Editorial policies for sex and gender analysis

Sex and gender are basic variables in preclinical and clinical scientific research.[1-4] Data show that physiology differs between male and female humans and animals beyond reproductive function to encompass all systems, including differences in cardiovascular, respiratory, musculoskeletal, immunological, gastrointestinal, neurological, and renal function.[5-7] Failure to account for sex and gender may result in the inability to reproduce scientific findings, and often translates into less than adequate care of, or even harm to, men and women.[8] For example, many drugs fail because sex and gender are not examined as variables in preclinical and translation research: between 1997 and 2000, ten drugs were withdrawn from the US market because of life-threatening health effects; eight of which posed greater health risks for women than for men.[9]

In recent years, granting agencies, including the Canadian Institutes of Health Research, the European Commission, and the US National Institutes of Health (NIH), have explicitly called for sex and gender analysis in health research. According to the NIH, both "sex and gender play a role in how health and disease processes differ among individuals, and consideration of these factors in research studies informs the development and testing of preventive and therapeutic interventions".[10-12]

Publishers can work in concert with funders to secure these mandates and enhance reproducibility in science by providing clear guidance to editors and authors for the scientific reporting of sex and gender.

A growing number of peer-reviewed journals have editorial policies that require sex-specific or gender-specific reporting.[13-15] For example, the International Committee of Medical Journal Editors (ICMJE) has long advocated that researchers "aim for inclusive representative populations in all study types" for "such variables as age, sex, or ethnicity" or "at a minimum provide descriptive data for these and other relevant demographic variables". In addition, the European Association of Science Editors has developed a set of recommendations for reporting sex and gender in study design, data analyses, results, and interpretation of findings.[16] But no standard has been broadly adopted. Reviews of basic science journals suggest that the sex of experimental material is not consistently reported: for example, sex was not reported for 22–60% of animals used in general biology and immunology, and about 75% of experiments using cultured cells.[17-21] Standards for transparent reporting of sex and gender are crucial to understanding and improving the health of both women and men.

We recommend that journal editors standardise guidelines for reporting sex and gender. Sex is a biological variable based upon chromosomal assignment, and generally male, female, or intersex. Gender is a constellation of sociocultural processes that interact with and have the potential to influence human biology. Sex and gender interact in individual males and females.[22,23] Pain, for example, has biological aspects (eg, sex differences in the physiology of pain signalling) and also cultural aspects (eg, gender differences in how men or women report pain, and how a physician's gender influences his or her understanding and treatment of pain in men or women).[14,24] Authors should specify how they analysed for sex and gender, and indicate where it is not possible to know whether a finding is driven by sex, gender, or both.

We propose adoption of the following guidelines designed for use by journal publishers, editors, reviewers,

For **ICMJE recommendations** see http://www.icmje.org/icmje-recommendations.pdf

***Panel:* Proposed guidelines on reporting sex and gender in medical journals**

1. Require correct use of the terms sex and gender. Using these terms precisely increases clarity, enables critical review, and facilitates meta-analysis.
2. Require the reporting of the sex, gender, or both of the study participants, and the sex of animals or cells. If males and females were not studied in appropriate proportions, these elements of study design should be justified in the Methods section, and considered in the Discussion section.
3. Consider analysing data by sex, gender, or both where appropriate, or providing the raw data in the main manuscript, supplemental material, or in an accessible data repository. Report on the approach chosen for sex and gender analysis and comment on it in the Discussion section. In studies that are underpowered to detect sex or gender differences, access to data allows for use of those data in meta-analyses and systematic reviews.
4. Analyse the influence (or association) of sex, gender, or both on the results of the study where appropriate, or indicate in the Methods section why such analyses were not performed. Where those analyses were not performed, consider covering this topic in the Discussion section. Readers need to know whether the results generalise to both sexes. Include negative results as well as results that show differences.
5. If sex or gender analyses were performed post hoc, indicate that these analyses should be interpreted cautiously. Negative post-hoc analyses may be underpowered, leading to a false conclusion of no difference. By contrast, if many such analyses were done, the additional comparisons may lead to spurious significance suggesting an erroneous conclusion of a sex-related or gender-related difference where no such difference was in fact present. To minimise this likelihood, authors could consider making a statistical adjustment (such as a Bonferroni correction).

and authors (panel). At the discretion of editors, they are suitable for journals' author instructions.

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Targeting tau protein in Alzheimer's disease

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Alzheimer's disease, the most common dementing illness, is a relentlessly progressive and fatal brain disorder that begins approximately 10–15 years before any symptoms manifest. More than 47 million people worldwide have Alzheimer's disease, and this number is expected to reach over 131 million by 2050.[1] With increasing prevalence, the global impact of the social, economic, and emotional costs associated with Alzheimer's disease is staggering, and the need for better treatments unquestionable, since currently approved medications provide only symptomatic benefit without affecting the underlying disease process. Despite remarkable advances in our understanding of the molecular pathogenesis of Alzheimer's disease, no new treatments have been approved globally in more than a decade.[2]

The two defining pathological hallmarks of Alzheimer's disease are extracellular amyloid plaques and intracellular tau protein tangles, and unsurprisingly, both have become therapeutic targets for disease modification. The amyloid cascade hypothesis, which is supported by genetic evidence from studies of autosomal dominant Alzheimer's disease, is the prevailing conceptual framework for Alzheimer's disease drug development.[3] Findings from biomarker studies have also indicated that Alzheimer's disease is most probably an amyloid-enabled tauopathy, whereby amyloid plaque positivity defines the preclinical or asymptomatic stage of Alzheimer's disease, whereas the occurrence of tau tangles beyond the medial temporal lobes of the brain correlates more closely with the onset of clinical symptoms and neurodegeneration.[4] Although many phase 3 clinical trials of anti-amyloid therapeutics have not met their primary endpoints,[5,6] some indication