Disparities in Female Hormone Research and Therapy

A Research Paper submitted to the Department of Engineering and Society

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

Samiyah Syeda

Spring 2024

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Advisor

Pedro A. P. Francisco, Department of Engineering and Society

STS Research Paper

Introduction

The underrepresentation of women as research participants has exacerbated the long-standing marginalization of women's health concerns in medical research. Whether deliberate or not, this exclusion has a significant impact on our knowledge of hormone imbalances and how they affect women's health. There are large discrepancies in diagnosis and healthcare effectiveness as a result of these differences, which make it difficult to conduct a thorough investigation of gender-specific symptoms, treatment responses, and outcomes (Ajayi & Akhigbe, 2020). This paper seeks to illuminate the significant ramifications of gender differences in research participation by looking at historical patterns, actual data, and the intricate web of players influencing research practices. In the end, it emphasizes how critical it is to develop inclusive and equitable strategies in order to improve women's healthcare and address the persistent gaps in diagnosis, treatment, and health outcomes.

Background

The underrepresentation of women in clinical research has been an issue throughout history. Despite the recognition of this problem, efforts to rectify it have been slow and incomplete. The safety and effectiveness of medical treatment begin at the start of research and clinical trials. It depends on how well-planned these trials are and how well the results are interpreted. Therefore, the population of subjects in these trials should be reflective of the general population that is affected by the disease or condition and whom the treatment is intended for. This is especially important when there is a lack of research and data on the condition the study is focusing on to protect vulnerable populations that are at higher risk for

complications from the potential treatment. Despite this, for conditions that affect both men and women, it has been shown that women, particularly women of color, have been severely underrepresented in clinical trials.

In the late 1950s and early 1960s, widespread use of thalidomide, a drug intended as a sedative and anti-nausea medication, was found to cause severe birth defects when taken by pregnant women. In an effort intended to protect women, in 1977, the US Food and Drug Administration (FDA) recommended that women of childbearing age should not be included in future clinical research to mitigate potential risks during pregnancy (The Office of Research on Women's Health, n.d.). This recommendation perpetuated gender disparities in research and fueled the exclusion of women from research studies for several years. Some estimates suggest that women only comprised 20-30% of participants in clinical trials as a result which led to the passing of the NIH Revitalization Act of 1993 (The Office of Research on Women's Health, n.d.). This legislation required the inclusion of women and minorities in clinical research funded by the National Institutes of Health (NIH) and mandated the analysis of research results by sex and minority status to ensure that findings were applicable to diverse populations.

There has been a reported increase in the proportion of women enrolled in NIH-funded clinical trials following the implementation of the Revitalization Act of 1993. Studies estimate that the representation of women in NIH-funded cardiovascular clinical trials increased from 22% before the Act to 38% after its implementation as well as the representation of women in NIH-funded cancer clinical trials from 38% before the Act to 48% after its enactment. Despite these upward trends of representation, barriers to participation such as structural barriers, logistical challenges, and cultural factors continue to hinder women's participation in clinical trials. These barriers may include a lack of awareness about research opportunities, difficulty

accessing trial sites, caregiving responsibilities, socioeconomic constraints, and language barriers. In addition, some clinical trials may still employ exclusion criteria that disproportionately affect women, such as age restrictions or pregnancy, and studies often fail to disaggregate data by sex or gender, making it difficult to identify sex-based differences in treatment outcomes or adverse effects (Pavlidi et al., 2021). Disparities in research participation are further compounded by factors such as race, ethnicity, socioeconomic status, sexual orientation, and disability status.

The consequences of excluding women from research are far-reaching and profound, particularly concerning conditions that disproportionately affect them. Women are at a higher risk of a large number of medical issues. For example, women make up two-thirds of people with Alzheimer's disease and are three times more likely to have a fatal heart attack than men (Fairweather & Rose, 2004). 78% of those affected by autoimmune diseases are women and rheumatoid arthritis, multiple sclerosis, and chronic pain conditions are just a few examples of health issues that exhibit significant sex-based differences in prevalence, manifestation, and treatment response (Fairweather & Rose, 2004). Yet, the lack of female representation in research has hindered progress in understanding and addressing these conditions, leading to suboptimal outcomes for women.

