PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019
AUTHORS	Guan, Bin; Anderson, David; Chen, Lingxiao; Feng, Shiqing; Zhou, Hengxing

VERSION 1 – REVIEW

REVIEWER	Tenovuo, Olli University of Turku
REVIEW RETURNED	01-Jun-2023

GENERAL COMMENTS	This is an update and slight extension of a paper published in Lancet Neurology in 2019, describing the global burden of traumatic brain injury (TBI) and spinal cord injury (SCI). The paper uses the same methodology and databases as previous reports from the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study. The main differences to the previous reports are that the statistics cover data up to 2019 (1990-2019), the results are presented for separate countries also what comes to the causes of injury, and that some new areas are included. In principle the paper is well written and mostly easy to follow. However, as most of the methodology used is presented by referring to earlier publications, without good knowledge of those it is difficult to understand how this data is derived. I have the following comments and suggestions. Major points: • All papers should be understandable without doing profound reading of previous papers. Therefore, the authors should include a short summary – e.g., as an information box – what kind of data is behind the statistics used. From the earlier 2019 publication it appears that the sources of data are heterogeneous depending on the country, most including only inpatient statistics. • Reliability of national statistics is the weakest point of these kinds of approaches. There are few studies which have tried to address the discrepancy between register-based data and true incidence, these have not been discussed. The difference between these two is probably highly dependent on the country and organization/administration of healthcare and collection of registry data. Basically, the reliability depends on a) how well the statistics cover cases that occur (= how many cases do not seek for medical care for different reasons, or are treated at facilities that are not covered by registries), b) how reliable is the clinical diagnostics, c) how carefully the persons in charge of diagnosis coding do their job, and d) how well does the registry cover all cases that should be included. These factors cause great variability between the country specific data, thus obscuring the true differences between

	the incidence and causes of injury. For example, Nordic countries are considered to have very reliable statistics, but knowing the true situation from inside the system in detail, cases with TBI remain unrecorded at least because a) those taken care by private healthcare or occupational healthcare are not included, b) often in patients with multitrauma TBI remains unrecorded (= doctors need to record one main diagnosis and others often remain unrecorded), c) many cases of mild TBI remain unrecorded because the symptoms are interpreted to be caused by confounders (e.g., inebriation). The reliability problems are well shown also by an US study doi: 10.1089/neu.2018.5772. In addition, clinical work has shown that codes for the cause of injury are often wrong, although choosing the cause is mandatory. These kinds of causes make great sources of error – for example, it is highly unlikely that the incidence of TBI in Finland is three times higher than in China or almost double the incidence of Sweden, or three times higher than in South Africa. Or is there any logical explanation that Slovenia indeed would have the highest incidence and prevalence of TBI of all countries? Or does anyone believe that New Zealand has four times higher incidence than Niger? It is also unlikely that falls have surpassed traffic accidents as the main cause in many population-rich Asian countries with a chaotic traffic. These differences probably reflect more the reliability of the data than differences in true incidence. Thus, the limitations concerning the incidence and causes of injury should be discussed in more detail. This is also reflected in the discrepancy between the reported global incidence here (27.16 million) and some other recent expert sources (>50 million, ref. 7). • The authors have mentioned as a limitation that due to diagnosis hierarchy in those with a SCI and eventual TBI is not recorded. As there are many studies on the coexistence of these two, why they have not been utilized in the estimates? • The definitions for TBI and SCI used are based on ICD-9 and ICD-10, and the details of this are described in the previous publication. There, on Appendix 1 page 1 “The ICD-10 codes for TBI are F07.2, F07.8, F07.81, F07.89, F07.9, S06, S07, T90.2, and T90.5. Among these, S06.1 designates minor TBI while the others designate moderate or severe TBI.” I guess this is an error probably not reflected in the results, but S06.0 (Commotio cerebri) can be considered to represent mild TBI, while S06.1 (Diffuse brain oedema) cannot be considered mild TBI. • Mortality from TBI is excluded from the statistics. This should be stated more clearly in the beginning, since the contribution to the total number of TBIs is significant. • For the study “estimates in some data-sparse countries and territories were modelled and predicted by borrowing estimates from data-rich countries and territories”. As there may be huge variations between countries depending on several issues, the error this may cause should be highlighted, and the countries where this has been applied mentioned clearly in the text. • The data on prevalence is probably the most problematic interpretation of the paper, and the discussion on the limitations of this data insufficient. This data is based on the GBD probabilities of permanent health loss, which data in turn is based on five long-term follow up studies mentioned in the 2019 publication. The response rate in these has mostly been around 30-40 %, expect the smallest study from China with 87 %. For a 40-44 yr old patient with an mTBI, taken care as an inpatient, the probability of permanent health loss is 0.124, for those treated as outpatients 0.017, and for those with moderate-severe TBI 0.119. The figures

	are gross underestimates, based on recent large studies, showing that about 50 % of those who are discharged from emergency departments in the US and Europe after an mTBI have not recovered at one year. The same estimates used in GBD show that in the age category 95+ the probability of permanent health loss after moderate-severe TBI is 0.230, which of course is full nonsense. Estimating the true prevalence of TBI is notoriously difficult, given the nature of the sequels. This is nicely shown in a large study from a Swedish registry, which showed that even an mTBI suffered at childhood caused significant risk of later sequels, compared to uninjured siblings (doi: 10.1371/journal.pmed.1002103). Consequently, the limitations of the prevalence data require more thorough discussion. • It is a bit confusing that the global numbers for SCI are not actually presented, since they have been published in a recent paper (ref. 6). In this paper, the authors only present country-specific data and causes. This should be more clearly reflected in the title and in the abstract. It is also confusing that the authors yet have a different interpretation on the global trends in SCI as the ref. 6 (page 17), to my understanding they interpret the figures differently, but this should be written more clearly. • The authors found that socio-demographic index associates positively with the incidence of TBI. This is contrary to what would be expected, and probably reflects more the more reliable statistics in countries with higher SDI than true trend and should be discussed. In this same connection the authors write about rates "higher than expected" – expected on what grounds? Please clarify. • In line 416-418 the authors discuss how some patients with an mTBI may not seek for medical help. I'd like to see discussions how these results reflect with the estimates that 1/3 – ½ of people sustain a TBI in their lifetime (e.g., ref. 7). I guess this could be calculated from the GBD data? Minor issues: • In the abstract: "Participants: Patients with TBI and SCI". This is confusing, giving an impression that this covers patients who have had both. • Lines 99-103: "Ding et al. reported the burden of SCI at the global and regional levels through the GBD 2019 data, but did not mention the burden of SCI in individual countries and territories [6]. However, it will not allow for identifying variations that can exist between countries and territories within a same world or a same region, which may bring biased information to health care professionals." – I would not call this biased information is the information does not exist. Please rephrase the latter sentence. • The time trends for conflict and terrorism, exposure to forces of nature, and executions and police conflict were not studied because these were "defined as random events due to not having predictable time trends". Although the trends are not predictable, isn't it worth recording how much these contribute to the global burden? • Lines 332-335: "One example, was in 2004, when the United Nations General Assembly and World Health Organization passed resolutions which called on preventive measures against road injuries [19]. The resolutions were championed in many countries and territories successively, including Oman, Russia, and Sweden [19]." – Please revise the language. • Lines 357-358: "Additional challenges to falls reduction is not just the ageing population, but the increased global life expectancy at birth from 65.4 years in 1990 to 73.5 years in 2019 [12]." – This

	sounds odd, isn't increased life expectancy in practice the same thing as increasing ageing population. • Lines 400-401. You can leave the last sentence out, this is self-evident.

