Sex and gender in health research: updating policy to reflect evidence

Australia needs to align with other nations and implement sex and gender analysis in health and medical research

Growing evidence from pre-clinical[1] and clinical research[2] demonstrates that females/women and males/men can differ significantly in susceptibility to common diseases and response to treatment, including efficacy and adverse events.[3] The mechanisms underlying sex and gender differences will include epigenetic, genetic, endocrine, environmental, social, economic and behavioural factors. Hence, ignoring sex and gender 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 health 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, behaviour 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 sex and gender differences in screening, risk factors, treatment and prognosis is emerging across a broad range of diseases, and differences are identified for those conditions conferring the greatest health burden in Australia and globally:[4] cancer,[2] cardiometabolic disease,[5] mental illness,[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] Failure to appreciate the differences between and across the sex and gender spectrum risks compromising the quality of care and increasing costs due to inappropriate allocation of resources.

As a consequence, growing numbers of countries, including the United States, Canada, Ireland and Germany, have introduced policies and practices that require the integration of sex and gender analyses in competitive research grants and publications in journals.[9,10] Whether similar policies and practices exist for Australian institutions has not previously been documented.

In this article, 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 sex and gender 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 sex- and gender-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 Institutes of Health (NIH) Office of Research on Women's Health was founded under an edict from the US Congress. The Office of Research on Women's Health was instrumental in the creation of the NIH *Agenda for research on women's health for the 21st century* in 1999;[11] 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 established the Understanding the Biology of Sex and Gender Differences committee, which produced the 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 (FDA) issued a safety announcement that the recommended dose of zolpidem should be halved for women,[12] after research demonstrated that women had significantly higher blood levels of zolpidem than men,[13] causing impaired next-day alertness and driving safety concerns. In response to these findings, the FDA informed manufacturers to reduce recommended doses accordingly for women.[12] Until this point, women and men had received the same dose. Canada followed the US dosage changes in January 2014.[14] An FDA update in 2017 stated "The recommended initial dose of certain immediate-release zolpidem products … is 5 mg for women and either 5 mg or 10 mg for men. The recommended initial dose of zolpidem extended-release … is 6.25 mg for women and either 6.25 or 12.5 mg for men. If the lower doses (5 mg for immediate-release, 6.25 mg for extended-release) are not effective, the dose can be increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release".[12] The fact that this issue continues to be debated[15] strengthens our stance that sex and gender disaggregated analysis should be included in all research analysis plans from the very beginning. The US 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,

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the NIH implemented a policy that required sex be included as a biological variable in pre-clinical research.[10] Given the cost implications, the policy direction was accompanied by increased funding to enable researchers to increase sample sizes to ensure they had sufficient power to analyse sex separately.[16]

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

- the Organization for the Study of Sex Differences (www.ossdweb.org), which enhances knowledge of sex and gender analyses in health by facilitating interdisciplinary communication and collaboration among scientists and clinicians;
- the International Society of Gender Medicine (www.isogem.eu), which connects national and professional societies dedicated to the study of sex- and gender-specific differences in health; and
- Gendered Innovations in Science, Health and Medicine, Engineering, and Environment (Stanford University and the European Commission; http://genderedinnovations.stanford.edu), which provides tools and training to enable clinicians, researchers and policy makers to understand and undertake sex and gender research.

In 2013, the Institute of Gender and Health (www.cihr-irsc.gc.ca/e/8673.html), of the Canadian Institutes of Health Research, was established with the aim of integrating sex and gender across the health research spectrum to assist development and implementation of research findings on policies, services and systems that support better health for all Canadians. The Canadian Institutes of Health Research requires all grant applicants to respond to mandatory questions about sex and gender in research proposals.[17] They also provide online training modules on sex and gender in biomedical research for scientists and peer reviewers, with the objectives of ensuring increased accuracy of nomenclature used in sex and gender science, identifying methods to conduct sex and gender science, and critically appraising the integration of sex and gender in protocols and publications.[18]

