

PEER-REVIEW REPORT

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Manuscript NO: 90590

Title: Can propensity score matching replace randomized controlled trials?

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05824612

Position: Peer Reviewer

Academic degree: PhD, PsyD

Professional title: Adjunct Professor, Assistant Lecturer, Reader in Health Technology Assessment, Research Assistant, Research Assistant Professor, Research Associate, Research Fellow, Research Scientist, Researcher, Science Editor, Statistician

Reviewer's Country/Territory: Iran

Author's Country/Territory: Singapore

Manuscript submission date: 2023-12-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-12-07 18:16

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty

Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I have thoroughly reviewed your paper and appreciate your efforts. I've given constructive feedback to improve your article's quality. Please consider my suggestions to enhance clarity and impact. Once you make revisions, I will gladly review the updated version. Your commitment to improvement is commendable, and I look forward to seeing how your article evolves. Best regards.

Abstract 1. While the abstract is informative, it might benefit from being more concise. Abstracts should quickly convey key points. Consider shortening some of the longer sentences and focusing on the most critical aspects of your study.

2. The abstract mentions the use of examples to demonstrate the versatility of PSM and RCT integration, but it doesn't provide any specific examples. Including at least one brief, illustrative example could enhance the reader's understanding.

3. While the abstract mentions the study examining applications, advantages, and considerations of using PSM with RCTs, it does not specify how this examination is conducted. Are you

conducting a meta-analysis, a systematic review, or using case studies? A brief mention of the methodology would be beneficial. 4. While the abstract discusses the potential of this integrated methodology, elaborating slightly on its implications for future research or clinical practice could add value. How might this integration change the way clinical trials are conducted or interpreted? 5. It might be useful to briefly specify what these ethical challenges are and how PSM integration with RCTs addresses them.

Introduction

- You mention the inception of PSM by Rosenbaum and Rubin in 1983. Briefly elaborating on how PSM has evolved since its inception and its impact on clinical research could provide valuable context.
- You've highlighted various challenges associated with RCTs. It might be beneficial to briefly discuss how these challenges have historically impacted the field of clinical research and decision-making.
- Elaborate on why integrating PSM with RCTs could be a solution to the challenges faced by RCTs. This would strengthen the argument for your study's significance.
- The introduction is dense with information. Consider breaking down complex sentences into shorter, clearer ones to enhance readability. This will make the introduction more accessible to a broader audience.
- Ensure that terms like EBM, PSM, and RCTs are clearly defined for readers who may not be familiar with them. This could either be done in the introduction or in a dedicated section for definitions.
- While you mention the intention to explore the strengths and limitations of both methodologies, it could be beneficial to hint at what unique contributions your study/review aims to make to the existing body of knowledge.
- You start by linking your discussion to EBM but don't revisit this connection later in the introduction. Drawing a clearer line between your study and its implications for EBM would strengthen your argument.

1. The description of the literature search is clear but could be enhanced by specifying the inclusion and exclusion criteria used for selecting studies. This would add transparency and reproducibility to your research process.

2. Both RCTs and PSM are well-explained, but consider emphasizing their distinct roles and applications in clinical

research more clearly. This could help readers better understand the rationale behind comparing these two methodologies. 3. While you've touched upon ethical considerations in RCTs, it would be beneficial to discuss ethical considerations in PSM as well, particularly regarding data privacy and the use of patient data from registries or electronic health records. 4. The section that compares RCTs and PSM is comprehensive. However, consider adding a brief summary at the end of each subsection to reinforce the key points and differences between the two methodologies. 5. You mention various models used in PSM, like logistic regression. It might be useful to discuss briefly how the choice of model can influence the outcomes and the limitations associated with these models. 6. The use of practical examples to illustrate the applications of RCTs and PSM is excellent. Ensure that these examples are relevant, recent, and accurately cited. 7. The discussion on the integration of RCTs and PSM is insightful. Expanding on how this integration could be implemented in practice, possibly with examples or case studies, would be beneficial. 8. Ensure that the methods section is aligned with the research question or hypothesis stated in your introduction. The connection between your methods and your research goals should be evident. 9. Discuss the limitations of your review method, such as potential biases in the literature search or limitations in the scope of the studies reviewed.

