**Author’s response to reviews**

**Title:** Reporting of sex and gender in randomized controlled trials in Canada: a cross-sectional methods study

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**Author’s response to reviews:**
Dear editors,

We would like to thank you for the conscientious and detailed peer reviewer comments and their positive comments regarding the importance and timeliness of this contribution to the literature. We appreciate that both reviewers had difficulty with the rationale for reporting single-sex and mixed-sex studies together, and have revised the manuscript substantially to report these separately.

In addition, we have responded to the comments from both peer reviewers point by point below.

Sincerely,

Vivian Welch on behalf of the author team

Reviewer reports:

Reviewer #1: Thank you for the invitation to review this interesting paper. This is a timely topic and the paper makes an important contribution. The paper is well-written, the design of the study well thought, methodology clear and sound. Results are presented in a comprehensive and clear way, and the discussion is based on the findings of the paper. My only concern is that the authors have included single-sex trials in the study, which skews their analysis. I suggest that the authors remove all trials that only recruited /enrolled one sex/gender from the analysis to be able to present a more accurate picture of the reporting of analysis of sex and gender differences in RCT. I recommend publication of this paper following this revision, and I command the authors for this important piece of work.

Author’s response:

Thank you for your positive and constructive comments. We agree that single-sex trials are different from studies which did not restrict eligibility by sex or gender. However, we feel that it is important to also describe these single-sex studies since our purpose was to document how sex/gender were considered and reported in any kind of randomized trial, not just to assess analysis of sex and gender differences. It is just as important for single-sex studies to consider the implications of their findings across sex/gender because the influence of sex/gender operates even in a single-sex study, given that gender captures social positioning and relationships not just identity.
Thus, in order to address this reviewer’s concern, we have separated the results for “single sex” and “mixed sex” studies. We chose these terms because they are used by Gendered Innovations to describe different types of studies, and we describe this in the paper.

Some comments that can help improve the paper:

The authors could explain why they decided to focus on papers published from January 01, 2013 to July 23, 2014. It would have been great to include a later time period to see whether the CIHR policy has had an impact. As the CIHR only introduce their policy in 2011 to ask all research grant applicants to indicate whether their research proposal addresses sex and gender and to provide justification for their response, most of the RCT findings reported in this time period would have been funded before 2011.

Author’s response:

The data collection for this study was completed in the summer of 2015. We chose to sample from 1 year prior to data collection because these studies would have been entered into the medical subject indexing according to author institutions. This process can take up to 1 year, and the effect would have been to provide a search that could not be reproduced in later years due to changes in indexing.

We recognize this is a limitation of our study and we agree that it will be important to determine the impacts of the CIHR policy as well as the Health Canada Guidance Document (2013) in future studies. which is why we conclude on page 21 that: “This study provides a baseline and methodological approach to compare and assess changes in reporting about sex and gender and in the application of sex and gender analysis in future Canadian RCTs”

Added: (p.9)

“We chose to search MEDLINE up to 1 year prior to data collection because most articles would be indexed according to Medical Subject Headings by this time, allowing the use of the specific filter for randomized trials above.”

Reference 31 is to a PowerPoint presentation by the EASE Gender Policy Committee in 2015. The committee has since published it’s guidelines in this same journal: 10.1186/s41073-016-0007-6

Author’s response:

Thank you- we have changed this reference
Methodology: the inclusion / eligibility criteria should be better articulated. For example, it is not clear whether or not single-sex trials were included (and if yes, why?)

Author’s response:

Thank you for suggesting we be specific in our eligibility criteria. Single-sex trials were included (as described above) because single-sex trials also need to consider applicability of results across sex/gender since the influence of sex/gender operates even in a single-sex study, given that gender captures social positioning and relationships not just identity. We considered the characteristics of single-sex studies to be an outcome of our study.

Added (p. 8)

We did not restrict inclusion on the basis of age (e.g., children, adolescents) or whether the trial focused on specific populations (including across sex and/or gender).

Line 203: "We screened 256 records from the top"… were these sorted based on most recent on the top? Perhaps clarify whether the most recent 256 records were screened.