REVIEWER	Corry, Daniel The University of Iowa College of Public Health, Epidemiology
REVIEW RETURNED	12-Jun-2023

GENERAL COMMENTS	This study aimed to update the burden of TBI and SCI through the use of the Global Burden of Disease (GBD) tool, encompassing data from 1990-2019. The researchers found that TBI decreased significantly across that timespan, but SCI did not, and also found that Eastern Europe (especially Slovenia) had the highest global burden of TBI. Falls were the most common cause of both TBI and SCI. Overall, this was a well-written paper with a very consistent logical flow from intro to results to discussion/conclusion. Methods were very detailed and would likely be repeatable. I only suggest minor revisions before resubmitting for publication. Additional comments: 1. The authors should more explicitly make the case in the discussion for how their research on the national level provides richer information than a regional analysis would. Devoting a short paragraph or a few sentences outlining within-region differences among nations might support the points made in the introduction about a need for national-level analysis. This might work best focusing on sub-Saharan Africa, where the leading causes of TBI vary greatly between countries. 2. If able to do so, the authors might indicate in the tables which countries are data-sparse and should be interpreted with caution. 3. The authors should include age-adjusted rates from 1990 in the tables to clearly delineate the numbers used to calculate the percent change. I look forward to reading the next iteration of this paper, whether it is revised and resubmitted or published.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Reliability of national statistics is the weakest point of these kinds of approaches. There are few studies which have tried to address the discrepancy between register-based data and true incidence, these have not been discussed. The difference between these two is probably highly dependent on the country and organization/administration of healthcare and collection of registry data. Basically, the reliability depends on a) how well the statistics cover cases that occur (= how many cases do not seek for medical care for different reasons, or are treated at facilities that are not covered by registries), b) how reliable is the clinical diagnostics, c) how carefully the persons in charge of diagnosis coding do their job, and d) how well does the registry cover all cases that should

be included. These factors cause great variability between the country specific data, thus obscuring the true differences between the incidence and causes of injury. For example, Nordic countries are considered to have very reliable statistics, but knowing the true situation from inside the system in detail, cases with TBI remain unrecorded at least because a) those taken care by private healthcare or occupational healthcare are not included, b) often in patients with multi-trauma TBI remains unrecorded (= doctors need to record one main diagnosis and others often remain unrecorded), c) many cases of mild TBI remain unrecorded because the symptoms are interpreted to be caused by confounders (e.g., inebriation). The reliability problems are well shown also by an US study doi: 10.1089/neu.2018.5772.

- **Reviewer #1: Thus, the limitations concerning the incidence and causes of injury should be discussed in more detail. This is also reflected in the discrepancy between the reported global incidence here (27.16 million) and some other recent expert sources (>50 million, ref. 7).**

Authors' response: We thank the Reviewer #1 for the comment. Referring to the comments, we discussed in detail the difference between the estimates of the TBI/SCI burden and the true incidence. Taking TBI as an example, we listed several possible reasons why the true incidence may be underestimated: 1) The register-based data may not cover all cases that should be included. We used the examples of the Nordic countries and the United States, which are considered to have very reliable statistics, to illustrate that there are still some TBI patients who seek medical treatment in non-registered places (e.g., private healthcare) or some mild TBI patients who do not receive treatment and are not recorded, resulting in an underestimation of the true incidence of TBI. 2) The clinical diagnosis codes may not be matched to the injuries, especially for patients with multi-trauma. We took the modelling strategies for estimating the burden of non-fatal injuries (including TBI and SCI) in the GBD Study as an example. After the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators tried to apportion co-occurring non-fatal injuries using regression methods, they found that there was an incredible number of long-term disabilities were assigned to seemingly trivial non-fatal injury categories, such as open wounds and bruises, thus pulling disability away from more serious non-fatal injury outcomes, including TBI and SCI [3]. Therefore, this study followed the method used in the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators' Lancet Neurology paper of assigning one non-fatal injury case to the most severe of any co-occurring non-fatal injuries according to the GBD severity hierarchy (SCI had a higher rank than TBI in the GBD severity hierarchy). However, for some patients who experience both TBI and SCI from a traumatic event, SCI but not TBI would be matched to the individual in this study, which may underestimate the true incidence of TBI.

We have added relevant contents in the Strengths and Limitations section in the Discussion as follows:

"This study also had some limitations. First, the data sources relied on patients having medical records, so reported estimates would underestimate the true incidence. For example, there was a discrepancy between the annual worldwide estimation of new TBI cases in this study (27.16 million) and other recent expert sources (more than 50 million) [4]. The underestimation may be attributed to two reasons.

The first reason for underestimation is that the register-based data may not cover all cases. For example, the Nordic countries and the United States are considered to have reliable statistics, but there are still patients treated at facilities that are not covered by registries (e.g., private healthcare) [4, 5]. Further, many patients with mild TBI go untreated and, therefore, unrecorded; population-based studies with a broad definition of TBI show significantly higher TBI incidence rates than those based on hospital discharge rates [4]. The second reason for underestimation is that

clinical diagnosis codes may not accurately match injuries, especially in patients with multi-trauma. For example, some patients may experience both TBI/SCI from a traumatc event, but TBI would not be matched to the individual because SCI had a higher rank than TBI in the GBD severity hierarchy [1]. This is because after the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators tried to apportion co-occurring non-fatal injuries using regression methods, they found that many long-term disabilities were assigned to seemingly trivial non-fatal injury categories (e.g., open wounds/bruises), thus pulling disability away from more serious non-fatal injury outcomes (e.g., TBI/SCI) [3]. Therefore, this study followed the method that assigns one non-fatal injury case to the most severe of any co-occurring non-fatal injuries according to the GBD severity hierarchy [1, 3]. This method was also utilized in the paper by the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators published in the Lancet Neurology [3]." (Pages 21-22, lines 458-481)

