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Title	Sex and gender considerations in Canadian clinical practice guidelines: a systematic review
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Reviewer 1	Dr. Mohamad Anas Hussain
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General comments (author response in bold)	Thank you for the opportunity to review this well-written paper that examines the important aspect of sex-based reporting in clinical practice guidelines. I have a few comments/questions that may help further enhance this manuscript. ABSTRACT 1. In the last sentence of the Results, section you state that, 'several important sex-specific recommendations were omitted from CGPs…' I do not think this is correct. Your paper indicates that sex-specific data from original research were not included in CGPs. Perhaps this sentence should be reworded to reflect this more accurately, such as 'several published sex-specific data were omitted from CGPs..' **The sentence has been removed.** INTRODUCTION 2. I think the introduction will benefit from clear definitions of sex vs. gender, as these terms seem to be used interchangeably throughout the paper. **The first paragraph now provides clear definitions of sex and gender according to the Sex and Gender Equity in Reporting guidelines.** METHODS 3. Please clarify if your systematic review protocol was registered with PROSPERO International prospective register of systematic reviews. **The review protocol was not registered with PROSPERO. The protocol is posted on Open Science Framework. We now indicate this in the first sentence of the methods section.** 4. Did your systematic review follow PRISMA or another similar systematic review reporting guideline? **Yes. Please see attached PRISMA checklist. This is now indicated in the methods section.** 5. Please justify limiting the inclusion of guidelines published after the year 2013. This limitation removed 56% of the papers in your initial search, which can be a source of significant bias. Many guidelines were published prior to 2013, and have not since been updated. For example, the Canadian Peripheral Arterial Guidelines were last published in 2005. I wonder if inclusion of these older guidelines can help strengthen (or weaken) your conclusions. **In 2009, the federal government issued the Sex and Gender Based Analysis Policy for the Health Portfolio. Although researchers and scholars have been discussing SGBA in clinical trials and practice before then, we saw that as a critical turning point in Canada, as it confirmed the SGBA requirements that the CIHR had already been developing for research. In considering that all evidence post-2009 would be required to have sex and gender integrated, and the fact that studies take at least one year to conduct and another year to be published, and that it takes approximately 2 years to review evidence and develop a CPG, it is was reasonable to consider that CPGs written in 2013 would be the earliest possible date to have new evidence on sex and gender considerations incorporated. Therefore, we searched only for CPGs written in 2013 or sooner as our cut-off. The end date of 2015 was selected for currency at the start of this review project. We now clarify this choice in the methods section.** 6. Please clarify your criteria for defining a guideline as 'Canadian,' especially the ones you found in your PubMed search. Many of these guidelines are multidisciplinary, and have several international collaborators. For example, did the senior author need to have a Canadian affiliation? Etc. **According to the CMA Infobase, the selection criteria for Canadian guidelines can be found here: https://www.cma.ca/En/Pages/submit-guideline.aspx , but essentially state that to be eligible, guidelines must be developed or endorsed by authoritative medical or health organizations in Canada. We could not find any information on how complete Infobase is, which is why we also searched Pubmed for the word Canadian, as well as provincial and professional websites.** 7. Please provide further explanation on the following statement "We strategically selected CPGs.." How was this done? And by whom? **The word "strategically" has been removed. We now provide references and appropriate**

	justification for the chronic disease states that were selected, in accordance with priorities of interest to policy makers. 7. How many authors screened the initial set of articles to establish eligibility? Was this done independently and in parallel? **Eligibility was established by two authors. Because the screening criteria for Canadian CPGs was already set by the CMA, there was no need to arbitrate inclusion. The electronic text search for keywords in the CPGs was decided upon by all authors. After the initial screening, 3 authors independently analyzed the data for classification purposes.** 8. I understand the risk-of-bias assessment was not possible using traditional tools, but did the authors examine any factors that can help establish quality of the guidelines? For example, single vs. multidisciplinary guidelines; guidelines that followed established reporting standards vs. those that did not; presence of male vs. female authors; provincial vs. national vs. international guidelines. This information can allow for a subgroup analysis of only the 'highest quality' guidelines to ensure your results are robust. **This is a great suggestion. Unfortunately we did not think of doing this as it was beyond the scope of our initial research question. The CMA Infobase does not a priori classify CPGs according to the quality/risk of bias factors you highlight. We include this as a limitation in the Abstract. We will definitely consider taking this approach in our next analysis, as we are already at our word limit for the current publication.