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

Featured Article

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

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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.

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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.

are incorporated, where appropriate, into the research design, outcome measurement, analysis, and properly reported in publications. This process involves six key components (see Fig. 2): executive oversight: guideline development and protocol planning, sex and gender training, research design collaboration, interim assessment of progress, results dissemination, and ongoing review of CCNA projects.

2.2. Six-component strategy for integrating sex and gender

2.2.1. Executive oversight

WGSD provide executive oversight of all matters pertaining to sex and gender in the CCNA. It is critical to have a sex and gender expert at an executive level advocating for sex and gender consideration in guidelines, policy and protocol development, publications, and knowledge translation. There is a sex and gender representative within the CCNA research executive council. Within this executive role, the WGSD contributed to two main phases: guideline development and protocol planning.

2.2.1.1. Phase 1: Guideline development

Prior to working with CCNA researchers, the WGSD group developed a set of six principles to facilitate and streamline the incorporation of sex and gender research within the CCNA. These principles state that all CCNA teams, platforms, and cross-cutting programs should endeavor to consider whether and how sex and gender are relevant to their work and how they may affect their findings, as well as to collect information that will permit the exploration of the role of sex and gender on neurodegeneration in aging. They further state that individual CCNA investigators should explicitly report on their plans for ensuring sex

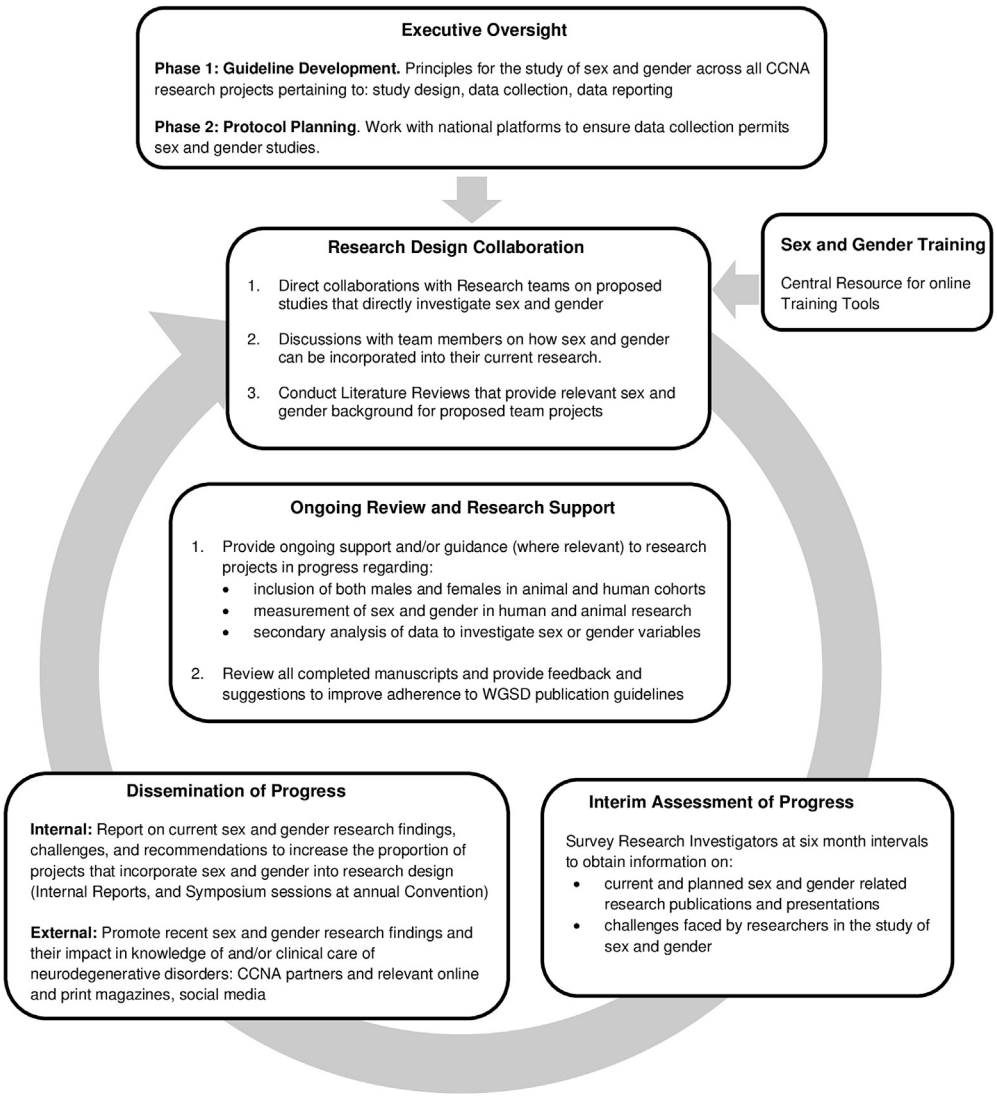

Fig. 2. WGSD's six-component strategy for integration of sex and gender in research. Abbreviations: CCNA, Canadian Consortium on Neurodegeneration in Aging; WGSD, Women, Gender, Sex and Dementia.

and gender balance in all projects and provide evidence-based rationales should sex and gender not be incorporated into research designs. These principles also apply to preclinical animal model studies that should be conducted on both male and female animals to provide the information necessary to establish knowledge about sex differences in early phases of drug discovery. Finally, the guidelines state that based on the availability of funds, competitive internal grant opportunities would be made available to all CCNA teams and platforms, allowing researchers to address the role of sex and gender on their studies.

In addition, in line with the CIHR, NIH, and European Association of Science Editors recommendations [15], the WGSD developed specific publication guidelines for sex and gender reporting. CCNA researchers are required to adhere to these guidelines in all manuscripts. These guidelines recommend that researchers use the terms sex and gender appropriately, indicate if only one sex was included in the project, and identify the sex of included animal or human subjects in the title of their paper. The guidelines also recommend that authors describe how sex and gender were taken into account, providing a rationale for inclusion or exclusion of these considerations. Results should also be provided separately by sex and gender, and sex- or gender-based analyses should be reported, irrespective of positive or negative findings. Finally, it is recommended that if sex and gender are not considered in the research project, and no rationale for this exclusion is provided, authors should list this as a limitation of their study.

