

Sex and gender in health research: updating policy to reflect evidence – an Australian call to action

Introduction

Growing evidence from pre-clinical(1) and clinical research(2) demonstrates that females/women and males/men can differ significantly in their susceptibility to common diseases and response to treatment, including efficacy and adverse events.(3) Whilst the mechanisms underlying sex and gender (S&G) differences are likely to include epi/genetic, endocrine, environmental, social, economic, and behavioural factors, it is clear ignoring S&G differences across the research lifecycle – from grant submissions through to clinical translation - has the potential to compromise the accuracy of science, result in detrimental health outcomes, increase healthcare costs, and have implications beyond health including social services and aged-care.

Sex refers to the biological and physiological characteristics that define humans (and other species) as male, female or intersex, based on chromosomal complement. Gender references roles, behaviours and activities that a given society, at a given time, considers appropriate for men, women and gender diverse persons. Disaggregation of data by sex and/or gender enables the identification of differences between females/women and males/men, facilitating an understanding of the roles of both biological and sociocultural factors in disease presentation and outcomes.

Knowledge of clinically significant S&G differences in screening, risk factors, treatment and prognosis are emerging across a broad range of diseases, and are identified for those conditions conferring the greatest health burden in Australia and globally(4): cancer,(2) cardiometabolic disease,(5) mental illness and substance use (6) and dementia.(7)

Historically and consistently across a broad-range of health domains, data have been collected from men and generalised to women,(8) although response rates and healthcare utilisation among women can be higher resulting in women potentially over-represented in some observational studies. The failure to appreciate the differences between and across the S&G spectrum risks compromising the quality of care and increasing costs due to inappropriate allocation of resources and interventions.

As a consequence, growing numbers of countries, including the United States of America (US), Canada, Ireland, and Germany have introduced policies and practices which require the integration of S&G analyses in competitive research grants and/or publications in

journals.(9, 10) Whether similar policies and practices exist for Australian institutions has not previously been documented

In this paper, we summarise the findings sourced from key documents that provide an overview of the history and mechanisms in place in North America and Europe which facilitate the integration of S&G into health research. We then provide data on the policies and practices of Australian funding agencies and peer-reviewed journals relating to the collection, analysis, and reporting of S&G-specific health data . Finally, we make recommendations, launching a call to action to key stakeholders to introduce such policies and practices in Australia.

The North American experience

In 1990, the National Institute of Health (NIH) Office for Research into Women's Health (ORWH) was founded under an edict from the U.S. Congress. The ORWH was instrumental in the creation of the NIH Agenda for Research on Women's Health for the 21st Century (1999); it extended the scope of research policies beyond involvement of women in studies, to also include an understanding of sex differences. In response, the Institute of Medicine (IOM) established the Understanding the Biology of Sex and Gender Differences committee which produced the IOM landmark report "Exploring the Biological Contributions to Human Health: Does Sex Matter?"(8)

Policy change in the US further progressed when in 2013, the US Food and Drug Administration issued a safety announcement that the recommended dose of zolpidem should be halved for women,(11) after research demonstrated that women (compared to men) had 45% higher blood levels, 12 and 24 hours after administration, causing impaired next day alertness and driving safety concerns.(11) Up until this point women and men had received the same dose. Canada followed the US dosage changes in January 2014.(12) However, this zolpidem recommendation has not been implemented in Australia.

Policies relating to the inclusion of females in research have now been extended beyond clinical research to include cell lines and animal models. (1, 10) In 2016, the NIH implemented a policy that required sex be included as a biological variable in pre-clinical research.(10) Given the cost implications of this policy, the policy direction was accompanied by increased funding to enable researchers to increase sample sizes to ensure they had sufficient power to analyse sex differences. (13)

Three additional US organisations have been key contributors to this issue:

1. The Organization for the Study of Sex Differences(14), which enhances knowledge of S&G analyses in health by facilitating interdisciplinary communication and collaboration among scientists and clinicians.
2. The International Society for Gender Medicine(15), which connects national and professional societies dedicated to the study of S&G-specific differences in health.
3. Gendered Innovations in Science, Health & Medicine, Engineering and Environment (Stanford University and the European Commission), which provides tools and training to enable clinicians, researchers and policy-makers to understand and undertake S&G research.(16)

In 2013, the Institute of Gender and Health in the Canadian Institutes of Health Research (CIHR)(17) was established with the aim of integrating S&G across the health research spectrum to assist development and implementation of research findings on policies, products, services and systems that support better health for all Canadians. The CIHR requires all grant applicants to respond to mandatory questions about S&G in research proposals.(18) They also provide online training modules on S&G in biomedical research for scientists and peer reviewers, with the objectives of ensuring graduates recognise nomenclature used in S&G science, identify methods to conduct S&G science and critically appraise the integration of S&G in protocols and publications.(19)

The European experience

The European Association of Science Editors established a Gender Policy Committee (2012), with the aim “to advance gender and sex-sensitive reporting and communication in science”(20) and published the Sex and Gender Equity in Research (SAGER) guidelines in 2016.(21) *The Lancet* recently published a commentary on editorial policies with respect to S&G analyses that proposed guidelines for medical journals including accurate use of S&G terms and reporting of sex, gender or both in study participants and sex of animals or cells(9).

