Gender Disparities in Medicine: Factors Contributing to the Biases Against Women in Clinical Care

Presented to the S. Daniel Abraham Honors Program in Partial Fulfillment of the Requirements for Completion of the Program

Stern College for Women
Yeshiva University
April 27, 2023

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Acknowledgements

I owe a tremendous amount of gratitude to my mentor, Dr. DiLorenzo, for her guidance on this endeavor. In addition to the formal support I received from Dr. DiLorenzo throughout the thesis writing process, many of the skills I have gained throughout college relating to academic writing and composing a literature review have stemmed from experiences in the four classes of hers which I have been privileged to learn from. I am further thankful to Dr. DiLorenzo for supporting and maintaining the public health minor, allowing me to explore and develop my passion for healthcare. My experience at Stern was highly enhanced by the presence of incredible professors such as Dr. DiLorenzo, who have become role models to me and have taught me lessons that I hope to take with me beyond the classroom. I would also like to specifically thank Professor Nechama Price, whom I have had the privilege of learning from during all but one of my semesters and has graced me with invaluable advice and guidance through the various ups and downs of my college career. Thank you for serving as a mentor and confidante and for showing your students how much you care about us.

I am tremendously appreciative to my parents for gifting me the ability to attend the Honors Program at Stern College for Women. I would also like to thank my grandmother for being one call away to listen to me flesh out a thought or idea and for supporting my interest in public health and allowing me to continue the legacy of my late grandfather, who was a professor in the Boston University School of Public Health.

Abstract

Research shows that gender disparities exist in the diagnosis and treatment of females across various diseases. Women are less likely to be given the appropriate tests and treatments and tend to wait longer for an accurate diagnosis and effective treatment and pain relief. This review examines the extent of these disparities and possible factors contributing to these differences. One of the more significant explanations found in the literature is the lack of females in clinical trials, and various rationales will be explored in an attempt to explain this fact. Even when females are included in studies, the results are often not analyzed by sex, and the implications are discussed. Finally, the policies that have been developed to address this disparity and their impact will be analyzed and recommendations regarding what contributions can be made to further the literature on this topic will be provided.

Introduction

Part of the Hippocratic Oath, famously uttered by graduating physicians, has them promise that "I will take care that they suffer no hurt or damage." However, when looking at the way women are treated in the medical system, one would wonder if half the population was excluded from this oath. Newspapers constantly display headlines such as "Why Won't Doctors Believe Women?," "Doctors Are Failing Women with Chronic Illness," and "Doctors Are More Likely to Misdiagnose Women Than Men" (Cleghorn, 2021). Stark disparities exist in the way that females are diagnosed and treated, which has detrimental effects on their health. Their symptoms are dismissed, they are misdiagnosed, and they are left with higher rates of mortality for certain diseases.

Medicine has evolved based on a male-centric model, treating the male as the norm and women as deviations from the norm. Textbooks include more diagrams of males, and doctors are taught typical symptoms, effective treatments, and appropriate doses for medications that were established based on studies performed on males. In addition, women have been viewed by the medical community as reproductive bodies, and, according to Jackson (2021), "because women had reproductive organs, they should reproduce, and all else about them was deemed uninteresting." Dr. Alyson McGregor, Associate Professor of Emergency Medicine at Brown University, describes that when she told people that she wanted to study women's health, everyone assumed that she was referring to the field of obstetrics and gynecology. She had to explain to them that the health of females does not relate just to their reproductive organs and that there are many other aspects relating to the care of women (McGregor, 2021).

It is critical to explore what has promoted those beliefs and how they have caused various disparities for women entering the medical system. While policies have been created to try to address some of these discrepancies, there is still much room for progress.