Author’s response:

Thank you for this suggestion

Added/changed p.10

“from the most recent to the oldest”

Line 218: "In the subset of multi-site trials that did report information on site location, 27/42 (64%) were conducted within Canada and 13/14 (93%) of those conducted outside of Canada included at least one site in Canada. " This is not clear. If these were all multi-site trials and Canada was one of the sites in all of them, why some are considered conducted in Canada and others outside Canada. It's confusing.

Author’s response:

Thank you for suggesting we improve this sentence. Only one study was conducted entirely outside of Canada.

Added/changed (line 238)
In the subset of multi-site trials that did report information on site location, 27/42 (64%) were conducted entirely within Canada and only one out of 15 included no sites within Canada.

Line 235: "Ten RCTs had eligibility criteria that restricted participation to women, and one RCT enrolled girls and one RCT enrolled boys". Were these excluded from the analysis? As they are single sex trials, there would not be a reason to look at sex / gender differences.

Author’s response:

As above, we aimed to identify the single-sex studies, describe their characteristics and assess whether they considered sex and gender analysis to understand “how and why different subpopulations (e.g., of diverse genders, ages, and social locations) may experience health conditions and interventions in different or similar ways.”(line 118). This does not require a subgroup analysis across sex and/or gender.

We added a section entitled :”Population” to define the single-sex and mixed-sex studies.

Population: Twelve RCTs were classified as “single-sex” studies because they had eligibility criteria that restricted participation to women, one RCT enrolled girls and one RCT enrolled boys. The remainder of RCTs were classified as “mixed sex” because they enrolled male and female participants. Eighty-five out of 88 mixed sex RCTs reported the number of enrolled male and female participants. For these, the median number of male participants was 45 (range 3 to 3843) and the median number of female participants was 53 (range 1 to 1712). As shown in Table 1, the median sample size of the 100 RCTs was 103 (range 20-1466) for single sex studies and 107 participants (range 12 to 6085) for mixed sex studies. As noted, we did not restrict inclusion on the basis of age or focus on specific populations. Two trials did not provide any information about the sex of the population, referring to the population as patients or nurses/care aides.

Line 245: "some trials used the term 'gender' when referring to the sex of their participants". This is not necessarily incorrect, as most trials do not perform a chromosome analysis to confirm the biological sex and rely on the self-reported gender of the participants. In this sense, the term gender is actually more accurate, as it refers to the way the participants identify themselves. This is worth discussing in the discussion section.

Author’s response:

Agree with your observation. We have changed the wording to remove the suggestion that this is incorrect use of the term “gender” and we have added this to the discussion.
Added/changed:

Line 263, changed to remove suggestion of incorrectness: “The terminology used by authors to describe the participant demographic composition by ‘sex or gender’ varied. For example, some trials used the term ‘gender’ and some used “sex”.

Line 394 (in discussion): added: “In RCTs, the use of the term “gender” may be more accurate since most RCTs rely on self-reported gender of participants.”

Line 263: "19 (19%) RCTs reported on some aspect of 'sex or gender'. For four of these, the study was focused on a specific population of women, men, boys or girls and this population was defined in the title." Were these all the single sex studies? You should perhaps mention that. I assume the 12 studies mentioned above are part of these 19?

Author response:

As suggested, we have separated the results into “single sex” and “mixed sex” studies since the expectation is different for some aspects of study design and reporting.

Added/changed:

In the title or abstract, 19 (19%) RCTs reported on some aspect of ‘sex or gender’.

Single Sex Studies: In the title or abstract, 11 out of 12 (92%) RCTs reported some aspect of ‘sex or gender’. For four of these, the population was defined in the title. For example, “Effect of a Novel Movement Strategy in Decreasing ACL Risk Factors in Female Adolescent Soccer Players: A Randomized Controlled Trial.”[34]

Mixed Sex Studies: 8 out of 88 (9%) RCTs reported on some aspect of ‘sex or gender,’ and this was mentioned only in the abstract.

Line 271: "sex or gender' was only mentioned in 11 (11%) of the RCTs". Were these all the single sex studies? That would make sense, as they probably need to justify why looking at only one sex/gender. Excluding these studies from your review is important in order to offer a more accurate picture of the extent to which sex/gender are considered important and worth mentioning in RCT that are meant to enrol both males and females.

