

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The global burden of musculoskeletal disorders and attributable factors in 204 countries and territories: A secondary analysis of the Global Burden of Disease 2019 study
AUTHORS	Liu, Shiwen; Wang, Binyan; Fan, Shuzhen; Wang, Yaxuan; Zhan, Yuxuan; Ye, Ding

VERSION 1 – REVIEW

REVIEWER	WU, Dongze Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology
REVIEW RETURNED	02-Mar-2022

GENERAL COMMENTS	Thank you for the author's great interest on musculoskeletal disorder and GBD study. However, there are two issues need to be addressed. Q1: What is the added value to previous GBD study? Eg: PMID: 32414807 Q2: I would like to encourage the authors to join GBD as registered collaborator, apply the research proposal, and go through internal circulation as the study use complete rather than partial data from GBD.
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REVIEWER	Santaguida, Pasqualina McMaster University, Health Research Methods, Evidence and Impact
REVIEW RETURNED	15-Mar-2022

GENERAL COMMENTS	Thank you for the opportunity to review this important manuscript. There is a need to keep up with changes in musculoskeletal burden as it impacts the quality of life of many people and is central to chronic conditions. In my judgement the analytic approach was robust and the findings interesting. Alas there is a need for some editing of the text (lack of prepositions, run on sentences) but this is a minor issue relative to the content of the study. I have tried to point out some of these in the comments below. It would be helpful if there were some subheadings.
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ABSTRACT:

Please note that the following is a RUN on sentence....difficult to understand. Please consider partitioning the sentence to be easier to understand.

RESULTS: In comparison with 1990, age-standardized incidence rate (3944.53 per 100,000, 95% uncertainty interval [UI] 3580.13 to 4325.84) and age-standardized DALY rate (1825.56 per 100,000, 95% UI 1322.52 to 2402.00) had decreased in 2019, with AAPCs of -0.32 (95% confidence interval [CI] -0.34 to -0.31) and -0.05 (95% CI -0.06 to -0.04), while age-standardized death rate (1.51 per 100,000, 95% UI 1.21 to 1.74) showed a stable trend from 1990 to 2019.

CONCLUSIONS: I do understand that at times abstract length is restricted, but using so many acronyms in the abstract also makes it difficult to comprehend. If SDI is sociodemographic index....how can this be a region?

STRENGTHS AND LIMITATIONS OF THE STUDY

Pag2 2: lines 10: What is the meant by “specific regions” and how are these different from SDI regions. Do you mean to say these are SDI “intervals”

Although these sections are tricky to write, in my judgement it is not so helpful to simply restate the methods. For example, why is trim trend assessed using Joinpoint regression model and uatified AAPC a strength. If for example you stated something like “ We used rigorous regression models (Joinpoint) to assess time trends that showed ...”. As I noted above restating your methods is not a strength, it is best if you explain why you view this as a strength.

INTRODUCTION

Your opening sentences are difficult to place into context. Perhaps you can describe what the purpose of the first sentence is in relation to the first reference.the reader has no frame of reference.

Line 12 page 6: It uses the past tense to describe 5 common conditions for which the reader has no frame of reference hence these common conditions are referring to.

Line 54 page 6: What is the sociodemographic index....there are many different ways that these characteristics can be described. Please consider adding a reference.

Page 7 line 7-12. You make reference to previous studies but cite only 1 (reference 5). Is this sentence referring to SDI of musculoskeletal injuries. I have no idea what you intend by this sentence.

Page 7 line 40: You “first used data from GBD) and then what did you use “second”. In my judgement this is also a run-on sentence.

METHODS

Page 8 line 12: The meaning of the following sentences was not clear: "Currently, the GBD study results in 2019 replaced GBD data from previous rounds, making some changes.". Did you mean to say that the GBD was updated with 2019 data (it is obvious that adding this makes changes to the information).

Page 8: lines 15-28. Should these sentences not be in the "statistical analyses section". It would be helpful to those of us who are not statisticians to understand why these analyses are used (to estimate prevalence, etc.)

Statistical Analyses:

This section was very well written. Thank you for those of us that are not statisticians.

RESULTS:

Burden of MSK disorders at the global, regional and national level

Page 10 line 48: Please consider some other way to begin sentences with a term other than "besides" as this in my judgment is colloquial language. I find this confusing to consider "beside" what specifically.