CONCLUSION 1. Start by briefly reiterating the key findings from your study to remind readers of the most significant points discussed. 2. Stress the importance of considering the context in which each method is applied. Highlight situations where one method may be more advantageous than the other. 3. Suggest areas for future research, particularly in improving the methodologies or exploring new ways of combining them for more robust research outcomes. 4. Acknowledge any limitations in your study or analysis, such as potential biases or aspects that were not covered but could be relevant. 5. Discuss the implications of your findings for evidence-based medicine, particularly how they can contribute to more informed decision-making in clinical practice.

ANSWERING REVIEWERS

Thank you very much for your feedback. We have incorporated your suggestions into this revision.

Abstract

Comment 1: While the abstract is informative, it might benefit from being more concise. Abstracts should quickly convey key points. Consider shortening some of the longer sentences and focusing on the most critical aspects of your study.

Reply 1: We have edited the abstract to make it more concise and convey key points.

Comment 2: The abstract mentions the use of examples to demonstrate the versatility of PSM and RCT integration, but it doesn't provide any specific examples. Including at least one brief, illustrative example could enhance the reader's understanding.

Reply 2: We have included the INTERACT2 trial as an example as suggested.

Comment 3: While the abstract mentions the study examining applications, advantages, and considerations of using PSM with RCTs, it does not specify how this examination is conducted. Are you conducting a meta-analysis, a systematic review, or using case studies? A brief mention of the methodology would be beneficial.

Reply 3: We have edited the abstract to mention that the article is a literature review. The methodology has also been updated with more details in the Methods section.

Comment 4: While the abstract discusses the potential of this integrated methodology, elaborating slightly on its implications for future research or clinical practice could add value. How might this integration change the way clinical trials are conducted or

interpreted?

Reply 4: We agree with the comment and have added a line suggesting researchers to consider adopting the integrated approach of PSM in RCT for better generalizability to patient populations for translation to clinical practice while maintaining the robustness of randomization.

Comment 5: It might be useful to briefly specify what these ethical challenges are and how PSM integration with RCTs addresses them.

Reply 5: We agree with the comment but feel that the ethical challenges might be better explained in the main text and have removed mention of ethical challenges in the abstract.

Introduction

Comment 6: You mention the inception of PSM by Rosenbaum and Rubin in 1983. Briefly elaborating on how PSM has evolved since its inception and its impact on clinical research could provide valuable context.

Reply 6: We agree with the comment and have included the emergence of newer models to compute propensity scores and the increase in uptake of use of PSM in clinical research.

Comment 7: You've highlighted various challenges associated with RCTs. It might be beneficial to briefly discuss how these challenges have historically impacted the field of clinical research and decision-making.

Reply 7: We agree with the comment and mentioned that the most common reason for premature discontinuation of RCTs is poor recruitment, and this premature termination of RCTs results in considerable waste of resources

Comment 8: Elaborate on why integrating PSM with RCTs could be a solution to the

challenges faced by RCTs. This would strengthen the argument for your study's significance.

Reply 8: We agree with the comment and mentioned that using the integrated approach allows for better generalizability due to greater external validity from use of PSM while still maintaining the robustness of randomization offered by RCT protocol.

Comment 9: The introduction is dense with information. Consider breaking down complex sentences into shorter, clearer ones to enhance readability. This will make the introduction more accessible to a broader audience.

Reply 9: We have revised the introduction section and tried to break down sentences to shorter and clearer ones

Comment 10: Ensure that terms like EBM, PSM, and RCTs are clearly defined for readers who may not be familiar with them. This could either be done in the introduction or in a dedicated section for definitions.

Reply 10: We have removed EBM as an abbreviation since it is not frequently mentioned. PSM and RCTs were defined before the abbreviations were used.

Comment 11: While you mention the intention to explore the strengths and limitations of both methodologies, it could be beneficial to hint at what unique contributions your study/review aims to make to the existing body of knowledge.

Reply 11: We agree with the comment and mentioned that the review aims to support the use of PSM in RCTs and supporting it with examples.

