PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Do biological disease-modifying anti-rheumatic drugs reduce the spinal fracture risk related to ankylosing spondylitis? A longitudinal multi-registry matched cohort study
AUTHORS	Robinson, Yohan; Olerud, Claes; Willander, Johan

VERSION 1 – REVIEW

REVIEWER	Abhijeet Danve Yale University, USA
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	The authors have attempted to answer a very important question about effect of TNF inhibitors on spinal fracture risk. However this study may not be a well-designed study as far as study design, methodology, description, clarity, fluency and justification. Below are few comments- Abstract- Page3 line 14- clarify “decelerated” Describe the study design- Cross sectional? Cohort? What was the control population? Methods in abstract need more details including description of statistical methods. Can confidence intervals contain the very number around which 95% other observations are? What about 2.5% observations below median 9 years and median 11 years? I ntroduction- Not all patients fuse. Please restructure the sentence. bDMARD now also includes IL-17 inhibitors. Methods= Participants AS pt data was from 1987 to 2014. But prescription data was from 2005 to 2014. What is the rationale of limiting age between 40 and 70? Patients can have active AS before age 40 years as well as after age of 70 years. Description of the statistical tests lacks clarity. Description of results is also not fluent and meaningful.

REVIEWER	Ernst Feldtkeller Deutsche Vereinigung Morbus Bechterewe, Germany
REVIEW RETURNED	08-Sep-2017

GENERAL COMMENTS	The manuscript answers important questions and should be accepted for publication. It contains, however, some severe errors that have to be corrected. 1) In the Key Points, in the abstract and in the Conclusions it is

	mentioned that “activity restrictions should not be changed”. This can easily be misunderstood. Physical activity (including appropriate sports like swimming or Nordic walking) is important for patients with ankylosing spondylitis to relieve inflammation and prevent stiffening. It should not be restricted. The only restriction is that dangerous sports like football etc. have to be avoided and that fall prevention has to be regarded. 2. In the Results paragraph of the abstract, “age 67±19” has to be replaced by “age 67±19 years”. 3. That 59% of the AS patients received their AS diagnosis in conjunction to their first spinal fracture, is a terrible result and should be discussed in detail. 4. AS is not a “rheumatoid disease” as mentioned in the Introduction, but a rheumatic disease. The word “rheumatoid” is only used in connection with rheumatoid arthritis (RA). 5. AS is not “affecting all joints of the axial skeleton” as mentioned in the Introduction. The affection may also be restricted to the sacroiliac joints or the lumbar spine. There is only a tendency to affect the whole spine. 6. The sentence “Since only patients with an active form of AS were of interest for this study, patients younger than 40 and older than 70 years in 2014 were excluded“ (page 8) is irritating. The disease is most active in the first years after disease onset. The exclusion of patients younger than 40 years is however reasonable because patients with a progressed ankylosis are more at risk of a spinal fracture. 7. The abbreviations CCI used in the results chapter and in the Tables has to be explained. 8. What do you mean with “AS was diagnosed within half a year from the first spinal fracture diagnosis”? Half a year before or after the fracture? 9. There is no “change in the classification criteria for AS during the last decade from the modified New York criteria to Assessment of Spondyloarthritis International Society (ASAS) criteria” (page 13). The modified New York criteria are the classification criteria for AS also today, and ASAS has created classification criteria for the disease group of axial Spondyloarthritis (AS and non-radiographic axial SpA). 10. The abbreviation SCI used in the tables has also to be explained. 11. Every reference has to be listed only once. Reference 33 is identical with reference 3. I have not checked for further duplicates. 12. In some of the references the year of appearance is missing Reference 3 appeared in 2011, reference 36 appeared in 2016. 13. In reference 20, Landewe has to be re

REVIEWER	Ennio Lubrano Università Del Molise, Campobasso, Italia
REVIEW RETURNED	13-Sep-2017

GENERAL COMMENTS	This is an interesting population based multi-registry study aimed to investigate whether the biologic treatment for AS patients reduced the spinal fracture incidence. The study is well written with a simple and clear design and methodologically correct. I have only a few considerations that authors might address: Even if bDMARDs can increase bone density (see ref 5-6) which, in

	turn, could reduce the spinal risk fracture, no clear data demonstrated that an increase of bone density are in keeping with lower risk. In other words, the data obtained from this study are very clear but obviously did not address the pathophysiological role of bDMARDs on osteoporosis. In my mind, as other possible explanation of the results obtained, the bDMARDs were prescribed in more severe AS patients with stronger bio-mechanical consequences of the disease.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Abhijeet Danve
Institution and Country: Yale University, USA
Competing Interests: I have no competing interests.

