PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between chiropractic spinal manipulation and lumbar discectomy in adults with lumbar disc herniation and radiculopathy: retrospective cohort study using United States' data
AUTHORS	Trager, Robert; Daniels, Clinton; Perez, Jaime; Casselberry, Regina; Dusek, Jeffery

VERSION 1 – REVIEW

REVIEWER	Yi Wong International Medical University, Centre for Complementary & Alternative M
REVIEW RETURNED	02-Oct-2022

GENERAL COMMENTS	1. Kindly define "newly diagnosed" 2. Kindly correct the error on page 8 (Eligibility criteria) Error! Reference source not found.

REVIEWER	Julie Fritz University of Utah, Physical Therapy and Athletic Training
REVIEW RETURNED	13-Oct-2022

| GENERAL COMMENTS | This manuscript uses data from the TriNetX, Inc, network to evaluate the association between chiropractic spinal manipulative therapy (CSMT) and discectomy for patients age 18-49 with ICD-codes indicating lumbar disc herniation and/or radiculopathy. This paper addresses an important topic of the pathways used to manage persons with back pain and the role of nonpharmacologic, non-surgical interventions like CSMT. Findings from this report support findings from other studies suggesting reduced risk of surgery as an outcome when nonpharmacologic interventions are received.

This paper is generally well-written and appropriately succinct. There are however several areas of clarification in the methods and data sources that would improve the paper as outlined below:

1. More information is needed about the TriNetX data source. What is known about the degree of completeness of data in the network? Are all the health care systems in the United States or is data included from other countries?

2. How was missing data elements handled in the dataset?

3. Did participants have to be continuously represented in the dataset some period of time before and after the index diagnosis date in order to be eligible? |
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| | 4. Additional information is also needed on the formation of the cohorts for analysis. Participants with a diagnostic code specifying LDH or LSR were identified, the text should explain the washout period used to identify the index date of diagnosis and the use of the washout period.

The timing of the CSMT receipt should be clarified. Could the CSMT occur anytime in the year following the index diagnosis or did the care have to occur within some time window after the index diagnosis? If CSMT could occur at anytime it may be difficult to presume the manipulative therapy was provided for LDH/LR and not some other condition. Among patients with both surgery and CSMT did the CSMT have to occur before the surgery or does this group include participants who received post-operative CSMT? Please clarify these timing issues.

5. The paper focuses on the potential limitation of the lack of socioeconomic data. Several important psychological characteristics with prognostic value for predicting outcomes are also missing including catastrophizing and self--efficacy for pain management and should also be mentioned as limitations. In addition, the lack of information about pain severity or impact could be a source of bias in the analyses.

6. Please clarify the date range for study participants which is listed as August 3, 2012 to August 3, 2022. Presumably the index date had to be between Aug 3, 2012 and Aug 3, 2020 to allow sufficient time for outcomes?

7. In the discussion section, page 18, please remove the statement that the results support the effectiveness of CSMT. The design precludes this statement. |

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Dr. Yi Wong, International Medical University Comments to the Author:
1. *Kindly define "newly diagnosed"*
    a. Thank you. This is an important point. In our study, we included patients at the first instance of the diagnosis in the medical record, which we defined as being newly diagnosed. We added more language to clarify this in the abstract accordingly:
        i. "Adults age 18-49 with newly-diagnosed LDH/LSR (first date of diagnosis) were included"
    b. We also added further information in the Methods to explain our definition of newly-diagnosed:
        1. This study identified patients with newly-diagnosed LDH and/or LSR by querying the TriNetX dataset with a custom set of codes (Supplemental Table 1). These patients were identified at the index date of diagnosis, which we defined as the first instance of LDH or LSR codes appearing in the medical record. This requirement created an infinite washout period preceding the index date in which patients had no previous diagnosis of LDH or LSR.
2. *Kindly correct the error on page 8 (Eligibility criteria) Error! Reference source not found.*
    a. Thank you. We ensured that this Error message did not appear in the revised draft.

Reviewer 2

Dr. Julie Fritz, University of Utah

Comments to the Author:
This manuscript uses data from the TriNetX, Inc, network to evaluate the association between chiropractic spinal manipulative therapy (CSMT) and discectomy for patients age 18-49 with ICD-codes indicating lumbar disc herniation and/or radiculopathy. This paper addresses an important topic of the pathways used to manage persons with back pain and the role of nonpharmacologic, non-surgical interventions like CSMT. Findings from this report support findings from other studies suggesting reduced risk of surgery as an outcome when nonpharmacologic interventions are received.

