

# Sex and Gender in Systematic Reviews

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## Introduction

Accurate and comprehensive evidence is critical to sound decision making, whether in the public or private sector. Systematic reviews represent one method for identifying, evaluating and synthesizing available evidence relating to a single issue. In this process, research that fits particular criteria is compiled, reviewed and assessed for quality and then synthesized in an attempt to provide a comprehensive picture of existing knowledge. In health, systematic reviews are an important means to transfer research findings into the development of policy, programs, regulatory initiatives and clinical practice. Reviews are used to appraise evidence about health care interventions, such as drugs, devices, and surgical techniques, as well as exercise, diet and other programs designed to improve, alleviate or cure particular health conditions.<sup>[3]</sup>

Increasingly, systematic reviews are regarded as one of the best tools to grapple with large amounts of evidence and are considered as particularly important for evidence-based medicine. Implicit in the label “systematic review,” is the idea that this approach to analyzing and assessing evidence is methodical, consistent, thorough and therefore reliable.<sup>[4]</sup> In particular, systematic reviews should help to answer the question: “To whom does this evidence apply?” Yet, despite guidelines that encourage researchers to include demographic and other population characteristics,<sup>[5]</sup> various studies of systematic reviews have revealed a lack of adequate attention to health equity factors, including sex and gender.<sup>[6-8]</sup> Without sex- and gender-based analysis, the policies, programs and clinical interventions that are based on systematic reviews may not be equitable and may have unintended or even harmful consequences for some people.

This case study describes the development of a *Sex and Gender Appraisal Tool* for systematic reviews and reports on its application with systematic reviews of cardiovascular diseases. As with other analyses, this case study reinforces the conclusion that current systematic review models are not sufficiently sensitive to sex and gender and suggests opportunities to address this situation.

## How Might We Use a Sex and Gender Lens to Evaluate Systematic Reviews?

Our research team, comprised of individuals with expertise in women’s health issues, sex- and gender-based analysis and who were familiar with systematic reviews, examined whether sex and gender were addressed in a sample of systematic reviews of cardiovascular disease. If gaps were found, we were also interested in addressing how sex- and gender-based analysis could best be integrated into the systematic review process to enhance the quality of reviews.

Because systematic reviews typically address a single issue or health condition, it was necessary to choose a topic for investigation. We chose to focus on systematic reviews of cardiovascular diseases because sex and gender differences have been well documented in relation to risk factors, age of onset, symptoms, disease progression, treatment-seeking behaviours, the efficacy of diagnostic tests and drugs and hospitalization and mortality rates.<sup>[9]</sup> For example, recent studies have

### What is a systematic review?

Systematic reviews provide a summary of the journal literature on a particular topic. By definition, systematic reviews summarize, appraise and communicate the results and implications of otherwise unmanageable quantities of research.<sup>[1]</sup> Systematic reviews bring together separately conducted studies (sometimes with conflicting findings), evaluate them against specific criteria and then synthesize the results.<sup>[2]</sup> In this way, they can contribute to the evaluation of both existing and new technologies and practices.<sup>[2]</sup>

shown that sex and gender are independent risk factors for complications after both coronary artery bypass graft surgery and angioplasty, technically known as percutaneous coronary intervention. Women experience more complications and higher rates of mortality after coronary artery bypass graft surgery,<sup>[10]</sup> and are more often admitted to intensive care units following both bypass surgery and angioplasty.<sup>[11]</sup> Given that the different experiences and health outcomes for women and men with heart diseases are well-known, we expected that systematic reviews would capture or reflect these – perhaps more so than systematic reviews of some other conditions or diseases.