Comment: The authors have attempted to answer a very important question about effect of TNF inhibitors on spinal fracture risk. However, this study may not be a well-designed study as far as study design, methodology, description, clarity, fluency and justification.

Below are few comments-

Abstract-
Page3 line 14- clarify “decelerated”

Response: We thank reviewer #1 for the criticism of our work. We agree that the study design is– as so often in our domain – a compromise of data quantity and quality. There is definitely room for improvement as reviewer #1 has clearly shown. We will address this below.

With decelerate, we mean reduction of the inflammatory development. Possibly “ameliorate” would be a better word.

Comment: Describe the study design- Cross sectional? Cohort?
Response: This was a longitudinal propensity score matched cohort study following patients throughout the time they were registered in the NPR. We added this information to the title and abstract.

Comment: What was the control population?

Response: The control population comprised of a matched cohort with no more than one bDMARD prescription prior to their spinal fracture – matched for year of birth, sex, CCI, spinal fracture, NSAID, MTX and Sulfa prescriptions, and years with AS-diagnosis.

Comment: Methods in abstract need more details including description of statistical methods.

Response: We added specific information on the statistical methods applied to perform the calculations.

Comment: Introduction-
Not all patients fuse. Please restructure the sentence.
bDMARD now also includes IL-17 inhibitors.

Response: We added information on ankylosis development and IL-17 inhibitors to the introduction chapter.

Methods=
Participants
AS pt data was from 1987 to 2014. But prescription data was from 2005 to 2014.

Response: Since we do not have prospective prescription data prior to 2005 on patients with AS, additional left-censoring would have complicated the fracture-free survival analysis. Instead we changed the study design to a matched cohort study, which simplifies adjusting for covariates at the cost of lesser sample size.

Comment: What is the rationale of limiting age between 40 and 70? Patients can have active AS before age 40 years as well as after age of 70 years.

Response: We agree that limiting the age to those between 40 and 70 years seems arbitrary, but was an attempt to exclude spinal fractures unrelated to an ankylosing spine disease. In line with to the reasoning of reviewer #2 we included all patients in risk of a spinal fracture related to AS (≥18 years). The revised manuscript includes therefore new data as marked in the word-file.

Comment: Description of the statistical tests lacks clarity.
Description of results is also not fluent and meaningful.

Response: We increased the information in the statistical tests section as well as worked on the transparency and content in the results section.

Reviewer: 2
Reviewer Name: Ernst Feldtkeller
Institution and Country: Deutsche Vereinigung Morbus Bechterew, Germany
Competing Interests: No competing interests

Comment: The manuscript answers important questions and should be accepted for publication.
It contains, however, some severe errors that have to be corrected.

Response: We thank reviewer 2 on the important criticism and valuable input with regard to this study.

Comment 1) In the Key Points, in the abstract and in the conclusions it is mentioned that “activity restrictions should not be changed”. This can easily be misunderstood. Physical activity (including appropriate sports like swimming or Nordic walking) is important for patients with ankylosing spondylitis to relieve inflammation and prevent stiffening. It should not be restricted. The only restriction is that dangerous sports like football etc. have to be avoided and that fall prevention has to be regarded.

Response 1. We agree that activity restrictions are dangerous, if these lead to avoidance behaviour. We rather recommend physiotherapeutic guidance for sports activities, improving balance, bone density, and minimising risk of falls.
We rephrased this in the revised manuscript.

Comment 2. In the Results paragraph of the abstract, “age 67±19” has to be replaced by “age 67±19 years”.

Response 2. We corrected the style in the abstract results.

Comment 3. That 59% of the AS patients received their AS diagnosis in conjunction to their first spinal fracture, is a terrible result and should be discussed in detail.

Response 3. In the revised manuscript we analysed a matched cohort which is not representative for the national cohort. The national cohort data will be published in a separate manuscript, since we are certain that the information of most AS patients with spinal fractures did not have their diagnosis registered.