Comment 12: You start by linking your discussion to EBM but don't revisit this connection later in the introduction. Drawing a clearer line between your study and its implications

for EBM would strengthen your argument.

Reply 12: We have decided to remove EBM as it is not frequently touched on in the manuscript.

Methods

Comment 13: The description of the literature search is clear but could be enhanced by specifying the inclusion and exclusion criteria used for selecting studies. This would add transparency and reproducibility to your research process.

Reply 13: We agree with the comment and have included the inclusion and exclusion criteria in the methods section.

Main text

Comment 14: Both RCTs and PSM are well-explained, but consider emphasizing their distinct roles and applications in clinical research more clearly. This could help readers better understand the rationale behind comparing these two methodologies.

Reply 14: We agree with the comment and mentioned that RCTs are used to establish cause and effect in medical treatments and have a role in regulatory requirement while PSM usually is done when RCTs are not feasible.

Comment 15: While you've touched upon ethical considerations in RCTs, it would be beneficial to discuss ethical considerations in PSM as well, particularly regarding data privacy and the use of patient data from registries or electronic health records.

Reply 15: We agree with the comment and have included a paragraph touching on the ethical considerations of PSM.

Comment 16: The section that compares RCTs and PSM is comprehensive. However,

consider adding a brief summary at the end of each subsection to reinforce the key points and differences between the two methodologies.

Reply 16: We have added brief summaries at the end of each subsection to reinforce key points and differences

Comment 17: You mention various models used in PSM, like logistic regression. It might be useful to discuss briefly how the choice of model can influence the outcomes and the limitations associated with these models.

Reply 17: We agree with the comment and have mentioned that different models do lead to different result, however there is no guidelines or consensus on which models should be used, but Baser et al. proposed a set of criteria which can be considered to select the most appropriate model.

Comment 18: The use of practical examples to illustrate the applications of RCTs and PSM is excellent. Ensure that these examples are relevant, recent, and accurately cited.

Reply 18: The examples have been checked again together with their citations.

Comment 19: The discussion on the integration of RCTs and PSM is insightful. Expanding on how this integration could be implemented in practice, possibly with examples or case studies, would be beneficial.

Reply 19: Case studies in the form of examples cited demonstrate the ways PSM and RCTs can be integrated to provide different advantages.

Comment 20: Ensure that the methods section is aligned with the research question or hypothesis stated in your introduction. The connection between your methods and your research goals should be evident.

Reply 20: The methods section has been edited to reflect the connection with research goals.

Comment 21: Discuss the limitations of your review method, such as potential biases in the literature search or limitations in the scope of the studies reviewed.

Reply 21: We have added in a limitations section right before the conclusion segment.

Conclusion

Comment 22: Start by briefly reiterating the key findings from your study to remind readers of the most significant points discussed.

Reply 22: We agree with the comment and have amended the conclusion segment as recommended.

Comment 23: Stress the importance of considering the context in which each method is applied. Highlight situations where one method may be more advantageous than the other.

Reply 23: We agree with the comment and have amended the conclusion segment as suggested.

Comment 24: Suggest areas for future research, particularly in improving the methodologies or exploring new ways of combining them for more robust research outcomes.

Reply 24: Currently, we suggest the integration of PSM into RCTs rather than using either method alone. Not many studies have used this integration approach now so this is relatively new.

Comment 25: Acknowledge any limitations in your study or analysis, such as potential biases or aspects that were not covered but could be relevant.

Reply 25: We have acknowledged the limitations of our study in the newly added limitations section right before the conclusion.

Comment 26: Discuss the implications of your findings for evidence-based medicine, particularly how they can contribute to more informed decision-making in clinical practice.

Reply 26: We reiterated that the combined implementation of PSM and RCTs can improve generalizability of results and maintain robustness of randomization and suggest that both methods should be considered together in future research if possible.

Once again, we would like to thank the reviewer for his/her valuable comments and we appreciate their precious time spent on our manuscript. We have tried to incorporate as much of the comments as possible. Thank you very much.