- **Reviewer #1: In addition, clinical work has shown that codes for the cause of injury are often wrong, although choosing the cause is mandatory. These kinds of causes make great sources of error – for example, it is highly unlikely that the incidence of TBI in Finland is three times higher than in China or almost double the incidence of Sweden, or three times higher than in South Africa. Or is there any logical explanation that Slovenia indeed would have the highest incidence and prevalence of TBI of all countries? Or does anyone believe that New Zealand has four times higher incidence than Niger? It is also unlikely that falls have surpassed traffic accidents as the main cause in many population-rich Asian countries with a chaotic traffic. These differences probably reflect more the reliability of the data than differences in true incidence. Thus, the limitations concerning the incidence and causes of injury should be discussed in more detail.**
- **Reviewer #1: For the study "estimates in some data-sparse countries and territories were modelled and predicted by borrowing estimates from data-rich countries and territories". As there may be huge variations between countries depending on several issues, the error this may cause should be highlighted, and the countries where this has been applied mentioned clearly in the text.**

Authors' response: We thank the Reviewer #1 for the comment. We agree with this comment. It is a fact that for some data-sparse countries/territories, it is very difficult to calculate the true disease burden. The GBD Study is an attempt to estimate the global disease burden. The GBD Collaborators have tried thir best to include more data sources and use more sophisticated modeling strategies to make the estimates as close as possible to the true disease burden, but it had to admit that there were still differences between the estimates and the true disease burden. This made the reliability of estimates for data-sparse countries/territories was much lower than for data-rich countries/territories. Furthermore, due to issues with the accuracy of data sources, there may be some differences in the estimates of the cause-specific disease burden (that is, leading cause) that are logically difficult to explain, especially in data-sparse countries/territories. For example, it is unlikely that falls have surpassed traffic accidents as the main cause in many population-rich Asian countries with a chaotic traffic.

We have added relevant contents in the Strengths and Limitations section in the Discussion as follows:

"*Third, a weakness of this study is the ability to estimate incidence in countries with lower-quality data. Estimates in some data-sparse countries/territories were modeled and predicted by borrowing estimates from data-rich countries/territories [1]. Therefore, the estimates of the data-sparse countries/territories (e.g., Democratic People's Republic of Korea) might have a greater deviation than the true incidence. Furthermore, the cause-specific burden (that is, the leading cause) of TBI/SCI in some data-sparse countries/territories should be interpreted carefully. For example, it is logically difficult to explain why falls have surpassed traffic accidents as the leading cause of SCI in many*

population-rich Asian countries/territories (e.g., Malaysia) with chaotic traffic." (Pages 22-23, lines 499-507)

We have also added a table listing the specific data sources used to estimate the burden of non-fatal injuries (including TBI and SCI) in 204 countries/territories, which can be found in the Supplementary Materials (eTable 1).

- **Reviewer #1: The authors have mentioned as a limitation that due to diagnosis hierarchy in those with a SCI and eventual TBI is not recorded. As there are many studies on the coexistence of these two, why they have not been utilized in the estimates?**

Authors' response: We thank the Reviewer #1 for the comment. This is because after the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators tried to assign co-occurring non-fatal injuries using regression methods, they found that there was an incredible number of long-term disabilities were assigned to seemingly trivial non-fatal injury categories, such as open wounds and bruises, thus pulling disability away from more serious non-fatal injury outcomes, including TBI and SCI. Therefore, this study followed the method of assigning one non-fatal injury case to the most severe of any co-occurring non-fatal injuries according to the GBD severity hierarchy, which was also utilized in the paper published by the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators in the Lancet Neurology [3].

We have added relevant contents in the Strengths and Limitations section in the Discussion as follows:

"The second reason for underestimation is that clinical diagnosis codes may not accurately match injuries, especially in patients with multi-trauma. For example, some patients may experience both TBI/SCI from a traumatic event, but TBI would not be matched to the individual because SCI had a higher rank than TBI in the GBD severity hierarchy [1]. This is because after the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators tried to apportion co-occurring non-fatal injuries using regression methods, they found that many long-term disabilities were assigned to seemingly trivial non-fatal injury categories (e.g., open wounds/bruises), thus pulling disability away from more serious non-fatal injury outcomes (e.g., TBI/SCI) [3]. Therefore, this study followed the method that assigns one non-fatal injury case to the most severe of any co-occurring non-fatal injuries according to the GBD severity hierarchy [1, 3]. This method was also utilized in the paper by the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators published in the Lancet Neurology [3]." (Pages 21-22, lines 469-481)

- **Reviewer #1: The definitions for TBI and SCI used are based on ICD-9 and ICD-10, and the details of this are described in the previous publication. There, on Appendix 1 page 1 "The ICD-10 codes for TBI are F07.2, F07.8, F07.81, F07.89, F07.9, S06, S07, T90.2, and T90.5. Among these, S06.1 designates minor TBI while the others designate moderate or severe TBI." I guess this is an error probably not reflected in the results, but S06.0 (Commotio cerebri) can be considered to represent mild TBI, while S06.1 (Diffuse brain oedema) cannot be considered mild TBI.**

Authors' response: We thank the Reviewer #1 for the comment. We have tried to verify the issue you raised. Unfortunately, in the GBD 2019 Study, the GBD Collaborators only provided a detailed description of the ICD-9/ICD-10 codes used to define cause-of-injury (e.g., falls, road injuries), but did not provide a detailed description of the ICD-9/ICD-10 codes used to define nature-of-injury (including TBI and SCI). Therefore, we were unable to verify whether the ICD-9/ICD-10 codes for mild TBI described in the GBD 2016 Study published by the GBD Traumatic Brain Injury and Spinal Cord Injury

Collaborators in the Lancet Neurology were correct. However, we have clarified this point clear in the Discussion and hope that readers will take note.

We have added relevant contents in the Strengths and Limitations section in the Discussion as follows:

"Finally, the GBD Traumatic Brain Injury and Spinal Cord Injury Collaborators defined TBI/SCI by ICD-9/ICD-10 codes through physician review. However, with reference to the reviewer's comments, there may be a minor error probably not reflected in the results in the Lancet Neurology paper; the ICD-10 code S06.0 (concussion) can be considered a mild TBI, but S06.1 (traumatic cerebral edema) in the published paper cannot [3]." (Page 23, lines 518-522)

- **Reviewer #1: Mortality from TBI is excluded from the statistics. This should be stated more clearly in the beginning, since the contribution to the total number of TBIs is significant.**

Authors' response: We thank the Reviewer #1 for the comment.

