Rapid Statistical Review Report for your manuscript

Title: Rheumatoid arthritis and cardiovascular risk: Retrospective matched cohort analysis based on the RECORD study of the Italian society for rheumatology.

Job Code: CATER_4795_5

Dear Author,

Welcome to Editage and thank you for giving us the opportunity to work with you!

For ease of understanding, this report is divided into the following sections:

Section 1	**TECHNICAL CHECKS** Details of the checks that we have undertaken as part of the review
Section 2	**OVERVIEW & NEXT STEPS** Recommended next steps for you
Appendix	Frequently Asked Questions

We will be happy to provide further clarifications or answer any queries you may have about this report.

We look forward to continuing to be your partner in your publication journey towards acceptance!

Best regards,
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Section 1: TECHNICAL CHECKS

➢ Review of research design & methods

- The study aimed to implement an algorithm to identify patients with rheumatoid arthritis (RA) using the administrative healthcare databases (AHDs) information and to measure the prevalence, incidence, and mortality of RA.
- The study utilized a retrospective matched-cohort design, which helps in minimizing selection bias and allows for comparison between RA and non-RA cohorts, providing valuable insights into CV risk factors and events in RA patients.
- Retrospective studies are susceptible to recall bias, incomplete data, and inability to establish causality.
- With a total of 21,201 RA patients and 249,156 non-RA subjects, the study had a large sample size, enhancing the statistical power and generalizability of the findings.
- The study followed patients from January 2009 to December 2013, providing a longitudinal perspective on CV events and risk factors, which is crucial for understanding the temporal relationship between RA and CV outcomes.
- The study lacked clinical data such as disease activity scores, smoking status, and body weight, which are important confounders in assessing CV risk.
- The study obtained ethical approval from the Pavia University Hospital Ethics Committee and adhered to the principles outlined in the Declaration of Helsinki, ensuring ethical conduct in research involving human participants.
- Although the study assessed persistence and adherence to CV risk-lowering therapies, it did not capture reasons for non-adherence or discontinuation of medications, limiting the interpretation of medication utilization patterns.
- The study primarily focused on the Lombardy region of Italy, which may limit the generalizability of findings to other populations.
- The study only captured CV events occurring during hospitalizations, potentially underestimating the true incidence of events, especially those occurring in outpatient settings or in patients who died before hospitalization.

➢ Data analysis

- The statistical analysis software employed in the article was R (version 3.3).
- The study conducted a thorough analysis of cardiovascular risk factors and events among rheumatoid arthritis (RA) patients compared to the general population, utilizing both univariate and multivariate statistical models.
- With a sizable RA cohort (N = 21,201) and matched non-RA subjects (N = 249,156), the study benefits from a large sample size, enhancing the statistical power and generalizability of the findings.

- The study adjusted for potential confounders such as gender, age, and cardiovascular (CV) risk factors in the multivariate analysis, which strengthens the validity of the results.
- While the study adjusted for gender, age, and CV risk factors in the multivariate analysis, other potential confounders such as disease duration, disease severity, and medication use were not accounted for.
- The results are presented clearly, with detailed tables (Tables 1 and 2) summarizing the incidence rates of CV events and the relationship between CV risk factors and events.
- Given the numerous comparisons conducted in the study (e.g., incidence rates of multiple CV events), there's a risk of Type I error inflation. Employing correction methods such as Bonferroni adjustment could address this issue.
- Additional statistical tests such as survival analysis (e.g., Kaplan-Meier curves, Cox proportional hazards models) could provide insights into time-to-event outcomes and account for censoring.
- Potential mediation pathways (e.g., inflammation, medication adherence) underlying the association between RA and CV risk through appropriate statistical methods could be done by causal mediation analysis.

➢ Critical appraisal of strengths/weaknesses

- The study utilized a large sample size, with 21,201 patients in the RA cohort and 249,156 subjects in the non-RA cohort. This large sample size enhances the statistical power of the study and increases the generalizability of the findings.
- Employing a retrospective matched cohort design allows for the comparison of outcomes between patients with RA and non-RA subjects, while controlling for potential confounders such as age and gender.
- The study comprehensively assessed cardiovascular risk factors and events, including hypertension, diabetes, dyslipidemia, atrial fibrillation, heart failure, stroke, and myocardial infarction.
- The study's retrospective design limits the ability to establish causal relationships between RA and cardiovascular events. It also relies on the accuracy and completeness of medical records, which may introduce information bias.
- The study relies on administrative healthcare databases, which may lack detailed clinical information such as disease severity, disease duration, medication adherence, lifestyle factors, and socioeconomic status.
- While the study matched patients on age and gender, there may still be unmeasured confounding factors that influence the association between RA and cardiovascular events. Variables such as smoking status, obesity, physical activity, and family history of cardiovascular disease could potentially impact the study outcomes.
- The study followed patients from January 2009 to December 2013, which may not capture long-term cardiovascular outcomes associated with RA.

