Sex and Gender Considerations in Canadian Clinical Practice Guidelines: A systematic review

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Abstract

Background: The importance of sex and gender in the pathophysiology, diagnosis, treatment and outcomes of many chronic health conditions is well established. The extent to which evidence about sex and gender differences is integrated into Canadian clinical practice guidelines (CPGs) remains unknown. We conducted a systematic review to investigate the penetration of sex and gender evidence into Canadian CPGs for selected common chronic diseases.

Methods: We searched the Canadian Medical Association Infobase, PubMed, and provincial websites. We included English-language Canadian CPGs published between January 2013 and June 2015. Citations and text were searched electronically using keyword terms related to sex and gender. Two independent reviewers extracted data. Text-positive CPGs were analyzed by health condition for the type, amount, and quality of evidence presented.

Results: One hundred fifteen CPGs met the inclusion criteria. Sixty-seven percent (n=77) were text-positive for sex and/or gender. CPGs addressing mental health conditions, stroke, and cardiovascular diseases most frequently cited evidence on sex differences. Analysis of the text-positive CPGs showed variability in the quality of the information. Many mentions of sex and gender were superficial in nature and of little value. The most useful information occurred in the form of actionable evidence-based evaluation and treatment recommendations stating whether care should be applied differently, or with a similar approach, to women/men, girls/boys.

Interpretation: Evidence on sex differences and gender considerations is inconsistently reported in CPGs for chronic disease in Canada. A structured approach to ensuring meaningful inclusion of evidence on sex and gender is needed.

Introduction:

Gender-responsive healthcare focuses on quality of care for both men and women, taking into account all sex- and gender-related factors (Box 1).[1, 2] Manifestations and outcomes of disease have long been known to differ between men and women, notably in the field of cardiology,[3-6] but also in immune disease,[7, 8] respiratory illness,[8-10] and mental health.[11, 12] A better understanding of molecular, cellular and epigenetic mechanisms underlying these differences has led to a steep rise in the number of sex and gender-specific research publications in all medical disciplines since the 1990s.[13] Despite the wealth of new evidence on sex and gender differences, the uptake of sex and gender research into clinical practice guidelines (CPGs) and clinical practice has been slow, and trails far behind the growth in the medical literature.[14] In the Netherlands, a preliminary study revealed that sex-related factors or effects were mentioned in only 20% of CPG recommendations for osteoporosis and were completely absent in CPGs on depression.[14] Research suggests that failure to integrate sex and gender considerations into CPGs results from lack of awareness and resources.[14-16]

The consequences of omitting sex and gender evidence from CPGs can be severe, ranging from missed opportunities to prevent the onset of Type 2 diabetes in the fathers of children born from mothers with gestational diabetes,[17] to inappropriate prescription of some cardiovascular drugs to women based on altered risk/benefit profiles.[18] An alarming recognition of harm occurred in 2001, when the US General Accounting Office reported that 8 of the 10 prescription drugs withdrawn from the US market by the Food and Drug Administration posed greater health risks for women than for men [19]. Three of these drugs caused potentially fatal Torsades de Pointes ventricular arrhythmias

(terfenadine, astemizole and cisapride).[19] In 2014, Health Canada issued a warning to cut by half the recommended dose of zolpidem for women, a common sleeping pill that has higher morning blood levels in women and increases the risk of next-day driving impairment.[20] Men are not exempt from harm. Rochon et al. discovered that in Ontario, men with dementia who were prescribed antipsychotic drugs had a significantly higher risk of hospital admission and mortality compared to women.[21] Similarly, social risk factors are associated with higher rates of suicide in older men, indicating that more aggressive screening and treatment may be required.[22-24]

The development of CPGs is a critical first step for translating research findings into clinical practice to narrow the "know-do" gap[25, 26] and improve patient care. The extent to which evidence about sex and gender differences in medicine are integrated into Canadian CPGs remains unknown. We conducted a systematic review to investigate the penetration of sex and gender evidence into 2013-2015 Canadian CPGs for common chronic diseases.