We have added relevant contents in the Overview section in the Methods as follows:

"Although TBI and SCI could cause death, they were not defined as a cause-of-death in the GBD 2019 study [1]. Therefore, in this study, we provided the burden of TBI and SCI by incidence, prevalence, and YLDs, but not mortality or YLLs." (Page 7, lines 136-139)

- **Reviewer #1: The data on prevalence is probably the most problematic interpretation of the paper, and the discussion on the limitations of this data insufficient. This data is based on the GBD probabilities of permanent health loss, which data in turn is based on five long-term follow up studies mentioned in the 2019 publication. The response rate in these has mostly been around 30-40 %, expect the smallest study from China with 87 %. For a 40-44 yr old patient with an mTBI, taken care as an inpatient, the probability of permanent health loss is 0.124, for those treated as outpatients 0.017, and for those with moderate-severe TBI 0.119. The figures are gross underestimates, based on recent large studies, showing that about 50 % of those who are discharged from emergency departments in the US and Europe after an mTBI have not recovered at one year. The same estimates used in GBD show that in the age category 95+ the probability of permanent health loss after moderate-severe TBI is 0.230, which of course is full nonsense. Estimating the true prevalence of TBI is notoriously difficult, given the nature of the sequels. This is nicely shown in a large study from a Swedish registry, which showed that even an mTBI suffered at childhood caused significant risk of later sequels, compared to uninjured siblings (doi: 10.1371/journal.pmed.1002103). Consequently, the limitations of the prevalence data require more thorough discussion.**

Authors' response: We thank the Reviewer #1 for the comment. Referring to the comments, we have emphasized that the probabilities of permanent health loss assessed in the GBD Study might be grossly underestimated across all age groups. In addition, we took TBI as an example and listed several possible reasons why the estimates might be lower than the true prevalence, including 1) accurate data on TBI validity is even more limited than data on incidence, especially in low/middle-income countries; 2) TBI can cause significant risks of various sequelae, such as dementia, stroke, epilepsy, etc. Furthermore, considering that the risk of TBI-induced sequelae has not been fully explored, which means that many other neurological sequelae caused by TBI have not been statistically analyzed, leading to an underestimation of the true prevalence.

We have added relevant contents in the Strengths and Limitation section in the Discussion as follows:

"Second, this study might also underestimate the true prevalence. The GBD 2019 Study calculated the prevalence of non-fatal injuries through probabilities of permanent health loss [1]. Permanent health loss relates to the probability of patients (one year after the injury) returning to a health status with more disablity than their pre-injury health status [1]. However, the probabilities of permanent health loss assessed in the GBD Study may be grossly underestimated, especially for TBI, because accurate TBI prevalence data is even more limited than incidence data, especially in low/middle-income countries; and TBI is not an isolated event but can have variable long-term consequences, including dementia, stroke, parkinsonism, and epilepsy [4]. For example, a large study from a Swedish registry found higher probabilities of premature mortality, psychiatric inpatient admission/outpatient visits, disability pension, welfare recipiency, and low educational attainment after even a mild TBI compared to uninjured siblings [6]. Furthermore, the associations between TBI and long-term neurological diseases remain poorly understood; many sequelae other than those mentioned above have not been considered, leading to an underestimation of the true TBI prevalence [4]." (Page 22, lines 483-497)

- **Reviewer #1: It is a bit confusing that the global numbers for SCI are not actually presented, since they have been published in a recent paper (ref. 6). In this paper, the authors only present country-specific data and causes. This should be more clearly reflected in the title and in the abstract.**

Authors' response: We thank the Reviewer #1 for the comment. In fact, this study included an analysis of the global, regional (21 GBD regions), and national (204 countries/territories) burden of both TBI and SCI through the GBD 2019 data. However, in the previous submission process, the result of the global and regional burden of SCI was published by Ding *et al* [7]. This led us to intentionally remove the result of global and regional burden of SCI when submitting to the BMJ Open to avoid duplicate publication of the result. However, in this round of revision, we kindly request the Editor and Reviewers to allow us to supplement the result of global and regional burden of SCI to make the paper more complete and easier for readers.

We have revised the Results section in the Abstract as follows:

*"**Results:** Globally, in 2019, TBI had 27.16 million new cases, 48.99 million prevalent cases, and 7.08 million YLDs. SCI had 0.91 million new cases, 20.64 million prevalent cases, and 6.20 million YLDs. Global age-standardized incidence rates of TBI decreased significantly by -5.5% (95% uncertainty interval, -8.9% to -3.0%) from 1990 to 2019, whereas SCI had no significant change (-6.1% [-17.3% to 1.5%]). Regionally, in 2019, Eastern Europe and High-income North America had the highest burden of TBI and SCI, respectively. Nationally, in 2019, Slovenia and Afghanistan had the highest age-standardized incidence rates of TBI and SCI, respectively. For TBI, falls was the leading cause in 74% (150/204) of countries/territories, followed by pedestrian road injuries (14%, 29/204), motor vehicle road injuries (5%, 11/204), and conflict and terrorism (2%, 4/204). For SCI, falls was the leading cause in 97% (198/204) of countries/territories, followed by conflict and terrorism (3%, 6/204)."* (Pages 2-3, lines 46-57)

We have also revised the Global, Regional, and National Disease Burden section in the Results as follows:

*"Globally, TBI had 27.16 (95% UI, 23.36 to 31.42) million new cases, 48.99 (46.84 to 51.32) million prevalent cases, and 7.08 (5.00 to 9.59) million YLDs in 2019 **(Table 1; eTables 8-10)**. There were 346 (95% UI, 298 to 401) cases per 100,000 population, 599 (573 to 627) cases per 100,000 population, and 87 (61 to 117) YLDs per 100,000 population for age-standardized incidence rates, age-standardized prevalence estimates, and age-standardized YLD rates of TBI in 2019, respectively (**Figure 1; eFigures 1-3**). SCI had 0.91 (0.71 to 1.16) million new cases, 20.64 (18.93 to 23.61)*

million prevalent cases, and 6.20 (4.47 to 8.16) million YLDs in 2019 ***(Table 2; eTables 11-13)****. There were 12 (9 to 15) cases per 100,000 population, 253 (231 to 290) cases per 100,000 population, and 76 (55 to 100) YLDs per 100,000 population for age-standardized incidence rates, age-standardized prevalence estimates, and age-standardized YLD rates of SCI in 2019, respectively (****eFigures 4-6****). Global age-standardized incidence rates of TBI decreased significantly by -5.5% (95% UI, -8.9% to -3.0%) from 1990 to 2019. By contrast, there was no significant change in global age-standardized incidence rates of SCI (-6.1% [-17.3% to 1.5%]) from 1990 to 2019."* (Page 12, lines 250-265)

Due to the manuscript word limit, we have removed the regional and national TBI/SCI burden; percentage changes of cause-specific TBI/SCI burden from the manuscript to the Supplementary Materials as follows:

"Regionally, Eastern Europe had the largest age-standardized incidence rates (737 [633 to 857] cases per 100,000 population), age-standardized prevalence estimates (1312 [1240 to 1393] cases per 100,000 population), and age-standardized YLD rates (193 [136 to 261] YLDs per 100,000 population) of TBI in 2019. High-income North America had the largest age-standardized incidence rates (23 [17 to 30] cases per 100,000 population), age-standardized prevalence estimates (438 [404 to 474] cases per 100,000 population), and age-standardized YLD rates (113 [80 to 146] YLDs per 100,000 population of SCI in 2019.