Thus far, in the results for global, national burden every single figure referenced in the manuscript directs the reader to the supplement. I believe you are allowed to include some of these in the manuscript. It is really difficult to follow key details in this section when the reader has to go to a separate document. Perhaps include at least one figure for this section.

Burden of MSK disorders by age and gender groups

Page 12: line 38: The sentence "over the years females, etc.". Is this a result? Perhaps you can simply present the difference between females and males from previous estimates. This would seem an important finding given that "over the years" this was not the case.

Risk factors attributable to MSK disorders and five common conditions in 2019

Page 15: line 38: What is meant by "other distributors"

Please note that it is not customary to add adjectives such as "of serious concern" and that every other sentence is "however" or "on the contrary" when there is no need to draw the readers attention to differences between some of the metrics that were never expected to be compared.

Generally, you have chosen to compare across time and then across regions and msk conditions. In my judgement it might be easier to consider WITHIN comparisons more explicitly. I am not sure it is so important that neck pain is different from back pain but rather that changes over time within these conditions changed. I cannot quite understand the focus of the comparisons in some of these sections.

DISCUSSION

	Generally the discussion was well written and the limitations were very clear but the strengths seemed less so to me. It would be helpful if there were some subheadings.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Q1: What is the added value to previous GBD study? Eg: PMID: 32414807

Response:

Thanks for your valuable question. Our study evaluated incidence, death and DALY of MSK disorders, along with its five common conditions from 1990 to 2019 at global, regional and national levels, while Jin et al. (PMID: 32414807) focused on assessing the trends of incidence between 1990 and 2017. Besides, we added to analyze the risk factors of MSK disorders and its five common conditions in the current study. Moreover, we used Joinpoint regression model to calculate AAPC, which allowed us to characterize the epidemiological trends of MSK disorders rigorously by connecting linear line segments on a log scale, which was not involved in the aforementioned article. These added values have been stated in the “Strengths and limitations of this study” section.

In the revised manuscript, we added to compare our results with previous reports in the Discussion section. We found that the numbers of incident cases, deaths, DALYs of MSK disorders increased from 1990 to 2019. Likewise, the increasing trend has been found in previous reports from GBD 2017 study¹⁻² (Line 327-329, Page 16). Gender differences were described in detail in our study, and the differences among five conditions were compared. At all ages, the burden on females was significantly heavier than that on males. After stratified by conditions, the burden of RA, OA, LBP and NP were consistently higher in females than males, except for gout. This was consistently found in the previous reports³⁻⁷ (Line 349-350, Page 17). As for age distribution, compared with the 2017 report,¹ the peak age of onset of MSK disorders moved from 45 to 49 years to 50 to 54 years (Line 333-334, Page 17). We also found that occupation risks contributed the most to MSK disorders, and tobacco use and high body mass index (BMI) were also major risk factors. On the other hand, the AAPC of ASIR and age-standardized of DALY rate had decreased significantly. To be noted, a significantly negative correlation between AAPC in ASRs and SDI was observed. For the five conditions, ASIR showed a decreasing trend for LBP (AAPC= -0.49, 95% CI -0.52 to -0.46) and NP (AAPC= -0.02, 95% CI -0.02 to -0.01), while increased for RA (AAPC= 0.21, 95% CI 0.18 to 0.21), OA (AAPC= 0.13, 95% CI 0.11 to 0.15) and gout (AAPC= 0.58, 95% CI 0.51 to 0.66). ASDR of RA showed a significant downward trend in global (AAPC= -0.37, 95%CI -0.54 to -0.2). Temporal trend for age-standardized DALY rate varied greatly, with the pronounced decrease for LBP (AAPC= -0.61, 95% CI -0.65 to -0.57) and increase for gout (AAPC= 0.71, 95% CI 0.61 to 0.80) (Online supplementary table S2-6).

Q2: I would like to encourage the authors to join GBD as registered collaborator, apply the research proposal, and go through internal circulation as the study use complete rather than partial data from GBD.

Response:

Thanks for your valuable suggestion. I have applied to join the GBD Collaborator Network, which has been recorded. However, applications may take up to 2 months to be reviewed and may take longer depending on the volume of applications. Therefore, I uploaded the application form along with the revised manuscript.