Disparities in Diagnosis and Treatment

Heart Attacks

Studies have shown that women are less likely than men to receive appropriate testing for heart attacks when they are having symptoms. This was clearly displayed by the results of a pivotal study in which professional actors were recorded impersonating patients with symptoms of coronary heart disease, each using the same script but differing in gender, age, race, and socioeconomic status. These video clips were shown to a random sample of 128 primary-care doctors in the United States, United Kingdom, and Germany, who were asked what follow-up questions they would ask the patient, what tests they would order, how they would diagnose the patient, and how they would treat him/her. The results showed that among all three countries together, doctors indicated that they would ask women significantly fewer questions and would be significantly less likely to ask about their medical histories, including smoking and alcohol consumption. Furthermore, doctors reported that they would be significantly more likely to order a test for a man for whom coronary heart disease was suspected than for a woman (Bönte et al., 2008). A similar finding relating to heart disease was found in a study of patients with potential acute coronary syndrome who presented to the emergency department at the Hospital of the University of Pennsylvania. Female patients received fewer diagnostic cardiac catheterizations than males and were less likely to receive noninvasive stress testing. These findings persisted

even after being adjusted for various demographics, risk factors, and specific clinical presentations (Chang et al., 2007).

Even once correctly diagnosed and hospitalized for a heart attack, females have been shown to be less likely to receive the proper treatment. In a retrospective analysis of over a million discharge records from U.S. hospitals for patients admitted with cardiac arrest, it was found that women were significantly less likely to undergo coronary angiography, percutaneous coronary interventions, and targeted temperature management (Kim et al., 2016). These are all important therapeutic options for heart attacks and have been associated with improved outcomes (Geri et al., 2015). Similarly, an investigation of records from all patients in Sweden who were hospitalized with acute myocardial infarction (heart attack) between 2003 and 2013 revealed that women were less likely to receive reperfusion and revascularization therapies while inpatient and were less likely to be prescribed the medication indicated by the standard protocol at the time of discharge. These disparities were not explained by confounding variables such as age and comorbidities and were therefore likely attributable to gender inequalities (Alabas et al., 2017). Another very large study looked at reports of all people who had used emergency medical services (EMS) for chest pain or out-of-hospital cardiac arrest, as reported in 2010-2013 to the National Emergency Medical Services Information System (NEMSIS). The NEMSIS consists of EMS patient care reports that are provided by local EMS agencies in participating states and submitted to state repositories for compilation. These data showed that females with chest pain received a lower percentage of the recommended treatments than men (Lewis et al., 2019).

Given these findings showing inadequate testing and treatment for females experiencing a heart attack, it is no surprise that women have been found to have a 50% higher chance of receiving an incorrect diagnosis after a heart attack (Mickle, 2017) and are more likely to be

incorrectly discharged from the emergency department while having a heart attack (Pope et al., 2000). Furthermore, for heart attacks, women have a higher rate of in-hospital mortality than men (Kim et al., 2016) and have worse relative survival and higher excess mortality than men. However, when evidenced-based treatments were used, these differences were no longer prevalent, providing evidence that the discrepancies in outcomes were likely due to gender disparities in appropriate treatments (Alabas et al., 2017).

Strokes

These gender disparities in appropriate testing and treatments do not exist only with heart attacks, however. Research has shown that women are 10% less likely to be admitted to the hospital within the first three hours after stroke onset (Foerch et al., 2007). This is critical, because tPa, a life-saving drug to treat strokes, is most effective when given in the first few hours after stroke onset (Marler et al., 2000). Even once a stroke is diagnosed, a female is 13% less likely to be given the proper treatment of thrombolysis than a male (Foerch et al., 2007), even after controlling for various confounding variables, including age and stroke severity (Reid et al., 2008). Women are also less likely than men to be properly evaluated for a stroke with the use of carotid duplex imaging, echocardiography, or angiography, according to a European study (Di Carlo et al., 2003). Furthermore, researchers from Johns Hopkins University used data from nine states collected in the years 2008-2009 and found that women were 33% more likely to be misdiagnosed in the week prior to sustaining a debilitating stroke, meaning that they were exhibiting early symptoms of a stroke but were incorrectly sent home from the emergency department without the correct diagnosis (Desmon & Nelson, 2014).