Nationally, for TBI, Slovenia had the largest age-standardized incidence rates (885 [768 to 1036] cases per 100,000 population), age-standardized prevalence estimates (1521 [1448 to 1595] cases per 100,000 population), and age-standardized YLD rates (223 [157 to 303] YLDs per 100,000 population) in 2019. For SCI, Afghanistan had the largest age-standardized incidence rates (44 [12 to 132] cases per 100,000 population), and Syrian Arab Republic had the largest age-standardized prevalence estimates (1049 [333 to 2942] cases per 100,000 population) and age-standardized YLD rates (403 [113 to 1150] YLDs per 100,000 population) in 2019.

By falls, the countries/territories with the top three largest increase in age-standardized incidence rates of TBI from 1990 to 2019 were Turkey (100.3% [88.8% to 114.5%]), Bhutan (96.7% [86.9% to 108.0%]), and Cambodia (73.5% [67.6% to 79.9%]), and the top three decreasing rates were in Democratic People's Republic of Korea (-38.1% [-40.2% to -35.8%]), Armenia (-35.1% [-41.2% to *-28.4%]), and Latvia (-34.6% [-38.4% to -30.9%]) (out of 150 countries/territories). By pedestrian road injuries, the top three countries/territories by increasing rates were Lesotho (49.5% [38.4% to 59.9%]), Cabo Verde (28.1% [19.2% to 37.2%]), and Ghana (18.3% [11.2% to 26.6%]), and the top three countries/territories by decreasing rates were Zimbabwe (-32.5% [-38.5% to -26.4%]), Rwanda (-30.3% [-34.9% to -25.3%]), and South Sudan (-19.2% [-24.3% to -13.9%]) (out of 29 countries/territories). By motor vehicle road injuries, the countries/territories with the top three largest increase in rates were Dominican Republic (38.5% [24.0% to 54.6%]), Sao Tome and Principe (28.9% [20.0% to 38.6%]), and Seychelles (26.8% [15.3% to 39.3%]), and there were only two countries/territories had a significant decrease in their rates: South Africa (-26.0% [-30.5% to -21.3%]) and Mauritania (-11.2% [-17.4% to -4.2%]) (amongst the 11 included countries/territories).*

Regarding change rates in falls (as a cause of SCI) from 1990 to 2019, the countries/territories with the largest increase in age-standardized incidence rates were Turkey (110.5% [97.3% to 125.4%]), Bhutan (101.1% [90.9% to 112.6%]), and Cambodia (76.5% [70.1% to 83.1%]), and the top largest declines were in Democratic People's Republic of Korea (-37.2% [-39.3% to -34.9%]), Latvia (-34.5% [-37.9% to -31.0%]), and Armenia (-33.9% [-39.3% to -27.9%]) (out of 198 countries/territories)." (Supplementary Materials)

- **Reviewer #1: It is also confusing that the authors yet have a different interpretation on the global trends in SCI as the ref. 6 (page 17), to my understanding they interpret the figures**

differently, but this should be written more clearly.

Authors' response: We thank the Reviewer #1 for the comment. Ding *et al*. estimated the change trend of the global age-standardized incidence rates of SCI from 1990 to 2019 through the indicator, Estimated Annual Percentage Change (EAPC), but did not use the indicator, Percentage Change, which was recommended in the GBD Study. More importantly, when Ding *et al.* calculated that the EAPC of the global age-standardized incidence rates of SCI from 1990 to 2019 was -0.08 [95% confidence interval, -0.24 to 0.09], they concluded that the global age-standardized incidence rates of SCI decreased from 1990 to 2019. Our study used the indicator, Percentage Change, to describe the change trend of the global age-standardized incidence rates of SCI from 1990 to 2019, and the results show that there is no significant change (-6.1% [95% uncertainty interval, -17.3% to 1.5%]). Ding *et al*.'s interpretation of the results only emphasizing the point estimates but neglecting the confidence interval is the reason why our conclusion is inconsistent with Ding *et al*.'s conclusion, even though we use the same GBD 2019 data for analysis. We believe that our conclusion was more reliable, and Ding *et al*.'s conclusion may cause confusion for readers and bring biased information to policymakers. Furthermore, Mohammadi *et al*.'s letter to the Editor on Ding *et al*.'s paper also pointed out that EAPC could be biased in modeling injuries from natural disasters or wars and, if included, would lead to inflated estimates in volatile regions when estimating the trend [8].

We have revised relevant contents in the Incidence of TBI/SCI section in the Discussion as follows:

"Unfortunately, the global age-standardized SCI incidence rates did not significantly change despite the decreases in TBI. Although we used the same GBD 2019 data, this conclusion differs from Ding et al.'s finding that the global age-standardized incidence rates of SCI decreased since 1990 [7]. Ding et al. calculated the temporal trends of the global age-standardized incidence rates of SCI using the Estimated Annual Percentage Change (EAPC) [7]. The EAPC was based on a linear regression mode of the age-standardized rates and the calendar year [9]. However, EAPC can be biased in modeling injuries from natural disasters or wars; if included, it inflates estimates in volatile regions [8]. Furthermore, Ding et al. misinterpreted their statistical results [7]. The EAPC was -0.08 but had a 95% confidence interval of -0.24 to 0.09 [7]. By focusing only on the point estimate of -0.08 and neglecting the confidence interval, they failed to convey that the confidence interval crossed zero. That approach may confuse and bring biased information to policymakers [10]. Our study showed a non-significant change in the global age-standardized incidence rates of SCI (-6.1% [-17.3% to 1.5%]). The lack of SCI change may be because motor vehicle accidents are a major cause of TBI but not SCI. As discussed below, other interventions may be required to reduce SCI [11, 12]." (Pages 15-16, lines 334-349)

- **Reviewer #1: The authors found that socio-demographic index associates positively with the incidence of TBI. This is contrary to what would be expected, and probably reflects more the more reliable statistics in countries with higher SDI than true trend and should be discussed.**

Authors' response: We thank the Reviewer #1 for the comment.

