Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 660-667

Featured Article

# Integrating sex and gender into neurodegeneration research: A six-component strategy

Mary C. Tierney[a,b,c,*], Ashley F. Curtis[b,c], Howard Chertkow[d,e], R. Jane Rylett[f,g]

[a]Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada
[b]Department of Family and Community Medicine, Primary Care Research Unit, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada
[c]Sunnybrook Research Institute, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada
[d]Department of Neurology & Neurosurgery, McGill University, Montréal, Québec, Canada
[e]Department of Clinical Neurosciences, Jewish General Hospital, Montréal, Québec, Canada
[f]Department of Physiology and Pharmacology, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada
[g]Molecular Medicine Research Laboratories, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada

**Abstract**

**Introduction:** Despite important sex differences, there remains a paucity of studies examining sex and gender differences in neurodegeneration. The Canadian Consortium on Neurodegeneration in Aging (CCNA), a national network of researchers, provides an ideal platform to incorporate sex and gender.

**Methods:** CCNA's Women, Gender, Sex and Dementia program developed and implemented a six-component strategy involving executive oversight, training, research collaboration, progress report assessment, results dissemination, and ongoing manuscript review. The inclusion of sex and gender in current and planned CCNA projects was examined in two progress reporting periods in 2016.

**Results:** Sex and gender research productivity increased substantially for both preclinical (36%–45%) and human (56%–60%) cohorts. The main barrier was lack of funding.

**Discussion:** The Women, Gender, Sex and Dementia strategy resulted in a major increase of sex and gender into research on neurodegenerative disorders. This best practice model could be utilized by a wide variety of large multidisciplinary groups.



*Keywords:* Sex; Gender; Sex differences; Sex and gender guidelines; Dementia; Neurodegeneration

## 1. Introduction

Studies that have focused on sex differences in neurodegenerative disorders have generated important differences between males and females. As a result of these studies, we now know that estrogen is neuroprotective in females [1,2], that the apolipoprotein ε4 allele increases risk of Alzheimer's disease (AD) to a greater degree in women than men [3], that women suffer more stroke events than men and are less likely to recover from them [4], that men with depressive symptoms are at greater risk for dementia, particularly AD, than women [5], and that there are important sex differences in response to cholinesterase inhibitors used to treat AD [6]. Despite the fact that knowledge about sex and gender differences has improved our understanding of etiology, progression, and treatment of neurodegenerative disorders, there remains a paucity of research in this area and a need to include sex as a variable in research designs and reporting [7–9]. Many studies fail to include adequate numbers of males and females to allow for sex- and gender-based analyses [10]. Moreover, even those studies

The authors have declared that no conflict of interest exists.

*Corresponding author. Tel.: +416-480-4291; Fax: +416-480-6776.
E-mail address: mary.tierney@sunnybrook.ca

https://doi.org/10.1016/j.trci.2017.10.006

with sex-balanced designs often do not examine sex differences. Furthermore, there is still a lack of examination of underlying causes of important sex and gender findings. For example, while it is well documented that the prevalence of AD is higher in women than it is in men [11], the underlying genetic, physiological, and social differences between men and women and how they interact to contribute to AD pathology are rarely examined, and thus not adequately understood.

Lack of sex and gender exploration is compounded by confusion in the research community regarding the meaning of these two terms [12]. The terms are conceptually distinct, with sex referring to biological and physiological differences between men and women, including chromosomes, hormones, and anatomy [8,13]. Gender, on the other hand, refers to social or cultural roles and characteristics used to describe masculinity and femininity within a given society [13]. Sex and gender terms have important implications for understanding etiology and prevention in neurodegeneration. For instance, we know from studies in Parkinson's disease (PD) that men have a higher prevalence and incidence of the disease (sex difference) and that men are at greater risk because they are more likely to have a higher occupational exposure to toxic environmental agents (gender difference) [14]. Thus, important sex and gender differences moderate the phenotypic expression of PD, and the ongoing confusion of these two terms in reporting continues to impede progress in this area.

If inconsistent sex and gender information is disseminated, data compiled in meta-analyses could provide inaccurate information to the research community [15]. This information could then result in negative consequences for men and women if applied to the management of sex- and gender-related factors that are thought to affect various types of disease. Therefore, it is important that researchers first educate themselves on the proper definitions of sex and gender. The Canadian Institute for Health Research (CIHR) and the National Institute of Health (NIH) now require all grant applicants to describe how sex and gender are incorporated into their research [8,10]. Since the CIHR policy change, there has been an increase in the number of clinical and population health research projects that are examining sex and gender, but no increase in the number of preclinical projects (e.g., cell models and animal studies) investigating sex and gender [8]. In addition, international Sex and Gender Equity in Research (SAGER) guidelines published by the European Association of Science Editors suggest a framework for researchers to disseminate their findings [15].

We herein report on the success of a new cross-cutting sex and gender research program within a national research network that has streamlined and facilitated the study of sex and gender in research projects across the spectrum of neurodegeneration. We discuss the approach, providing a best practice model for the facilitation of sex and gender integration in research, and present data regarding the effect of the program on sex and gender research productivity as well as discuss challenges faced by researchers in the area. Our proposed model could be applied to a wide range of research disciplines and topics.

## 2. Methods

### 2.1. Overview of the Women, Gender, Sex and Dementia Program

The Canadian Consortium on Neurodegeneration in Aging (CCNA) is a Canada-wide network of researchers, clinicians, and students that conducts independent and collaborative research on neurodegenerative disorders. There are 20 research teams within the CCNA, focused on three core areas (see Fig. 1), and each team has several research projects currently underway or planned. The teams obtain data from eight national platforms (see Fig. 1), which act as data gathering vehicles and facilitate collaboration across the CCNA. One of the strengths of the CCNA is the Clinical Cohort Platform that is used for recruitment and will include 1600 patients from a variety of diagnostic groups. Many of the teams will access data being collected as part of the Clinical Cohort (Comprehensive Assessment of Neurodegeneration and Dementia [COMPASS-ND]) to conduct their investigations. Some CCNA teams have been funded to conduct human studies that represent distinct cohorts from COMPASS-ND, and five teams conduct preclinical, cell-based, or animal model studies. Finally, there are four cross-cutting programs that collaborate with CCNA teams (see Fig. 1). The Women, Gender, Sex and Dementia (WGSD) cross-cutting program works with all research teams and platforms to ensure that sex and gender


Fig. 1. Structure of CCNA: research teams and platforms.