Other Diseases

In addition to heart attacks and strokes, disparities in diagnosis extend to other diseases as well. For example, an analysis of data from the English National Audit of Cancer Diagnosis in Primary Care showed that women with bladder and renal cancers are more likely than men to require three or more pre-referral consults with a general practitioner before being sent to an appropriate specialist and have longer intervals between presentation of symptoms and referral, even when experiencing the same symptoms (Lyratzopoulos et al., 2013). Furthermore, data from the Clinical Practice Research Datalink in the United Kingdom showed that the diagnostic interval, meaning the time elapsed from symptom onset to diagnosis, was longer in females for six non-gender-specific cancers, including bladder, colorectal, gastric, head/neck, and lung cancers, as well as for lymphoma. Moreover, for all cancers together, there was a longer mean diagnostic interval for females (Din et al., 2015). With rheumatoid arthritis as well, "physician's delay," which refers to the time between a patient's first encounter with a physician and the referral to a specialist (in this case the rheumatology department), was much longer for women than for men. More specifically, the median delay for men was three weeks, while for women the median delay was ten weeks (Palm & Purinszky, 2005).

An analysis of over 20,000 severely-injured patients showed that EMS personnel were less likely to transport females from the site of the injury to a trauma center than males, limiting females' ability to receive adequate treatment (Gomez et al., 2012). In addition, Lewis et al.'s (2019) study of patients with chest pain or out-of-hospital cardiac arrest who used EMS showed that females were significantly less likely than men to be transported to the hospital with lights flashing and sirens blaring (Lewis et al., 2019). These findings on the disparities in getting women to the emergency department at all and within a reasonable time frame are consistent

with the discrepancies that exist between genders in securing an appropriate diagnosis and treatment.

Pain

In addition to studies showing significant gender disparities relating to appropriate diagnosis and treatment, various data show that there are gender disparities in the way that pain is approached and treated, despite the fact that women have been shown to report more severe levels of pain, more frequent pain, and pain of longer duration than men (Unruh, 1996). A prospective study of 55,000 nonpregnant adults presenting to an emergency department with acute nontraumatic abdominal pain observed that even after controlling for age, race, specific diagnosis, and pain score, women were between 13 and 25 percent less likely to receive opioid pain medication, and even when they did receive it, they had to wait longer for the drugs than men (Chen et al., 2008). Likewise, in a study of those 55 years of age or older who had undergone abdominal surgery, doctors gave females fewer pain medication than males (Faherty & Grier, 1984). An analysis of medication records of patients who had undergone coronary-artery bypass graft surgery in a Rhode Island hospital yielded similar results, observing that male patients received pain medication significantly more frequently than female patients (Calderone, 1990). Not only did female patients receive less pain medications than males, but they were also shown to be significantly less likely to receive the appropriate analgesic therapy according to World Health Organization (WHO) guidelines (Breitbart et al., 1996). In other words, females were not only treated unequally when being compared to men, but females were not even treated up to the standard of adequate healthcare guidelines.

In addition to receiving less pain medication than males, females tend to wait longer to have their pain recognized and to be given the appropriate attention. Of 188 patients at a pain clinic, the women had experienced pain for a longer duration than the men before eventually being referred by their doctor to the clinic for treatment (Lack, 1982). The above-mentioned study of over 55,000 nonpregnant adults presenting to an emergency department with acute nontraumatic abdominal pain also showed that females waited an average of sixteen minutes longer to receive pain management than males, even after the study was controlled for other clinical factors (Chen et al., 2008).

Research clearly shows that disparities exist between men and women with regard to obtaining the appropriate diagnoses in a timely fashion, receiving an adequate treatment, and addressing pain. It is important to examine what factors may contribute to these gender differences.

Why do These Disparities Exist?

Females Perceived as Anxious

Although women were given less pain medication than men as demonstrated by multiple studies, they were given anxiety-related medications to treat their pain more often than men. For example, among the patients who had undergone coronary-artery bypass graft surgery, despite females receiving narcotics much less often than males, they were shown to have received sedatives more frequently than men (Calderone, 1990). Furthermore, another study showed that while men were given more opioids, women were given more minor tranquilizers, antidepressants, and non-opioid analgesics than men (Lack, 1982). These studies show that females tend to be perceived as anxious, rather than being in pain (Hoffmann & Tarzian, 2001).