2.2.1.2. Phase 2: Protocol planning

Given the structure of the CCNA network, with eight national platforms gathering data from clinical cohorts, and big data, it was necessary for the WGSD to ensure data gathered in the clinical cohort and biomarker platforms would permit sex or gender studies. To operationalize this goal, the lead of the WGSD program was present on virtually all committees involved in the establishment of the platforms and the national cohort study. The presence of the WGSD member provided a "sex and gender lens" which was brought consistently into discussions of particular questionnaire questions, planned biosamples, sample size, and sex ratio of the subgroups.

2.2.2. Sex and gender training

The WGSD group organized an online resource that provides information regarding various online training tools for sex and gender research. This central resource is utilized by all CCNA teams who are interested in learning more about the distinction between the concepts of sex and gender, challenges in the study of sex and gender in human and preclinical research, and measurement tools that can be used to assess sex and gender in research studies. The online training tools were developed by the WGSD and derived from a wide variety of sources including the CIHR Institute for Gender and Health (IGH), NIH, Health Canada, Public Health Agency of Canada, European Commission, and the European Curriculum in Gender Medicine. We recommend this type of training as an important first step not just for trainees but also for all researchers who are planning to examine sex or gender in their work.

2.2.3. Research design: Direct collaboration and support

The WGSD works with CCNA investigators in various capacities, depending on the nature of the research project. For instance, the WGSD can provide support in preliminary research design stages, providing evidence-based sex and gender research questions (with supporting background literature) that could be examined in a team's proposed project. The WGSD also synthesizes new research ideas regarding sex or gender differences in neurodegenerative disorders and participates in direct collaborations with several team investigators in every facet of the research process. These collaborations involve experts across various project themes within the CCNA, resulting in a multidimensional perspective in the research design, data acquisition, results interpretation, and dissemination processes.

2.2.4. Interim assessment of progress of WGSD cross-cutting program

To assess the effects of the WGSD program on sex and gender research productivity within the CCNA, interim progress assessments are conducted. All lead investigators of team projects are required to complete biannual progress reports describing their research development, preliminary findings, and future research plans. The WGSD group designed a survey that is included in the biannual progress reports. This survey asks investigators to state whether they are currently conducting or planning to conduct sex and gender research and to describe the type of research. This allows the WGSD team to determine in which capacity teams are integrating sex and gender: (1) incorporating sex and gender into the design of their research projects, to directly examine sex and gender questions; (2) covarying sex and gender in the analysis of their data; or (3) not conducting sex and gender research. If investigators report no sex and gender current or planned research, they are asked to provide reasons for this. The WGSD survey allows for evaluation of the WGSD program, regarding its effectiveness in incorporating sex and gender either directly (by research design) or indirectly (by covariate analysis) into team research projects.