We chose to focus our research on systematic reviews developed by the Cochrane Collaboration, an international network of more than 20,000 specialists who regularly review and analyze clinical trials and other types of health research. Cochrane reviews are based on a standardized method and are widely considered to meet very high standards.<sup>[12]</sup>

Drawing from the research literature on sex- and gender-based analysis,<sup>[13-15]</sup> we developed a *Sex and Gender Appraisal Tool for Systematic Reviews* (SGAT-SR) to determine whether sex and gender were being addressed in systematic reviews and, if so, how. The tool is composed of 35 questions that are aligned with the nine standard sections of a Cochrane review (see textbox). We designed the tool to facilitate ease of use by systematic reviewers who might not be familiar with sex- and gender-based analysis, using plain language to ensure accurate responses about whether sex and gender were addressed or not throughout the review process. For example, in the section on Discussion and Conclusions, the tool asks: “Does the review report that primary studies analyzed or failed to analyze results by sex?” The draft tool was then reviewed both by subject experts to ensure consistency with standard sex and gender definitions and concepts, and by an individual familiar with Cochrane reviews to ensure compatibility with the Cochrane review process.

Once the design, review and revisions were complete, the tool was applied by an independent reviewer to a random sample of Cochrane Systematic Reviews on interventions for high blood pressure, heart and other vascular diseases. Thirty-eight separate reviews were included, spanning eight broad topic areas, with the largest number of reviews focusing on drug therapies. Together these reviews analyzed a total of 668 research trials, which in turn represented investigations with 473,666 participants.

### **Do Cochrane Reviews of Research on Cardiovascular Diseases Consistently Address Sex and Gender?**

Our study found that while a majority of the topics addressed in the reviews had sex and/or gender implications – such as differences in symptoms or treatment – the data presented in the research reviewed were rarely broken down by sex. In other words, it was frequently impossible to learn from these trials whether or not women and men reacted differently to treatments or had different outcomes.

In the past, the exclusion of women from health research was usually responsible for our lack of knowledge about women’s health. However, this was not necessarily the case for the Cochrane reviews we examined: close to 75 percent

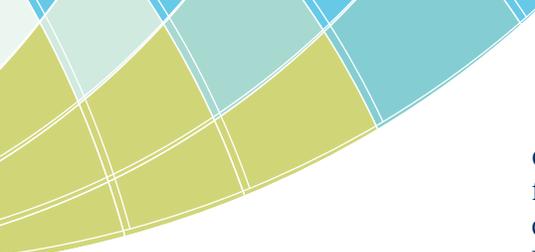
#### **What Does a Systematic Review Include?**

The Cochrane Collaboration has developed a handbook for systematic reviewers, which outlines the steps involved and the issues to be addressed. According to the *Cochrane Handbook*,<sup>[5]</sup> a systematic review consists of seven steps:

1. Formulating a problem
2. Locating and selecting studies
3. Critical appraisal of studies
4. Collecting data
5. Analyzing and presenting results
6. Interpreting results
7. Improving and updating reviews

The final systematic review should generally contain nine main sections:

1. Background
2. Objectives
3. Criteria for inclusion/exclusion of research
4. Search strategy
5. Methods of the review
6. Analysis
7. Discussion and conclusions
8. Quality assessment
9. Table of included studies



of the reviews – 28 out of 38 – were based on research studies that included both females and males.<sup>a</sup> Despite this fact, 20 of the 38 reviews reported on adverse outcomes of treatment, but none of these reported adverse outcomes by sex. Furthermore, only two of the 38 reviews commented on research gaps related to sex or gender and only 25 percent of the reviews included a rationale as to why they had not analyzed results for any “subgroup” of participants, including males and females. Only one review reported sex and/or gender implications for clinical practice and not one of the reviews discussed the sex and/or gender implications of research for health policy or regulation. In summary, the *Sex and Gender Appraisal Tool* revealed that none of the 38 reviews systematically addressed sex and gender in health research.

## Conclusions and Implications

Despite the accumulation of significant evidence for the relevance of sex and gender in the management of cardiovascular health, this pilot project demonstrated that sex and gender were not adequately taken into account in the systematic reviews sampled. There are likely a variety of reasons for this, including the possibility that the primary studies included in the systematic reviews did not identify the participants by sex, and/or did not report their findings by sex and gender. Thus, the limitations of these original studies would be reflected in the systematic reviews. But systematic reviews – by definition and design – are meant to help researchers, clinicians and policy makers assess the quality of evidence and identify significant gaps in our knowledge: they should not replicate or perpetuate flaws in health research, including a lack of attention to the influence of sex and gender. It seems, then, that some authors of systematic reviews may be unaware of established or potential sex and gender differences in health research and that the systematic review tools currently used for quality assurance are not sufficiently sensitive to sex- and gender-related variables.