It is not only with pain that women are made to feel that what they are feeling is of psychological origin. One study showed, in contrast with findings in many of the previously mentioned studies, that women and men presenting with traditional symptoms of coronary heart disease (CHD) were equally likely to be appropriately diagnosed and referred to a cardiologist. However, when CHD symptoms were presented in the context of a stressful life event, women were less likely than men to be referred to a cardiologist. This study gave light to the fact that women are often seen as stressed and anxious, which clouds providers from appropriately listening to and believing their accounts of their physical symptoms, whether it be pain or another unusual body indication (Chiaramonte & Friend, 2006).

Knowledge/Teaching of Women's Health

There is a clear knowledge gap in what medical professionals know about women's bodies and how they work, which is ultimately a factor behind various disparities in their medical care. In her book *Doing Harm: The Truth About How Bad Medicine and Lazy Science Leave Women Dismissed, Misdiagnosed, and Sick*, Maya Dusenbery (2018) writes that "the average doctor does not know as much about women's bodies and the health problems that afflict them."

The most prominent example of this relates to cardiovascular disease, which has been identified as the number one killer of women and has been recognized to be the cause of death for more women than men (Go et al., 2013). A study of 500 randomly selected providers from three different specialties (cardiology, primary care, and obstetrics and gynecology) who filled out online questionnaires revealed that less than 20% of physicians from any of the specialties were aware that more women than men die each year of cardiovascular disease. In addition,

physicians were more likely to assign a lower risk category to a female patient than to a male patient with a comparable risk level. This is significant because awareness of the problem and identification of an individual's risk are the first steps towards reducing the risk and practicing effective prevention (Mosca et al., 2005). A survey from the World Heart Association found that only 22% of primary care providers and 42% of cardiologists felt extremely well-prepared to assess cardiovascular disease risk in women, which makes sense considering that only about half the providers of both specialties felt that they were adequately trained in assessing women's cardiovascular disease risk. Seventy-five percent of them agreed that women's heart disease needs more attention in medical training (Bairey Merz et al., 2017).

This lack of knowledge not only persists among medical providers, but permeates among women themselves. A national survey conducted by the American Heart Association in 1997 found that less than one-third of women were able to correctly identify heart disease as the leading cause of death in women and overwhelmingly indicated that they felt they were not well informed about heart disease and stroke (Mosca et al., 2000). A follow-up study was conducted in 2012, which observed that the percentage of women who were aware that cardiovascular disease was the leading cause of death in women nearly doubled, to about 56% of women being able to correctly identify the top killer of women (Mosca et al., 2013). A smaller survey by the World Heart Association in 2014 had comparable results, noting that 45% of women were not aware that heart disease was the top killer of women (Bairey Merz et al., 2017).

It is quite plausible that the attention to women's health in medical schools and the attitude with which it is taught has a lasting effect on the way that physicians approach women throughout their career. In her article "What Medical Schools Teach About Women," Dr. Mary Howell (1974) writes that "it is widely taught, both explicitly and implicitly, that women patients

(when they receive notice at all) have uninteresting illnesses, are unreliable historians, and are beset by such emotionality that their symptoms are unlikely to reflect real disease" (Howell, 1974). She also notes that patients in most medical lectures are referred to with the pronoun "he," following standard linguistics, but when discussing a hypothetical patient with a disease of psychological origins, the lecturer often automatically uses the pronoun "she" (Howell, 1974). Furthermore, in her book *Why Would a Girl Go into Medicine?: Medical Education in the United States: A Guide for Women*, Campbell (1973) presents data from a survey of over 100 female students in 41 American medical schools, with participants recounting that "their lectures were filled with references to women as 'hysterical mothers', 'hypochondriacs', and 'old ladies whom doctors must manage'" and that they were taught that "women's illnesses are assumed psychosomatic until proven otherwise." In an interview with ABC7, cardiologist Dr. Adam Spalver similarly recalls that "in training, we were taught to be on the lookout for hysterical females who come to the emergency room" (ABC7, 2011).

