



Sex/Gender Biases in Pain Research and Clinical Practice

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What are sex/gender biases in pain research and clinical practice?

- Sex/gender biases describe a tendency to (un)favor a group of individuals over another based on their sex/gender categorization^[1]. They reflect unjustified stereotypical preconceptions and prejudiced attitudes towards females/women, males/men, or gender-diverse people, that may lead to discriminatory actions. In patriarchal societies, such biases often reflect a tendency to favor males/men over females/women and gender-diverse people. They are culture-bound, contextual and intersect with other social positions and identities like age, ethnicity, sexual orientation and/or socioeconomic status.
- Sex/gender biases can be explicit (i.e., conscious) or implicit (i.e., unconscious). Explicit and implicit biases can be contradictory^[1]. For example, health care professionals or researchers may be explicitly committed to egalitarian values but implicitly hold gender stereotypical beliefs that shape their clinical judgements or their conceptual/methodological approaches, respectively.
- Two main types of sex/gender biases can be found in the health field^[2]:
 - Disregarding real or potentially relevant sex/gender differences under the assumption that females/women and males/

men are “the same” or have similar needs, e.g., when females/women are excluded from clinical trials under the assumption that findings may be generalizable from male/men samples.

- Assuming differences between the sexes/genders when similarities should be acknowledged, e.g., underassessing a woman’s pain compared to a man’s pain despite similar complaints and needs.

Are there sex/gender biases in pain research?

Sex biases in preclinical research:

- Preclinical studies of pain have been historically performed exclusively in male rodents (rats and mice), because of the fear that cycling gonadal hormones (i.e., estrogen and progesterone) would “complicate” things in females and lead to higher levels of variability in the data, necessitating the use of more animals and raising costs. This fear was shown to be unfounded in studies of pain^[3] and in biomedicine more generally. If anything, it is male rodents that feature higher levels of variability.
- A review of preclinical research published in the journal *Pain* from 1996–2005 showed that 79% of studies featured the exclusive use of male rats/mice, with an additional 3% of studies not even specifying the sex of the research subject^[3]. A similar review of *Pain* papers published in 2015 showed that nothing had changed over 20 years; again, 79% of studies used males only^[4].

- This use of male rodents to model conditions overwhelmingly affecting women is clearly unethical. In response, funding agencies around the world are instituting sex-as-a-biological-variable (SABV) mandates, i.e., policies recognizing sex as a variable to consider in research design, analysis and reporting. At the National Institutes of Health in the U.S., such a mandate was announced in 2014 and went into effect in 2016 [6].
- A review of preclinical papers published in *Pain* from 2015–2019 showed that by 2019, only 50% of papers used males only [6]. However, of 127 identified studies in which both sexes were tested, and the experimental manipulation was found to “work” in one sex but not the other, 72% of the time it worked in males but not females [6]. This suggests that the literature is now thoroughly biased such that findings in males generate hypotheses that are found to be true only in males. We are thus likely only at early stages of understanding female pain biology in animal models.

Sex/gender biases in clinical research:

- Most current pain theories do not integrate sex/gender factors and most pain research with humans does not analyze nor report sex/gender differences. A systematic review of publications in *Pain* from 2012–2021 concluded that less than 20% presented data disaggregated by sex [7].
- Although recent studies have a more balanced representation of the sexes [7], sampling bias can still be found. As females/women are more likely to seek support or attend pain clinics, there is an overrepresentation of females/women in clinical studies. Conversely, experimental studies have a higher proportion of males/men in their samples, as masculine-identifying individuals are more likely to volunteer for experimental pain studies [8].
- Assessment of demographic characteristics is still often unable to tap the diversity of the sexes and gender identities, going little beyond “female/woman, male/man, other”. Furthermore, gender-diverse populations are often lumped together or excluded from the data analysis, contributing to their marginalization in knowledge production [8].
- Dominant stereotypical sex/gender binary views still shape most research conceptual assumptions and designs [8]. For example, within-sex variations in biological factors (e.g., sex hormones) that may be linked to pain experiences have been less investigated. Also, research has mostly been focused on traditional western conceptions of femininity and masculinity, sometimes seen as mutually exclusive, instead of coexisting within all human beings. Indeed, little pain research has

explored the diversity and fluidity of femininities and masculinities, which are often shaped by situational cues and other social positions (e.g., age, culture, ethnicity, social class).

Are there sex/gender biases in clinical practice?

- Sex/gender biases can influence pain communication, assessment and treatment decisions occurring within clinical encounters. Many studies have shown sex/and gender biases in acute and chronic pain contexts.
- Regarding acute pain, various studies have been conducted in emergency medical settings and post-operative pain contexts:
 - A scoping review of articles published from 1960–2021 on biases in emergency medical services (EMS) in the US [9] concluded that although women are quicker in recognizing the signs and symptoms of acute coronary syndromes (such as chest pain), they wait longer to access the EMS system after seeking help compared to men. However, there was no clear consensus on sex/gender biases in prehospital interventions for acute coronary syndrome (e.g., ECG, aspirin or nitroglycerin) nor prehospital pain management.
 - A systematic review of studies on biases in post-operative pain and pain management published from 1992–2022 [10] showed women reported higher postoperative pain scores than men in most studies but received less pain medication than men in more than half the studies.
- Regarding chronic pain, a theory-driven review of quantitative and qualitative studies published from 2000–2015 on gender bias in pain care [11] showed that, compared to men, women more often:
 - must struggle for their pain to be seen as legitimate in the context of clinical encounters: their pain is more psychologized, mistrusted and judged as unreliable depending on their appearances (e.g., looking too good or not looking good enough).
 - receive more referrals to psychological treatments, less effective pain relief, fewer opioid analgesics, and more antidepressants.
- This review [11] also showed that pain-related gender norms – stereotypical expectations regarding how men and women are and should behave when in pain – may partially account for such sex/gender biases in clinical practices. Indeed, there are widely shared expectations across various cultures that, in public spaces such as the clinical encounter:
 - men with chronic pain are stoic, autonomous, in control, pain tolerant, avoid talking about pain and seeking help. They are also expected to prioritize paid work over household duties.

