Inequality in Medicine: A Call to Analyze by Sex

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Abstract. Sexual dimorphism, the differences between males and females, widely exists in various perspectives of physiology. However, for a long period, such differences were not properly addressed in both biomedical research and clinical trials. The ignorance of women’s health led to many tragedies. With more female scientists and doctors and more solid scientific bases regarding the existence of sexual dimorphism, the inclusion of females has become the center of mainstream medicine. However, with the underrepresentation of females in the biomedical field, women currently still have a significantly higher likelihood to suffer from various aversive drug reactions and bear a lower possibility to have effective treatments. To make difference, people inside and outside the biological fields need to call for awareness and advocacy of sex-based research practices continuously. Balanced sample size from both sexes and sex-specific analyses should be the standard requirements for future research. At the same time, they should be used to recalibrate the medication and health guides that were developed from male-only research. The scientific understanding of health and diseases for both sexes will be clear to facilitate the reality of personalized medicine.

1 Introduction

The differences between sexes and genders can affect health differently. While sex and gender are two different concepts, they are often associated. One obvious difference between males and females is related to reproduction. However, it is only a small portion of the human body, and sex differences are way beyond the reproduction systems. Sex differences are widely existing on multiple levels, from the genetic, cellular, and molecular to physiological levels. In addition, woman’s and man’s body respond to external stress, such as cultural influence, differently. So, sexual dimorphism exists and widely affects human health. The main purpose of biomedical and clinical research is to know how the human body functions and use the knowledge to improve overall health outcomes. To be truly generalizable and useful, it needs to represent the populations that it intends to help.

2 The history of medicine inequality

Prior to the 1990s, omitting females as subjects of biomedical research was a routine operation (figure.1). In 1977, it was recommended by a Food and Drug Administration (FDA) policy to exclude women who have childbearing potential from Phase I and early phase II clinical trials, and it was generalized to exclude women who used contraception and whose husbands were vasectomized1-2. Phase I and II are the stages where researchers identify safe and effective doses. Without female data from those stages of drug trials, it was a mystery regarding how drugs affect women. This led to many tragedies. Thalidomide, a sedative, was an infamous example. This drug would affect embryonic development. It was not known until thousands of females in Canada and Europe took it during pregnancy which resulted in having infants with limb deformities3,4. Ignorance of women’s health was not limited to it. A study conducted between 1973 and 1982 to find the correlation among blood pressure, coronary heart disease, smoking, and cholesterol involved 12,866 men and 0 women5. Despite the fact that two third of the elderly population (>65 years old) were women, the National Institute of Aging’s Baltimore Longitudinal Study of Aging, from 1958 to 1974, excluded female subjects6.

The root of this prevalent ignorance of women’s health was implanted from basic biomedical research. Up until recent years, most basic scientific research has been done on exclusively male animals. Due to lacking monthly hormonal cycles, male animals were thought to be less variable7. Without testing drugs in any female vertebrates, it was not known whether or not certain drugs could be tested in women at all. Shocked by tragedies, and with more females working in the biomedical fields, more voices asked for more scientific attention towards women’s health.

The 1980s was the awakening of mainstream medicine to consider issues of female health (figure.1). It was recommended by the 1985 report of the Public Health Service Task Force on Women’s Health Issues to conduct a longitudinal study on how different factors affect women’s health8. In 1987, the NIH Guide for Grants and Contracts published a policy to encourage the

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Inclusion of female subjects. In 1991, Dr. Bernadine Healy was named to be the first female NIH director and launched the Women’s Health Initiative. Before 1993, the inclusion of females in biomedical trials founded by NIH was policy. In 1993, it become law: Congress wrote those NIH policies into the Federal law through a section in the NIH Revitalization Act of 1993, and the title is Woman and Minorities as subjects in Clinical Research. Since then, NIH published reports about the sex, race, and ethnicity of people who are involved in biomedical trials funded by NIH. With more and more attention to the inclusion of females in biomedical research and clinical trials, women’s health is moving towards a promising future.