GBD Collaborator Application

Thank you for your interest in joining the GBD Collaborator Network; your application has been recorded. Please note, applications may take up to 2 months to be reviewed and *may take longer* depending on the volume of applications. **You will receive a status update via email once your application is reviewed.** If you have any questions about your application or need to make changes, please contact the GBD Secretariat at gbdsec@uw.edu.

Reviewer: 2

Q1: There is a need for some editing of the text (lack of prepositions, run on sentences) but this is a minor issue relative to the content of the study. I have tried to point out some of these in the comments below. It would be helpful if there were some subheadings.

Response:

Thanks for your valuable comment. We are delighted to resubmit a revised version of the manuscript which improves the quality of our writing using the language editing service by Editage. We have also attached the Certificate of English Language Editing.

Moreover, we added some subheadings in the Discussion section to help readers understand the principal findings and strengths and weaknesses of the study.

Q2: ABSTRACT: Please note that the following is a RUN on sentence....difficult to understand. Please consider partitioning the sentence to be easier to understand. RESULTS: In comparison with 1990, age-standardized incidence rate (3944.53 per 100,000, 95% uncertainty interval [UI] 3580.13 to 4325.84) and age-standardized DALY rate (1825.56 per 100,000, 95% UI 1322.52 to 2402.00) had decreased in 2019, with AAPCs of -0.32 (95% confidence interval [CI] -0.34 to -0.31) and -0.05 (95% CI -0.06 to -0.04), while age-standardized death rate (1.51 per 100,000, 95% UI 1.21 to 1.74) showed a stable trend from 1990 to 2019.

Response:

Thank you for the suggestion to split the long sentences properly. In the revised abstract, we modified this sentence to "The age-standardised incidence rate and age-standardised DALY rate in 2019 (incidence: AAPC = -0.32, 95% confidence interval [CI]: -0.34 to -0.31; DALYs: AAPC = -0.05, 95% CI: -0.06 to -0.04) were lower than those in 1990. However, the age-standardised death rate showed a stable trend (AAPC = 0.05, 95% CI: -0.05 to 0.15) from 1990 to 2019". To be noted, we deleted ASRs that be directly provided by GBD 2019 database, and focused on showing the trends of MSK disorders by using AAPC value.

Q3: CONCLUSIONS: I do understand that at times abstract length is restricted, but using so many acronyms in the abstract also makes it difficult to comprehend. If SDI is sociodemographic index....how can this be a region?

Response:

Thank you for the suggestion. We should apologize for the ambiguous expression, which might confuse readers. To be specific, we revised this sentence to "This study demonstrates that the burden of MSK disorders tends to be lower in high-SDI regions than in lower-SDI regions".

Q4: STRENGTHS AND LIMITATIONS OF THE STUDY

Pag2 2: lines 10: What is the meant by "specific regions" and how are these different from SDI regions. Do you mean to say these are SDI "intervals"

Response:

Thank you for the question. The 204 countries and territories in GBD 2019 study were classified into 21 regions according to geographic location, and regions with low-, low-middle-, middle-, high-middle-, and high-SDIs. Also, we modified the description to avoid misunderstanding (Line 54-55, Page 4).

Q5: Although these sections are tricky to write, in my judgement it is not so helpful to simply restate the methods. For example, why is trim trend assessed using Joinpoint regression model and unadjusted AAPC a strength. If for example you stated something like “We used rigorous regression models (Joinpoint) to assess time trends that showed ...”. As I noted above restating your methods is not a strength, it is best if you explain why you view this as a strength.

Response:

Thank you for the suggestion. It's convincing to use average annual percentage change (AAPC) through Joinpoint regression model to quantify the global trends. The AAPC is calculated

by
$$AAPC = \left[\exp \left(\frac{\sum \beta_i t_i}{\sum t_i} - 1 \right) - 1 \right] \times 100$$
, which means the weighted average of the individual

annual percentage changes (APC) during observed time, where β_i is the slope of each stage, and t_i is the time length of each stage. The AAPC takes account of the transition in trend, which is preferred as tool to show the trends which may not stay constant over time.

In the revised manuscript, we summarized the strength as “We used joinpoint regression model to calculate the average annual percent changes, which allowed us to rigorously characterise the epidemiological trends of MSK disorders by connecting linear line segments on a log scale”.

Q6: INTRODUCTION: Line 12 page 6: It uses the past tense to describe 5 common conditions for which the reader has no frame of reference hence these common conditions are referring to.