When the vital impact of sex and gender is not taken into consideration, it can lead to catastrophic gaps in research. Excluding women from clinical trials can lead to a limited understanding of how diseases manifest differently in women compared to men resulting in women being misdiagnosed or receiving ineffective treatments that were developed based on research conducted primarily on men. This can exacerbate health disparities and worsen health outcomes eventually contributing to unnecessary suffering and mortality among women.

According to the American Cancer Society, the five-year survival rate for women diagnosed with lung cancer is significantly lower than that for men, and this is just one of the many conditions in which women are disproportionately being impacted (American Cancer Society, 2023). Additionally, women experience health conditions that are unique to their sex, such as pregnancy-related complications, autoimmune diseases, and gynecological disorders. Excluding women from research studies therefore limits our understanding of the underlying mechanisms, risk factors, and optimal treatments for these conditions, hindering progress in women's healthcare and contributing to disparities in diagnosis and treatment. Studies also show that women are less likely than men to receive advanced and therapeutic intervention, furthering the gaps in existing disparities in healthcare access and outcomes (Bierer et al., 2022).

Methodology

In order to investigate how disparities in women's research contribute to gaps in understanding the impact of hormonal imbalances the following methodology was used. First, a systematic review and meta-analysis of randomized controlled trials (RCTs) across various medical disciplines were conducted to quantify the representation of women as research participants. This involved screening studies based on predefined inclusion criteria to determine the proportion of female participants in RCTs. Additionally, qualitative analyses of historical and contemporary literature were analyzed to explore the rationale behind excluding women from research studies, including examining regulatory guidelines and institutional policies. Case studies and empirical evidence were also analyzed to assess the impact of underrepresentation on healthcare outcomes, with a focus on identifying disparities in diagnosis and treatment efficacy among women.

The Actor-Network Theory (ANT) provides a lens through which the various actors, both human and non-human, interact within networks to shape the understanding of how the gaps in understanding hormonal imbalances and women's health issues come to be (Cresswell et al., 2010). The primary actors in this network are the regulatory bodies and funding agencies, FDA and NIH, due to their level of influence as the lawmakers that govern the requirements that clinical researchers have to reach and as the main financial providers that approve the projects before funding them.

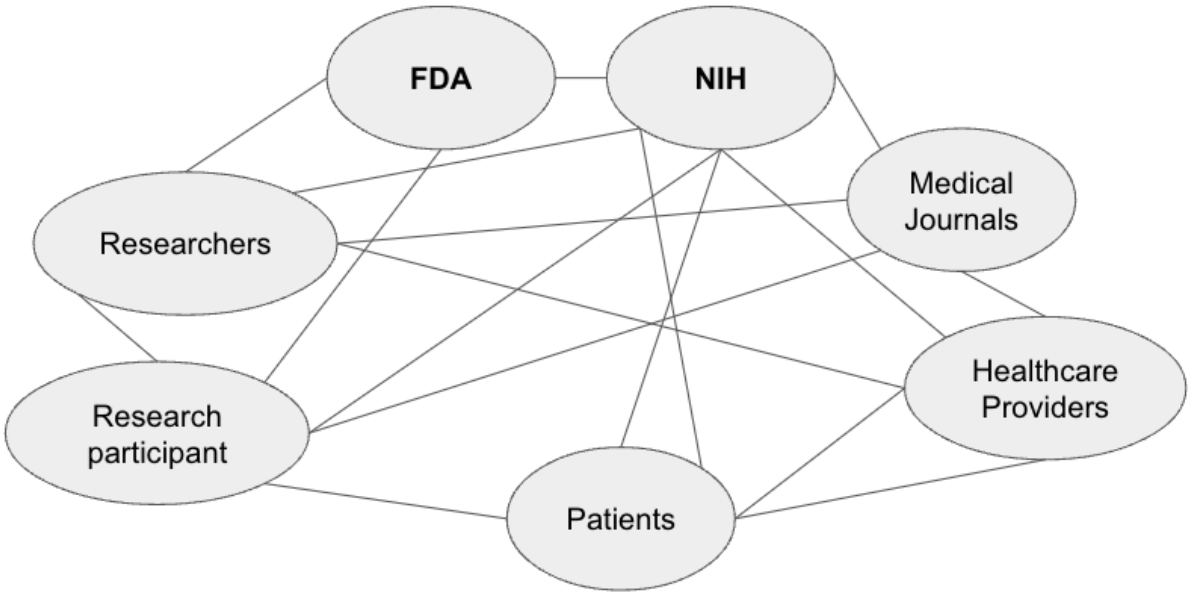

Figure 1. Actor-network theory diagram showing the system of actors involved in the clinical research process. The FDA and the NIH are placed at the top as the primary actors.