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Events</th>
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<tr>
<td>1975</td>
<td>National commission for the protection of human subjects and biomedical and behavioral research includes the concept of as vulnerable subjects for research</td>
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<td>1977</td>
<td>FDA guideline “general considerations for the clinical evaluation of drugs: excluding females for early stages of trials”</td>
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<tr>
<td>1985</td>
<td>Report of the Public Health Service Task Force on Women’s Health Issues to conduct a longitudinal study on how different factors affect women’s health</td>
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<td>1986</td>
<td>Recommends granting applicants that includes women in studies</td>
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<td>1987</td>
<td>The NIH guide for grants and contracts published a policy to encourage the inclusion of female subjects</td>
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<td>1990</td>
<td>Office of Research on Women’s Health established at the NIH</td>
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<td>1993</td>
<td>Congress mandates adequate inclusion of women in NIH sponsored clinical trials to determine differences between the sexes.</td>
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<tr>
<td>1994</td>
<td>Office of Women’s Health Established at the FDA</td>
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<tr>
<td>1998</td>
<td>FDA regulation states that FDA must present safety and efficacy data by sex</td>
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Fig. 1. The history of the inclusion of women in medicine.

### 3 The consequences of medicine inequality

Medications provide relief for symptoms at the same time pose some risks to everyone who takes them. However, deeply rooted in a long history of the underrepresentation of females in biomedical research, women have to face more risks regarding side effects than men and bear a lower likelihood that a treatment will actually work. Based on the FDA reports, between 2004 and 2013, women experienced 2 million drug-related side effects cases, compared with 1.3 million cases in men. Men and women have different patterns of blood concentration and elimination time of most drugs, which are closely correlated with adverse drug reactions (ADRs), or side effects. ADRs have a wide range of symptoms, and they can be clustered into three large groups, including physical, mood, and cognitive side effects. The physical ADRs are symptoms related to general malaise from the body; The mood side effects are mood fluctuations; the cognitive ones are related to declined cognitive functions. Figure 2A shows that 86.7% of FDA-approved medications lead to side effects in females, but only 5% of them cause ADRs in males, which is a significant sex difference. Women suffer from all three categories of ADRs. Figure 2B shows that 79% of ADRs are related to the physical category, 11.3% are related to cognitive symptoms, and about 5% are mood-related ADRs. Figure 2 shows that females are indeed suffering unacceptably higher amounts of side effects than males at all times. Those are the consequences of a history of the underrepresentation of women in biomedical research.

The true scope of the scientific question of women’s health can be missed, when females are studied through a male lens. Despite the fact that affective and anxiety disorders are twice as prevalent in women than that in men, the common behavior tests used to model relevant symptoms in rodents were estimated and validated in males. Using male-based behavior tests to evaluate the emotional states of females is clearly not the most accurate way to know the neural mechanisms underlying disease susceptibility in women. The current standard evaluations in disease models, especially psychiatric ones, may need to be recalibrated to incorporate female-specific behaviors. With more attention towards the inclusion of females, more and more studies start to have female subjects. In 2019, 356 out of 841 articles (49%) from high-impact journals reported using both males and females in their research, which is significantly higher than 28% in 2009. Among different disciplines of biomedical research, the field of neuroscience showed the largest increase in sex-inclusive studies (29% vs. 63%). It is a promising direction, but it is still less than 45% of depression or anxiety-related studies that involve females. There is a long way to go to better understand women’s health.

Fig. 2. Distribution of sex-biased clinical ADRs of certain drugs and distribution of physical, mood, and cognitive ADRs of certain drugs.

### 4 The scientific evidence of sexual dimorphism

It has been widely accepted that sexual dimorphism does exist. However, most people do not know how exactly females’ system is different from males’ system. It has been shown that the drug pharmacokinetics of the two sexes is different, which predicted the direction of...
sex-biased ADRs. Is that sole due to the different body sizes? What have scientists known regarding how females are different from males fundamentally?