This paper is generally well-written and appropriately succinct. There are however several areas of clarification in the methods and data sources that would improve the paper as outlined below:

1. *More information is needed about the TriNetX data source.*
   a. *What is known about the degree of completeness of data in the network?*
      i. Response: TriNetX includes basic data quality checks to ensure a minimum standard level of completeness. This standard is consistent with broader norms/levels utilized by other federated/national records databases. Please see the added references[1,2] which detail these standards more thoroughly. Our strategy to compare the mean number of data points between cohorts showed that cohorts had a high and similar number of data points, suggesting that a difference in data completeness would not explain our results. This strategy has been used in previously as a method to examine for the potential for differential data completeness.[3,4] However, considering the data is de-identified from several institutions, we could not verify the exact level of completeness of data against for all variables a gold standard of chart review. Please see this added statement in the Methods:
         1. "The TriNetX dataset routinely undergoes automated and manual assessments to ensure data conformance, completeness, and plausibility.[1,2] One previous study estimated a completeness of at least 87% for medications in the TriNetX dataset,[5] however the completeness of other variables has not been examined to our knowledge."
      ii. We did have access to see the percentage of unknown values for patients' demographics. Please note that the ethnicity data is frequently recorded as "unknown" in medical records data even beyond TriNetX and the presence of "unknown" may not indicate that the variable is altogether missing.[6,7] In order to describe this information concisely, we reported it in the Descriptive data section where we provide the results for data density and completeness. Please see this added statement in the Results:
         1. After propensity matching, the frequency of unknown demographic variables was the same both cohorts, with 15% having unknown race, 14% having unknown ethnicity, and 0% having unknown sex or age.
      iii. Please see this added statement in the Limitations:
         1. We were also unable to examine data completeness for all variables at an individual patient level.
   b. *Are all the health care systems in the United States or is data included from other countries?*
      i. Response: All the health care systems included in TriNetX are in the US. We made this clearer by introducing the network as the "TriNetX US research network" in the Setting and data source section, and also added "in the US" as follows:
         1. "Data in this network is de-identified, aggregated, and frequently updated from the health records of multiple health care organizations in the US, which are typically large, academically affiliated health centers and their ambulatory offices."
      ii. Please note that we define "United States" as "US" earlier in the text.
2. *How was missing data elements handled in the dataset?*
   a. Response: It is currently not possible to make any imputations for missing data in the TriNetX dataset. We were only able to examine the mean number data points per

patient between cohorts. This analysis suggested that between-cohort differences in missing data / data completeness would not explain our outcomes. We added the following statement:
- i. We did not perform any imputations for missing data.

3. *Did participants have to be continuously represented in the dataset some period of time before and after the index diagnosis date in order to be eligible?*
   a. Response: Patients were required to be continuously represented in the dataset <u>after</u> the index diagnosis date to be eligible. This ensured that patients were not lost to follow-up. This was achieved by requiring the presence of any healthcare visit for at least two years' follow-up after the index date of diagnosis, a period which corresponded to our longest follow-up window. Patients were not required to be continuously represented in the dataset <u>prior to</u> the index date of diagnosis, as our study focused on a new user design including young to middle-aged adults, and we expected many patients to be presenting for care for LDH/LSR for the first time in the health care organization. We added the following statement to our Methods:
      - i. Patients were required to be represented in the dataset for at least two years after the index diagnosis date to be eligible.

