INCORPORATING THE SEX AND GENDER PERSPECTIVE IN RESEARCH CONTENT: A TOOLKIT

Community Hipàtia



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DEFINITIONS AND CONCEPTS

SEX

Sex refers to biology. In humans it refers to the biological attributes that distinguish male, female, and/or intersex. In non-human animals, sex refers to biological attributes that distinguish male, female, and/or hermaphrodite. Sex may be defined according to:

- 1. Genetic sex determination: chromosomal make-up, generally XX/XY for most mammals. The presence of sex-determining genes means that every nucleated human cell has a sex.
- **2.** Gametes: germ cells. In species that produce two morphologically distinct types of gametes, the egg-sperm distinction is the basis for distinguishing between females and males.
- **3.** Morphology: physical traits that differentiate female and male phenotypes.

GENDER

Gender refers to sociocultural norms, identities, and relations that: 1) structure societies and organizations; and 2) shape behaviours, products, technologies, environments, and knowledge (Schiebinger, 1999).

How we speak, our mannerisms, the things we use, and our behaviours all signal who we are and establish rules for interaction. Gender is one such set of organizing principles that structure behaviours, attitudes, physical appearance, and habits. Gender attitudes and behaviours are complex and change across time and place. They are not fixed nor universal but culturally constructed and learned through the socialization process.

- Gender Norms are produced through social institutions (such as families, schools, workplaces, laboratories, universities or boardrooms), social interactions (such as between romantic partners, work colleagues, or family members), and wider cultural products (such as textbooks, literature, film and video games).
- Gender Identities refer to how individuals or groups perceive and present themselves in relation to gender norms. Gender identities may be contextspecific and interact with other identities, such as ethnicity, class or cultural heritage. Gender is commonly referred to a binary model (male/female); however, there are several forms of gender identities
- Gender Relations refer to how we interact with people and institutions in the world around us, based on our sex and our gender identity. Gender relations encompass how gender shapes social interactions in families, schools, workplaces and public settings, for instance, the power relation between a man patient and a woman physician.

SEX AND GENDER INTERACTION

Although gender is distinct from sex, it is important to stress that sex and gender interact in unexpected ways. Gendered experiences can affect biology; sex and gender interact to influence health and disease processes across the lifespan. The term "Embodiment" refers to the fact that human beings are simultaneously social beings and biological organisms (Krieger 2005).

For example, pain exhibits biological sex differences in the physiology of signalling. Pain also incorporates sociocultural components in how symptoms are reported by women, men and gender-diverse people, and how physicians understand and treat pain according to a patient's gender.

CISGENDER AND TRANSGENDER

Transgender is an umbrella term which describes a range of gender identities, including individuals whose gender identity differs from that typically associated with the sex they were assigned at birth. (Marshall et al, 2019; Scandurra et al, 2019). This is in contrast to what some authors name cisgender, which describes individuals whose self-identified gender matches their birth sex assignment. Other individuals refuse the concept of gender as binary altogether, and may self-identify as genderqueer, nonbinary, genderfluid, or bigender (Hyde et al, 2018).

INTERSECTIONALITY

Intersectionality describes overlapping or intersecting forms of discrimination related to gender, sex, ethnicity, age, socioeconomic status, sexuality, geographic location, and other social axes of inequality. Gender should not be considered in isolation: gender identities, norms and relations both shape and are shaped by other social attributes (Buolamwini & Gebru, 2018). An intersectional framework assumes that an individual's experiences are not simply equal to the sum of their parts but represent intersections of axes of social power. For example, health-related experiences of immigrant women may be different from those of immigrant men and non-immigrant women.

When setting research priorities, developing hypotheses and formulating study designs it is important to take an intersectional approach as it can better predict variations in health outcomes and determine user needs, and ultimately lead to more inclusive research and engineering solutions (Weber et al, 2007).

WHY IS IT IMPORTANT TO CONSIDER SEX AND GENDER IN HEALTH RESEARCH?