Round 2

Specific Comments to Authors:

I have comprehensive review of your paper. I have provided constructive feedback aimed at enhancing the quality and impact of your article. I encourage you to consider these suggestions to improve clarity and overall effectiveness. Upon implementing revisions, I am eager to review the updated version. Your commitment to refining your work is admirable, and I am eager to witness the evolution of your article. Best regards.

1. The abstract mentions the limitations of traditional RCTs but doesn't provide a clear introduction or definition of propensity score matching for readers who may not be familiar with the concept. Consider incorporating a brief explanation of what PSM entails to ensure a comprehensive understanding.
2. Explicitly state how PSM addresses the limitations of RCTs. While it is mentioned that PSM increases external validity, providing specific examples or mechanisms through which PSM achieves this would enhance the clarity of the abstract.
3. The abstract mentions the application of PSM in an RCT related to the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2). While this is a good example, providing a concise summary of the specific findings or improvements achieved by integrating PSM in this study would strengthen the abstract.
4. Connect the findings to practical implications for clinical research and healthcare. How can the integration of PSM with RCTs benefit clinicians, researchers, and ultimately patients? Elaborate on the broader impact of adopting this combined approach.
5. The introduction effectively sets the stage for the importance of establishing causality in clinical research. However, consider breaking down the lengthy sentences for better readability. Particularly, the second sentence is quite dense and could be divided into more concise statements.
6. Expand on the limitations of RCTs, especially the statement, "poor recruitment is the most frequently reported reason for RCT termination." Provide examples or statistics to illustrate this point and enhance the understanding of the challenges faced in RCT implementation.
7. Clearly articulate how PSM addresses the limitations of RCTs. While the abstract mentions the potential benefits, it would be beneficial to elaborate on how PSM specifically helps overcome the ethical, external validity, and feasibility concerns associated with RCTs.
8. Consider providing brief explanations or definitions for terms such as "propensity score matching" to cater to a broader audience, including those less familiar with statistical methodologies.
9. Provide specific examples of studies that have successfully adopted an integrated approach, combining PSM with RCTs. Discuss the outcomes and advantages observed in these studies to highlight the practical implications of such integration.
10. Emphasize the need for a comprehensive literature review by briefly mentioning the scope of the review, including the types of studies, methodologies, and outcomes that will be explored.
11. Make sure to include specific citations for the studies mentioned in the text, such as Leinonen et al and Gui CH et al. This will enhance the credibility of your arguments and provide readers with the opportunity to explore these studies for further context.
12. Discuss potential limitations of both RCTs and PSM methodologies. Acknowledging limitations adds depth to the discussion and helps readers understand the contexts in which each method may be more or less appropriate.
13. check for the most recent studies or developments in the field, especially since your literature search was conducted up to November 2023.
14. Consider breaking down the content into subsections with clear headings to enhance readability and navigation for readers.
15. Ensure that the flow of information is logical and cohesive throughout the manuscript. Consider revisiting the

structure to maintain a smooth transition between sections. 16. Ensure that these are appropriately labeled, and consider including captions that provide a brief overview of the content. 17. Consider adding more visual elements (graphs, charts) to aid in conveying complex information, especially when discussing statistical models. 18. Check the consistency and formatting of the references. Ensure that the citation style is uniform throughout the manuscript. 19. If available, consider adding DOI numbers to facilitate easy access to cited articles. 20. Some sentences are complex and may benefit from simplification for better clarity. Ensure that the language used is accessible to a broad audience, including those who may not be experts in the field. 21. Proofread the manuscript for grammatical errors and typos. Clear and concise language enhances the overall quality of the manuscript. 22. While the manuscript discusses limitations related to the lack of studies directly comparing PSM and RCTs, consider expanding on potential biases or challenges in the studies reviewed. Addressing the limitations in the existing literature could provide a more nuanced perspective. 23. The conclusion is well-structured and provides a concise summary. Consider emphasizing the practical implications of the integration of PSM and RCTs and suggesting potential areas for future research. 24. Given the focus on ethical considerations throughout the manuscript, consider discussing the ethical implications of PSM in more detail, especially in the context of data privacy and the use of patient data. 25. Ensure that the information is up-to-date, especially if there have been significant developments or changes in the field since the last knowledge update in January 2022.

