Author's response to reviews

Title: Management of hyperlipidemia among patients with rheumatoid arthritis in the primary care setting

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BMC Musculoskeletal Disorders

Dear Editorial Board and Reviewers,

Please accept our revised manuscript titled, “Management of hyperlipidemia among patients with rheumatoid arthritis in the primary care setting.” We thank the reviewers for their thoughtful comments regarding our manuscript and have addressed these comments in a point-by-point fashion below.

Thank you for your consideration of our manuscript.

Sincerely,

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Reviewer 1

1. Title: Management of hyperlipidemia among patients with rheumatoid arthritis in the primary care setting.

2. Abstract: The abstract does describe the study design of a retrospective observational study that defines a cohort of rheumatoid arthritis (RA) patients from the administrative health database of one academic center.

3. Is the question posed original, important and well defined? Yes, this study does address an important issue for clinicians taking care of rheumatoid arthritis patients. In the background, the authors review the literature for the increased prevalence of coronary artery disease (CAD) for people with RA. The authors’ rationale for the study presents the importance of primary health prevention for CAD in RA patients and questions whether a care gap exists for the identification and management of cardiovascular risk factors.

4. Objectives: This study has three objectives. First objective is to determine the prevalence of hyperlipidemia screening in RA patients. The second goal is to ascertain if lipid lowering therapy is initiated in RA patients with an indication. Finally the authors assess the performance of the Framingham cardiovascular risk score with European League Against Rheumatism (EULAR) modifier to identify further RA patients at risk.

5. Methods – Setting: This is a retrospective cohort study set in the University of Pennsylvania Health System and utilizes data from the electronic medical record of this academic health system. The recruitment of the cohort takes place from January 2005 to February 2010. Follow up for the cohort is a minimum of one year and a maximum of three years from cohort entry.

Minor Essential Revision - In the description of the study population (third paragraph in Materials and Methods), It is not clear what proportion of the cohort were followed before 2010 and how many were followed after 2010. The authors themselves cite that the EULAR guidelines for the management of cardiovascular risk factors were published at the end of the cohort recruitment period. The dissemination of the guidelines may have influenced a change in practice and therefore the temporal context of the data retrieval could be important.

We apologize for the confusion. We have only included data up to the date of the publication of the EULAR guidelines. We have clarified this in the text. (page 6, lines 33-34)

6. Methods – Participants: The criteria used for identification of the cohort is only one physician diagnosis code for RA which is interesting as most administrative health database studies find that case definitions for RA using more than one outpatient physician diagnostic code is optimal unless the code is from a specialist such as a rheumatologist. However one of the inclusion criteria for the study was receipt of
medical care for 2 or more outpatient visits which is in keeping with increasing validity of case definitions with repeated visits.

Other inclusion criteria (third paragraph under Materials and Methods) included age greater than 18, care from a primary physician (internal medicine, geriatrics or family medicine) and one year of follow up time. Note-worthy was the outpatient visits could also be provided by a physician extender such as a nurse practitioner or physician assistant.

Minor Essential Revision - Regarding the validation (fourth paragraph under Materials and Methods), the positive predictive value (PPV) for the case algorithm is high but this is a cohort from one health system. I would suggest the authors provide the data for the validation of case identification in a supplemental file to also include sensitivity, specificity, PPV and negative predictive value (NPV).

The reviewer is correct: we used only one code for RA to define rheumatoid arthritis and found that, within this population, the positive predictive value (PPV) was sufficiently high that additional codes were not required. We reported this validation step in order to assure readers of the accuracy of this code in our health system’s database. We do not intend for this to serve as a validation with external validity for other data sources. In a typical “code” validation, all cases with the code are identified (“test positive”) and then within those with the “positive tests,” those that are “true positive” and “false positive” are defined. Thus, the only statistic that can be computed based on these data is the positive predictive value. Defining sensitivity, specificity and negative predictive value would necessitate drawing patients without codes for rheumatoid arthritis and determining how many patients actually have RA based on chart review. Given the low yield of this exercise in supporting the study methods and results, we did not perform this task. Given the remarkably high PPV, we also did not assess the sensitivity and specificity of adding additional codes to a single code for RA.


7. Variables: The authors include appropriate covariates in their analysis. Minor Essential Revision - One question for the authors is why biologic agents were left out and what impact this could have on the results (Sixth paragraph under Materials and Methods)?

We apologize for the confusion. By “DMARDs” we meant both biologic and non-biologic DMARDs and have added this for clarity to the methods section. (page 8, line 87)

8. Results:
Discretionary Revision - A third of the cohort is being treated with DMARDs
(Table 1 - Patient Demographics). The authors may want to comment whether they feel that this is reflective of a certain level of RA disease activity and contribute to the cardiovascular risk of their cohort?