What clinicians know about the diagnosis, treatment, and prevention of disease originates from studies mostly done on male cells, male mice, and men (Clayton 2016). Therefore, medicine and health care are less evidence-based for women than for men. Within the biological studies, it has been a common and preferential practice to utilize male research subjects in basic and preclinical research (Beery and Zucker, 2011; Kong et al., 2016; Sugimoto et al., 2019; Yoon et al., 2014). This male bias stems from the misconception that female animals increase experimental variability due to cyclical fluctuating hormones and the historical belief that no major differences exist between the sexes outside of reproductive functions (Institute of Medicine, 2001

NEW DISCOVERIES WITH X CHROMOSOME LINKED GENOME STUDIES

An exponential rise in biomedical discoveries is expected, now that new computational biology and statistical genetics software facilitates the exploration of X chromosome related expression in complex diseases (Gao et al, 2015). Until recently, sex chromosomes were excluded from most genome wide association studies because of the difficulty in distinguishing the active from the inactive X chromosome in females, and because of a mismatch in chromosomal size (Khramtsova et al, 2019) —the X chromosome has 1,669 known genes and the smaller Y chromosome contains only 426. Including sex chromosomes in genome wide association studies, as well as including and analysing adequate numbers of female and male cells, tissues, animals and humans in research, will broaden our understanding of why women and men are affected differently by certain diseases and how we can adapt lifesaving therapies to their specific needs.

A recent review of 2,347 articles, 618 of which included animals, in basic biomedical science and translational surgery showed pervasive sex bias (Yoon, 2014). (i) 80% of publications included only males, 17% only females and 3% both sexes; (ii) of all animals studied 84% were males and 16% females; (iii) 76% of publications on cells did not mention the lines' sex; (iv) only 1% (n=7) of all studies specifically reported sexbased results; (v) 44% of publications on diseases prevalent in women did not report the sex of the subjects or specimens studied.

SEX-LINKED DISPARITIES IN GENE EXPRESSION AND MALIGNANCY IN TUMOURS DEVELOP IN DROSOPHILA

Epidemiological studies show that in a wide range of cancer types unrelated to reproductive function, men have a worse prognosis than women. A research have found that the tumours that develop in Drosophila I(3)mbt mutant larvae are strongly dimorphic: malignant traits are much more prominent in males than in females, to the extent that they can be used to objectively stratify mbt tumour samples into two populations that correlate tightly with the sex of the tumour bearer. By quantitative proteomics, it is possible to identify a signature of proteins that are differentially expressed between male and female tumour samples. Many of the proteins that belong to these signatures have homologs in humans and are therefore promising leads for future research (Molnar et al, 2019).

These biases are not limited to basic sciences, but extend into clinical and public health research as well (Geller et al., 2018; Prakash et al., 2018; Scott et al., 2018). Eight out of ten drugs that were withdrawn from the market in the US between 1997 and 2000 were found to have worse side-effects in women than in men (US General Accounting Office, 2001).

OPPORTUNITIES FOR GENDER MAINSTREAMING IN CANCER IMMUNOTHERAPY

Cancer immunotherapy is benefitting from a deeper understanding of previously recognized genetic and hormone-mediated sex differences in immunity. Patients with melanoma or lung cancer, who are treated with checkpoint inhibitors, respond differently based on their sex, with a higher proportion of male patients achieving successful remission. Designed to outsmart the defence tactics of the cancer cells, checkpoint inhibitors stimulate natural killer cells to attack tumour cells. Natural killer cells are sensitive to oestrogen and testosterone, which may explain these observed sex differences. Understanding the underlying mechanisms will enable us to fine-tune future therapies (Giefing-Kröll et al, 2015).

Hence, gender bias in medicine is shown threefold: first, incorrectly assuming that health problems and risks of women and men are the same; second, on the basis that there are biological and psychological differences where there are only similarities; and third, on underestimate biological differences on top of cultural and social reasons, without further interferences based on biological differences (Valls-LLobet 2020).

MEN'S DEPRESSION AND SUICIDE

Depression in men may be more common than we think. Men's global suicide rates are even higher than those reported for male depression, suggesting depression in men could be going undetected and untreated (Oliffe et al, 2012). Social expectations about gender-appropriate reactions to depression have a significant influence on men's symptoms, coping strategies, and help-seeking behaviours. Until recently, men's experiences with depression have been largely overlooked by researchers and health care professionals. Although many men with depression and suicidal thoughts want help, pressure to conform to traditional masculine ideals can make reaching out difficult.

Indeed, research has shown sex/gender differences in health and its outcomes. Many diseases have been identified that affect women more heavily than men, such as cancer, rheumatoid arthritis, autoimmune diseases, osteoporosis, depression or anxiety, while others such as cirrhosis, Parkinson's disease, or aortic aneurism are more common in men than women (Alswat 2017, Beery et al 2011, Giefing-Kröll et al 2015, Hayter et al 2012, Schmitt et al 2014, Taylor et al 2011). It is increasingly recognised that women and men may manifest and experience diseases differently, respond differently to treatment and, metabolise drugs in a different way (DiPietro et al, 2017). Some female/male variations can occur as early as during pregnancy and birth. Female infants, for instance, are more likely than males to contract HIV perinatally, regardless of weight and mother's viral load, while male infants are more likely to be infected through breastfeeding. The differences between the sexes can be found at a very fundamental level, namely even in cells, cell lines and cell regulatory practices (Mittelstrass, 2011).