Thank you for your comprehensive review and feedback. We have incorporated your suggestions to further refine the manuscript as much as possible.

Comment 1: The abstract mentions the limitations of traditional RCTs but doesn't provide a clear introduction or definition of propensity score matching for readers who may not be familiar with the concept. Consider incorporating a brief explanation of what PSM entails to ensure a comprehensive understanding.

Response: We have added the sentence "... new frontiers in establishing causation in clinical research were opened up. PSM predicts treatment effects using observational data from existing sources such as registries or electronic health records, to create a matched sample of participants who received or did not receive the intervention based on their propensity scores, which takes into account characteristics such as age, gender and comorbidities. ..." to incorporate a brief explanation of what PSM entails to ensure a comprehensive understanding.

Comment 2: Explicitly state how PSM addresses the limitations of RCTs. While it is mentioned that PSM increases external validity, providing specific examples or mechanisms through which PSM achieves this would enhance the clarity of the abstract.

Response: We have added the sentence "... Given its retrospective nature and its use of observational data from existing sources, PSM circumvents the aforementioned ethical issues faced by RCTs. By matching study patient characteristics to that of the population of interest..." to explicitly state how PSM addresses the ethical limitations of RCTs. We have also revised the sentence "By matching study patient characteristics to that of the population of interest, PSM greatly increases the external validity and facilitates generalization of results to the wider

population.” to “Majority of RCTs exclude elderly, pregnant women and young children; thus, evidence of therapy efficacy is rarely proven by robust clinical research for this population. On the other hand, by matching study patient characteristics to that of the population of interest, including the elderly, pregnant women and young children, PSM allows for generalization of results to the wider population and hence greatly increases the external validity.” in order to explain the mechanism through which PSM increases external validity.

Comment 3: The abstract mentions the application of PSM in an RCT related to the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2). While this is a good example, providing a concise summary of the specific findings or improvements achieved by integrating PSM in this study would strengthen the abstract.

Response: We have revised the sentence “For example, in an RCT investigating the impact of mannitol on outcomes among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2), PSM was incorporated in its analysis to account for the variability in baseline covariates between the treatment and control arms, thus providing a fairer comparison.” to “For example, in an RCT investigating the impact of mannitol on outcomes among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2), the baseline characteristics of comorbidities and current medications between treatment and control arms were significantly different despite the randomization protocol. Therefore, PSM was incorporated in its analysis to create samples from the treatment and control arms that were matched in terms of these baseline characteristics, thus providing a fairer comparison for the impact of mannitol.” in order to provide a concise summary of the specific findings and improvements achieved by integrating PSM in this study.

Comment 4: Connect the findings to practical implications for clinical research and healthcare. How can the integration of PSM with RCTs benefit clinicians, researchers, and ultimately patients? Elaborate on the broader impact of adopting this combined approach.

Response: We have added the phrase “... Future research should consider integrating the use of PSM in RCTs to better generalize outcomes to target populations for clinical practice and thereby benefit a wider range of patients, while maintaining the robustness of randomization offered by RCTs.” to connect the findings to explain how the integration of PSM with RCTs can benefit patients. The benefits to clinicians and researchers have been mentioned which are to better generalize outcomes to target populations for clinical practice.

Comment 5: The introduction effectively sets the stage for the importance of establishing causality in clinical research. However, consider breaking down the lengthy sentences for better readability. Particularly, the second sentence is quite dense and could be divided into more concise statements.

Response: The sentence “Determining the degree to which an intervention can modulate changes in a patient’s health lays the groundwork for evidence-based medicine to take shape, ensuring the best health outcomes can be attained for patients.” has been revised to “The foundation for evidence-based medicine depends on the influence of interventions on patients’ health. To attain the best outcomes for patients, causal relationships must be studied objectively.” for better readability.

Comment 6: Expand on the limitations of RCTs, especially the statement, "poor recruitment is the most frequently reported reason for RCT termination." Provide examples or statistics to illustrate this point and enhance the understanding of the challenges faced in RCT implementation.