The European experience

The European Association of Science Editors established a Gender Policy Committee in 2012, with the aim "to advance gender- and sex-sensitive reporting and communication in science"[19] and published the Sex and Gender Equity in Research (SAGER) guidelines in 2016.[20] *The Lancet* recently published a commentary on editorial policies with respect to sex and gender analyses that proposed guidelines for medical journals, including accurate use of sex and gender terms and reporting of sex, gender or both in study participants and the sex of animals and cells.[9]

In Sweden, the Karolinska Institutet's Centre for Gender Medicine supports research and education with a particular focus on how the promotion and implementation of sex and gender analyses can drive innovation in health care (http://ki.se/en/research/centre-for-gender-medicine). The League of European Research Universities published a paper in 2015 with 20 recommendations about how universities can improve treatment of sex and gender in research and innovation, stating that it must be better integrated into research funding, curriculum and clinical practice.[21]

Finally, The European Commission has undertaken work in this field, including supporting the development of the European Gender Medicine Network in 2013, which provides an innovative framework for implementation of sex and gender in health research. In 2014, the European Commission put in place a condition for Horizon 2020 funding that requires applicants to "describe how sex and/or gender analysis is taken into account in the project's content".[22]

The Australian situation

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 on the collection, analysis and reporting of sex- and gender-specific health data. In addition, major medical granting agencies in Australia were identified through the University of New South Wales (UNSW) Grants Management Office. The top ten peer-reviewed Australia-based medical journals were identified through Journal Citation Reports. Ethics approval was provided by the UNSW Ethics Committee (HC17866).

A web-based search, performed between 1 and 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 and 14 March 2018 with key informants from these organisations. The semi-structured interviews covered four main questions:

- Does your organisation have a policy on sex and gender research integration?
- Does your organisation have plans to develop one in the near future?
- What in your view are barriers to changing current policies and practices?
- What in your view are facilitators to changing current policies and practices?

Box 1 and Box 2 provide information on the 20 organisations that were included in the study. As a result of the web-based search, eight of the ten 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 the 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 ten journals did not have policies on the collection,

1 Sex- and gender-specific policies of the top ten granting agencies in Australia,* according to a web-based search in December 2017

Organisation	Presence of policy	Policy
National Health and Medical Research Council (NHMRC)	Yes	The NHMRC does not have a single policy document on sex and gender research integration. However, advice is provided in several policy documents and in a number of different sources: • Best practice methodology in the use of animals for scientific purposes (2017) (https://www.nhmrc.gov.au/guidelines-publications/ea20), in specific terms under Section 3.1, "Quality of experimental design", "the failure to consider the use of both sexes in pre-clinical studies involving animals (unless there is a valid reason not to do so) can affect the validity of the outcomes from such studies, which may then impact on the validity of their use as the basis for clinical trials in humans" • The *National Statement on Ethical Conduct in Human Research* (2015) (https://www.nhmrc.gov.au/guidelines-publications/e72) includes reference to principles of scientific merit, integrity and justice. A clinical trial designed with scientific merit and integrity would ensure that the size and profile of the sample to be recruited is adequate to answer the research question. An appropriate balance of male and female participants may be necessary to ensure the profile of participants is representative of the community in which the new drug or device, for example, will be used. If one sex is to be excluded from a clinical trial, a researcher would need to justify this to the reviewing Human Research Ethics Committee Policy accessed 19 December 2017
National Heart Foundation of Australia	No	No policy at this level at the time of the search
Cancer Council Australia	No	No policy at this level at the time of the search
Medical Research Future Fund	No	No policy at this level at the time of the search
New South Wales State Government (Office for Health and Medical Research)	No	No policy at this level at the time of the search
Victoria State Government (Cancer, Specialty Programs, Medical Research and International Health, Health and Wellbeing Division)	No	No policy at this level at the time of the search
Diabetes Australia	Yes	Applicants must comply with the NHMRC's general principles (https://static.diabetesaustralia.com.au/s/fileassets/diabetes-australia/3c9b4f5f-38c4-4cfb-a8f1-68689c906dae.pdf) Policy accessed 19 December 2017
Leukaemia Foundation	No	No policy at this level at the time of the search
Australian Research Council	No	No policy at this level at the time of the search
Cancer Australia	No	No policy at this level at the time of the search