Author’s response

Thanks for your detailed review. We agree this was confusing, and have separated into single-sex and mixed sex studies to make this clear. As the reviewer suspects, there is more description of sex/gender in single-sex studies.
Added/changed:

Line 292- remained the same: Background /rationale of RCTs

In the rationale or background section, ‘sex or gender’ was only mentioned in 11 (11%) of the RCTs.

Single Sex Studies: 5 out of 12 single-sex RCTs (42%) reported on ‘sex or gender’ in the background section. Three of the RCTs reported information on prevalence or importance of a condition in subpopulations. Two of these studies reported a rationale related to ‘sex or gender.’

Mixed Sex Studies: Six out of 88 mixed sex RCTs (7%) reported information in the background section. One RCT reported information on prevalence across ‘sex or gender’. For example, one RCT stated that “…symptomatic knee OA (ed: osteoarthritis) occurs in 10% of men and 13% of women ages >59 years (pg.1837)” [35]. Five RCTs reported a rationale related to why the intervention might work differently across ‘sex or gender’ or provided background evidence about differential effects. For example, one study of compression technologies for leg ulcer care stated in the background that, “women did more poorly according to one study, but two other studies found no significant effect of gender (pg. 1834)” [36]. Of these 6 studies, none report analyzing the effect of sex or gender but three RCTs discuss applicability of results with regards to sex or gender.

Line 284: now here it gets a bit confusing. Earlier in the paper you mention that there were 12 RCT that enrolled only women, girls or boys. Then there is another statement about 19 papers (see my comment above) and now there is "Thirty-three of RCTs (33%) described exclusion criteria based on 'sex or gender'. Does this mean that they excluded one sex or gender? That's how I read it. Of the "Nineteen of the 100 RCTs excluded pregnant/breastfeeding women (n=14), women of child-bearing age (n=1) or both (n=4)" how many included women outside these groups? Can you clarify these figures?

Author’s response

We agree this was confusing, and have separated into single-sex and mixed-sex studies, as follows:

Added/changed (line 314)

Single Sex studies: All twelve single sex RCTS described an exclusion based on ‘sex or gender’. Two of these 12 RCTs (1 with pharmacological intervention and 1 with non-pharmacological intervention) excluded pregnant / breastfeeding women.

Mixed sex studies: Twenty-one of 88 RCTs (24%) described exclusion criteria based on ‘sex or gender.’ Seventeen RCTs excluded pregnant/breastfeeding women (n=12), women of child-
bearing age (n=1) or both (n=4). Thirteen of these 17 RCTs (77%) evaluated pharmacological interventions. For example, one pharmacological intervention using “low (50 mg/day) or high (200 mg/day) dose of Losartan” excluded “pregnant and lactating women” (pg. 590) [37] and another using a “supplement with a high-dose micronutrient, mineral and antioxidant preparation (K-PAX UltraH) or an identically appearing 100% RDA preparation of multivitamins and minerals” had exclusion criteria that included “HIV-2 infection alone, pregnancy or not willing to practice barrier method of birth control” (pg. 3) [38]. Of the remaining 4 RCTs that excluded pregnant/breastfeeding women or women of child-bearing age, 2 RCTs were non-pharmacological interventions, one surgical, and one organizational intervention. No studies discuss the rationale or risk considerations for excluding on the basis of pregnancy.

Line 308: "Almost all RCTs (98%) reported demographic characteristics by 'sex or gender' by identifying number of male/female participants in text or as part of their demographic table describing baseline characteristics." Did the author look at whether sex or gender was reported for recruited, enrolled and completed the study, including for those who was lost to follow up or those who discontinued the trials?

Author’s response

We did not collect this data, and have described this in the limitations.

Added/changed

Line 471: We did not collect whether the flow of participants was reported according to gender (e.g. recruited, enrolled, completed), and this information would be important for conducting a sex and gender based analysis.

Line 315: you should remove the single sex studies from your analysis, as your findings are skewed. Naturally, the single sex trials will not carry out a gender analysis in the sense to look at sex or gender differences. And explain what you mean with "discrete analyses".