Methods:

Data sources and inclusion criteria

We searched the Canadian Medical Association's database of CPGs (called the Infobase)[27] and used the term "clinical practice guideline" to search PubMed and all 13 Canadian provincial/territorial websites for English-language CPGs (Figure 1). According to the CMA's website, the Infobase includes approximately 1,200 CPGs developed or endorsed by authoritative medical or health organizations in Canada.[27] Only documents published in Canada within the preceding two years (January 2013 –

June 15, 2015) were included. Duplicates were removed. Original research publications, reviews, opinion pieces, and editorials were excluded. CPGs dealing with single sex health conditions such as erectile dysfunction, menopause, and prostate or gynecologic cancers were also excluded.

CPG selection

We strategically selected CPGs addressing chronic health conditions identified as priorities by policy makers and practitioners, including diabetes, cardiovascular disorders, specific cancers, mental illness, and pain (Appendix 1)[28, 29, 30-34]

Data extraction and quality assessment

The CPG citations and text were searched electronically using these keywords: “sex”, “gender”, “male”, “female”, “men”, “women”, “man”, “woman”, “boy”, “girl”. Two broad categories were created: text-negative for sex and/or gender keywords; text-positive for sex and/or gender keywords. Risk-of-bias assessments were not performed, as no validated strategy exists for conducting risk-of-bias assessments for sex and gender integration into CPGs.

Data synthesis and analysis

CPGs that covered more than one health condition were assigned to the condition that was most emphasized in the text. Text-positive and text-negative CPGs were treated separately. Text-positive CPGs were analyzed by health condition for the type, amount, and quality of evidence presented on epidemiology, risk and screening, pathophysiology,

symptoms and diagnosis, and treatment/interventions.[35] Examples of the evidence included in each of these sections were extracted. As there was significant overlap in these categories, the data were synthesized qualitatively. CPGs that were text-negative for sex and/or gender keywords but included citations in the reference lists for research that addressed sex and/or gender considerations were separated out for further analysis.

Outcomes

The primary outcome of the review was the proportion of CPGs that considered sex and/or gender, defined as the number of CPGs that were text-positive for sex and/or gender, over the total number of CPGs included in the review.

Results:

CPG characteristics

A total of 347 Canadian CPGs were identified that addressed one or more of the chronic diseases under consideration (Figure 1). Thirty CPGs were excluded because they were published in French: 90% of these were French versions of CPGs already published in English. Our initial search was not limited by date; a further 194 CPGs were excluded because they were published in 2012 or earlier. Seven CPGs were excluded because they addressed sex-specific topics – one for males and six for females. A total of 115 CPGs comprised the final sample. Table 1 lists the distribution of CPGs by chronic disease.

Proportion of CPGs integrating sex and/or gender considerations

Over two-thirds (n=77) of CPGs were text-positive for sex and gender (Table 1). CPGs addressing mental health issues, stroke and cardiovascular diseases were most likely to report evidence on sex differences. Table 2 illustrates the breakdown of sex and gender mentions by epidemiology, risk and screening, pathophysiology, diagnosis and treatment category. Five of the 38 text-negative CPGs included one or more citations to sex-specific evidence or evidence of sex differences. For example, a 2014 CPG on the pharmacological management of chronic neuropathic pain made no reference to sex or gender in the body of the text, but cited two articles on the effects of sustained-action opioids on women and men.[36]

Type of evidence cited in the text-positive CPGs

There was a wide range in the ways text-positive CPGs reported epidemiological data with respect to sex and gender, even for the same disease state. One colorectal cancer CPG stated that "Colorectal cancer is the third most common cancer …in both sexes, with an estimated 8700 new cases in 2012".[37] Others provided more precise sex-disaggregated risk and mortality data: "The probability of developing colorectal cancer increases with age and varies with sex … approximately 1 in 13 men and 1 in 16 women will develop invasive colorectal cancer within their lifetime. Males have a greater chance of dying from colorectal cancer than females, i.e., 1/32 males and 1/36 females will die of invasive colorectal cancer."[38, 39]

Two-thirds of CPGs that mentioned sex as a risk factor did so only in absolute terms, noting for example that female sex is a risk factor for depression in diabetic patients,[40] or that adolescent women with Type 1 diabetes are at risk of developing eating disorders.[41] In rare instances, estimates of the magnitude of the risk difference were explicitly reported, "Estimates of risk of ischemic stroke in people with diabetes range from a 2- to 3-fold increase in men and a 2- to 5-fold increase in women."[42] Sometimes the comparative risk of different adverse outcomes in men and women were mentioned in broad terms, such as following stroke, when women are at greater risk of depression while men are at greater risk of vascular dementia.[43] Gender was recognized as a modifier of pain perceptions and interpretations of pain.[44]