4. *Additional information is also needed on the formation of the cohorts for analysis.*
   a. *Participants with a diagnostic code specifying LDH or LSR were identified, the text should explain the washout period used to identify the index date of diagnosis and the use of the washout period.*
      - i. Response: Thank you. We added a statement explaining the washout period used to identify the index date of LDH or LSR diagnosis as follows:
        1. This study identified patients with newly-diagnosed LDH and/or LSR by querying the TriNetX dataset with a custom set of codes (Supplemental Table 1). These patients were identified at the index date of diagnosis, which we defined as the first instance of LDH or LSR codes appearing in the medical record. This requirement created an infinite washout period preceding the index date in which patients had no previous diagnosis of LDH or LSR.
   b. *The timing of the CSMT receipt should be clarified. Could the CSMT occur anytime in the year following the index diagnosis or did the care have to occur within some time window after the index diagnosis? If CSMT could occur at anytime it may be difficult to presume the manipulative therapy was provided for LDH/LR and not some other condition. Among patients with both surgery and CSMT did the CSMT have to occur before the surgery or does this group include participants who received post-operative CSMT? Please clarify these timing issues.*
      - i. Response: For the reasons you mentioned about potential confounding, the CSMT was required to occur on the same day of index diagnosis for patients to be included in the CSMT cohort. Accordingly, the other care cohort could not receive CSMT on this day. We expect that considering we excluded cases of serious pathology in which chiropractors would need to refer patients for imaging, most chiropractors would perform CSMT on the index diagnosis date.[8,9] We made this clearer by adding a statement as shown below:
        1. Patients in the CSMT cohort were required to receive CSMT on the date of index date of diagnosis of LDH or LSR (i.e., the first instance of the diagnosis in the medical record), while those in the cohort receiving other care could not receive CSMT on the index date of diagnosis.
      - ii. Regarding patients with both surgery and CSMT: The CSMT had to occur prior to surgery. Please see our statement above which should help clarify this. For patients in the CSMT cohort, CSMT was required on the date of index diagnosis of LDH/LSR, rather than after its diagnosis. Also note that we excluded patients with <u>any previous</u> lumbar spine discectomy, fusion, arthrodesis, and postlaminectomy syndrome as part of our eligibility criteria, as we aimed to exclude patients who received CSMT post-operatively for LDH/LSR.
        1. "Participants: Adults age 18-49 with newly-diagnosed LDH/LSR (first date of diagnosis) were included. Exclusions were prior lumbar

surgery, absolute indications for surgery, trauma, spondylolisthesis, and scoliosis."
2. Also note the exclusions in the Supplemental file:

Table 2: Exclusions for both cohorts

Diagnosis codes*	Definition (excluded days -365 to 0)
C00-C96	Malignant neoplasm
G83.4	Cauda equina syndrome
M41	Scoliosis
M43.16	Spondylolisthesis, lumbar region
M43.17	Spondylolisthesis, lumbosacral region
M48.0	Spinal stenosis
M48.46	Fatigue fracture of vertebra, lumbar region
M48.56	Collapsed vertebra, not elsewhere classified, lumbar region
M48.57	Collapsed vertebra, not elsewhere classified, lumbosacral region
M84.40	Pathological fracture, unspecified site
M84.48	Pathological fracture, other site
M84.58	Pathological fracture in neoplastic disease, other specified site
M84.60	Pathological fracture in other disease, unspecified site
M96.1	Postlaminectomy syndrome, not elsewhere classified
N31	Neuromuscular dysfunction of bladder, not elsewhere classified
R15	Fecal incontinence
R32	Unspecified urinary incontinence
S22.08	Fracture of T11-T12 vertebra
S30-S39	Injuries to the abdomen, lower back, lumbar spine, pelvis and external genitals
S32.0	Fracture of lumbar vertebra
Z98.1	Arthrodesis status
Lumbar discectomy codes	**Definition (excluded any time to day 0)**
Multiple	See Supplemental File Table 4
* International Classification of Diseases (ICD-10)	

a.

5. *The paper focuses on the potential limitation of the lack of socioeconomic data. Several important psychological characteristics with prognostic value for predicting outcomes are also missing including catastrophizing and self-efficacy for pain management and should also be mentioned as limitations. In addition, the lack of information about pain severity or impact could be a source of bias in the analyses.*
   a. Response: Thank you, we agree. We added to our Limitations section, so it now reads as follows:
      i. There are several variables unavailable in the TriNetX dataset that could lead to unmeasured confounding such as those relating to socioeconomic status, clinical examination findings,[10] detailed spinal imaging data such as measures of disc herniation,[11] self-reported pain severity and impact, and measures of catastrophizing, self-efficacy, and disability.
6. *Please clarify the date range for study participants which is listed as August 3, 2012 to August 3, 2022. Presumably the index date had to be between Aug 3, 2012 and Aug 3, 2020 to allow sufficient time for outcomes?*
   a. Response: Thank you for pointing this out. We believed that TriNetX would automatically account for this and reduce the inclusion window to 2 years prior to the final outcome window, to allow for sufficient follow-up time to capture all outcomes. However, we were unable to determine if the software was doing this. Therefore, we revised our cohort query in TriNetX to ensure that the inclusion window was from 2012 to 2020, rather than 2012 to 2022, as it was previously. This change led to similar outcomes in the model. Despite these changes, because the TriNetX network is continuously growing and changing, we found an increase in our CSMT cohort sample size. This can be explained by different health care organizations reporting data or participating in the network at the time of the query.
   b. With the stricter cohort query, larger sample size, and more recent/updated query date (October 24, 2022) it made the most sense for us to update our results in the manuscript. This is reflected throughout the manuscript and the Tables. We also updated the propensity matching density graph in the Supplemental file.
   c. Please note that while the outcomes change slightly, the directionality of the association remains the same (i.e., reduced odds of discectomy in the CSMT cohort). Therefore, our Discussion and Conclusion remains almost identical.