2.2.5. Dissemination of progress

The WGSD program utilizes the survey information to create internal reports on sex and gender research productivity that is distributed biannually to the CCNA executive committee. This process allows the WGSD to identify growth and areas for future opportunity related to the pursuit of sex and gender research integration. The WGSD also uses the survey information to disseminate important sex and gender findings within the CCNA to the broader community through articles in local and national research media outlets

(e.g., CIHR's IGH, http://www.cihr-irsc.gc.ca/e/49629.html), often working with CCNA partners such as Women's Brain Health Initiative, who publish noteworthy findings on sex and gender (http://womensbrainhealth.org/better-thinking/mind-over-matter), as well as social media platforms (e.g., Facebook and Twitter). The WGSD program also organizes symposium sessions at annual CCNA meetings where recent sex and gender research findings are presented to members. These symposia are particularly useful for stimulating discussion among CCNA researchers and partner organizations, with the goal being to foster interest in the integration of sex and gender into current and planned projects. Communicating novel sex and gender research findings and their implications help facilitate the necessary integration of sex and gender into planning, measuring, and interpreting research findings.

2.2.6. Ongoing guidance and review: Manuscripts of completed projects

The WGSD program works to ensure that all CCNA research manuscripts follow the sex and gender publication guidelines. WGSD reviews all CCNA manuscripts according to these criteria and provides a summary of adherence and recommendations to improve sex and gender integration and reporting to the authors. This process helps to encourage all authors of manuscripts that are published in the CCNA to carefully consider sex and gender, and by doing so will facilitate sex and gender education within the CCNA and the broader research community.

3. Results

3.1. Sex and gender research productivity

Since the inception of the CCNA in 2014, there have been four progress reporting periods. The 20 team leaders and 36 subproject leaders (see http://ccna-ccnv.ca/en/about-us/) were asked to provide in these progress reports a description of their current and planned work involving sex and gender. However, teams were not fully formed until 2015 and thus, here, we present reports of teams' current work from progress report three (October 2015–March 2016) and four (April 2016–September 2016). We also present reports of teams' planned future work that they described in progress report four.

Overall, survey responses were received from 55 of the 56 team projects (98%) across and within the 20 CCNA teams. This included 11 team projects that conducted research using preclinical models (i.e., cell-based, rodent, and nonhuman primate models), and 44 projects involving human subjects. For human research, there were 25 currently active projects. There were an additional 19 proposed human research projects that planned to use data from the COMPASS-ND cohort which will be available in 2018. As shown in Fig. 3, the survey results show an increase in the proportion of sex and gender research projects across reporting periods for both preclinical (36%–45%) and human (56%–60%) studies. Moreover, we observed an increase across reporting periods in the proportion of studies that incorporated sex and gender into the design of their research projects, as opposed to covarying sex and gender in data analysis, particularly for preclinical studies. Regarding future research plans, the proportion of planned studies on sex and gender (design and covariate combined) increased relative to currently active projects described in the fourth reporting period for both preclinical (increased 19%) and human (increased 8%) cohorts (see Fig. 3).

Survey results also provided details regarding recent sex- and gender-related publications in the CCNA. For example, a collaborative human epidemiological study between the WGSD team and investigators in team 16 (driving and dementia) found that women with dementia stop driving sooner than men with dementia [16]. WGSD, in collaboration with teams 1 (Clinical Genetics and Gene Discovery) and 13 (Frontotemporal Dementia) conducted a large meta-analysis which revealed important sex differences in the prevalence of pathogenic mutations in frontotemporal dementia and amyotrophic lateral sclerosis [17]. Team 9 (Developing New Biomarkers) recently reported that men and women who are genetically at risk for AD differ in the type of biomarkers and risk factors associated with memory resilience [18].

Other CCNA studies currently underway include animal-based investigations by team 4 (Early Synaptic Changes and Metabolomics) examining sex differences in the timing and development of amyloid pathology, inflammation, and cognitive decline. Team 18 (Effectiveness of Caregiver Intervention) is investigating differences between men and women on their dementia caregiving experiences. Team 20's (Issues in Dementia Care for Rural and Indigenous Populations) work examines gender perspectives in dementia health care in Indigenous populations. WGSD is collaborating with team 8 (Lewy Bodies, Aging, and Dementia) to conduct a meta-analysis examining sex differences in cognitive profiles of PD patients.