* Identified through the University of New South Wales Grants Management Office. ◆

analysis and reporting of sex- and gender-specific health data. Six of the journals (*The Medical Journal of Australia*, *Immunology and Cell Biology*, the *Australian and New Zealand Journal of Psychiatry*, the *Australian and New Zealand Journal of Public Health*, *Respirology*, and the *Australian and New Zealand Journal of Surgery*) indicated they either followed the reporting guidelines of the International Committee of Medical Journal Editors[23] or the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.[24]

Of the 20 key informants invited to the interview, 12 agreed to participate. Among the participants, seven were heads of funding agencies and five were editors of peer-reviewed journals. Five 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 was seen as a facilitator 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 participants indicated that policies could be developed within 2 years, 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

2 Sex- and gender-specific policies of the top ten peer-reviewed journals in Australia,* according to a web-based search in December 2017

Journal	Presence of policy	Policy
Journal of Gastroenterology and Hepatology	No	No policy at this level at the time of the search
The Medical Journal of Australia (*MJA*)	Yes	"The *MJA* follows the guidelines of the International Committee of Medical Journal Editors [ICMJE] and the World Association of Medical Editors on publishing and editorial matters, including peer review, conflict of interest and confidentiality" (https://www.mja.com.au/journal/mja-instructions-authors) Policy accessed 19 December 2017
Clinical and Experimental Pharmacology and Physiology	No	No policy at this level at the time of the search
Immunology and Cell Biology	Yes	"Authors are encouraged to adhere to animal research reporting standards, for example the ARRIVE reporting guidelines for reporting study design and statistical analysis" (https://onlinelibrary.wiley.com/page/journal/14401711/homepage/ForAuthors.html#5) Policy accessed 19 December 2017
Australian and New Zealand Journal of Psychiatry	Yes	"This Journal recommends that authors follow the *Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals* formulated by the [ICMJE]" (https://au.sagepub.com/en-gb/oce/Journal/australian-new-zealand-journal-psychiatry#submission-guidelines) Policy accessed 19 December 2017
Journal of Paediatrics and Child Health	No	No policy at this level at the time of the search
Australian and New Zealand Journal of Public Health	Yes	The journal endorses "the guidelines set out by the [ICMJE] in *Uniform requirements for manuscripts submitted to biomedical journals*" (http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1753-6405/homepage/ForAuthors.html) Policy accessed 19 December 2017
Respirology	Yes	"Manuscripts should conform to the revised guidelines of the [ICMJE], published as ICMJE *Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals*" (http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1440-1843/homepage/ForAuthors.html) Policy accessed 19 December 2017
ANZ Journal of Surgery	Yes	"The journal complies with the [ICMJE's] *Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication*" updated February 2006 (http://www.ICMJE.org)" (http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1445-2197/homepage/ForAuthors.html) Policy accessed 19 December 2017
Clinical and Experimental Ophthalmology	No	No policy at this level at the time of the search

ARRIVE = Animal Research: Reporting of In Vivo Experiments. * Identified through Journal Citation Reports. ◆

countries, will soon be effectively implemented in the Australian research funding environment. Further, Australian peer-reviewed journals can follow the proposed guidelines on reporting on sex and gender in medical journals.[20]

Recommendations and a call to action to key stakeholders in Australia

All Australian Government departments and agencies are required to progressively 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.[25] The Standard for Sex and Gender Variables of the Australian Bureau of Statistics is consistent with these guidelines.[26] However, as identified in the study reported above, Australian medical research has fallen behind North America and Europe in recognising sex and gender as key determinants of health and their importance for health research and improved health outcomes.

