Gender Bias in Clinical Research

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GENDER BIAS IN CLINICAL RESEARCH

Gender bias can be defined as stereotypes about people based on their gender or sex, and it can manifest in several different ways. For example, it can sometimes be seen in our language choices, such as *male* nurse or *female* doctor, or in our assumptions, such as women being more emotional or men being stoic. These biases can lead to inequities in how people treat others. This paper will explore what factors contribute to gender bias in clinical research and how these biases affect treatment outcomes for female patients in clinical settings.

Because gender bias in clinical research is complex, it should be explored through an interdisciplinary lens. The causes of these gender biases are rooted in disciplines such as history and public policy, while the effects impact disciplines such as medicine and public health. The interdisciplinary process allows us to bridge information between these disciplines to understand the problem of gender bias in clinical research holistically instead of in its parts. Interdisciplinarity also shows us how these disciplines connect and influence each other.

The factors contributing to these gender biases will be examined through the following disciplines: history, law and public policy, medicine, and public health.

Through the disciplinary lens of history, we may examine the events that set precedence for gender bias in clinical research. These historical events influenced how lawmakers wrote legislation and how public policies were interpreted in an effort to protect women. Public policy directly impacts how clinical research should be carried out and who should be included. Lastly, through the disciplinary lenses of medicine and public health, we see the impacts that gender bias has had on women and their health.

History

Gender bias in medicine and medical research reaches as far back as the Ancient Greeks. Historically, female anatomy was considered an immature version of male anatomy (Lippi et al., 2020). For instance, early medical academics believed that ovaries were inverted testicles, and anatomical knowledge was "limited to [women's] reproductive capabilities" (Lippi et al., 2020). Because of this idea that female bodies are simply immature or imperfect versions of the male body, male bodies were considered the norm and "representative of the human species" (Merone et al., 2022). Therefore, data collected from clinical studies with male participants have been generalized to female patients (Merone et al., 2022).

Aside from the idea that clinical information from males can be generalized to females, females have been historically excluded from clinical research for several reasons. Reasons include male researchers preferring male subjects and, most notably, the concerns that clinical research could cause infertility issues or harm pregnancies (Merone et al., 2021, 2022). For example, in the 1950s, people thought a sedative called Thalidomide was safe because it had proven difficult to complete suicide using the drug (Dally, 1998). Then, in the 1960s, women were provided with the drug to manage morning sickness in early pregnancy (Dally, 1998). Many of the unborn children of these women had congenital malformations due to the Thalidomide (Dally, 1998). The backlash from this tragedy resulted in a change in public policy in the 1970s.

Public Policy and Law

In 1977, the Thalidomide scandal caused the Food and Drug Administration (FDA) to release strict guidelines that excluded women of reproductive potential from early phases of clinical trials (The US Department of Health and Human Services, n.d.). This guideline was

implemented broadly to exclude women using birth control, women with infertile partners, and those without partners simply because they *could become* pregnant (the US Department of Health and Human Services, n.d.). Historically, men have been more interested in preserving a female's ability to have children rather than her health (Lippi et al., 2020). Then, thirty years ago, Congress passed the NIH Revitalization Act of 1993, which required the inclusion of women and marginalized people in clinical research. The NIH Revitalization Act of 1993 reversed the 1977 guideline that excluded women with reproductive potential from clinical research (Institute of Medicine et al., 1994).

The European Union passed similar recommendations as late as March 2011 to reduce health inequalities (EU Parliament, n.d.). In these guidelines, The EU Parliament (n.d.) recommends promoting investments in pharmaceutical research for diseases mostly affecting women "with reference to all phases of [a woman's] life," including "the health status of women" and "gender impact assessments" in public policy, and accounting for "social determinants in health and lifestyle risk factors."

According to a study conducted by Mirin (2021), gender bias in clinical research goes beyond the underrepresentation of women in clinical studies. Gender bias in clinical research includes disparities in funding allocation to diseases mostly affecting women and discrimination in awarding women researchers with research grants (Mirin, 2021).