We have added relevant contents in the TBI/SCI Burden by Socio-demographic Index section in the Discussion as follows:

"The burden of TBI was generally higher in countries/territories with higher SDI. One of the reasons for the difference may be disparities in access to healthcare resources . Medical resources are sufficient and easily available in locations with higher SDI, so patients with TBI can be treated and recorded in time. However, medical resources are insufficient in locations with lower SDI, and patients

may die of treatable TBI and even fail to receive a diagnostic code. Furthermore, data from countries/territories with higher SDI may be more reliable than locations with lower SDI, so estimates in locations with higher SDI may be closer to the true disease burden [1]." (Page 19, lines 414-421)

- **Reviewer #1: In this same connection the authors write about rates "higher than expected" – expected on what grounds? Please clarify.**

Authors' response: We thank the Reviewer #1 for the comment. In this study, the correlations between SDI levels and age-standardized rates were measured by Spearman's rank sum correlation tests, and visualized by Locally Weighted Scatterplot Smoothing curves. We used the term, "expected value", after referring to a GBD paper published in JAMA Network Open that used the same statistical anlysis [13]. However, we were unable to find a reasonable explanation for the term, "expected value" in the paper we referenced, and we also read other GBD papers, but in the end, we were still unable to find a reasonable explanation. Therefore, in order to avoid confusions for readers, we have removed the relevant content.

We have revised relevant contents in the Disease Burden by Socio-demographic Index section in the Results as follows:

"Generally, a positive association was found between age-standardized YLD rates of TBI and SDI in 204 countries/territories in 2019 (ρ=0.42, P<.001) ***(eFigure 7)****. SCI on the other hand, had no statistical association with SDI (ρ=-0.05, P=0.49), although the SCI burden in a few countries/territories, such as Afghanistan, far exceeded those of others."* (Page 14, lines 301-306)

- **Reviewer #1: In line 416-418 the authors discuss how some patients with an mTBI may not seek for medical help**. **I'd like to see discussions how these results reflect with the estimates that 1/3 – ½ of people sustain a TBI in their lifetime (e.g., ref. 7). I guess this could be calculated from the GBD data?**

Authors' response: We thank the Reviewer #1 for the comment. We have read some papers on the calculation of lifetime prevalence of TBI and found that the types of studies commonly used to calculate lifetime prevalence are longitudinal cohort or survey analysis. Unlike this, the GBD Study is a cross-sectional analysis conducted iteratively on an annual basis. The prevalence estimates of non-fatal injuries in the GBD Study were calculated from the incidence data by short-term disability (that is, the duration was less than one year) and long-term disability (that is, the duration was more than one year) separately. The GBD Study assumed that there was no remission and thus integrated incidence over time to arrive at prevalence estimates for long-term disability. For shrt-term disability, the prevalence was approximated by the incidence multiplied by the associated duration. However, given that short-term disability was assumed to last less than one year in the GBD Study, and the GBD Study iterated on an annual basis, this meant that short-term disability caused by non-fatal injuries in a given year would not be estimated for prevalence in future iterations. Therefore, unfortunately, we were unable to calculate lifetime prevalence of TBI and SCI through the GBD data. However, we have mentioned this in our expectations for the future studies in this revision.

We have added relevant contents in the Strengths and Limitations section in the Discussion as follows:

"Fourth, the GBD 2019 Study did not link TBI/SCI with risk factors such as behavioral factors (e.g., alcohol use), so we could not assess any associations between the two [14]. Furthermore, while longitudinal cohort or survey analysis is commonly used to calculate lifetime prevalence [15, 16], the GBD Study is a cross-sectional analysis conducted iteratively on an annual basis [1]. Short-term disability caused by non-fatal injuries is assumed to last less than one year in the GBD Study, which

means that the short-term disability after TBI/SCI in a given year may not be calculated for prevalence in future iterations [1]. Therefore, we could not calculate the lifetime prevalence of TBI/SCI through the GBD data." (Page 23, lines 509-516)

We have also added relevant contents in the Implications for Future Studies section in the Discussion as follows:

"First, population-based epidemiological studies may be improved in the future through standardized definitions (e.g., standardized criteria for diagnosis), methods (e.g., case ascertainment based on multiple, overlapping sources of information, such as hospitals, outpatient clinics, general practitioners, and death certificates), and data presentation (e.g., collection of a complete calendar year of data) [4]. These improvements would be especially helpful in data-sparse locations to facilitate comparisons between countries/territories. Second, there is a need for better ways to characterize the currently under-recognized risk of long-term disabling sequelae to bring estimates closer to the true prevalence, especially for mild TBI. Last, we hope that the GBD Collaborators will include the burden of TBI/SCI attributable to risk factors; this would provide more detailed results on the causes of TBI/SCI and allow for more targeted preventative strategies. Furthermore, we hope that the GBD Collaborators include lifetime prevalence in future iterations to estimate the global impact of TBI/SCI accurately." (Page 24, lines 526-538)

- **Reviewer #1: In the abstract: "Participants: Patients with TBI and SCI". This is confusing, giving an impression that this covers patients who have had both.**

Authors' response: We thank the Reviewer #1 for the comment.

We have revised the Participants section in the Abstract as follows:

*"**Participants:** Patients with TBI/SCI."* (Page 2, line 39)

- **Reviewer #1: Lines 99-103: "Ding et al. reported the burden of SCI at the global and regional levels through the GBD 2019 data, but did not mention the burden of SCI in individual countries and territories [6]. However, it will not allow for identifying variations that can exist between countries and territories within a same world or a same region, which may bring biased information to health care professionals." – I would not call this biased information is the information does not exist. Please rephrase the latter sentence.**

Authors' response: We thank the Reviewer #1 for the comment.

We have revised relevant contents in the Introduction as follows:

"Ding et al. reported the burden of SCI at the global and regional levels through the GBD 2019 data, but did not mention the disease burden in individual countries/territories [7]. However, it will not allow for identifying variations that can exist between countries/territories within a same world or a same geographical region." (Pages 5-6, lines 107-111)

- **Reviewer #1: The time trends for conflict and terrorism, exposure to forces of nature, and executions and police conflict were not studied because these were "defined as random events due to not having predictable time trends". Although the trends are not predictable, isn't it worth recording how much these contribute to the global burden?**

Authors' response: We thank the Reviewer #1 for the comment.

We have added two tables that showing the global, regional, and national cause-specific burden (including conflict and terrorism, exposure to forces of nature, and executions and police conflict) of TBI and SCI in 1990 and 2019, as well as the percentage changes from 1990 to 2019, which can be found in the Supplementary Materials (eTables 12-13).

- **Reviewer #1: Lines 332-335: "One example, was in 2004, when the United Nations General Assembly and World Health Organization passed resolutions which called on preventive measures against road injuries. The resolutions were championed in many countries and territories successively, including Oman, Russia, and Sweden." – Please revise the language.**

Authors' response: We thank the Reviewer #1 for the comment.