Medical textbooks tend to endorse the false notion that male and female bodies are generally the same, leading providers to misdiagnose women when their symptoms do not conform to the male model they have typically learned about. In a screening of eleven textbooks on the fields of internal medicine, cardiology, pharmacology, and psychiatry, gender-specific information was either absent or severely lacking, and when it was present, it was hardly accessible through the index or table of contents (Dijkstra et al., 2008). In another study of illustrations in 12 commonly used anatomy and physiology textbooks, women were severely underrepresented in the illustrations of non-reproductive anatomy, perpetuating the belief that the male body is the typical standard for medical care (Mendelsohn et al., 1994).

Lack of Females in General in Clinical Trials

Throughout all areas of medicine, females have been entirely excluded from clinical trials or included in a very limited capacity. A report written by the U.S. General Accounting Office in 1992 indicated that one quarter of drug manufacturers admitted that they deliberately did not recruit a representative number of women to participate in drug trials. The report also included a comparison of the proportion of women included in phase II and phase III trials for a drug with the proportion of women in the target audience of the drug, which showed that for over 60% of drugs women were underrepresented in the trials, with women severely underrepresented for 23% of those drugs (U.S. General Accounting Office, 1992).

In 2004, Geller et al. (2006) performed an analysis of randomized, controlled trials published in nine prominent medical journals during the year 2004 that were relevant to both sexes in the fields of general internal medicine, infectious disease, oncology, and cardiology. They found that for drug trials, women on average represented only 24% of the sample, and for all trials together, women represented 37% on average (Geller et al., 2006). A follow-up analysis was done, examining randomized, controlled trials published in 2009, with a goal to assess improvement from the underwhelming results in the previous study. This evaluation showed that there was no significant improvement in inclusion of women in randomized, controlled trials between 2004 and 2009 (Geller et al., 2011). A search of the NIH registry of clinical trials funded by the National Heart, Lung, and Blood Institute that analyzed phase III and IV randomized, controlled trials published between 1997 and 2006 found that the mean percentage of women enrolled in the trials was 27% (Kim et al., 2008).

Some more recent evidence has shown that this trend of including a disproportionate number of women in clinical trials has been continuing. A study published in *Circulation*, the

journal of the American Heart Association, analyzed data from 740 clinical trials on cardiovascular diseases that were completed between 2010 and 2017 on ClinicalTrials.gov, a clinical trial registry managed by the National Institutes of Health. Their research showed that in all of the trials, only 38% of participants were women (Jin et al., 2020). In 2019, Woitowitch et al. (2020) performed a systematic review of 34 journals across nine different disciplines, as a follow-up to a 2009 study which had found that only 28% of studies included any female participants. In the follow-up, they found that the proportion of studies including female participants increased to 49%. Across almost all disciplines, the percentage of studies including females had increased, but in pharmacology, there were actually fewer studies including women than there had been in 2009. Even though in most fields the number of studies that included females at all had increased, there was still a large discrepancy in the number of males and females actually participating in the studies, with a 5.8:1 ratio of males to females as participants in all the studies that included both sexes. This was an increase from the 5:1 proportion in 2009 (Woitowich et al., 2020).

Exclusion of Pregnant Women from Clinical Trials

While the inclusion rates for women in general are low, involvement in clinical trials is even lower for pregnant women. To show just how significant the exclusion is, Shields and Lyerly (2013) performed a review of phase IV trials on ClinicalTrials.gov completed between 2011 and 2012 that were studying conditions that could be experienced by but are not limited to pregnant women and not studying a medication that was specifically teratogenic. They found that among those studies, 95% excluded pregnant women (Shields & Lyerly, 2013).

Many researchers and institutional review boards (IRBs) view pregnancy as a reason for automatic exclusion from a clinical trial. This is likely because they are worried about the safety of medications during pregnancy, since medications can cross the placenta and directly affect the fetus. Furthermore, a fetus cannot give consent, so some argue that therefore there need to be extra protections on the fetus's wellbeing, such as abstaining entirely from trials (Lyerly et al., 2008).