SEX AND GENDER DIFFERENCES IN STUDIES ON HIV

According to the clinics, the HIV transmission risk varies by type of exposure. For example, in heterosexual intercourse, the risk of transmission for a woman (receptive vaginal intercourse) is 1 in 1000, while for a man (insertive vaginal intercourse) the risk is 1 in 1,219 (UK Guideline for the use of HIV Post-Exposure Prophylaxis 2021). On the other hand, among men who have sex with men (MSM), the HIV epidemic continues to spread in most countries, and is 25 times higher among gay men and other MSM. Therefore, perform a gender perspective allows a deeper analysis of how the concept of masculinity contributes to the spread of HIV. A systematic review conducted on masculinities and HIV found that most studies on HIV and masculinity show a gender bias by not address the sexual identity of the population. In addition, the most widely investigated topic was sexuality and risk behaviour, demonstrating that men were cultural

legitimised by always being ready for sex. On the other hand, studies on masculinity and HIV were invisible from Western culture. It would seem, therefore, that western men are not seen as suitable for study from the gender perspective (Jacques-Aviñó, 2018).

Therefore, consideration of sex and gender in biomedical and health research is essential for informed decision making, reduction of harm, and for the promotion of health equality. Men, women and people of diverse gender identities can have different vulnerabilities, symptoms, and responses to health interventions.

Studies of both males, females and diverse people are essential to the advancement of human health, since the influences of sex and gender on the prevalence, presentation, and progression of many disease states is profound. Both sex and gender affect molecular and cellular processes, genetic expression and cell regulatory processes, the pharmacokinetics of drugs, onset, prevalence and severity of diseases, clinical traits, response to treatments, recognition and diagnosis of conditions; access to and utilization of health services; patient-practitioner interactions and how health and disease are experienced by individuals. Thus, sex and gender influence health at multiple levels, ranging from subcellular processes to interactions at the societal or global level.

INCORPORATION OF THE GENDER PERSPECTIVE IN COMMUNITY HEALTH

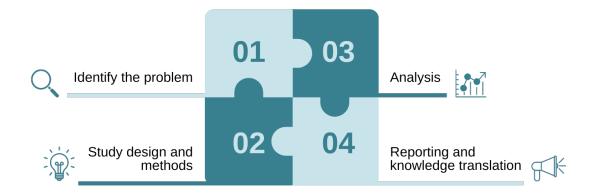
The concepts of community health and gender perspective are often misunderstood or interpreted differently between distinct sectors and disciplines. Gender norms determine different pathways and opportunities for people according to their sex, which are associated with gender inequalities in health and therefore must be incorporated into community health interventions. The gender perspective requires considering gender inequalities in power, in the access to and control over resources, the sexual division of labour and gender socialization in all phases of community health strategy implementation. A gender impact assessment must be carried out before the implementation of the interventions. The evaluation must consider gender equity, both in the process and in the effectiveness of the interventions. Incorporating a gender perspective in community health is not only a matter of ethics and justice but also of the effectiveness of interventions. (Artazcoz et al, 2018)

Thus, incorporating sex and/or gender analysis into research can improve reproducibility and experimental efficiency, help to reduce bias, enable social equality in scientific outcomes and foster opportunities for discovery and innovation (Tannenbaum et al, 2019).

THE SEX AND GENDER PERSPECTIVE IN RESEARCH TOOLKIT

The Sex and Gender Perspective in Research Toolkit is designed to guide researchers in considering accounting for sex and/or gender in basic science, clinical, health system and population health studies where appropriate. The Toolkit is a list of **questions** tackling the integration of sex/gender into research, a list of **subquestions** to illustrate each question, and **inputs** regarding how to incorporate sex and gender aspects.

The Toolkit captures each phase of the research process:



Investigating sex and/or gender may not be significant for all study analyses. Whenever the research subjects are organisms which can be differentiated by sex, the research study should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected (involve human subjects, use human cells or tissues or animal tissues/cells/other that serve as a model for human biology or physiology). Whenever subjects can be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this level of distinction.