Medicine and Public Health

According to The Institute of Medicine et al. (1999), researchers often prefer male participants in clinical studies because men do not have the hormonal fluctuations that women

do. The Institute of Medicine et al. (1999) goes on to say that hormonal fluctuations and cycles "confound or confuse research results." This phenomenon is *not* isolated to human subjects. A study carried out in 2019 found that in the past, scientists preferred male mice to female mice in early clinical research for some of the following reasons: the hormonal fluctuations in the females, the spending of funding used to house the sexes separately, and "increased variability around a combined mean" that "reduces statistical power and slows progress" (Beery, 2019). In other words, if scientists decide to use both sexes of mice, then they are concerned that if they don't separate out the groups (sexes), then the combined data would have increased variation. Then, if they were to separate them into different groups based on sex, they would have fewer samples per group, which would decrease the statistical power of the data. If scientists continue to study only males, then the results will only apply to males until proven otherwise.

Monitoring drug reactions in women may be difficult because of how hormones like estrogen and progesterone can affect the metabolism of a drug (Lippi et al., 2020). Lippi et al. (2020) assert that women may have severe adverse reactions to drugs for the following reasons: women are vulnerable to drug-induced cardiac issues and the reactions between hormonal contraceptives and other medications. There is not enough data from female participants in clinical trials (Lippi et al., 2020; Merone et al., 2022; Beery, 2019). "It is not possible to determine whether a drug is effective and safe in women if there are no relevant clinical trials" (Lippi et al., 2020).

The Effects of Gender Bias

A US-based cross-sectional study conducted by Steinberg et al. (2021) found that in the years 2000-2020, "sex bias in clinical trial enrollment persists within medical specialties." So,

fewer participants of one sex or the other were enrolled in clinical research in certain specialties, causing sex bias. For example, Steinberg et al. (2021) note women are underrepresented in specialties like “oncology, neurology, immunology, urology, cardiology, and hematology.” Steinberg et al. (2021) assert that this is a concerning finding because cancer and cardiovascular disease are the leading causes of death in women in the United States meaning that women are not adequately represented in clinical research on diseases that could be fatal to them.

In 2022, Merone and colleagues conducted a meta-analysis using literature found across several databases spanning the years 2009-2019. This meta-analysis found that only 37% of participants represented females across studies, and “only three studies noted limitations and lack of diversity.” In other words, there was an underrepresentation of females participating across all the studies included in the meta-analysis, but only three of those studies noted that a lack of diversity was a problem. This is an issue because if the differences between sexes are not studied, then claims of safety or efficacy in clinical treatments cannot be generalized to all sexes. Also, the fact that these studies did not state that lack of diversity was a limitation suggests that the researchers did not view it as a problem. If studies continue to omit this limitation, then future researchers may continue down the same path, which may perpetuate the sex bias in clinical research.

The effects of sex bias may manifest in a clinical setting in several ways. For instance, because women are seen as overly emotional and dramatic, their symptoms are more likely to be downplayed (Merone et al., 2021; Ng et al., 2024). Women must prove they are “as unwell as their male counterparts” (Merone et al., 2022). This attitude towards women has made them distrustful of medical providers because those providers may label them as depressed or anxious instead of addressing their symptoms (Merone et al., 2022). Merone et al. (2022) assert that

"women wait longer for diagnosis, pain relief, and are more likely to be misdiagnosed or discharged during a serious medical event." For example, a review by Cabral and Dillender (2023) notes a connection between sex and treatment. The colleagues go on to cite that females received less aggressive treatments for cardiac conditions and were less likely to receive preventative care for blood clots when admitted to the hospital (Cabral & Dillender, 2023).

"Lack of research evidence from female patients may result in delay in treatment; applying inappropriate, ineffective, or harmful treatments; or the withholding of effective treatments" (Merone et al., 2022). In other words, women may experience a delay in treatment because clinical research has not examined how women experience a disease (Merone et al., 2021) or how the treatments affect women (Lippi et al., 2020).

Sex is an important factor when treating people because women and men do not always experience illness and disease the same, and they often metabolize medications differently (Merone et al., 2021). Merone and colleagues (2022) put it most succinctly, "Clinical research informs the development of clinical guidelines and clinical guidelines directly impact the lives of patients."