The reviewer correctly notes that approximately one third of our cohort was using DMARDs in the baseline period. (Of note, some of these patients later started therapy during the period of observation). While this seems like a very low percentage, this has been noted in other primary care populations as well. A recent paper describes this phenomenon in the US (as well as 3 preceding papers by the same group) and another population-based study of RA in the UK in 2002 demonstrated that only approximately one third of patients were receiving a DMARD at that time. We have added a comment regarding the possibility of missing DMARD prescriptions to the discussion (page 12, lines 196-199).

References:


Discretionary Revision - It would be of interest to know what proportion of visits were provided by the physician extender and whether the authors would be concerned about any potential bias as a result.

We did not include indicators of care provider type (including physician extenders) in the final datasets, but from the original data pull, approximately 6-7% of visits were conducted by physician extenders. We do not believe this should have induced bias nor affected generalizability as physician extenders commonly provide primary care.

Minor Essential Revision - For the flow diagram in figure 1, please add explanation of why the numbers do not add up between second last box of RA patients screened and the final box of RA patients with lipid levels and no contraindications for therapy (likely overlap between exclusion criteria).

We apologize for this mistake. We have corrected figure 1. Thank you for pointing this out!
Minor Essential Revision - The labelling of the categories of the pie charts for figure 2 is not immediately clear (‘after start’, ‘before start’).
As recommended by reviewer 2, we have removed Figure 2.

9. Do the figures appear to be genuine, i.e. without evidence of manipulation? Yes

10. Is the interpretation (discussion and conclusion) well balanced and supported by the data? The study does identify a care gap in the identification and management of cardiovascular risk factors. As the authors have stated, this has been seen in other studies. However it is not clear what proportion of the observed events took place before and after the publication of EULAR 2010 Recommendations for Cardiovascular Risk Management in RA Patients.

Minor Essential Revision - It would be helpful for the authors to place the results of the study in the temporal context of the EULAR guidelines (e.g. this study shows a care gap exists after the dissemination of EULAR recommendations).
Thank you for this suggestion. We have added a comment regarding the temporal relationship to the EULAR recommendations in the conclusion (page 14, lines 230-231).

10. Are limitations of the work clearly stated? Yes, the authors identify some of the limitations of the study including decreased generalizability of this one center study, incomplete data on several variables that may lead to an underestimation of cardiovascular risk and possible selection bias with the exclusion of participants who did not have complete lipid panels. One strength of the study is that it sought to assess the performance of the cardiovascular risk score with the EULAR multiplier for RA patients.

Discretionary revision - It would be interesting to have more discussion about the execution of this risk calculation and whether the authors have any comments about if their results can influence future research (First and second paragraphs under discussion).
Thank you for this suggestion. We have added a comment regarding the need for better risk stratification methods in the discussion (page 12-13, lines 202-206).

11. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes.

Reviewer 2
Research Article: Management of hyperlipidemia among patient with rheumatoid arthritis in the primary care setting

Minor Essential Revisions:
1. It would strengthen clarity in the manuscript for the authors to include within the methods, how the covariate definitions are determined.
We apologize for this omission. We identified diagnoses via ICD-9 codes. This has been added to the methods (page 8, lines 91-92).
2. Please further clarify whether the outcome measure related to lipid lowering therapy is the dispensing of a prescription for lipid lowering therapy or the compliance with the filling of the prescription.  
This is also an important point and has been added to the methods as well (page 7, lines 70-73).

Major Compulsory Revisions:
1. If the data source permits, utilization of BMI categories rather than ‘obesity’ would be preferable.  
A significant proportion of patients had missing height and weight data. We have added BMI to Tables 1 and 2 but did not include in the model given the significant amount of missing data.

2. The authors should expand on and hypothesize as to why application of the EULAR multiplier did not have a larger effect.  
Thank you for this suggestion. We have added a paragraph to the discussion about the use of the EULAR multiple. (page 12, line 189-206)

3. The authors may wish to consider whether patients had preferred or had been advised in regards to non-pharmacologic means of addressing hyperlipidemia including diet and exercise.  
This is an important point and has been added to the limitations (page 11, lines 193-195).

4. Figure 2 does not appear to be providing additional information, nor does it appear to be referenced within the manuscript text and therefore can be removed  
We agree and have removed figure 2.

Editorial Requests
1) Requesting Ethics statement:  
Research involving human subjects (including human material or human data) that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html). A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.  
This is located within the Methods section, lines 115-118.

2) Requesting consent statement:  
Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.  
This has been added to the Methods section, lines 116-117.