In this toolkit, we used the term '**sex/gender**' not to imply that the two concepts are synonymous, but to serve as shorthand for 'and/or' throughout the metrics. If the answer to any of the questions is **negative**, a reasonable explanation should inform the decision why it is not possible or relevant to consider a sex/gender perspective.

Identify the problem

Questions / Subques	tions		Input
Was sex/gender issues addressed in previous studies? Compare your research efforts to existing literature with the help of the table below to assess how you are dealing with sex/gender issues:		Perform literature searches with adequate terms for "gender" and "sex" (Oertelt-Prigione et al, 2010). Include the term sex	
Sex/gender differences (or lack thereof)	Documented in the literature	Not documented in the literature	and gender or sex differences or gender differences in your literature search along with the condition or phenomenon of interest (Song et al, 2016). During the literature review, expand your perspective beyond biology to reflect on how
Addressed in your research	Adequate	Innovative: new knowledge, gaps or questions developed	psychosocial factors may influence health outcomes and consider the multidimensionality of gender (identity, norms and relations), if applicable. Search for relevant factors intersecting with 'sex' (e.g. genetic, physiological, hormonal,
Not addressed in your research	Missing relevant aspects: you will need to look further into how sex/gender can play a role in your research	Sex/gender aspects remain to be studied	anthropometric, biomechanical, injury thresholds, levels of pain tolerance, etc.) or 'gender' (age, socio-economic status, ethnicity, etc.) that could be relevant to your research study.
 Does the research question(s) or hypothesis/es make reference to sex/gender issues? ✓ Can the research project identify or explain sex/gender differences in the intervention/treatment/outcomes under study? ✓ Can the research project establish that there are no sex/gender differences in the intervention/treatment/outcomes under study? ✓ Has the research project the intention to study sex/gender as confounder or interaction variable while testing study hypothesis? 		ain sex/gender differences in er study? at there are no sex/gender outcomes under study? on to study sex/gender as	Clearly state who is likely to benefit from the study. Detail the research questions so that it reflects the population under investigation (and avoid unspecified terms like 'adult' or 'patient'). Clear articulation of the type of research question being considered with respect to sex/gender. When investigating diverse individuals, make sure the research questions don't take the man/male as the 'standard' by which the woman/female is evaluated. Consider what output may be missing by failing to analyse sex/gender and intersecting

•	Questions / Subquestions	Input
	Can the research project establish sex/gender mechanism under study?	similarities in the factors. Use the terms sex and gender properly. Scientifically sound justification for proposing a single-sex/gender study, if
	Can the research project investigate about s pathways underlying a common phenotype?	sex/gender-specific applicable.
	☑ Is the study equally important to all populations?	

Study Design and Methods

Questions / Subquestions	Input
 Does the proposal explicitly and comprehensively explain how sex/gender issues will be handled in the design of the study? ✓ Does the methodology ensure that (possible) sex/gender differences will be investigated: that sex/gender differentiated data will be collected and analysed throughout the research cycle and will be part of the final publication? ✓ Do you have a Gender Advisory Committee to help guide the project? 	It might be advisable to explain why sex/gender is a research component. Consider which methods (qualitative and quantitative) are suited for examining the sex/gender dimensions of relevance to your project (Tannenbaum et al, 2019). Form an Advisory Committee to help guide the project, especially when a specific health issue or population is the focus of interest.

Questions / Subquestions	Input
 Has sex/gender been considered in the inclusion and exclusion criteria? Is it substantiated why women/female or men/male or diverse individuals are included (or excluded)? Are some populations inappropriately excluded on the basis of sex/gender by the inclusion/exclusion criteria? Do you identify the sex of the cells, tissues or animals being used? Are those factors that intersect with sex/gender considered in the inclusion/exclusion criteria? 	Consider the risk of stereotyping or excluding relevant groups. Consider how to involve diverse groups of research subjects/end- users in the project life-cycle to ensure inclusive solutions. Consider other factors that intersect with sex/gender that are of relevance to the research question (e.g. physiological, hormonal, anthropometric, biomechanical aspects; reproductive stages and cycles; or social environment factors, etc.).
 Has sex/gender been considered in the recruitment and retention strategies to ensure as broad as possible study participation? ✓ How will you guarantee equal numbers of sex/gender-diverse individuals? ✓ Is oversampling needed to ensure a sufficient number of sex/gender-diverse participants? (Vaughan, 2017). ✓ Has sex/gender been considered as a potential barrier to participation? 	Provide a clearly articulated plan to ensure the broadest possible range of participation. Design recruitment strategies to accommodate those with caregiving responsibilities, income challenges, etc. Be sensitive to culture and stigma associated with identity or health condition.