** 9. Please clarify how the 3 investigators that independently extracted the data resolved disagreements, and if any measure of agreement (such as kappa) was done. **We now clarify in the methods section that disagreements were resolved by discussion and consensus. Several discussions and arbitrations were required, as refinement of the categories was an iterative process. Our records for documenting change do not allow for kappa statistics to be calculated from each set of discussions, as we updated working Excel sheets and often changed the codes during the discussions.** RESULTS/DISCUSSION 10. As you have alluded to, it's difficult to gauge if sex-based evidence that was omitted in guidelines was due to low-quality data, or simply due to being overlooked. I think one thing you can do to strengthen this argument is compare some Canadian guidelines to other international guidelines, and examine if these other guidelines have included sex-based data that Canadian guidelines have overlooked. **Excellent suggestion. We now cite work from the Netherlands in the discussion section. and point out that our findings are in line with other international efforts to investigate this issue.** 11. The discussion can be further strengthened by highlighting that current CPG reporting instruments such as GRADE II do not specifically require sex-based reporting. **We agree this is a valid point, and now make reference to the AGREE II, GRADE II and SAGER guidelines in the discussion section of the manuscript.**
Reviewer 2	Dr. Pierre Durieux
Institution	Département de Santé Publique, Hôpital Européen Georges Pompidou, Paris, France
General comments (author response in bold)	This article represents an interesting peace of work. The subject is original, in my knowledge the first attempt to synthetize data on sex and gender considerations in guidelines. My remarks: 1) The authors differentiate sex and gender (they propose a box where they present definitions of these two terms). However, in their results they do not discuss this aspect: whether guidelines use the term gender or sex and which term should be used (and when). **Thank you for encouraging us to conduct and report this sub-analysis. We included it as a third objective, and now report that 34% of text-positive CPG's used the terms correctly. We believe these findings enhance the quality of the resubmission.** 2) The authors differentiate text-positive and text-negative guidelines. They analyze in detail text positive but not text negative guidelines (one short paragraph page 11 where they state that five text negative guidelines contained citations alluding to the presence of sex differences). More generally, it is not clear to understand whether or not a text negative guideline means that the problem of sex or gender should be addressed. **We now clarify this point and add a sentence in the discussion stating that further work is necessary to systematically identify whether relevant sex and gender information should have been included in the text-negative CPG's.** 3) The paragraph "omission of sex and gender difference" (page 11) is interesting and examples are given in Table 3. However, it is difficult for the reader to relate these results to the main results (analyze of text positive and text negative guidelines). In other words, data could have been

	analyzed as a diagnostic test with true positive, true negative, false positive and false negative guidelines. May be this work could have been done on a subset of guidelines addressing specific topics such as cardiovascular diseases or diabetes. **Thank you for pointing out the complexities and lack of clarity surrounding the "omission" analysis. Table 3 was added based on a suggestion from one of the initial reviewers from the CMAJ (who suggested that we re-submit the manuscript for publication to its sister journal CMAJ-Open). Given the 2,500 word limit we do not feel that we were able to do justice to the question. We like your suggestion to conduct the "omission" analysis on a subset of guidelines related to cardiovascular disease. After much discussion among the authors, we've decided to remove Table 3 and make this the focus of a separate article, with a more comprehensive search strategy, using some of the risk of bias indicators suggested by Reviewer 1.** 4) The authors state in their last paragraph that guidelines and handbooks for developing guidelines be revised to emphasize this issue. They do not give references on this subject. They could also have analyze main tools or recommendations on how to appraise guidelines (tools such as AGREE or GLIA, or at least Canadian recommendations) to see if these tools address this issue, and therefore they could propose more specific recommendations at the end of their paper on how sex or gender issue should be addressed. **We now devote a paragraph in the discussion section to the AGREE II, GRADE II and SAGER guidelines and what the limitations and opportunities of these tools are for improving the integration of sex and gender in CPGs.** 5) A limit of this work is its limitation to Canadian guidelines. Clinical guidelines development is now an international process and authors could have analyzed a subset of guidelines published in the world (may be limited to one or two topics)… but it is another work. **Please see our response to the Editor and Reviewer 1. We selected Canadian CPGs based on the Canadian Medical Association definition of guidelines that were produced in Canada or endorsed by Canadian professional organizations. It would certainly be interesting to compare Canadian CPGs to international CPGs. This is a topic we will consider for future publication. In the meantime we make reference to work done by the Netherlands on the integration of sex and gender in CPGs and report the similarity of our findings.**