Response:

Thank you for the valuable comment. We used present tense to describe the five common conditions of MSK disorders in the revised manuscript. Moreover, we added the corresponding references about the global burden of each condition to help readers be able to understand the issue (Line 71-74, Page 5).

Q7: Line 54 page 6: What is the sociodemographic index....there are many different ways that these characteristics can be described. Please consider adding a reference.

Response:

Thank you for your suggestion. We added the related references⁸⁻⁹ (Line 89 in Page 5) and described the characteristics in more details (Line 89 in Page 5 and Line 90-92 in Page 6) in the revised manuscript.

Q8: Page 7 line 7-12. You make reference to previous studies but cite only 1 (reference 5). Is this sentence referring to SDI of musculoskeletal injuries. I have no idea what you intend by this sentence.

Response:

Thank you for the question. We have added more references^{1-2,10-11} to clarify the relationship between ASRs of MSK disorders and SDI found in previous reports (Line 92-95, Page 6). In the current study, we aimed to provide the MSK disorders burden in regions with different SDI scores using updated data. Consequently, we found that there was a significant decrease in AAPCs of ASIR and ASDR in high- SDI regions, while a slight increase in AAPC of age-standardized rate was observed. In addition, there was a significantly negative correlation between AAPC in ASRs and SDI.

Q9: Page 7 line 40: You “first used data from GBD) and then what did you use “second”. In my judgement this is also a run-on sentence.

Response:

Thank you for your question. Sorry for the unclear description, we modified the sentence to “This study is the first to use data from the Global Burden of Disease Study 2019 (GBD 2019) to examine the global patterns and trends of MSK disorders from 1990 to 2019 in detail...”.

Q10: METHODS: Page 8 line 12: The meaning of the following sentences was not clear: “Currently, the GBD study results in 2019 replaced GBD data from previous rounds, making some changes.”. Did you mean to say that the GBD was updated with 2019 data (it is obvious that adding this makes changes to the information).

Response:

Thank you for the question. To avoid misunderstanding, we deleted the sentence in the revised manuscript, as its meaning is consistent with the sentence “GBD study updates, and adds new data and methodological enhancements to the estimation of the entire time series after each change to adjust for bias” in Line 116-117 in Page 7.

Q11: Page 8: lines 15-28. Should these sentences not be in the “statistical analyses section”. It would be helpful to those of us who are not statisticians to understand why these analyses are used (to estimate prevalence, etc.)

Response:

Thank you for the suggestion. According to your judgement, we have revised this part for better understanding. To be specific, the GBD study estimated incidence, prevalence, mortality, cause-specific mortality and remission of various diseases. A Bayesian meta-regression tool, DisMod-MR 2.1, was used as the main estimation method to ensure the consistency of data for each disease9 (Line 117-120, Page7).

Q12: Statistical Analyses:

This section was very well written. Thank you for those of us that are not statisticians.

Response: Thank you for your appreciation.

Q13: RESULTS:

Burden of MSK disorders at the global, regional and national level

Page 10 line 48: Please consider some other way to begin sentences with a term other than “besides” as this in my judgment is colloquial language. I find this confusing to consider “beside” what specifically.

Thus far, in the results for global, national burden every single figure referenced in the manuscript directs the reader to the supplement. I believe you are allowed to include some of these in the manuscript. It is really difficult to follow key details in this section when the reader has to go to a separate document. Perhaps include at least one figure for this section.

Response:

Thank you for the suggestion. We have deleted “besides” in the revised manuscript. In addition, we have moved Online supplementary table S1 to Table 1 in the main text, and the corresponding description also have supplemented in the manuscript (Line 171, Page 9).

Q14: Burden of MSK disorders by age and gender groups

Page 12: line 38: The sentence “over the years females, etc.”. Is this a result? Perhaps you can simply present the difference between females and males from previous estimates. This would seem an important finding given that “over the years” this was not the case.

Response:

Thank you for the question. We figured the time trends of ASRs in global and five SDI quintiles for males and females from 1990 to 2019 (Supplementary figure S1B and C), and added the corresponding annotations (Line 216-217, Page 11) in the revised manuscript. Accordingly, we found that the MSK disorders burden on females were much heavier than males.