Response: We have revised the sentence "... need for resources to conduct trials, and lack of feasibility to continue trials for a prolonged duration.(2) In particular, poor recruitment is the most frequently reported reason for RCT termination, leading to a considerable waste of scarce research resources.(3)" to "... need for resources to conduct trials, and lack of feasibility to continue trials for a prolonged duration due to manpower and resource constraints^[2]. In particular, a retrospective cohort study of 1017 RCTs found that poor recruitment is the most frequently reported reason for RCT termination, accounting for up to 40% of the total discontinuations^[3]. This in turn leads to a considerable waste of scarce research resources." in order to provide statistics to illustrate this point.

Comment 7: Clearly articulate how PSM addresses the limitations of RCTs. While the abstract mentions the potential benefits, it would be beneficial to elaborate on how PSM specifically helps overcome the ethical, external validity, and feasibility concerns associated with RCTs.

Response: The elaboration on how PSM specifically helps overcome the ethical, external validity, and feasibility concerns associated with RCTs is discussed in the main body of the manuscript and can be found under the main heading "Can propensity score matching replace randomized controlled trials?". How PSM addresses ethical concerns can be found under the sub-heading "Context and objectives" paragraph 3 beginning with "Moreover, there is the need to consider the ethicality of using placebos, which is often done in the control group in RCTs...". How PSM overcomes external validity concerns can be found under the sub-heading "Better external validity". How PSM addresses feasibility concerns can be found under the sub-heading "Feasibility".

Comment 8: Consider providing brief explanations or definitions for terms such as "propensity score matching" to cater to a broader audience, including those less familiar with statistical methodologies.

Response: We have added the sentence "... new frontiers have opened to establish causality in clinical research^[4]. PSM predicts treatment effects using observational data from registries to create a matched sample of participants who received or did not receive the intervention based on their propensity scores, which is associated with baseline characteristics such as age. Since then, newer models of computing propensity scores have emerged and the uptake of PSM in research has increased exponentially...".

Comment 9: Provide specific examples of studies that have successfully adopted an integrated approach, combining PSM with RCTs. Discuss the outcomes and advantages observed in these studies to highlight the practical implications of such integration.

Response: The examples of studies that have successfully adopted an integrated approach and their outcomes and advantages can be found under the main heading "Use of propensity score matching in randomized controlled trials" and its subsequent sub-headings: "Randomized controlled trials with imperfect randomization", "Non-compliance to protocol", "Translation of randomized controlled trial data to clinical practice".

Comment 10: Emphasize the need for a comprehensive literature review by briefly mentioning the scope of the review, including the types of studies, methodologies, and outcomes that will be explored.

Response: We have revised the segment “Therefore, this literature review aims to explore the integration of PSM studies as a potent adjunct to RCTs in establishing causality in healthcare, potentially circumventing the concerns and quandaries surrounding RCTs as a research modality. We report the current use of PSM in RCT studies and its advantages as compared to either method alone. It is hoped that the findings of our review would help guide researchers and clinicians alike to consider adopting the use of PSM in RCTs in future clinical research.” to “Therefore, this literature review aims to explore the integration of PSM studies as a potent adjunct to RCTs in establishing causality in healthcare, potentially circumventing the concerns and quandaries surrounding RCTs as a research modality. We report the advantages and limitations of RCTs and PSM studies, as well as their synergistic implementation and its advantages as compared to either method alone. It is hoped that the findings of our review would help guide researchers and clinicians alike to consider adopting the use of PSM in RCTs in future clinical research.” in order to mention the scope of the review, types of studies (RCTs and PSM studies), methodologies (literature review), and outcomes that will be explored.

Comment 11: Make sure to include specific citations for the studies mentioned in the text, such as Leinonen et al and Gui CH et al. This will enhance the credibility of your arguments and provide readers with the opportunity to explore these studies for further context.

Response: The specific citations for the studies mentioned in the text have been updated.

Comment 12: Discuss potential limitations of both RCTs and PSM methodologies. Acknowledging limitations adds depth to the discussion and helps readers understand the contexts in which each method may be more or less appropriate.