3.2. Challenges to sex and gender integration in neurodegenerative research

The WGSD survey responses reveal several challenges to the integration of sex and gender into CCNA research. The most widely cited reason for not examining sex and gender is a lack of funding. To have appropriately powered research designs, it is necessary to have animal and human cohorts with sufficient numbers of males and females, which can be costly. However, this cost is arguably outweighed by the benefit of properly investigating sex and gender differences, which leads to better science, by increasing our understanding of how sex and gender can affect various outcomes in health research such as disease mechanisms, drug

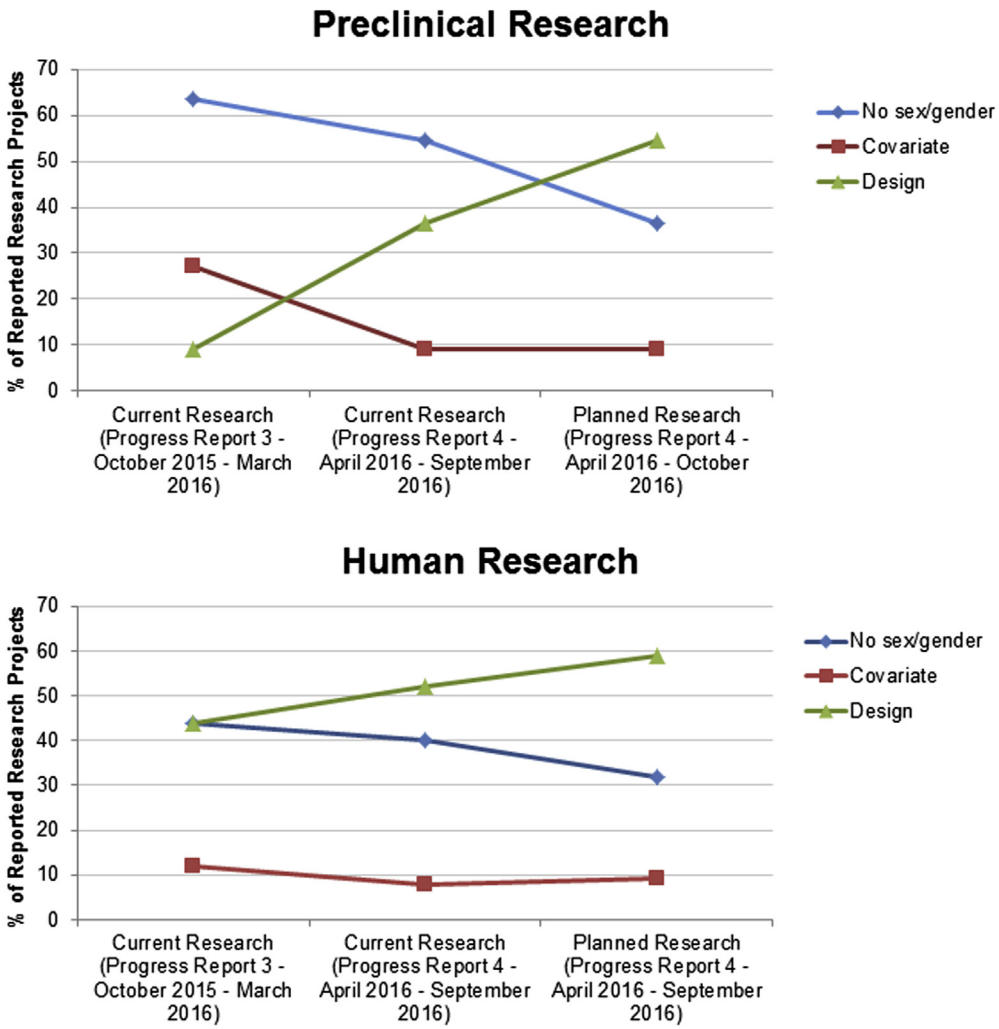

Fig. 3. WGSD survey results: incorporation of sex and gender in research projects on neurodegenerative disorders.

interactions, side effects, and metabolism [12]. Therefore, another important role of the WGSD program currently and particularly in the future will be to disseminate relevant funding opportunities to CCNA researchers. By highlighting grant competitions that support research projects that are directly investigating important sex and gender research questions at the local (i.e., within CCNA) and national (e.g., CCNA partner organizations such as the CIHR's IGH) level, our aim is to promote the study of sex and gender and create an infrastructure that can support these types of investigations.

