PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Sex and gender differences in health care utilization trajectories: A cohort study among Quebec workers living with chronic pain
AUTHORS	Lacasse, Anaïs; Nguena Nguefack, Hermine Lore; Page, G; Choinière, Manon; Samb, Oumar; Katz, Joel; Ménard, Nancy; Vissandjée, Bilkis; Zerriouh, Meriem; on behalf of the TorSaDE Cohort Working, .

VERSION 1 – REVIEW

REVIEWER	Gazerani, Parisa Aalborg Universitet
REVIEW RETURNED	02-Dec-2022

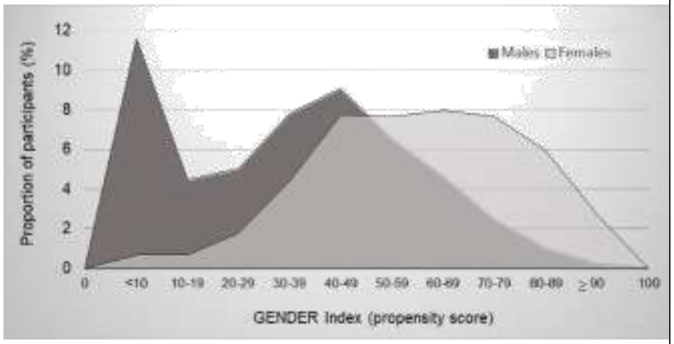
GENERAL COMMENTS	• Did the authors identify a discrepancy in the definition of sex versus gender in their data set? What do the authors suggest for registries considering gender fluidity that is now accepted in society but less implemented in health care systems, and what will be the influence of this point in the retrospective data obtained from already existing databases and registries? do the authors have a suggestion or recommendation? • How the findings presented in this study can be implemented at 3 levels for patients, clinicians, for policymakers, please elaborate. • Did the authors identify any change in gender in the longitudinal dataset? it seems that from adolescence to adulthood some cases might change gender from one to another or back later in adulthood. How such changes can be accommodated in the analysis? • Can healthcare utilization be defined in a more detailed way in future studies? Any alternative way or addition to health care visits for example? • Please elaborate and comment on the internal versus external validity of this study. Can the findings be generalized for an expanded conclusion? • Please add the sources of bias in this study and the attempts made to minimize those

REVIEWER	de Meij, Nelleke Maastricht University Medical Centre+, Anesthesiology and Pain Medicine
REVIEW RETURNED	29-Jan-2023

GENERAL COMMENTS	This is a nice written manuscript, with important sex en gender information in the CP population. I have no commments on the manuscript, except maybe that tI underline the need for furhter research on sex and gender.

VERSION 1 – AUTHOR RESPONSE

Reply to Reviewer 1 - Dr. Parisa Gazerani, Aalborg Universitet

Comments and suggestions	**Reply and page numbers in the “Track [redacted] changes” version of the manuscript**
1. Did the authors identify a discrepancy in the definition of sex versus gender in their data set?	We would like to thank the reviewer for the valuable and constructive comments. As published in our paper about the GENDER Index development (Lacasse, Pagé, et al., 2020), sex and GENDER Index scores appeared related but partly independent in the TorSaDE Cohort (e.g., incomplete histogram overlap, variability of gender scores within each sex group):  *Fig. 1 Distribution of GENDER Index scores in males and females.* *Higher scores on the 0–100 GENDER Index can be interpreted as a* *higher level of characteristics associated with being female/having*

	more feminine characteristics. This precision about our index was added to our methodology (**p. 9**).
What do the authors suggest for registries considering gender fluidity that is now accepted in society but less implemented in health care systems, and what will be the influence of this point in the retrospective data obtained from already existing databases and registries? do the authors have a suggestion or recommendation?	We would suggest all federal and provincial survey and patient registry developers to plan the measurement of sex at birth, gender identity (which was not available in our data), in addition to gender-related variables (e.g., responsibility for caring for children, occupation, number of hours of work). The inclusion of such measures would allow for more relevant, equitable, diversified, and inclusive future research. This is now underlined in our manuscript (**p. 17**).
2. How the findings presented in this study can be implemented at 3 levels for patients, clinicians, for policymakers, please elaborate.	Implications for knowledge users are now covered all together in the discussion (**p. 17-18**). Our discussion now reads as follows: **Implications for Knowledge Users** ***For clinicians.*** It will be important for clinicians to be aware of their clientele who are heavy healthcare users. Be vigilant about the presence of sex disparities vs. inequities is relevant. Disparities are not undesirable as such, unless they result in