The FDA is a regulatory agency of the United States Department of Health and Human Services (HHS), responsible for promoting public health by regulating the approval, marketing, and labeling of drugs, including hormone therapies, ensuring that they meet safety and efficacy standards (Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the

Inclusion of Women in Clinical Studies et al., 1999). Any hormone-related research findings that may have implications for drug development, treatment guidelines, or healthcare practices are subject to FDA oversight and regulation. It also oversees the conduct of clinical trials for investigational drugs to ensure that they adhere to ethical and regulatory standards ((Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies et al., 1999). This includes reviewing study protocols, monitoring participant safety, and evaluating trial results submitted as part of the drug approval process. As mentioned, the FDA was responsible for the 1977 recommendation of excluding women from clinical trials to mitigate risks during pregnancy. This led to studies being dominated by male participants for years leading to severe gaps in the understanding of female research.

The NIH is the primary agency of the United States government responsible for biomedical and public health research. It provides funding and support for biomedical and health-related research, including studies focused on hormones, hormonal imbalances, and women's health (Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies et al., 1999). Researchers conducting studies related to women's hormone research may apply for NIH grants to support their research activities, covering expenses such as equipment and research materials. As mentioned, the NIH was responsible for the Revitalization Act of 1993 which required the inclusion of women and minorities in clinical research they funded. These two agencies play complementary roles in the regulation of biomedical research and work together to support research that addresses critical gaps in knowledge and informs regulatory decision-making. They have to power to fund research that has an inclusive population of participants to properly reflect the target population who will receive treatment or benefit from the research.

Likewise, researchers play a huge role within this framework. They are the clinicians and scientists who are involved in the designing, conducting, and publishing of their own research. They investigate the underlying mechanisms, risk factors, and consequences of their research, and have the most knowledge when it comes to the potential negative impacts of excluding certain groups and demographics from their studies. They have control over who participates in their clinical research and therefore have the potential to publish studies that are reflective of the population. They undergo FDA regulations and must comply with the standards of research set in place. They also mentor and train other researchers and clinicians and therefore have the capacity to teach the importance of inclusivity and practices to prevent gaps within female research.

Medical providers including physicians and nurses play a critical role in this network as well. They integrate and apply research findings from published studies into their clinical practice to inform treatment decisions. They rely on evidence-based guidelines, clinical trials, and expert recommendations to guide their approach to issues like hormonal imbalances, ensuring that patients receive the most effective and appropriate care based on the latest scientific evidence. Medical providers also contribute to data collection efforts related to women's research by documenting patient encounters, medical histories, treatment outcomes, and adverse events. They play a crucial role in reporting data to research registries, clinical trial databases, and surveillance systems, helping to build evidence and monitor trends in hormonal health over time.

Medical journals and publications serve as crucial actors in the dissemination, validation, and advancement of knowledge in women's hormone research and related fields. They are the source of findings that researchers obtain, where they present their research methods, results, and

conclusions to the broader scientific community. Through publication and dissemination, researchers contribute to the accumulation of scientific knowledge, stimulate further research inquiry, and inform clinical practice, policy development, and public health initiatives.

Patients are integral actors in the network and provide firsthand experience and insight into their symptoms, experiences, and concerns that can be the consequence of exclusion and gender misrepresentation areas of research. Patients provide feedback on their experiences with treatment modalities, healthcare providers, and healthcare systems, helping to identify gaps, barriers, and opportunities for improvement in the delivery of hormone-related care.

Literature review

The comprehensive review of existing literature shows how actors such as the FDA and medical journals contribute to the network of factors involved in the clinical research process and the creation of gaps in understanding of women's health issues. The Actor-Network Theory helps describe the network of the actors and how their influence and reach impact the level of representation of women in health.