Q 15: Risk factors attributable to MSK disorders and five common conditions in 2019

Page 15: line 38: What is meant by “other distributors”? Please note that it is not customary to add adjectives such as “ of serious concern” and that every other sentence is “however” or “on the contrary” when there is no need to draw the readers attention to differences between some of the metrics that were never expected to be compared.

Response:

Thank you for the suggestions. This study describes the contribution of four risk factors (occupational risks, tobacco use, high BMI and kidney dysfunction) to DALYs of MSK disorders. We revised the corresponding description in the manuscript (Line 285-287 in Page 14 and Line 288-290 in Page 15) and added Supplementary Table 13 to present the DALYs caused by the risk factors.

As you mentioned, some differences in the contributions of the four risk factors to DALYs were not the main findings involved in the current study, thus we described the related results in plain language in the revised manuscript. The emphasis is on regional differences and temporal trends in the second and third paragraph in the “Risk factors for MSK disorders in 2019” part of the Results section.

Q16: Generally, you have chosen to compare across time and then across regions and msk conditions. In my judgement it might be easier to consider WITHIN comparisons more explicitly. I am not sure it is so important that neck pain is different from back pain but rather that changes over time within these conditions changed. I cannot quite understand the focus of the comparisons in some of these sections.

Response:

Thanks for your valuable comment. We agreed to that the focus in the “Risk factors for MSK disorders in 2019” part should be the time trends and regional difference. Therefore, we additionally showed that the distribution of risk factors globally and within five-SDI or 21-geographic regions (Supplementary Table S13). Figure 4a and Supplementary Figure S7 show the temporal trend of MSK disorders attributable to the certain risk factors from 1990 to 2019, and Figure 4b presents the overall DALYs and the most pronounced one attributable to specific risk factors. On the other hand, we deleted the difference in attributable risk factors across the five common conditions of MSK disorders in the revised manuscript.

Q17: DISCUSSION: Generally the discussion was well written and the limitations were very clear but the strengths seemed less so to me. It would be helpful if there were some subheadings.

Response:

Thank you for the suggestions about the Discussion section. We added some subheadings in Discussion to help readers read more clearly.

References

1 Jin Z, Wang D, Zhang H, et al. Incidence trend of five common musculoskeletal disorders from 1990 to 2017 at the global, regional and national level: results from the global burden of disease study 2017. *Ann Rheum Dis* 2020;79(8):1014-22.

2 Safiri S, Kolahi AA, Cross M, et al. Prevalence, Deaths, and Disability-Adjusted Life Years Due to Musculoskeletal Disorders for 195 Countries and Territories 1990–2017. *Arthritis Rheumatol* 2021;73(4):702-14.

3 Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. *Nat Rev Rheumatol* 2020;16(7):380-90.

4 Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73(6):968-74.

5 Safiri S, Kolahi AA, Hoy D, et al. Global, regional, and national burden of neck pain in the general population, 1990-2017: systematic analysis of the Global Burden of Disease Study 2017. *BMJ* 2020;368:m791.

6 Safiri S, Kolahi AA, Hoy D, et al. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis* 2019;78(11):1463-71.

7 Safiri S, Kolahi AA, Smith E, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020;79(6):819-28.

8 GBD 2019 Demographics Collaborators. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396(10258):1160-203.

9 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396(10258):1204-22.

10 GBD 2019 Viewpoint Collaborators. Five insights from the Global Burden of Disease Study 2019. *Lancet* 2020;396(10258):1135-59.

11 Clark P, Denova-Gutierrez E, Razo C, et al. The burden of musculoskeletal disorders in Mexico at national and state level, 1990-2016: estimates from the global burden of disease study 2016. *Osteoporos Int* 2018;29(12):2745-60.

VERSION 2 – REVIEW

REVIEWER	WU, Dongze Third Affiliated Hospital of Sun Yat-Sen University, Department of Rheumatology
REVIEW RETURNED	07-May-2022

GENERAL COMMENTS	Thank you for your continuous work on MSK disorders. I think the paper the suitable for publication now.
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REVIEWER	Santaguida, Pasqualina McMaster University, Health Research Methods, Evidence and Impact
REVIEW RETURNED	24-May-2022

GENERAL COMMENTS	The authors have made some good modifications to clarify areas within the manuscript. I was not clear if all had been copy edited (I only had time to focus on the red font areas).
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