Comment 4. AS is not a “rheumatoid disease” as mentioned in the Introduction, but a rheumatic disease. The word “rheumatoid” is only used in connection with rheumatoid arthritis (RA).

Response 4. Thank you for identifying the misclassification of the rheumatic disease of AS. We corrected this.

Comment 5. AS is not “affecting all joints of the axial skeleton” as mentioned in the Introduction. The affection may also be restricted to the sacroiliac joints or the lumbar spine. There is only a tendency to affect the whole spine.

Response 5. We agree that AS in many cases affects only few joints in the axial skeleton, while all axial joints are at risk.

Comment 6. The sentence “Since only patients with an active form of AS were of interest for this study, patients younger than 40 and older than 70 years in 2014 were excluded“ (page 8) is irritating. The disease is most active in the first years after disease onset.
Response 6. We agree, that this meaning with the “active disease” is incorrect. According to the comments of reviewer #1 and #2 we only exclude paediatric patients (<18 years).
The exclusion of patients younger than 40 years is however reasonable because patients with a progressed ankylosis are more at risk of a spinal fracture.

Since it is difficult to exclude types of fracture just by age exclusion, we performed a new analysis including all age groups ≥18 years. We discussed this reasoning in the manuscript.

Comment 7. The abbreviations CCI used in the results chapter and in the Tables has to be explained.

Response: 7. We explained the abbreviations of the Charlson Comorbidity Index to tables and manuscript text.

Comment 8. What do you mean with “AS was diagnosed within half a year from the first spinal fracture diagnosis”? Half a year before or after the fracture?

Response 8. In the revised manuscript, we did not exclude patients by interval from diagnosis to fracture, we excluded while matching the control group.

Comment 9. There is no “change in the classification criteria for AS during the last decade from the modified New York criteria to Assessment of Spondyloarthritis International Society (ASAS) criteria” (page 13). The modified New York criteria are the classification criteria for AS also today, and ASAS has created classification criteria for the disease group of axial Spondyloarthritis (AS and non-radiographic axial SpA).

Response 9. We agree with reviewer 2. We omitted this misleading paragraph.

Comment 10. The abbreviation SCI used in the tables has also to be explained.

Response 10. All abbreviations used in the tables are now explained.

Comment 11. Every reference has to be listed only once. Reference 33 is identical with reference 3. I have not checked for further duplicates.

Response 11. We identified the duplicate reference and screened for more duplicates.

Comment 12. In some of the references the year of appearance is missing Reference 3 appeared in 2011, reference 36 appeared in 2016.

Response 12. We checked the completeness of references

Comment 13. In reference 20, Landewe has to be re

Response 13. ok

Reviewer: 3
Reviewer Name: Ennio Lubrano
Institution and Country: Università Del Molise, Campobasso, Italia.
Competing Interests: none declared

Comment: This is an interesting population based multi-registry study aimed to investigate whether the biologic treatment for AS patients reduced the spinal fracture incidence. The study is well written with a simple and clear design and methodologically correct.

I have only a few considerations that authors might address:

Even if bDMARDs can increase bone density (see ref 5-6) which, in turn, could reduce the spinal risk fracture, no clear data demonstrated that an increase of bone density are in keeping with lower risk. In other words, the data obtained from this study are very clear but obviously did not address the pathophysiological role of bDMARDs on osteoporosis.

Response: We thank reviewer 3 for his positive comment regarding our study.

We agree that the quality of osteoporosis data in this study are insufficient, thus we focused on the fracture-free survival instead. Osteoporosis databases should be targeted if this question is to be answered.

Comment: In my mind, as other possible explanation of the results obtained, the bDMARDs were prescribed in more severe AS patients with stronger bio-mechanical consequences of the disease.

Response: In the revised manuscript, we matched treatment groups 1:1 with an untreated cohort. Matching was performed for year of birth, gender, comorbidity, years with AS, and other anti-rheumatic medication. We strongly believe that the new dataset answers the research question in a statistically safer way.

VERSION 2 – REVIEW

REVIEWER	Ernst Feldtkeller Deutsche Vereinigung Morbus Bechterew e.V., Germany
REVIEW RETURNED	14-Nov-2017

GENERAL COMMENTS	N/A