Multiple key stakeholders can act to raise awareness and facilitate the development and implementation of sex and gender analysis in health and medical research, educate researchers, scientists and clinicians, and drive change through funding and publication requirements. We suggest a number of recommendations to these stakeholders and a call for action (Box 3). 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 will reduce international partnership opportunities

3 Recommendations for stakeholders

Stakeholder	Recommendation
Universities and other training institutions	• Universities and other higher education training institutions, with the support of multi-institutional organisations (such as Medical Deans Australia and New Zealand), should commit to developing systematic and nationally consistent curricula that acknowledge and explore biological differences between males and females and the role of gender and sociocultural factors in disease presentation and outcomes. This recommendation has relevance across a range of faculties and disciplines, including medicine, public health, pharmacy, nursing, allied health, and science ► There are multiple texts that support this initiative as well as example curricula from Charité University Hospital in Berlin and Gendered Innovations at Stanford University[18] • University and other higher education ethics committees should ensure that implementation of sex and gender analyses in research is managed as an ethical issue
Learned academies and professional societies	• The Australian Academy of Health and Medical Sciences should encourage its members to champion the integration of sex and gender analysis in research. Similarly, we ask that the Australian Academy of Science creates a special interest group to ensure that the following committees champion the integration of sex and gender analysis in research: Mechanical and Engineering, Data in Science, Biomedical and Cellular and Developmental Biology • The Council of Presidents of Medical Colleges should ensure that medical colleges include evidenced-based sex and gender integration in clinical guidelines, requirements for funding for research, training and professional development • Australian-based professional societies, such as the Australasian Epidemiological Association, the Australian Society of Clinical and Experimental Pharmacology and Toxicology, and many more, should promulgate the integration of sex and gender analysis in research by developing policies, position papers, and sex- and gender-specific guidelines
Governments	• The Therapeutic Goods Administration should require all new applications for registration to address sex and gender differences • The Pharmaceutical Benefits Advisory Committee should consider how best the Pharmaceutical Benefits Scheme might incorporate knowledge of sex and gender differences in facilitating timely, reliable and affordable access to necessary medicines for Australians • Federal and state government health data bodies should develop a standard approach to analysing sex and gender in all health reporting, ensuring that sex and gender are treated as separate constructs when appropriate. Given its commitment to dealing with this issue, the Australian Institute of Health and Welfare is well placed to lead this initiative and provide policy direction for other health data groups and agencies. We similarly ask that all federal and state health departments and agencies align their data collection practices with the *Australian Government guidelines on the recognition of sex and gender* and the Australian Bureau of Statistics Standard for Sex and Gender Variables • The National Health and Medical Research Council (NHMRC) Australian Health Ethics Committee should review content relating to sex and gender in the *National Statement on Ethical Conduct in Human Research* and revise as required to ensure that the implementation of sex and gender analyses in research is managed as an ethical issue • Health funding bodies including the Independent Hospital Pricing Authority and Medicare should consider sex and gender analyses in cost-weighting calculations • The Australian Commission on Safety and Quality in Health Care should undertake to include integration of sex and gender data collection and analyses in guidelines for Clinical Quality Registries and ensure adherence to practice according to clinical guidelines, where sex and gender differences occur in accreditation standards
Medical and health research funders	• The Medical Research Future Fund, the NHMRC, and other federal and state government health funders, as well as the National Heart Foundation of Australia, Cancer Council Australia, Diabetes Australia, and other health-related, not-for-profit funders and researchers should promulgate the development of policies and practices, requiring consideration be given to the inclusion of sex and gender analysis, or demonstrate why it is not required, and guidelines to address the implementation of sex- and gender-specific clinical care and health promotion and prevention • Funders should develop a funding pool to cover the extra costs associated with including sex- and gender-specific analyses and they should make funding available to train researchers and clinicians in how to undertake research that includes comprehensive sex and gender analyses
Peer-reviewed journals	• Australian-based, peer-reviewed journal editors should develop and monitor the implementation of policies to ensure researchers include sex and gender in reporting of research. We ask that they support the implementation of unified policies in the requirements for the publication of sex and gender analyses and we call on them to challenge submitted manuscripts that do not address inclusion of sex and gender analyses in their reporting
Industry	• Health industry stakeholders, such as pharmaceutical companies and medical device companies, should ensure that all new products are developed, consistent with US Food and Drug Administration regulatory policies, requiring the involvement of both males and females in clinical trials and the integration of sex and gender analyses

with overseas organisations. By implementing these recommendations, Australia will align with other 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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