A paper published in 2022 on the underrepresentation of women in randomized controlled trials reviews randomized controlled trials (RCTs) across various medical disciplines to assess the representation of women as participants. On completion of an extensive meta-analysis, it found that women constitute only 38% of participants in RCTs, indicating a significant underrepresentation compared to their proportion in the general population (Daitch et al.). It also found that certain medical specialties experience higher levels of underrepresentation than others. For example, trials in cardiology and surgery tend to have lower female participation rates, sometimes below 30% compared to trials in areas like obstetrics and gynecology which

often exceed 50%, which translates into higher mortality rates for these specialties with the lower percentages (Daitch et al.). These clinical trials can compromise the generalizability and validity of research findings if they inadequately represent women, leading to further disparities in healthcare outcomes.

Besides the FDA's recommendation to exclude women from studies to protect them from potential pregnancy risk, a huge reason why women are historically excluded from studies is due to the assumption that the hormone cycle in females causes behavioral variation that could lead to unreliable results. A huge branch of biomedical research uses mice as test subjects, due to the fact that they share a significant portion of their genome with humans and can be manipulated to mimic human genetic mutations associated with specific diseases. They are relatively inexpensive to purchase and maintain compared to other animal models, such as primates.

Even within animal research, researchers have preferentially used male mice in experiments. A study from 2011 reported that within neuroscience specifically, there were over five times as many studies using male mice than those using female mice (Daitch et al.). This trend has led to a poor understanding of the female brain and has over time contributed to a misdiagnosis of neurological conditions in women. It has also contributed to the development of drugs for women that have significantly more side effects for women. This is all due to a lack of studies including female mice due to assumptions about the variability of results as a result of the hormonal cycle present in females. Female mice go through the estrous cycle, which refers to the reproductive cycle in rodents that is similar to the menstrual cycle in humans (Ajayi and Akhigbe).

A Harvard Medical School Journal published in 2023 challenged the assumption that the hormone cycle in female mice causes behavioral variation in research. Researchers studied

genetically identical male and female mice and placed them in a 5-gallon bucket for 20 minutes each and used a camera to record their movements and behaviors (Levy et al., 2023). The female mice were swabbed and underwent vaginal cytology, a procedure that is used to determine the estrous cycle stage they were in. They repeated this bucket test multiple times with each individual mouse and analyzed the videos to break down the specific movements of each.

The researchers found that the specific estrous cycle stage that the mice were in had very little effect on the behavior in female mice. They also found that despite the hormonal fluctuations, female mice exhibited much more stable behavior than male mice (Levy et al.). They concluded that although male mice are preferred by the majority of researchers due to the assumption that male mice can be used to make reliable comparisons across experiments, it's actually female mice that exhibit more stable behavior and therefore the case for excluding female mice is completely invalid. Based on their findings, the lab eventually switched their male mice groups to female groups, especially for the experiments that involved circular open-field testing (Levy et al.).

Ultimately, this case has broader implications beyond basic neuroscience research. It raises questions about the generalizability of findings from animal studies to humans, particularly regarding the impact of hormonal fluctuations on behavior and cognition. It also underscores the importance of considering individual differences and variability in research design and interpretation, especially in studies involving hormonal factors and behavioral outcomes. It suggests that factors beyond hormonal fluctuations, such as genetic differences, environmental influences, and individual temperament, play a substantial role in shaping mouse behavior and highlight the complexity of behavior and the limitations of assuming a direct link between hormonal status and behavior in female mice. By recognizing the importance of

individual variation, researchers can better understand the underlying mechanisms driving behavior and develop more nuanced approaches to studying hormonal influences on brain function and behavior.

A study released by the Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies journal highlights the health consequences that women as a population suffer from as a result of their exclusion from or underrepresentation in clinical studies (Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies et al., 1999). There currently exists extensive deficits in information relating to the prevention and treatment of conditions associated with the female reproductive organs and conditions related to female aging, including menopause. There are also deficits in conditions that affect both sexes, including cardiovascular disease and lung cancer, which are both leading causes of death in both men and women. The negative health consequences to women as a result of these deficits are reflected in morbidity and mortality as well as diagnosis and treatment patterns (Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies et al., 1999). Women have been shown to consistently experience more frequent adverse effects and poorer outcomes when given treatments developed and tested from studies from men, which can be attributed to the failure to study the impact of hormone interactions in drug trials. This was the case with the development and administration of antidepressants, which have been shown to raise issues with varying levels of estrogen during the menstrual cycle, pregnancy, postpartum, perimenopause, and menopause (Pavlidi et al., 2021). It has been shown that in women, there is a higher level of mortality in procedures like coronary artery bypass surgery and in conditions like ischemic heart disease. The study shows that these gaps in information result in a shift in the distribution of

risks to women, allowing them to receive treatment that hasn't been properly studied in female populations. These risks can be mitigated by simply increasing the number of female participants in studies.