We have revised relevant contents in the Incidence of TBI/SCI section in the Discussion as follows:

"Globally, the age-standardized incidence rates of TBI significantly decreased since 1990. This improvement may reflect the benefits of global initiatives to reduce TBI rates. For example, major efforts have focused on road safety and reduced road-related injuries, a leading cause of TBI globally [17]. In 2004, the United Nations General Assembly and the World Health Organization passed resolutions calling for preventive measures against road injuries [18]. The resolutions were championed in many countries/territories successively [18]. The age-standardized TBI incidence rates decreased significantly from 1990 to 2019 by -7.2% (-11.9% to -2.0%) in Oman, -20.3% (-22.5% to -17.9%) in Russia, and -9.8% (-13.6% to -5.4%) in Sweden, demonstrating the effectiveness of their interventions." (Pages 14-15, lines 316-324)

- **Reviewer #1: Lines 357-358: "Additional challenges to falls reduction is not just the ageing population, but the increased global life expectancy at birth from 65.4 years in 1990 to 73.5 years in 2019." – This sounds odd, isn't increased life expectancy in practice the same thing as increasing ageing population.**

Authors' response: We thank the Reviewer #1 for the comment.

We have deleted relevant contents in the Cause of TBI/SCI section in the Discussion as follows:

"Additional challenges to falls reduction is not just the ageing population, but the increased global life expectancy at birth from 65.4 years in 1990 to 73.5 years in 2019. With an older population, that is living longer, falls is likely to remain a high-priority area for health care professionals." (Page 17, lines 368-371)

- **Reviewer #1: Lines 400-401. You can leave the last sentence out, this is self-evident.**

Authors' response: We thank the Reviewer #1 for the comment.

We have deleted relevant contents in the Cause of TBI/SCI section in the Discussion as follows:

"It also suggests the importance of an appeal for peace in these war-torn countries and territories." (Page 18, lines 409-410)

- **Reviewer #2: This study aimed to update the burden of TBI and SCI through the use of the Global Burden of Disease (GBD) tool, encompassing data from 1990-2019. The researchers found that TBI decreased significantly across that timespan, but SCI did not, and also found**

that Eastern Europe (especially Slovenia) had the highest global burden of TBI. Falls were the most common cause of both TBI and SCI.

- **Reviewer #2: Overall, this was a well-written paper with a very consistent logical flow from intro to results to discussion/conclusion. Methods were very detailed and would likely be repeatable. I look forward to reading the next iteration of this paper, whether it is revised and resubmitted or published. I only suggest minor revisions before resubmitting for publication.**
- **Reviewer #2: Additional comments: The authors should more explicitly make the case in the discussion for how their research on the national level provides richer information than a regional analysis would. Devoting a short paragraph or a few sentences outlining within-region differences among nations might support the points made in the introduction about a need for national-level analysis. This might work best focusing on sub-Saharan Africa, where the leading causes of TBI vary greatly between countries.**

Authors' response: We thank the Reviewer #2 for the comment.

We have added relevant contents in the Strengths and Limitations section in the Discussion as follows:

"This study had some strengths. First, it provided the most up-to-date global, regional, and national burden of TBI/SCI from 1990 to 2019. The findings can help policymakers acquire the most up-to-date epidemiological characteristics of TBI/SCI in 21 GBD regions and 204 countries/territories. Secondly, it presented variations of leading causes of TBI/SCI in 204 different countries/territories even within a same geographical region. For example, the leading cause of TBI in the Sub-Saharan Africa region varied from falls in Angola to pedestrian road injuries in Namibia to motor vehicle road injuries in South Africa and conflict and terrorism in the Central African Republic. Falls were also the leading cause of SCI in most countries/territories in the North Africa and Middle East (e.g., Saudi Arabia, Egypt, Qatar); however, conflict and terrorism were the leading cause in Afghanistan, Iraq, Libya, Syrian Arab Republic, and Yemen. The presentation of variations in different countries/territories can provide richer information than a regional analysis and help policymakers identify which causes should be targeted to improve the effectiveness of preventive interventions." (Pages 19-20, lines 425-438)

- **Reviewer #2: If able to do so, the authors might indicate in the tables which countries are data-sparse and should be interpreted with caution.**

Authors' response: We thank the Reviewer #2 for the comment. We have tried to describe the specific data sources from 204 countries/territories used to estimate the burden of non-fatal injuries in a table and put it in the manuscript. However, considering that the BMJ Open requires a maximum of five boxes, tables, and figures, all the current five tables and figures in the manuscript were important enough for readers to interpret the results, so we can only place this table in Supplementary Materials to enable readers to understand the reliability of the estimates in different countries/territories.

We have added a table listing the specific data sources used to estimate the burden of non-fatal injuries (including TBI and SCI) in 204 countries/territories, which can be found in the Supplementary Materials (eTable 1).

- **Reviewer #2: The authors should include age-adjusted rates from 1990 in the tables to clearly delineate the numbers used to calculate the percent change.**

Authors' response: We thank the Reviewer #2 for the comment. We have added the absolute incidence numbers and age-standardized incidence rates of TBI in 1990 in Table 1

and the absolute incidence numbers and age-standardized incidence rates of SCI in 1990 in Table 2. However, considering the size limitations of the tables, we have moved the prevalence estimates in Table 1/Table 2 to the Supplementary Materials. In addition, in this re-submission, the Editor informs us that the BMJ Open allows a maximum 2 pages for tables embedded in the main document. Therefore, we have moved the TBI/SCI incidence burden of 204 countries/territories in Table 1/Table 2 to the Supplementary Materials, but have retained the results of 21 GBD regions.

The revised Table 1 and Table 2 can be found in the revised manuscript. (Pages 32-33)

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VERSION 2 – REVIEW

REVIEWER	Tenovuo, Olli University of Turku
REVIEW RETURNED	15-Aug-2023

GENERAL COMMENTS	I thank the authors for doing a profound revision based on the comments. At least the limitations behind the figures are now much more understandable, and I do not have further requests.

REVIEWER	Corry, Daniel The University of Iowa College of Public Health, Epidemiology
REVIEW RETURNED	29-Aug-2023

GENERAL COMMENTS	This is a revised and resubmitted version of a study examining incidence/prevalence rates of TBI and SCI on a national level using data from the Global Burden of Disease 2019 Study. I appreciate the time and effort taken by the authors to address comments from the two reviewers. The methods and discussion of limitations are more detailed, and these details have greatly improved the manuscript. However, some of the additions remain unclear and do not quite follow a logical flow that is present within the rest of the manuscript. I suggest minor revisions to this manuscript, and my comments follow below. I worked off of the manuscript copy with tracked changes, so references to specific lines reflect that copy, not the clean copy at the beginning of the submission.