	unfairness and injustice. On the other side, inequities are undesirable and should be subject to moral criticism as they imply unfairness and injustice [(76, 77)]). One may wonder, for example, if males receive similar medical follow-up and prescription opportunities as females do to manage their pain. Our results provide valuable information to identify, early on, patients who are more likely to experience heavy health care utilization—i.e., females—and adapt health care services accordingly (e.g., assess if heavy health care use is useful and necessary). ***For patients.*** It will be important to raise awareness among persons living with chronic pain, especially women, regarding the trends found in this study. Partnership with patients and the public could help explore the causes and potential solutions. ***For policymakers.*** We would suggest all federal and provincial survey and patient registry developers to plan the measurement of sex at birth, gender identity (which was not available in our data), in addition to gender-related variables (e.g., responsibility for caring for children, occupation, number of hours of work). The inclusion of such measures would allow for more relevant, equitable, diversified, and inclusive future research. ***For researchers.*** Our results underline the importance of considering both sex

	and gender in CP healthcare utilization research. This approach allows for a better understanding of whether differences are explained by biological factors or indirect measurement of social factors, and consequently helps identify modifiable risk factors for unfavourable outcomes. Although the non-pain-related medical literature abounds with findings demonstrating the tendency of females to have more health service contacts (74), our study is novel as it represents a first step in demystifying distinct subgroups of health care users among females and males living with CP. Future studies should build upon our work and enhance and diversify the operationalization of healthcare utilization and care trajectories. For example, they could focus on a specific type of visits (e.g., emergency department visits), examine transitions between different care sectors (primary, secondary, tertiary), or analyze sequences of care events over time (e.g., sequence analysis (59)). Further studies should also examine the reasons for sex differences (e.g., qualitative studies allowing an in-depth understanding of the behaviours and experiences specific to people living with CP).
3. Did the authors identify any change in gender in the longitudinal dataset? it seems that from adolescence to	This is a valid point. However, in our study, gender was assessed using the GENDER Index, which was computed using cross-sectional survey variables

adulthood some cases might change gender from one to another or back later in adulthood. How such changes can be accommodated in the analysis?	(Canadian Community Health Survey-CCHS). Although some Canadians may have participated multiple times in the CCHS, our sample was limited to only one CCHS participation (Figure 1), and we cannot accommodate such changes in the analysis. We have now highlighted this limitation in the manuscript (**p. 20**). The cross-sectional nature of the CCHS is also better underlined now (**p. 9 and 19**). We will keep this good idea for

	another study that could be conducted exclusively among individuals who have participated in the ESCC more than once.
4. Can healthcare utilization be defined in a more detailed way in future studies? Any alternative way or addition to health care visits for example?	The reviewer is absolutely right. Our study applied trajectory analysis for the first time to investigate the association between sex, gender, and healthcare trajectories among persons living with chronic pain. Future studies should build upon our work and enhance and diversify the operationalization of healthcare utilization and care trajectories. For example, they could focus on a specific type of visits (e.g., emergency department visits), examine transitions between different care sectors (primary, secondary, tertiary), or analyze sequences of care events over time (e.g., sequence analysis (Nguena Nguefack et al., 2020)). This is now underlined in the discussion of the manuscript (**p. 18**).
5. Please elaborate and comment on the internal versus external validity of this study. Can the findings be generalized for an expanded conclusion? 6. Please add the sources of bias in this study and the attempts made to minimize those	The *Strengths and limitations* section of our manuscript provided a description of the potential biases of our study as well as its external validity. To enhance the clarity of this section, we have reformulated the information and added various clarifications that enable the reader to identify the specific type of bias or validity being discussed (**p. 18-20**). It now reads as follows: *“Selection bias and external validity.* The TorSaDE Cohort, a unique database harnessing the strengths of longitudinal