Relatively few studies have been conducted on conditions that severely impact women specifically, including ovarian and endometrial cancer as well as preeclampsia, which is a major cause of maternal morbidity and mortality (Institute of Medicine (US) Committee on Women's Health Research, 2010). Despite women being disproportionately affected by autoimmune diseases, making up 78% of the population, there is little to no information on how women specifically are impacted (Fairweather & Rose, 2004). Sex differences are rarely studied when researching the prevention of Alzheimer's disease, obesity, and diabetes, all conditions that disproportionately affect women. Despite the fact that females are at a higher risk for developing all these conditions, factors such as biological differences and how the physical and social environment of the population affect the development of these conditions are rarely researched. There also is a desperate need to study how these factors result in health disparities in marginalized populations.

Results/Discussion

Disparities in women's research contribute to gaps in understanding the impact of hormonal imbalances by hindering the comprehensive study of gender-specific manifestations, treatment responses, and outcomes. The investigation into disparities in women's research provides an understanding of the profound consequences of underrepresentation on our comprehension of hormonal imbalances and other health conditions. Analyzing historical trends,

empirical data, and case studies sheds light on the intricate dynamics and far-reaching implications of gender disparities in research participation.

The Actor-Network Theory offers valuable insights into the intricate network of actors influencing women's health research. Regulatory bodies such as the FDA and NIH wield significant influence by setting research standards and allocating funding. Researchers, including scientists and clinicians, play a critical role in generating and disseminating knowledge through rigorous study design and publication. Medical providers translate research findings into clinical practice, while medical journals serve as platforms for disseminating scholarly work. Patients contribute essential perspectives by sharing their lived experiences, shaping research priorities, and advocating for inclusivity.

Men and women exhibit notable differences in their anatomical, physiological, and hormonal makeup, leading to variations in disease manifestation and progression. Hormonal fluctuations, such as those experienced during menstruation, pregnancy, and menopause in women, can significantly influence the onset and progression of certain conditions like migraines, mood disorders, and autoimmune diseases. Genetic variances also contribute to differences in disease susceptibility and presentation, with certain genetic factors predisposing individuals to specific diseases or influencing their response to treatments. For instance, women are more prone to autoimmune diseases like lupus and rheumatoid arthritis, influenced by genetic predispositions and hormonal factors. This is why it is essential to include women in clinical trials, as results for one gender cannot necessarily be applied the same way to the other.

Case studies provide tangible examples of how gender disparities perpetuate gaps in understanding and healthcare outcomes. Biases towards using male subjects in research, such as in neuroscience studies utilizing male mice, lead to a limited understanding of the female

experience and contribute to misdiagnosis and ineffective treatments. Excluding women from clinical trials exacerbates these issues, hindering our ability to understand how diseases manifest differently in women compared to men.

The reasoning behind the exclusion of female subjects, whether due to the misunderstanding of the impact of hormones on the variability and reliability of results or due to a need to overprotect potentially pregnant women from adverse effects, has shown to have little to no scientific backing and have actually proven to counterintuitive. The assumption that hormone cycles present in women have a huge impact on the behavioral variability of results wasn't supported by research, which shows that spontaneous behavior in female mice is primarily driven by individual variation rather than being strictly tied to their hormonal cycle stage.

Empirical evidence underscores the detrimental effects of excluding women from medical research. Studies consistently reveal that women face higher risks of various health conditions, yet their underrepresentation impedes our ability to understand and address these issues effectively. It compromises the generalizability and validity of research findings, as findings derived primarily from male participants may not accurately reflect the responses and outcomes experienced by women. This limitation in research inclusivity hinders our capacity to develop tailored and effective interventions for women's health conditions. By inadequately capturing the nuances of how diseases manifest and progress in women, research findings may fail to inform evidence-based practices that cater to the unique healthcare needs of female patients, allowing women to receive suboptimal or inappropriate treatments, leading to poorer health outcomes and exacerbating existing health disparities between genders. For example,

women undergoing coronary artery bypass surgery have a higher mortality rate than men, reflecting the impact of gender biases in research and clinical practice.