Section 2: OVERVIEW & NEXT STEPS

SUMMARY

The research article titled "Rheumatoid Arthritis and Cardiovascular Risk: A Retrospective Matched Cohort Study" delves into the relationship between rheumatoid arthritis (RA) and cardiovascular (CV) risk using data from the RECORD project in Italy. The study adopts a retrospective matched cohort design and analyzes data from administrative healthcare databases to assess the prevalence, incidence, and mortality of RA and associated CV events. Noteworthy findings include higher rates of CV risk factors such as hypertension and diabetes mellitus among RA patients, along with increased incidence rates of AF, heart failure, and myocardial infarction compared to non-RA subjects.

Strengths of the study lie in its large sample size, comprehensive assessment of CV risk factors and events, and rigorous statistical analysis. However, several limitations should be considered. These include the retrospective nature of the study, potential data limitations from administrative databases, and the presence of unmeasured confounding factors. Additionally, the study's reliance on short-term follow-up limits insights into long-term cardiovascular outcomes in RA patients.

To enhance the study's reliability and applicability, future research could validate findings in larger, longitudinal cohorts, address potential confounding variables, and incorporate additional clinical information to provide a more comprehensive understanding of the relationship between RA and cardiovascular risk.

RECOMMENDATIONS

We have listed focus areas that should be addressed to improve the robustness of your study.

Major issues:

	Focus area	Recommendations
1.	Retrospective design	Longitudinal studies can capture long-term cardiovascular outcomes in RA patients.
2.	Potential type I errors	Correct for multiple comparisons using appropriate statistical methods, such as Bonferroni correction.
3.	Selection bias	Rigorous matching criteria will minimize selection bias and ensure comparability.
4.	Generalizability	Conducting the study in diverse populations will enhance the generalizability of the results.
5.	Bias and their effects	Different biases that have been considered, and the efforts taken to address them, should be mentioned.

6.	Short term follow-up	Extending follow-up duration will capture long-term cardiovascular outcomes accurately.

Minor issues:

	Focus area	**Recommendations**
1.	Confidence intervals	Confidence intervals would have indicated the precision of estimates.
2.	Effect sizes	Reporting effect sizes alongside significance tests would facilitate interpretation of the magnitude of observed effects.
3.	Inadequate reporting of results	Comprehensive reporting of results, including sensitivity analyses and subgroup analyses could be done.

If you would like us to run the analysis on your dataset to validate your results and verify reproducibility, please ask us about our full Statistical Check service. We can also conduct additional analysis, if needed. You can look at our website for the full suite of Statistical Analysis and Review Services.

Write to us at request@editage.com for a quote customized to your requirements.

Best regards,

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Appendix: FREQUENTLY ASKED QUESTIONS

Q: What is the technical experts' qualification?
A: Our experts reviewers have a minimum qualification of a PhD in your relevant subject area and have extensive experience in publishing and peer-reviewing manuscripts. These experts also have experience of writing and publishing their own manuscripts in peer-reviewed journals. Many of our experts even serve as peer reviewers on journal editorial boards.

Q: The expert has advised collection of additional data. Will the analysis be redone free of charge, once this is collected?
A: Data analysis is not included as part of this service. You can write to us with your requirements for data analysis – we will give you a quote based on the type and complexity of the analysis needed.

Q: I would like the Results and Discussion sections to be written down, based on the data analysis results. Can you do this as part of the service?
A: No, writing parts or all of the manuscript is not included as part of this service. Please ask us about our Writing Lite service for this. Please note that this service may not be available in your country (depending on the local policies).

Q: The Rapid Statistical Review did not reveal significant gaps in my work. Since this is not of use to me, will you provide me a refund?
A: The Rapid Statistical Review will be carried out to meet the full scope of the service. We will only make suggestions for rework when it is warranted and is needed to improve the statistical robustness of your study. We will not provide a refund in such cases, since the service scope has been met. If your manuscript is returned after peer review with comments that point out gaps in statistical methods or analysis that could have been identified during this service, we will offer you a full refund.