The results provide a cautionary tale: if we are going to rely on systematic reviews as the basis for decisions about patient care, health policy and regulation, systematic reviews must routinely include information on sex and gender, including positive and negative results and they must clearly address when and why such information is not available. Without this kind of evidence, we risk creating policies or practices that may not be effective, safe or equitable for women and men, girls and boys in Canada.

These findings also underscore the need to address the methodological challenges of understanding the health status of different populations – or sub-groups – and how differences among people may affect symptoms, access to care, treatment outcomes and mortality. As Bailey and others point out, even slight variations in the design of research studies can affect the interpretation provided in a systematic review<sup>[16]</sup> and it is important to recognize that analyses of subgroups within the entire participant sample may not necessarily be more accurate than overall results.<sup>[17]</sup> We support Blauwet and colleagues who recommend universal sex-specific reporting of trial results, since such reporting “may reveal unexpected sex differences worthy of further study and, at the least, provide data for subsequent meta-analyses.” <sup>[19,p169]</sup>

<sup>a</sup> Each Cochrane Systematic Review includes a section entitled, “Table of included studies,” which allowed the researchers to discern whether or not males and females were represented in the research under review.

## Next Steps

To build a robust base for future work, we propose that the methodologies of systematic review and of sex- and gender-based analysis be refined and brought together to enhance the collection, synthesis and analysis of evidence for decision-making. Specifically, this study recommends:

- Developing appraisal tools for SGBA in systematic reviews;
- Establishing quality indicators for SGBA in primary research and in systematic reviews;
- Addressing the methodological challenges involved in analyzing potential sex and gender differences in health status, outcomes and experiences within and between sub-groups;
- Fostering collaboration and knowledge sharing about systematic reviews and SGBA among researchers, systematic reviewers, peer review committees, health care providers, sex/gender experts as well as patients and the public.

Our research team is addressing the recommendations in a number of ways. We are working to refine and validate the SGAT-SR appraisal tool and are collaborating with the relevant Cochrane Review Groups and with the Cochrane Health Equity Field. We are also involved in constructive discussions with biostatisticians, health researchers, systematic reviewers and health care providers about the development of quality indicators for the application of sex- and gender-based analysis to all stages of the collection and analysis of evidence – from protocol development to knowledge translation of systematic reviews.

Rigorous and appropriate application of sex- and gender-based analysis to the evidence synthesized by systematic reviews can best be advanced through creative collaboration across disciplines. A wide range of stakeholders generate, analyze and use research results for health policy, regulation and clinical practice to improve individual and population health. Increasingly, governments and research agencies are learning about SGBA and requiring that it be applied in health research to improve outcomes and reduce harm.<sup>b</sup> These goals can be achieved by carefully refining an understanding of the interrelationships between sex and gender as well as other health determinants, developing robust indicators for quality assurance of evidence<sup>c</sup> and demonstrating how sex- and gender-based analysis is integral to sound science, policy and clinical practice.

<sup>b</sup> In Canada, the application of sex- and gender-based analysis to policies, programs and research was mandated through the Federal Plan for Gender Equality (1995) and is required by the Treasury Board of Canada Secretariat in the preparation of Treasury Board submissions ([www.tbs-sct.gc.ca/pubs\\_pol/opepubs/TBM\\_162/gptbs-gppct03-eng.asp#Toc171392121](http://www.tbs-sct.gc.ca/pubs_pol/opepubs/TBM_162/gptbs-gppct03-eng.asp#Toc171392121)). Health Canada's Gender-based Analysis Policy (2000) has been updated and revised to a Health Portfolio Sex- and Gender-Based Analysis Policy (2009). For other examples internationally see: Caron J. Report on Governmental health research policies promoting gender or sex differences sensitivity. Ottawa: Institute of Gender and Health, Canadian Institute for Health Research; 2003. Available from [www.cihr-irsc.gc.ca/e/pdf\\_25502.htm](http://www.cihr-irsc.gc.ca/e/pdf_25502.htm)

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