Conclusion

In conclusion, including women in medical research to address the pervasive gaps in understanding hormonal imbalances and their impact on women's health should be of utmost importance to not all actors involved in the interconnected web of clinical research. Through an examination of historical trends, empirical evidence, and the complex network of actors shaping research practices, it is evident that the exclusion of women from clinical trials and studies has profound consequences. By inadequately representing women in research, the generalizability and validity of findings are compromised, leading to disparities in healthcare outcomes and exacerbating existing health inequities.

Moving forward, it is imperative for researchers, policymakers, and funding agencies to prioritize inclusivity and diversity in medical research. This requires efforts to overcome structural barriers and cultural biases that hinder women's participation in clinical trials. Strategies such as targeted recruitment efforts and policy interventions can help enhance the representation of women in research studies across various medical disciplines.

Furthermore, there is a pressing need for greater transparency and accountability in reporting sex-disaggregated data and analyzing research findings by gender. This ensures that research outcomes are applicable to diverse populations and contribute to the development of evidence-based practices tailored to the unique healthcare needs of women. Fostering interdisciplinary collaborations and knowledge exchange between researchers, healthcare providers, and policymakers is essential for advancing women's health research. This can lead to

comprehensive insights into the biological and environmental factors influencing women's health outcomes.

Ultimately, addressing disparities in women's research requires a multifaceted approach that prioritizes equity, inclusivity, and collaboration. By acknowledging and rectifying historical biases and systemic barriers, we can pave the way for more equitable and effective healthcare practices that benefit all individuals, regardless of gender. It is vital to have continued efforts to bridge the gender gap in medical research and ensure that women's health remains a priority in scientific inquiry and healthcare delivery.

Works Cited

Ajayi, A. F., & Akhigbe, R. E. (2020). Staging of the estrous cycle and induction of estrus in experimental rodents: An update. Fertility Research and Practice, 6(5), Article 5. https://doi.org/10.1186/s40738-020-00074-3

American Cancer Society. (2023). Lung cancer survival rates | 5-year survival rates for lung cancer. Retrieved from https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html

Bierer, B. E., White, S. A., Barnes, M., & Kornetsky, S. (2022). Advancing the inclusion of underrepresented women in clinical research. Cell Reports Medicine, 3(4), Article 100553. https://doi.org/10.1016/j.xcrm.2022.100553

Cresswell, K. M., Worth, A., & Sheikh, A. (2010). Actor-network theory and its role in understanding the implementation of information technology developments in healthcare. BMC Medical Informatics and Decision Making, 10(1), Article 67. https://doi.org/10.1186/1472-6947-10-67

Daitch, V., Zhu, X., & Tarasoff-Conway, J. M. (2022). Underrepresentation of women in randomized controlled trials: A systematic review and meta-analysis. Trials, 23(1), Article 70. https://doi.org/10.1186/s13063-022-07004-2

Fairweather, D., & Rose, N. R. (2004). Women and autoimmune diseases. Emerging Infectious Diseases, 10(11), 2005-2011. https://doi.org/10.3201/eid1011.040367

gazetteterrymurphy. (2023, March 8). Study confirms why we need female mice in neuroscience research. Harvard Gazette. Retrieved from https://news.harvard.edu/gazette/story/2023/03/study-confirms-why-we-need-female-mice-in-neuroscience-research/

Institute of Medicine (US) Committee on Women's Health Research. (2010). Women's health research: Progress, pitfalls, and promise. PubMed. National Academies Press (US). https://pubmed.ncbi.nlm.nih.gov/24983027/

Levy, D. R., Arzua, T., & Kimchi, T. (2023). Mouse spontaneous behavior reflects individual variation rather than estrous state. Current Biology, 33(7). https://doi.org/10.1016/j.cub.2023.02.035

Pavlidi, P., Giaginis, C., & Sfiniadakis, I. (2021). Antidepressants' effects on testosterone and estrogens: What do we know? European Journal of Pharmacology, 899, 173998. https://doi.org/10.1016/j.ejphar.2021.173998

Institute of Medicine (US) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies, et al. (1999). Health consequences of exclusion or underrepresentation of women in clinical studies (I). National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK236583/

The Office of Research on Women's Health. (n.d.). The office of research on women's health: A history of fostering diversity and inclusion in biomedical research. Office of Research on Women's Health. Retrieved from https://orwh.od.nih.gov/about/mission-history/office-research-womens-health-history-fostering-diversity-and-inclusion