Questions / Subquestions	Input
 Do the data collection tools capture information relevant to sex/gender? Do the participant intake forms and other tools (e.g. questionnaires, interview guides) capture sex/gender-diverse identities? Is it possible to collect sex/gender disaggregated data? How can gender-diverse populations be identified without stereotyping and discrimination? Will the tools used to collect data include factors that interact with sex/gender? Have sex/gender relations between participant and researchers been considered? 	Consider how to collect information on diverse population (e.g. intersex, hermaphrodite, transgender, female/male, woman/man, etc.). Ensure language is inclusive of those whose gender identity is fluid or non-binary, and provide culturally and ethnically suitable options. Record information on factors that interact with sex/gender (e.g. age, life-style, socioeconomic status, hormonal status, anthropometric variables, etc.). Consider how gender relations between researchers and participants may impact data collection (Chapman et al. 2018). Consider a two-step method for collecting about sex and gender identity. Choice of questionnaires that are validated, not gender biased and are sensitive and responsive to sex/gender issues. Consider sex/gender interactions that can affect interview dynamics and the type of information divulged in qualitative studies. Describe the method for documenting/controlling the hormonal status of experimental female animals, if applicable. Identify the sex of the cells, tissues or animals being used, if applicable. When using an established dataset where there is no direct measure of sex/gender, the use of existing theoretical frameworks and empirical evidence can inform how we might interpret the data from a sex/gender perspective.

Analysis

Questions / Subquestions	Input
 Has sex/gender been considered in the calculation of sample size? ☑ Do sample size calculations show adequate power for testing hypotheses with respect to sex/gender differences? ☑ Is your sample appropriate to capture sex/gender-based factors? 	Sample size should be calculated to, at minimum, support sex disaggregated analysis. Studies too small to detect interaction can still report the main effects of the exposure or treatment by sex/gender; however, they cannot claim to have tested a sex/gender difference. In experimental studies, consider factorial designs to reduce the sample size required for sex-based
Does the project analyse the impact of sex/gender on study findings?	Consider If sex/gender is believed to have an independent effect on the outcome; if sex/gender may modify the direction or strength of the relationship between independent variables and the outcome; or if
As what kind of variable do you analyse sex/gender: as an independent variable, as an effect modifier or as a confounder, and why?	common methods for analysing sex/gender: stratifying by sex/gender; testing the significance of sex using modelling techniques, and testing sex/gender in
Is there a plan to investigate differences within any of the sex/gender identities?	different sex/gender groups. Examine how observed sex/gender differences
Are other relevant variables analysed with respect to sex/gender?	vary by interactive factors (e.g. age, life-style, socioeconomic status, hormonal status, anthropometric variables, genetic factors, etc. and gender
Will a possible interaction between sex and gender be part of the analysis?	norms, identities and relations). Overlooking confounding factors may result in overemphasising sex differences. When using existing data, consider the
Do qualitative analyses consider gendered language, gendered interactions and gendered themes?	cultural or institutional contexts in which the data were generated for potential sex/gender biases. In longitudinal studies, examine how observed sex/gender variations evolve over time.

Report & Knowledge Translating

Quest	ions / Subquestions	Input
Has se ☑	ex/gender been considered in the reporting? Is there a plan to go through the findings with a 'sex/gender lens'? Are you going to tailor the content of the message: the what?	Report all results: positive, negative, and inconclusive. Discuss the potential implications of sex/gender on the study results and analyses. Avoid overemphasising sex/gender differences. Interpret apparent sex/gender differences in the light of biological plausibility and social context and factors. Discuss if future research on this topic should pay attention to sex/gender issues. If only one sex/gender is included in the study, or if the results of the study are to be applied to only one sex/gender, the title and the abstract should specify this. Use gender sensitive language in all dissemination and communication activities Consider if the publishing medium have specific requirements for reporting gender
Has se plan?	ex/gender been considered in the knowledge translation	Consider how the information on sex/gender differences can be
V	Are different strategies been considered in the knowledge translation and impact plan in relation to diverse populations?	translated into preventive, diagnostic and therapeutic practice. Consider how the knowledge translation strategies are intended to maximize uptake by men, women, or gender-diverse people (e.g. will the content,
	Will you identify and reach the appropriate audience: the who?	messages or products vary by sex or gender). Determine if knowledge translation strategies should be customized for relevance to a range of
	Will you select the best medium for delivery of the message: the how?	populations.

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