With respect to the pathophysiology of disease and the impact of sex differences on screening and diagnosis, a CPG on the use of spirometry in asthma noted that women's and men's lungs reach maturity at different ages and that adult males have higher lung volumes than adult females of the same age and height.[45] Hemoglobin and lipid levels have different reference values in men and women.[46 ,47] A CPG on colorectal cancer screening warned that female anatomy has been associated with more adverse events, longer duration, and incomplete examinations.[48] Making a diagnosis of heart failure in women is considered to be more difficult, because the cardinal triad of edema, fatigue, and dyspnea are neither sensitive nor specific manifestations and atypical presentations occur more frequently.[49]

The most useful CPG evidence on sex differences appeared in the form of actionable items, supported by physiologic data. Such information was found in CPGs on alcohol consumption that recommended a lower diagnostic screening threshold for risky drinking behaviour in women compared to men,[50-52] but only one explained biological differences in alcohol absorption rates by sex.[50] Evidence that women respond more favourably than men to outpatient care during alcohol withdrawal can reasonably inform treatment algorithms and resource allocation for the management of alcohol addiction.[53] Two CPGs on hypertension alluded to hormonal causal pathways for aggravated hypertension in women, highlighting modifiable treatment strategies in the form of discontinuation of oral contraceptive and exogenous sex hormone therapies.[54, 55] Recommending the avoidance of antidepressants with strong CYP2D6 inhibition (e.g. paroxetine, fluoxetine, high-dose sertraline, bupropion) for treatment of depression in pre-menopausal breast cancer survivors requiring tamoxifen therapy is practical guidance that clinicians can easily apply.[56] A CPG on heart failure in children and youth warned that treatment with spironolactone can lead to irreversible gynaecomastia in males.[57] This piece of information should be shared with patients and their parents, as it could significantly impact long term psychological outcomes.

By comparison, a CPG on childhood diabetes that underscored differences in response to medication between male and female children and adolescents with type 2 diabetes without providing details about or explanations for these differences, is of little use to practitioners during clinical decision-making on the choice of treatment.[41] Similarly, clinicians are left without guidance from CPGs that described a higher rate of adverse

drug effects in women due to use of statins but that offered no assistance for selecting an alternate lipid lowering therapy.[58-60]

CPGs reporting that sex differences are not evident or salient in decisions about care hold value. One CPG on obesity in adults concluded that there are no differences in outcomes of interventions based on sex.[61] Two CPGs indicated that the benefits of stroke rehabilitation are the same for women and men.[62, 63] One CPG on stroke noted that research on the benefits of carotid endarterectomy in women showed mixed findings. The CPG cautioned that female sex in isolation is not an exclusion criterion for surgery, but should be considered as part of the overall risk benefit assessment with specific attention to co-morbid disease and general health status.[64]

Interpretation:

Our review suggests that the uptake of evidence on sex and gender differences is occurring for a majority of CPGs in Canada. Given historical trends in the early recognition of sex and gender differences in mental health and cardiovascular diseases, it is unsurprising that these fields most commonly highlighted sex and gender in their CPGs[13]. Recent attention to sex differences in oncology,[65-67] lung disease,[8-10] and diabetes[68-70] explains why there is growth in these latter areas. The degree of detail and extent to which evidence on sex and gender was incorporated into CPG sections addressing epidemiology, risk, screening, diagnosis and treatment strategies varied considerably across health conditions, and within different CPGs for the same disease. What our review adds is a better understanding of the nature of the integration of

sex and gender evidence into Canadian CPGs. Although some CPGs incorporated sex and gender data in a way that meaningfully guides practice, many of the sex and gender mentions were superficial and of limited value. The most useful integration occurred when the data were translated into actionable practice recommendations that directed care.