Conflicts and Common Ground

During the research process, conflicts have been identified in disciplinary insights. The biggest conflict found was between the studies conducted by Steinberg et al. and Merone et al. Steinberg et al. (2021) note in the years 2000-2020, female and male representation in clinical studies may be similar in all clinical trials. Merone et al. (2022) found that only 37% of participants represented women across the studies in their meta-analysis. On the surface, these

studies appear to contradict each other. However, upon closer examination, Merone et al. examined English-only literature from several databases (e.g., PubMed, PsycINFO). Researchers found literature using limited search words like "sex, gender, sexism, and aesthetic research" (Merone et al., 2022). Merone and colleagues also note they used strict inclusion and exclusion criteria and described a study as misogynistic if it mentioned female participants' aesthetics (Merone et al., 2022). Because of limited search words, strict criteria, and their use of misogyny, Merone and colleagues may not have collected all relevant literature, meaning their data may be skewed. Steinberg and colleagues (2021) analyzed all clinical studies from the United States from the years 2000-2020 registered with ClinicalTrials.gov. Then, they "compared the enrollment data with the 2016 Global Burden of Disease database" to examine the disparities between participant enrollment and the severity of disease processes (Steinberg et al., 2021). These two studies, while similar, look at different data. Merone et al. examine 17 articles published in English from around the world. Steinberg et al. analyzed thousands of clinical studies from the United States registered with ClinicalTrials.gov. Both studies note that clinical research suffers from sex biases and that researchers should find ways to mitigate these issues to benefit the minorities in their studies.

The next conflict is a finding by Merone et al. (2022). The finding states that there was a higher representation of females in diseases "perceived to affect women more," like hypertension and stroke. However, a study carried out by Mirin (2021) categorizes hypertension and stroke as gender-neutral diseases. This is a conflict because Mirin's study finds that the disease processes that Merone et al. claim are "perceived to affect women more" are gender-neutral. This may not be a true conflict because Merone et al. note these diseases are "*perceived* to affect women more." According to Connelly et al. (2022), men are more likely to develop hypertension;

however, women have more significant complications. Merone et al. may be referring to the severity of the disease in females as opposed to the prevalence. Connelly et al. (2022) also find that by age 60, the prevalence of the disease is similar between the sexes, so in that regard, the disease could be seen as gender-neutral.

Another conflict that was found was that studies may underrepresent, adequately represent, or overrepresent a certain group of people depending on the disease process. For instance, Merone et al. (2022) note that diseases "perceived to affect women more" may adequately or even overrepresent females in a study. However, a study conducted by Steinberg et al. (2021) found that men were underrepresented in "8 disease categories" like musculoskeletal diseases and trauma. Men are underrepresented in categories that are more likely to be female-dominated, like breast cancer (Mirin, 2021). Men are also underrepresented in categories like trauma, but this may be because trauma is "associated with a higher mortality rate in male populations" (Steinberger et al., 2021). If this is the case, then men less often survive trauma and, therefore, cannot be included in medical research about treatment outcomes of living participants if they are deceased, which may cause a sex bias against men.

The last conflict was found in a 2019 study conducted by Beery. Beery (2019) found that female mice were *not* more variable [due to hormones] than male mice, but rather, the opposite. "Male mice appeared to exhibit slightly, but significantly, greater mean variability than female mice" (Beery, 2019). This conflicts with the oft given reason for using only male mice, that female mice have greater variability (Beery, 2019).

Common ground can be drawn from the idea that all gender bias in clinical research has profound effects that could harm the groups they discriminate against. It can also be drawn from

the fact that males and females have their own hormones and experience disease differently, which should be considered when conducting research.

Conclusion

Scientists have been doing clinical research for a long time, with ample opportunities to include female participants. As demonstrated throughout this paper, historically, females have been excluded or underrepresented in clinical research for reasons like the early idea that females were immature males, assumptions that hormones would confound results, and the fear of causing infertility in women. Several studies cited above show connections between gender bias in clinical research and adverse effects on treatment in women. The only way to study and holistically resolve this issue is through interdisciplinarity. Disciplines like medicine, public health, history, and public policy must work together to combat gender bias in clinical research so women may be diagnosed correctly, have access to effective treatments, and have the ability to use robust empirical data in order to make appropriate healthcare decisions for themselves.

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