claim data from Canadian universal health care coverage linked to cross-sectional patient-reported outcomes, allowed to increase the generalizability of our results to various persons living with CP in Canada and possibly in countries with a similar gender norms and health care system. In fact, probability sampling and diversity of profiles are strengths of the CCHS. Also, CCHS allowed to work with a community sample and include people with little or no contact with the health care system, as compared to studies using administrative databases alone, using medical charts, or involving clinic-based recruitment). A limitation is, however, that the GENDER Index was only available to workers (Lacasse, Pagé, et al., 2020) limiting our capacity to study older adults who are more likely to have CP. Still, various socioeconomic and health impairment profiles (e.g., participants reporting severe pain) could be taken into account in the multivariable analysis.

Information bias. Available data did not allow us to apply the new accepted definition of CP (persistent or recurrent pain lasting over three months (Treede et al., 2019)). However, our CCHS-based CP definition has been used in many

	epidemiology studies (Gilmour, 2015; Hogan et al., 2016, 2017; Ramage-Morin, 2008; Ramage-Morin &

Gilmour, 2010; Reitsma et al., 2012; Reitsma et al., 2011) and provides prevalence estimates comparable to studies using more traditional definitions (Moore et al., 2014). In our study, the index date (defined as CCHS date of completion) was not related to a significant event in the care trajectory of CP patients (e.g., first diagnosis). Consequently, trajectories modelled in this study represent a random picture of a part of the life course of participants, and patterns of health care utilization were quite stable over time. A limitation of our study is also that we had to study all-cause health care visits (as medical claims do not allow reliable identification of CP-related health care contacts/visits) (Lacasse, Cauvier Charest, et al., 2020; Lacasse et al., 2015). Nevertheless, this allows the patient journey to be viewed as a whole, which could also be seen as a strength.

Next relevant aspect, gender was assessed using the GENDER Index, which was computed using cross-sectional CCHS variables. Although some Canadians may have participated multiple times in the CCHS, our sample was limited to only one CCHS participation (Figure 1), and we could not accommodate change in gender over time in the analysis. Overall, the strengths of using the TorSaDe Cohort clearly outweigh the disadvantages since, to our knowledge at the time of this study, no pain-specific Canadian data

	source outside tertiary care settings links self-reported data from thousands of patients to longitudinal administrative databases (the only way to study bio-psycho-social determinants of health care trajectories). *Confounding*. The use of multivariable analysis in a large sample of participants and the availability of many potential confounders chosen according to recognized models (Andersen, 1995; Babitsch et al., 2012; Bauer, 2021; Mena et al., 2019) allowed us to control confounding.

Reply to Reviewer 2 - Dr. Nelleke de Meij, Maastricht University Medical Centre

Comments and suggestions	**Reply and page numbers in the “Track [redacted] changes” version of the manuscript**
1. This is a nice written manuscript, with important sex en gender information in the CP population. I have no comments on the manuscript, except maybe that to underline the need for further research on sex and gender.	We truly appreciate the positive comment provided about our manuscript and thank the reviewer for the helpful recommendation. The need for further research that takes into account both sex and gender have been reinforced in the discussion of our manuscript (**p. 18**): “*Our results underline the importance of considering both sex and gender in CP healthcare utilization research. This approach allows for a better understanding of whether differences are explained by biological factors or indirect*

	measurement of social factors, and consequently helps *identify modifiable risk factors for unfavourable outcomes.”*

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VERSION 2 – REVIEW

REVIEWER	Gazerani, Parisa Aalborg Universitet
REVIEW RETURNED	06-Jul-2023

GENERAL COMMENTS	The authors have addressed the points raised and accordingly revised the manuscript.