	● The paragraphs adding more detail about the limitations of this work should be rearranged slightly. In particular, the paragraph at Lines 511-518 lacks complete logical flow. The authors mention in the first sentence of that paragraph on Line 511 that the GBD study "did not link TBI/SCI with risk factors," but then focus on lifetime prevalence of TBI/SCI without mentioning risk factors at all beyond that first sentence. Additionally, it seems that the sentences mentioning the difficulty/impossibility of calculating "lifetime prevalence" might be better suited to the paragraph at Lines 485-499, which focuses on potential underestimation of the true prevalence of TBI/SCI. ● The authors may also wish to distinguish between "prevalence" and "lifetime prevalence". The way it reads currently, it seems that the authors intend for these to be viewed as distinct (albeit related) concepts, where "prevalence" has been approximated by GBD and in their manuscript, but "lifetime prevalence" cannot be calculated. Indeed, the way GBD calculates prevalence seems to be more akin to period prevalence over the timeframe of data collection. Mentioning that the prevalence at Line 485 is a period prevalence may help to further distinguish this from lifetime prevalence and might allay any possible confusion, especially if the sentences focusing on lifetime prevalence are moved to the paragraph focusing on underestimating the true prevalence.

VERSION 2 – AUTHOR RESPONSE

Point-by-point Reply to the Reviewers' Comments

We thank all the Reviewers for their insightful comments and suggestions. Below, we have endeavored to respond to all questions and suggestions from the Reviewers.

- **Reviewer #1: I thank the authors for doing a profound revision based on the comments. At least the limitations behind the figures are now much more understandable, and I do not have further requests.**

Authors' response: We thank the Reviewer #1 for the comment.

- **Reviewer #2: This is a revised and resubmitted version of a study examining incidence/prevalence rates of TBI and SCI on a national level using data from the Global Burden of Disease 2019 Study.**

I appreciate the time and effort taken by the authors to address comments from the two reviewers. The methods and discussion of limitations are more detailed, and these details have greatly improved the manuscript. However, some of the additions remain unclear and do not quite follow a logical flow that is present within the rest of the manuscript. I suggest minor revisions to this manuscript, and my comments follow below. I worked off of the manuscript

copy with tracked changes, so references to specific lines reflect that copy, not the clean copy at the beginning of the submission.

The paragraphs adding more detail about the limitations of this work should be rearranged slightly. In particular, the paragraph at Lines 511-518 lacks complete logical flow. The authors mention in the first sentence of that paragraph on Line 511 that the GBD study "did not link TBI/SCI with risk factors," but then focus on lifetime prevalence of TBI/SCI without mentioning risk factors at all beyond that first sentence. Additionally, it seems that the sentences mentioning the difficulty/impossibility of calculating "lifetime prevalence" might be better suited to the paragraph at Lines 485-499, which focuses on potential underestimation of the true prevalence of TBI/SCI.

The authors may also wish to distinguish between "prevalence" and "lifetime prevalence". The way it reads currently, it seems that the authors intend for these to be viewed as distinct (albeit related) concepts, where "prevalence" has been approximated by GBD and in their manuscript, but "lifetime prevalence" cannot be calculated. Indeed, the way GBD calculates prevalence seems to be more akin to period prevalence over the timeframe of data collection. Mentioning that the prevalence at Line 485 is a period prevalence may help to further distinguish this from lifetime prevalence and might allay any possible confusion, especially if the sentences focusing on lifetime prevalence are moved to the paragraph focusing on underestimating the true prevalence.

Authors' response: We thank the Reviewer #2 for the comment.

We have revised relevant contents in the Strengths and Limitations section in the Discussion as follows:

"Second, this study might also underestimate the true period prevalence. The GBD 2019 Study calculated the period prevalence of non-fatal injuries through probabilities of permanent health loss [1]. Permanent health loss relates to the probability of patients (one year after the injury) returning to a health status with more disability than their pre-injury health status [1]. However, the probabilities of permanent health loss assessed in the GBD Study may be grossly underestimated, especially for TBI, because accurate TBI prevalence data is even more limited than incidence data, especially in low/middle-income countries; and TBI is not an isolated event but can have variable long-term consequences, including dementia, stroke, parkinsonism, and epilepsy [2]. For example, a large study from a Swedish registry found higher probabilities of premature mortality, psychiatric inpatient admission/outpatient visits, disability pension, welfare recipiency, and low educational attainment after even a mild TBI compared to uninjured siblings [3]. Furthermore, the associations between TBI and long-term neurological diseases remain poorly understood; many sequelae other than those mentioned above have not been considered, leading to an underestimation of the true TBI period prevalence [2]. Referring to the reviewer' comments, we also attempted but could not calculate the lifetime prevalence of TBI/SCI through the GBD data because, while longitudinal cohort or survey analysis is commonly used to calculate lifetime prevalence [4, 5], the GBD Study is a cross-sectional analysis conducted iteratively on an annual basis [1]. Short-term disability caused by non-fatal injuries is assumed to last less than one year in the GBD Study, which means that the short-term disability after TBI/SCI in a given year may not be calculated for prevalence in future iterations [1]." (Pages 22-23, lines 484-504)

"Fourth, the GBD 2019 Study did not link TBI/SCI with risk factors such as behavioral factors (e.g., alcohol use), so we could not assess any associations between the two (e.g., disease burden attributable to certain risk factors) [6]." (Page 23, lines 516-518)

We have also revised relevant contents in the Strengths and Limitations of This Study

section as follows:

"One of the limitations was that this study might underestimate the true incidence and period prevalence of TBI/SCI; was unable to calculate lifetime prevalence of TBI/SCI through the GBD data." (Page 4, lines 76-78)

"The third limitation was that this study could not assess associations between risk factors and TBI/SCI burden through the GBD data." (Page 4, lines 83-84)

Additionally, we have revised relevant contents in the Implications for Future Studies

section in the Discussion as follows:

"First, population-based epidemiological studies may be improved in the future through standardized definitions (e.g., standardized criteria for diagnosis), methods (e.g., case ascertainment based on multiple, overlapping sources of information, such as hospitals, outpatient clinics, general practitioners, and death certificates), and data presentation (e.g., collection of a complete calendar year of data) [2]. These improvements would be especially helpful in data-sparse locations to facilitate comparisons between countries/territories. Second, there is a need for better ways to characterize the currently under-recognized risk of long-term disabling sequelae to bring estimates closer to the true period prevalence, especially for mild TBI. Furthermore, we hope that the GBD Collaborators include lifetime prevalence in future iterations to estimate the global impact of TBI/SCI accurately. Last, we hope that the GBD Collaborators will include the burden of TBI/SCI attributable to risk factors; this would provide more detailed results on the causes of TBI/SCI and allow for more targeted preventative strategies." (Page 24, lines 528-540)

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