In Sweden, the Karolinska Institute’s Centre for Gender Medicine supports research and education with a particular focus on how the promotion and implementation of S&G analyses can drive innovation in healthcare(22). The League of European Research Universities published a paper in 2015 with 20 recommendations about how universities can improve treatment of S&G in research and innovation, stating that it had to be better integrated into research funding, curriculum and clinical practice.(23)

Finally, The European Commission (EC) has undertaken work in the S&G field including supporting the development of The European Gender Medicine Network (2013) which provides an innovative framework for implementation of S&G in biomedicine and health research. In 2014 the EC put in place a condition for Horizon2020 funding that requires applicants to “...describe how sex and/or gender analysis is taken into account in the project’s content”.(24)

Australian data

A mixed methods analysis was undertaken by Carcel, Wainer, McKenzie, Webster and Norton, to determine whether funding agencies and peer-reviewed journals in Australia have policies and practices on the collection, analysis, and reporting of sex and gender-specific health data. The top 10 medical granting agencies in Australia were identified through the University of New South Wales (UNSW) Grants Management Office. The top 10 peer-reviewed Australia-based medical journals were identified through Journal Citation Reports.

A web-based search, performed between 1 to 5 December 2017, sought to identify the existence of sex and gender-specific policies or practices, of these agencies and journals. Telephone interviews were undertaken between 5 January to 14 March 2018 with key informants from these organisations. The semi-structured interviews covered four main questions: 1. Does your organisation currently have a policy on sex and gender research integration? 2. Does your organisation have any plans to develop one in the near future? 3. What in your view are some barriers to changing current policies and practices? 4. What in your view are some facilitators to changing current policies and practices?

Data were analysed using combined deductive and inductive methods. Ethics approval was provided by the UNSW Ethics Committee.

Tables 1 and 2 provide information on the 20 organisations that were identified for inclusion in the study. As a result of the web-based search, eight of the 10 funding agencies were identified as not having policies. The National Health and Medical Research Council (NHMRC) and Diabetes Australia had policies on the collection, analysis or reporting of sex and gender-specific health data. However, only NHMRC specifically recommended the analysis and reporting of sex and gender-specific data.

There was a mix of pre-clinical and clinical peer-reviewed journals identified through InCites. Four of the 10 journals did not have policies on the collection, analysis and reporting of sex

and gender-specific health data. Six of the journals (Medical Journal of Australia, Immunology and Cell Biology, Australian and New Zealand Journal of Psychiatry, Australian and New Zealand Journal of Public Health, Respiriology, Australian and New Zealand Journal of Surgery) indicated they followed the reporting guidelines of the ICMJE(25).

Of the 20 key informants invited to interview, 12 agreed to participate. Among the participants, seven were heads of funding agencies and 5 were editors of peer-reviewed journals. Five of the 12 participants were women. The findings of the web-based search were confirmed as correct by the 12 key informants. Key informants from journals shared that despite no publicly available policies on sex and gender health data, there were internal rules that the editors, reviewers and authors followed. Lack of awareness of the issue as well as the high cost of funding sex and gender-specific research were perceived as barriers to changes in policy. The evidence of a need for policy change and guidance from larger organisations were seen as facilitators for change within and across organisations. Overall, the majority of key informants were positive about creating specific policies on the collection, analysis and reporting of sex and gender-specific health data. Most indicated that policies could be developed within two years (of the interview) and some said that a necessary factor in this would be involving key individuals such as those from advisory and/or editorial committees.

Based on the positive responses to this Australian study, there is high expectation that new policies, consistent with those adopted in many overseas countries, will soon be effectively implemented in the Australian research funding environment. Additionally, rather than broadly referring to the reporting guidelines of ICMJE, given there are now proposed guidelines on reporting sex and gender in medical journals(21), Australian peer-reviewed journals will likely follow.

Recommendations and a call to action to key stakeholders in Australia

All Australian Government departments and agencies were required to align their business practices with the Australian Government Guidelines on the Recognition of Sex and Gender, which provide guidance about data collection, by 1 July 2016. The Australian Bureau of Statistics, Standard for Sex and Gender Variables, is consistent with these guidelines. However, as identified in the in the study reported above, Australian medical research has fallen behind North America and Europe in recognising S&G as a key determinant of health, and its importance for health research and improved health outcomes.

There are multiple key stakeholders who can act to raise awareness of and facilitate the development and implementation of S&G analysis in health and medical research, provide training for researchers, scientists and clinicians and drive change through funding and publication requirements. In the accompanying table (Table 3), we have made a number of recommendations to these stakeholders and a call for action. In the absence of implementing these there is a risk that Australia will fail to keep pace with the rest of the world and in turn will become increasingly less competitive when applying for funding from international bodies and reduce international partnership opportunities with overseas organisations. By implementing these recommendations, Australia will align with other major nations in improving health research and practice to the benefit of the women, men, girls and boys of Australia. This is not simply a women's or men's health issue, but an issue for all Australians.

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