These findings reflect the paucity of evidence on sex and gender differences in medicine. Historically, biomedical investigators conducted basic science experiments predominantly on male animals, and women were underrepresented in clinical trials.[71, 72] Although rates of publication are rising, in 2010 less than 25% addressed differences in management decisions for patients based on sex or gender.[13] Another explanation for the suboptimal integration of sex and gender evidence into CPGs relates to the long lag-time between research discovery and practice transformation.[73, 74] We now know that microglial cells play a role in mediating pain pathways in males, and T-cells are likely responsible for this same function in females.[75] When and how this information will translate into different analgesic drug targets for men and women remains unknown. Pharmaco-epidemiological findings and post-marketing drug safety warnings on the differential risk of adverse drug reactions in men and women do not seem to dramatically change prescribing patterns that are firmly entrenched in routine practice care.[76] It will be interesting to see whether a future CPG on insomnia incorporates Health Canada's 2014 recommendation to cut the dose of sleeping pills in half for women.[20] Finally, a standard method for synthesizing sex and gender evidence to help answer key questions framing the development of a CPG is lacking.[77] Unless a CPG working group

specifically asks a question about whether the evidence differs by sex or gender, it is unlikely that the correct search terms will be used to query the evidence. Sex and gender interact, but represent distinct concepts that can affect health recommendations (Box 1). Without a clear understanding of sex and gender effects in medicine, and how these factors should be incorporated into recommendations, CPG working group members may miss opportunities to appropriately influence clinical care.

A strength of our systematic review is that Canadian, provincial, and academic web sources were all used to search for CPGs. The search terms related to sex and gender were broad and inclusive. However, our findings may overestimate the meaningful integration of sex and gender evidence into Canadian CPGs, as mentions of sex and gender in text-positive CPGs were frequently superficial and of limited value. We did not systematically search for sex and gender evidence that was omitted from CPGs, so could not gauge the quality or comprehensiveness of the choice of data to include in the text-positive and text-negative CPGs. The fact that five text-negative CPGs cited references that alluded to sex differences, suggests that omission, rather than lack of evidence *per se*, may have occurred in certain circumstances.

The implications of this systematic review on future CPG development are two-fold. First, guidelines and handbooks for developing CPGs could be revised to emphasize the importance of including sub-questions and search terms aimed at revealing existing and emerging evidence on sex and gender differences in medicine. Second, a focus on gender-responsive interventions should be prioritized not only in CPGs, but also in

medical school curricula and continuing medical education resources to consolidate Canadian innovation in personalized care.

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Box 1: Sex and Gender

"Sex" refers to the biological and physiological characteristics that distinguish males and females in any species, including humans.

"Gender" consists of the socially constructed roles and relationships, personality traits, attitudes, behaviours, values, relative power and influence that society ascribes to the two sexes.

Sex and gender are understood to be not strictly binary (i.e., there are continua between "female" and "male")

The influence of "sex" and "gender" can overlap and intersect, affecting health and well-being.

Figure 1. Inclusion and exclusion of clinical practice guidelines (CPGs) in review