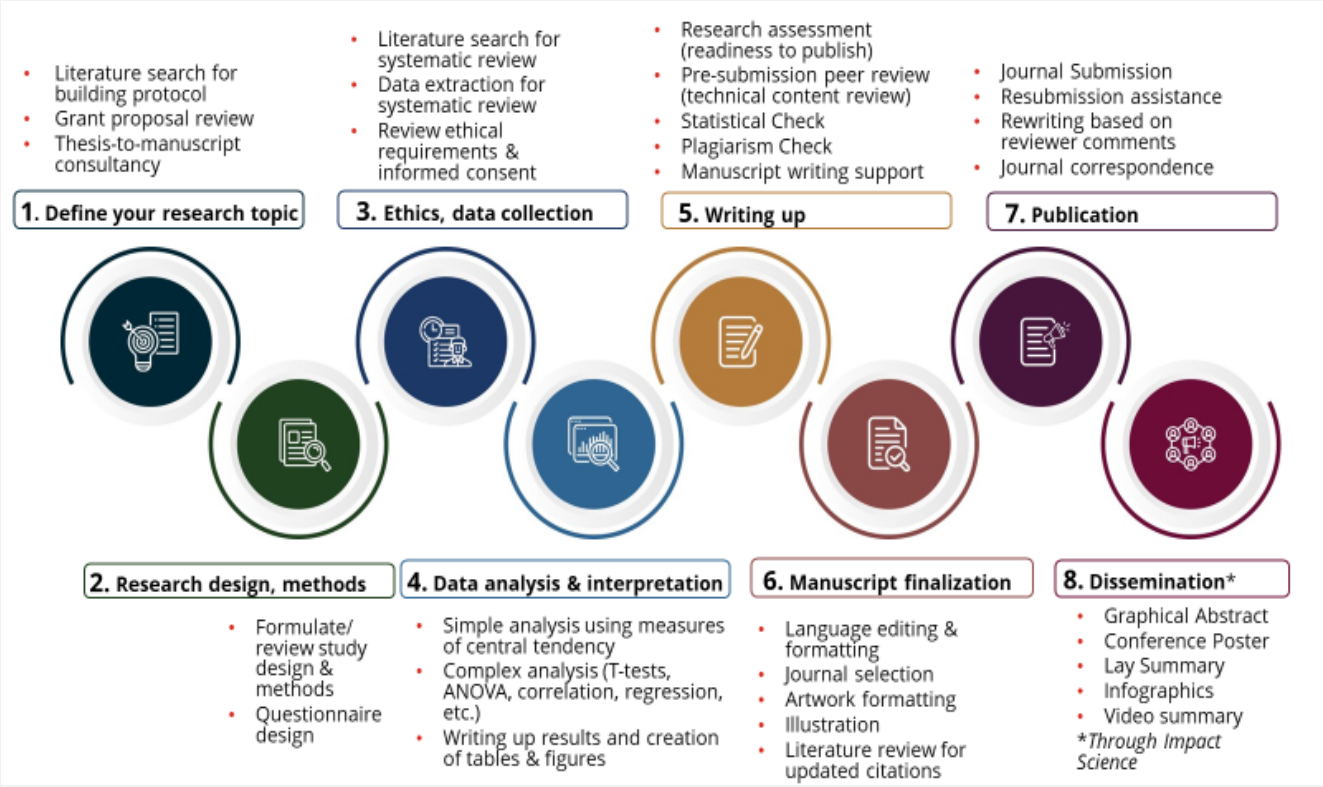
Q: Is there post service support?
A: This is a one-round service. However, if you have any queries about any of the deliverables, you can get in touch with us at any time.

Appendix: Other service offerings - Example pack with timelines*

This is an example of a publication support 'pack' that includes services to help improve scientific content and check for overlapping text, recommending appropriate journals, editing and formatting the manuscript, and submitting the manuscript to the selected target journal. You can choose to use these and many other services (including literature review, graphical abstract, etc.) as you see fit for your manuscript. We will be happy to customize a pack/service to your needs!

Appendix: Comprehensive support through your research and publication journey

We understand that support could be needed at any stage of your research and publication journey – so we have service offerings to work with you from the point of thinking about a research topic, all the way until publishing and disseminating your work. We will be happy to customize a pack/service to your needs!



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