Author’s response

We agree. We report only on mixed sex studies here, and have removed the term “discrete”

Added/changed:

Line 386: Mixed sex studies: Twenty of the 88 RCTs (23%) reported analyses related to ‘sex or gender’ in the methods section,
Line 334: see my previous comment re excluding the single sex studies.

Author’s response
As above, we have specified these studies which include methods related to sex and or gender are mixed-sex studies

Line 346: "For example, only 6% (six studies) of our sample…” were there any particular area or discipline that did better than others? It would be worth discussing it.

Author’s response
We did not feel it was appropriate to identify areas, disciplines or study design characteristics specifically for these 6 studies since it is too small a sample to make any generalizations

No changes made

Line 359: "sex-treatment interactions" it is a rather awkward term. I suggest revising to: the effect of sex on treatment response or outcome, or something similar.

Author’s response
Thanks, we have changed, using your suggestion.

Added/changed

Line 416: A recent meta-synthesis found that statistically significant effects of sex on treatment response in randomised trials were rarely reported…

Line: 374: "and a tool for peer reviewers…” Specify that this is for grant proposals?

Author’s response
Thanks- it is for grants and/or papers

Added/changed

For example, the Canadian Institutes of Health Research has published a casebook [65] and a tool for peer reviewers of grants and/or papers
Discussion: The discussion could be better organised and strengthened. The authors give examples of why and sex and gender reporting is important, and on and off refer to inconsistencies in terminology but do not meaningfully engage in a more-in-depth discussion on the complexities of sub-group analyses, the different underlying reasons for this failure to report sex-disaggregated data or gender analysis.

Author’s response

We organized the discussion to report the main findings, discuss subgroup analysis which is a major concern (as mentioned by both reviewers), report existing guidance available, and discuss limitations. We respectfully do not think that a major reorganization is needed.

Regarding the limitations and difficulties of subgroup analyses, we have added to the paragraph about subgroup analyses across sex to acknowledge these.

Added:

Line 414: The credibility and clinical importance of sex-based subgroup analyses must be carefully scrutinized since there is a risk of spurious findings due to under-powered tests and multiple testing.

Also, the discussion heavily focuses on "sex"-based differences and biomedical examples, and rarely discusses the importance of considering gender and how. That is a much harder task and most researchers are ill-equipped to address gender-dimensions beyond the biological sex within their research design or analysis, as there is a lack of understanding what tools there are and how these nuances should be captured and analysed.

Author response

We heartily agree that gender dimensions are rarely addressed, even when there are opportunities to do so. For example, over 50% of our sample of RCTs evaluated non-pharmacologic interventions such as decision aids, cognitive therapy, self-help education tools and community-based interventions where gender may play an important role in how the intervention is delivered (by whom and in what context) and received. We do think that our discussion covers the lack of consideration of gender. In the first paragraph, we emphasized this point.

Added/changed:

Line 395: Where sex or gender were considered, these considerations were often limited and mainly focused on biomedical analysis of differences across sex. For example, no studies considered the influence of gender. Only six studies of our sample reported subgroup analyses across ‘sex or gender’. This was despite the fact that over 50% of our sample of RCTs evaluated non-pharmacologic interventions such as decision aids, cognitive therapy, self-help education
tools and community-based interventions where gender may play an important role in how the intervention is delivered (by whom and in what context) and received. Furthermore, of the six with subgroup analysis, only one commented in any depth on the methodological challenges of conducting sub-group analysis or on the significance of their findings and implications for clinical practice.

It would also be useful approaches, if there are any, that have improve sex/gender reporting.

Author’s response:

We did not find studies in our literature review of tools that had been shown to improve reporting, however, we provide a list of relevant tools and guidance that can be used to improve reporting of sex and gender considerations in RCTs (line 422). Based on the second reviewer’s comments (below), we also added a tool providing reporting guidelines for health equity relevant RCTs, which is inclusive of sex/gender considerations, and extends the internationally recognized and widely used CONSORT statement.

Added/changed

Line 436: Members of our team have recently developed reporting guidelines for health equity relevant RCTs, as an extension of the CONSORT statement (Consolidated Reporting of Randomized Trials) [Welch et al 2017]. All of these tools can be used by authors of RCTs to improve report of sex and gender.