7. *In the discussion section, page 18, please remove the statement that the results support the effectiveness of CSMT. The design precludes this statement.*
   a. Response: Thank you. We removed the following statement as advised: "These results provide real-world evidence that CSMT is effective in reducing the likelihood of discectomy among adults with LDH/LSR, and support previous studies showing efficacy in reducing pain related to LDH and LSR.[12–14]"

VERSION 2 – REVIEW

REVIEWER	Julie Fritz University of Utah, Physical Therapy and Athletic Training
REVIEW RETURNED	08-Nov-2022

GENERAL COMMENTS	The authors have provided very helpful clarifications to the prior review comments. I have only a few remaining recommendations: 1. In the third bullet point of the article summary, please acknowledge the other variable domains that are not available in the dataset (psychosocial, etc.) 2. In the Methods section, Eligibilty requirements, please revise the statement that reads "This requirement created an infinite washout period preceding the index date in which patients had no previous diagnosis of LDH or LSR". Your participants have a finite amount of time during which they are represented in your data and this could be a rather short time period for some patients. It is not an infinite amount of time for any participant.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

1. The authors have provided very helpful clarifications to the prior review comments. I have only a few remaining recommendations:
   a. Thank you
2. In the third bullet point of the article summary, please acknowledge the other variable domains that are not available in the dataset (psychosocial, etc.)
   a. Thank you, we agree this is important to mention. We revised this bullet point to describe additional data items that were unavailable in the TriNetX dataset as follows:
      i. While an extensive propensity matching model was utilized to control for confounding variables, several variables were unavailable in the dataset including those relating to socioeconomic status, examination and imaging findings, pain severity and impact, catastrophizing, self-efficacy, and disability.

3. In the Methods section, Eligibilty requirements, please revise the statement that reads "This requirement created an infinite washout period preceding the index date in which patients had no previous diagnosis of LDH or LSR". Your participants have a finite amount of time during which they are represented in your data and this could be a rather short time period for some patients. It is not an infinite amount of time for any participant.
   a. Thank you. This is a great idea to improve the clarity of our methods. We revised the sentence as follows, mainly by changing "infinite" to "any time available:"
      i. This effectively required that patients had no previous instance of LDH or LSR diagnosis occurring over any time available in the dataset preceding the index date. As the length of time patients were available in the dataset prior to inclusion varied, this washout window also varied per patient.
   b. Note that we had another sentence which used the term "infinite" in a similar manner (i.e., As an additional measure of ensuring patients had no previous discectomy, any

prior occurrence of discectomy was excluded over an infinite time window preceding and including the date of index diagnosis). Accordingly, we also revised this sentence as follows:

     i. As an additional measure of ensuring patients had no previous discectomy, we excluded patients with any instance of discectomy occurring over any time available in the dataset preceding and including the index date of diagnosis.

c. Also please note that we updated the Figure 1 caption to explain the washout periods that we previously described as "infinite." The Schneeweiss et al. manuscript provided a Creative Commons template for creating this figure,[1] which we adapted appropriately for our study. Consistent with the original reference, our figure also uses the "∞" symbol to represent washout periods that extended as far back in time as possible. In keeping with the convention established by Schneeweiss et al's key reference on this topic, we kept the "∞" symbol as-is in the figure, however we explained that the windows extended as far back in time as data were available for each patient:

     i. **Figure 1: Study design. The vertical gray arrow represents the date of index diagnosis of lumbar disc herniation (LDH) or lumbosacral radiculopathy (LSR). Assessment windows to the left of this arrow represent time periods occurring before this date over a span of days [#,#]. The "∞" indicates that the time window extends as far as data are available in the dataset for each patient. The follow up window occurs after the index diagnosis and is represented by a green rectangle representing 1- and 2-years' follow-up. Figure created by RT using Creative Commons template from Schneeweiss et al.[1]**