4. Discussion

The WGSD cross-cutting program of the CCNA was conceived and developed to ensure appropriate integration of sex and gender into research on neurodegenerative disorders that ranges from preclinical models to psychosocial aspects of disease. We have had considerable success in achieving this goal within a 3-year period. Through contributing to decision making processes at the executive level, providing educational tools, background research, direct research support and guidance, ongoing review of research progress, assessing adherence to sex and gender publication guidelines, and promoting relevant research findings, the WGSD program has been effective in facilitating the integration of sex and gender into research on neurodegeneration. Through the tracking of CCNA research projects over biannual reporting periods, we observed a substantial increase in projects that incorporate sex and gender into their design and analysis. Furthermore, while challenges of integrating sex and gender into animal-based biomedical research has been noted in previous reports of CIHR grant applicants [8], the steady increase of CCNA projects utilizing preclinical models that are investigating sex and gender either directly or indirectly suggests that the active encouragement and monitoring carried out by WGSD is an important aspect of integrating sex and gender into research

practice. This strategy could be adapted and utilized across a wide variety of research disciplines and may be particularly relevant for preclinical research, which may be able to more quickly integrate sex considerations into their work, as human studies often involve longer recruitment and experimental protocol timeframes. Given that our survey results showed that the most frequently cited barrier to sex and gender integration in both pre-clinical and human studies is lack of funding, it will be critically important to encourage granting agencies to continue to provide and create a larger number of funding opportunities to financially support sex and gender research projects.

WGSD will continue its strategy implementation in the next phase of CCNA research. Subsequent program evaluation will be conducted once data from teams utilizing the nationwide clinical cohort (COMPASS-ND) is available. Based on the planned research reported in the latest progress report, as well as the richness of data on sex and gender being collected, we anticipate a large set of projects on this topic emerging from COMPASS-ND. This work will contribute to the increasing knowledge of how sex- and gender-related factors affect the risk and progression of neurodegenerative disorders—critical information for the therapeutic and clinical management of neurodegenerative diseases. Dissemination of the present sex and gender strategy could have broad impact and encourage researchers at an international level to facilitate sex and gender considerations and monitor its development. As sex and gender research continues to grow, it will be important for programs such as the WGSD to collaborate with similar institutions outside of the CCNA to establish best practice principles and a framework that could be adopted internationally.

The WGSD program advocates strongly for appropriate inclusion of sex and gender in study design, outcomes, interpretations, and results dissemination so that we can continue to improve our understanding of the etiology, progression, and treatment of neurodegenerative disorders. The WGSD joins a growing number of sex- and gender-based guideline [15] and curriculum development [19] groups and presents a framework for the integration of sex and gender in research. This work is important, timely, and will ultimately benefit science.

Acknowledgments

M.C.T. is the lead of the cross-cutting WGSD program of the Canadian Consortium on Neurodegeneration in Aging (CCNA) and is supported by a Clinician Scientist Award from the Department of Family and Community Medicine, University of Toronto and Sunnybrook Health Sciences Centre. A.F.C. is the WGSD program coordinator and was funded through a Postdoctoral Fellowship award from the CCNA. H.C. is the scientific director of the CCNA. R.J.R. is a member of the WGSD program. The CCNA is supported by a grant from the Canadian Institute of Health Research (CAN 137794), with funding from several partners. The funders were not involved in any aspect of study conception, design, data collection, analysis, manuscript preparation, or submission of manuscript for publication.

RESEARCH IN CONTEXT

1. Systematic review: Authors reviewed literature using PubMed. Several articles presented guidelines for the reporting of sex and gender and highlighted the importance of as well as challenges to conducting sex- and gender-related research. There were no articles describing and evaluating a best practice model of sex and gender integration implemented within a national neurodegenerative disorders research network called the Canadian Consortium on Neurodegeneration in Aging (CCNA).
2. Interpretation: The Women, Gender, Sex and Dementia program's six-component strategy for incorporating sex and gender was successful in increasing research productivity within the CCNA that directly examines sex and gender questions in neurodegenerative research.
3. Future directions: The Women, Gender, Sex and Dementia program will continue to monitor sex and gender research productivity in future projects within the CCNA that examine clinical cohort data across the spectrum of neurodegenerative disorders. Our presented strategy could be applied across a wide variety of health research disciplines.

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