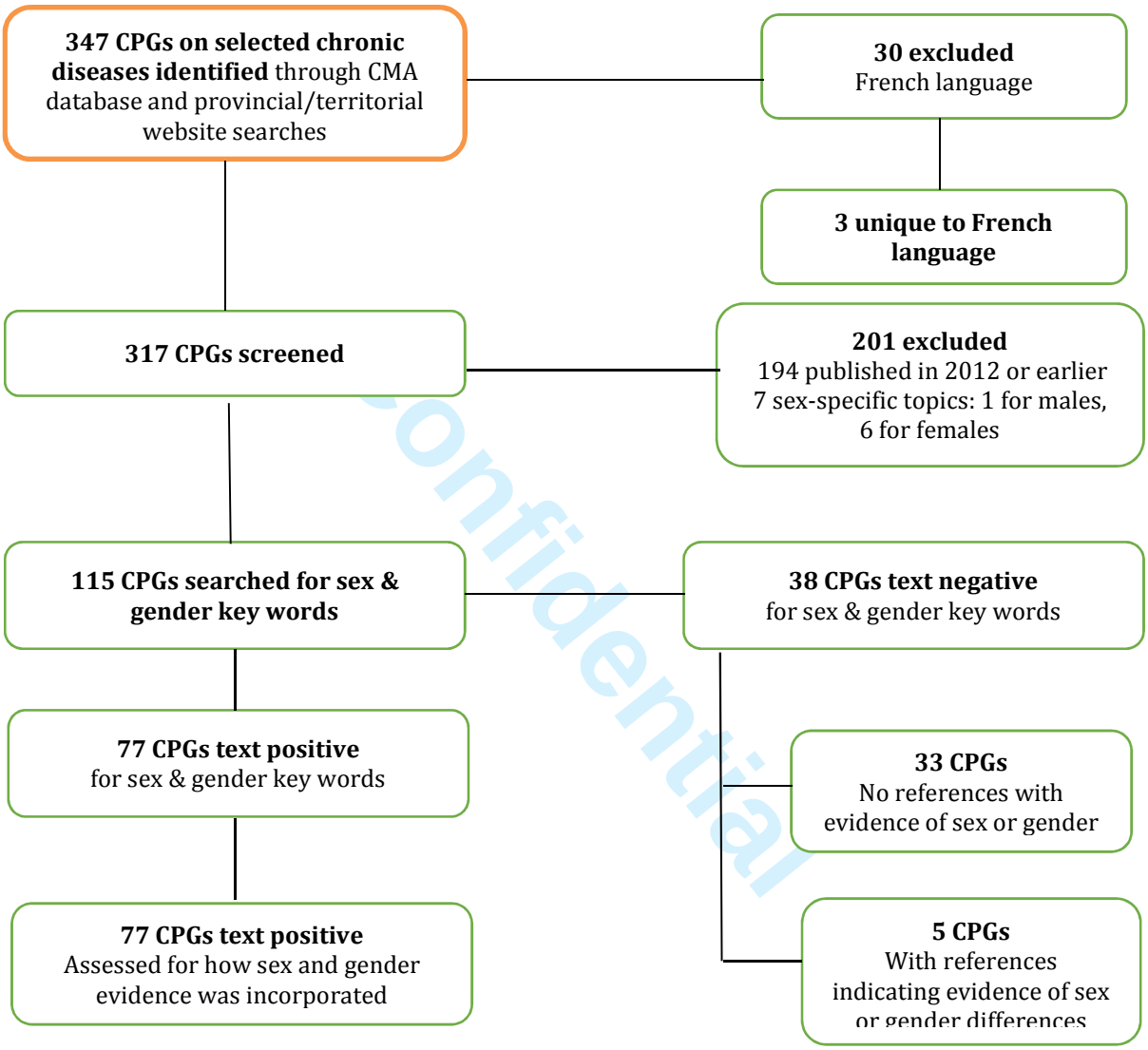

Table 1: Number and proportion of text-negative and text-positive CPGs by chronic health condition

Health Condition	Text-positive		Text-negative	
	n	%	n	%
Cardiovascular Diseases	24	70.5	10	29.4
Diabetes	18	52.9	15	47.1
Mental Illness and Substance Use	12	92.3	2	7.6
Cancer	8	57.1	6	42.9
Stroke	8	88.9	1	11.1
Obesity	3	100	0	0
Pain	3	50.0	3	50.0
Asthma	1	50.0	1	50.0
Total	77		38	

Table 2. Number and proportion of text-positive CPGs by subject

	Number	Percentage
Risk and Screening	32	41.5
Treatment and Interventions	24	31.2
Pathophysiology	23	29.8
Epidemiology and Prevalence	19	24.6
Symptoms and Diagnosis	13	16.9

Appendix 1

Final list of health conditions (and sub-conditions) searched for CPGs	
Health condition	Sub-conditions
Asthma	Asthma
Cancer	Cancer, colorectal
	Cancer, general
	Cancer, lung
	Polyps
Cardiovascular Diseases	Acute coronary syndrome
	Angina pectoris
	Atrial fibrillation
	Cardiomyopathies
	Cardiovascular diseases
	COPD
	Coronary artery disease
	Dyslipidemias
	Heart failure
	Hypertension
	Myocardial ischemia
	Pulmonary embolism
	Pulmonary hypertension
	Thrombosis
	Venous thromboembolism
Diabetes	Diabetes
	Diabetic nephropathies
	Diabetic retinopathy
Mental illness and substance use	Addictions
	Alcohol drinking
	Anxiety disorders
	Dementia
	Depression
	Generalized anxiety disorder
	Insomnia
	Mental health
	Substance dependence
Obesity	Obesity
Pain	Back pain
	Fibromyalgia
	Migraine
	Neuralgia
	Osteoarthritis
	Pain
Stroke	Stroke
	Peripheral vascular disease
	Transient ischemic attacks