Response: The limitations of each method are discussed under the main headings “Can propensity score matching replace randomized controlled trials?” and “When are randomized controlled trials better?” and their subsequent sub-headings. The former describes the limitations of RCTs and the contexts in which PSM may be more appropriate. The latter heading and subsequent sub-headings describes the limitations of PSM and the contexts in which PSM may be more appropriate.

Comment 13: check for the most recent studies or developments in the field, especially since your literature search was conducted up to November 2023.

Response: We have checked and have not found any new significant developments in the field within the past 2 months as of 5 February 2024.

Comment 14: Consider breaking down the content into subsections with clear headings to enhance readability and navigation for readers.

Response: We have reformatted the main headings and sub-headings for better clarity, readability and navigation for readers.

Comment 15: Ensure that the flow of information is logical and cohesive throughout the manuscript. Consider revisiting the structure to maintain a smooth transition between sections.

Response: We have reviewed the manuscript and revised it accordingly.

Comment 16: Ensure that these are appropriately labeled, and consider including captions that provide a brief overview of the content.

Response: We have added captions to Figures 1 and 2.

Comment 17: Consider adding more visual elements (graphs, charts) to aid in conveying complex information, especially when discussing statistical models.

Response: Thank you for your suggestion, we have decided not to include figures to discuss the randomization methods, methods of computing propensity scores and matching methods as it is not the main focus of the review and a brief summary of each method is provided in Tables 1-3.

Comment 18: Check the consistency and formatting of the references. Ensure that the citation style is uniform throughout the manuscript.

Response: We have revised the references accordingly.

Comment 19: If available, consider adding DOI numbers to facilitate easy access to cited articles.

Response: We have revised the references accordingly

Comment 20: Some sentences are complex and may benefit from simplification for better clarity. Ensure that the language used is accessible to a broad audience, including those who may not be experts in the field.

Response: We have revised the manuscript accordingly.

Comment 21: Proofread the manuscript for grammatical errors and typos. Clear and concise language enhances the overall quality of the manuscript.

Response: We have revised the manuscript accordingly.

Comment 22: While the manuscript discusses limitations related to the lack of studies directly comparing PSM and RCTs, consider expanding on potential biases or challenges in the studies reviewed. Addressing the limitations in the existing literature could provide a more nuanced perspective.

Response: We have revised the limitations section: “There are some limitations to our review. The studies reviewed in this article were not able to do a direct comparison between PSM and RCTs due to the nature of their investigation. Nevertheless, these studies were able to describe the advantages and disadvantages of each method collectively. In addition, there is a lack in reporting of the disadvantages of integrating PSM into RCTs. Further studies are therefore required to examine the limitations of the synergistic implementation of PSM and RCTs concurrently.”

Comment 23: The conclusion is well-structured and provides a concise summary. Consider emphasizing the practical implications of the integration of PSM and RCTs and suggesting potential areas for future research.

Response: We have revised the sentence “The combined implementation of both approaches can help improve the generalizability of results to a wider range of patients and specific patient populations of interest for translation to clinical practice, while maintaining the robustness of randomization and high internal validity.” Potential areas for future research have been suggested in the limitations section and we feel that including it in the conclusion section would break the overall flow and structure of the conclusion.

Comment 24: Given the focus on ethical considerations throughout the manuscript, consider discussing the ethical implications of PSM in more detail, especially in the context of data privacy and the use of patient data.

Response: We have added more details: “... particularly regarding data privacy and the use of patient data from electronic health records and registries. As it is often not practical to seek the consent of individuals to utilize observational data for retrospective studies, institutional review boards usually waive the need to obtain consent for using personal data in most circumstances. This is provided that the results are published in the form that does not identify the individual. Despite that, the issue of data privacy in the face of the retrospective nature of PSM studies must not be ignored. Nevertheless, the advent of methods such as propensity score-based pooling and combining distributed linear regression with propensity score modelling can avoid the need for individual-level data while maintaining analytic integrity, thereby offering protection of patient privacy^[39,40]. Hence, PSM could still prove to be the better method when ethical issues arise.”

Comment 25: Ensure that the information is up-to-date, especially if there have been significant developments or changes in the field since the last knowledge update in January 2022.

Response: We have checked and have not found any new significant developments in the field within the past 2 months from our search date as of 5 February 2024.