Reviewer #2: In the present manuscript, Welch and colleagues address the incorporation of sex and gender specific analysis into Canadian randomized controlled trials. A MEDLINE search provided a large number of Canadian led or funded trials, of which the first 100 were selected for analysis.

Overall, the authors detected little to no incorporation of sex and gender specific analysis in the sample publications, although the Canadian research environment is actively promoting the incorporation of this kind of investigation into biomedical and clinical research.

The paper addresses a very important issue in times where the incorporation of sex and gender specific analysis is being increasingly mandated by funding bodies and journals. The translation of these requirements into practice is of relevance to the research community well beyond the field of sex and gender specific medicine, since all researchers might eventually have to apply these requirements.
The main issue that should be addressed further is the heterogeneity of the publications retrieved through this kind of approach. Selecting the first 100 Canadian RCTs led to a very diverse group of studies and research topics, making it difficult to compare the quality of the performed analysis among these publications. I can understand the approach, yet I feel it needs some more data and specifics. The number of participants ranges from 3 to 3843 males and 1 to 1712 females with medians around 50 in both groups. This leads me to believe that most of the trials were small - and most likely underpowered for any sort of subgroup analysis. Would it be possible to add a table detailing the number of participants within these 100 RCTs?

Author’s response

We agree the types of trials are diverse, however they are not unrepresentative of Canadian RCTs. Table 1 does include the median sample size, which is 100, which we agree is small for a subgroup analysis. However, even without subgroup analysis, this does not limit the ability to discuss the relevance of these results across sex and or gender in the discussion, therefore we feel this is a contribution to the literature by assessing a baseline of sex and gender analysis in Canadian RCTs.

Regarding being underpowered, we agree this is important and have added to the discussion.

Added/changed

Line 464: Also, this sample of RCTs includes mostly relatively small RCTs (with a median of 100 participants), thus they would be underpowered to detect differences in response across sex or gender.

Furthermore, since the criticism many scholars in the field of sex and gender specific medicine have to face is the raise in costs due to the need of inclusion of more individuals in order to perform sex-specific analysis, the question of statistical power becomes essential (and frequently controversial). This should be discussed. Were the studies powered to detect any kind of subgroup difference? Were the sex-specific analyses (if performed) done rigorously? What does it mean for the researchers to perform this kind of analysis? What needs to be considered? The discussion should probably refer to this point as well.

Author’s response

Thank you. We decided a priori not to assess the quality of these analyses nor the power to conduct these subgroup analyses since we expected very few studies would have these analyses and the results would not be generalizable to other situations. We have added this in the discussion of limitations.
Added/changed

Line 466: In the six RCTs which did conduct a subgroup analysis across sex or gender, we did not assess the power for this analysis, nor the quality of these analyses because we expected there to be too few studies with these analyses to be generalizable to other situations.

My second point is linked to the first one. Were any specific aspects/commonalities identifiable in the publications that performed some sort of sex and gender specific analysis? Were the trials larger? Did the type of funding matter? Did authorship matter? Did the publishing journals have some sort of requirement to include this type of analysis? Although not statistically significant, it would be interesting to know whether any trends appear in these manuscripts.

Author’s response

As above, and in response to reviewer 1, we agree these are important questions for further research but were beyond the scope of this preliminary survey. There would be too few studies with subgroup analyses to assess the characteristics related to type of funding, authorship.

Added/changed

No changes made

Finally, the authors point to a forthcoming publication about comprehensive sex and gender specific reporting in RCTs, yet it would be desirable to have at least some short recommendations in this manuscript as well. Based on these results, what would the essentials for reporting be?

Author’s response

We agree that recommendations on how to improve the reporting of sex and gender in RCTs is needed. However, we felt that it would go beyond the aim and objective of this paper to provide recommendations or reporting guidelines. Members of our group have just concluded a 1.5 year project to develop reporting guidelines for health equity considerations in RCTs, as an extension of the CONSORT statement, and we have added this reference to the discussion.

Added/Changed

Line 436: Members of our team have recently developed reporting guidelines for health equity relevant RCTs, as an extension of the CONSORT statement (Consolidated Reporting of Randomized Trials) [Welch et al 2017]. All of these tools can be used by authors of RCTs to improve report of sex and gender.