The mouse model is one of the main model organisms in biomedical research. The social behavior of mice involves many drug-targeting brain regions and hormones. From the figure 3, people can see why certain medications work for both sexes, but many others do not. The preoptic hypothalamus area (POA), the medial amygdala (MeA), and the ventromedial hypothalamus (VMH) are three critical brain regions involved in social behaviors in both female and male mice (figure 3A). There are mainly three actions in mouse social behavior, including aggression, mating, and parental care. Indeed, there are similarities between female and male brains. The POA is a brain region that is closely associated with parental care. The stimulation of galanin-expressing neurons in the POA increases parental care in both females and mated males (figure 3B). In general, virgin male mice show aggressive behaviors towards pups. Activating those neurons results in decreased pup-directed aggression and eliciting parental behaviors in virgin male mice. So, the POA is the brain region critical for eliciting parental care in both male and female mice. The POA is not the only similarity in the central nervous system, and these kinds of similarities are the reasons why many medications work similarly between males and females. However, sexual dimorphism widely exists in the central nervous systems, which is probably the reason why women experience much more aversive side effects. Both male and female mice have the VMH, but the VMH mediates different functions in the two sexes. Progesterone-expressing neurons in the VMH are important for female receptivity, namely mating behavior, but have no effects on male sexual behavior (figure. 3C). Estrogen receptor alpha neurons in VMH are both sufficient and necessary for male aggression but have no effects on female aggression. Another example here is the aromatase-expressing neurons in MeA (figure.3D). In male mice, those neurons in MeA are important for male mating behavior, but in females, they are critical for maternal aggression, namely protecting pups from intruders. The same neurotransmitter-secreting neurons in the same brain regions control two different behaviors. So, the significantly higher ADR in women is much more than just the dosage of certain medications. involving females in biomedical research is to test how medications fit both sexes. It is likely that the same drug may treat different symptoms in two sexes based on the scientific evidence shown above. To minimize ADR in women, revisiting male-only based medications, involving female subjects, and modifying the ingredients will be a potential solution.

5 Discussion

Since the 1980s, policies have encouraged the inclusion of females in biomedical research and clinical trials. For example, only 17% of articles in Nature in 2011 included both sexes, but the ratio increased to 35% in 2021, which is a significantly higher ratio (figure 4). With more understanding of sexual dimorphisms, women’s health has improved significantly. However, women still have a much higher possibility to have side effects and lower therapeutic efficacy. To cope with such conditions, women have been suggested to take change the medication dosage to reduce the side effects. For example, females are recommended to take a lower dose of the sleeping pill, Ambien (zolpidem), since 2013. However, sexual dimorphism is much more than the body size difference between the two sexes. It is not reasonable in the first place to create disease models solely based on male animals. Also, it is not rational to directly generalize the results from the male-only research to females. Due to the long history of the ignorance of females in biomedical research, many diagnosis standards and health guides were generated based on male-only data points. Properly addressing women’s health issues did not require novel technical breakthroughs or simply more female doctors and scientists, although the latter would help a lot. It is important to quantify the sample size by sex and perform sex-based analysis. Such analysis will increase the possibility to uncover sex differences for given medical conditions, facilitating the estimation of sex-specific diagnosis, drug targets, prevention strategies, or other therapeutic benefits to both sexes. On the other hand, sex-based analysis can provide scientific grounds to aggregate and analyze data together from both sexes if no sex differences have been shown for given traits. With this information involved and published, redundant research efforts can be avoided, and biological resources, such as funding, time, and money can be used to further advance our scientific understanding. Considering sex difference as a biological variable is not only important for future biomedical research but also should be used to recalibrate the medicine and health standard developed solely on males in the past. To truly improve the healthcare quality for both males and females, biomedical research and clinical trials need to include
both sexes and perform sex-specific analyses to characterize the similarities and differences.

**Fig. 4.** Comparison of numbers of sex-biased papers published in Nature in 2021(A) and 2011(B). The representations of subjects based on sexes are being counted and categorized into female only, male only, both, and not specific.

**References**