This exclusion of pregnant women from clinical trials has had detrimental effects. Because pregnant women are included in drug research so infrequently, only 12 medications have been approved by the FDA for use during pregnancy, and they are all for birth-related issues, such as induction of labor (Haire, 2001). Therefore, any medication to treat a condition that occurs during pregnancy, such as gestational diabetes or hypertension during pregnancy, is used without FDA approval (Lyerly et al., 2008). This is significant since 90% of women take medications during pregnancy (Center for Disease Control and Prevention, 2022), and the average woman receives 1.3 prescriptions during an obstetric visit (Lee et al., 2006). While the FDA has tried to give direction as to which drugs are safe during pregnancy, more than 80% of drugs are labeled as "undetermined" with respect to fetal safety (Lo & Friedman, 2002).

In addition to the importance of assessing the drug's safety for the fetus, it is just as important to ensure that a treatment is both safe and effective for the mother. Since body changes during pregnancy, such as increases in blood volume, decreases in gastric emptying time, changes in concentration of sex hormones, and alterations in liver enzymes, can affect the way a drug is metabolized (Mattison & Zajicek, 2006), research to assess the appropriate dosages of a drug for pregnant women and its effects on the woman's body must be conducted. However, since there is very limited research on the way drugs are metabolized by pregnant women,

providers are often prescribing medications that are a wild card in terms of correct dose and effectiveness for a pregnant woman. Alternatively, providers may be reluctant to prescribe a medication that could be very helpful to the pregnant woman since they are fearful of the ambiguity, despite the fact that not treating certain conditions can be very harmful.

Lack of Female Animals/Cells

It is not only in human studies that an underwhelming proportion of female subjects is included. In research using cells and animals too, females are consistently excluded from studies. In the period of 1996-2005, 80% of the animal studies published in the journal *Pain* utilized only male animals (Mogil & Chanda, 2005). In the *Journal of Pharmacology and Experimental Therapeutics* and the *Journal of Physiology*, 50% of articles using non-human subjects written from 1969-2009 utilized only male animals, while only 15% used both, and 30% did not specify the gender of the animals. In a literature review of studies published in 2009 in ten disciplines, eight disciplines showed a bias towards male-only studies, with the highest biases in neuroscience, pharmacology, and physiology (Beery & Zucker, 2011). The same authors sampled the Thomson Reuters Web of Science database for 2009 and compared the proportion of animal studies that included females with the prevalence among females in society of the disease being studied. They found staggering disparities; for example, although women have more strokes than men, female animals were included in only 38% of studies on strokes. Similarly, although anxiety and depression are more than twice as common in females than males, only 45% of animal studies for those diagnoses used females (Zucker & Beery, 2010). According to Beery and Zucker's (2011) literature review, spanning a sixty-year period, there was no increase in studies including female animals (Beery & Zucker, 2011). In discussing the lack of female

animals in studies, Annaliese Beery, assistant professor at Smith College, recaps various excuses she has heard over the years, including “I just want to do things like everybody else does them” and even "female mice have smellier urine" (Schumaker, 2015).

In addition to studies using animals, research utilizing cells also fails to include females at appropriate amounts. In an analysis of articles in ten cardiovascular journals published in 2010, 68.9% of the articles that reported the sex of the organism from which the cells were taken used only used cells from males, and none exclusively used cells from females (Taylor et al., 2011).

With the literature consistently showing that females are underrepresented in human research as well as in both cell and animal studies, there is a need to explore why this exclusion of females exists.

Why are Females Underrepresented in Clinical Trials?

During the late 1950s, thalidomide was commonly used in Europe as a treatment for nausea during pregnancy. However, in the 1960s, there were thousands of reports of birth deformities in babies born to mothers who had taken thalidomide during pregnancy (Kim & Scialli, 2011). As a result of this experience, in 1977, the FDA issued guidelines aimed to protect women and fetuses from harmful effects of drugs, such as those from thalidomide. The document, titled “General Considerations for the Clinical Evaluation of Drugs,” stated that women of childbearing potential should be excluded from all phase I and phase II clinical trials, except when testing drugs for a life-threatening illness (U.S. Food and Drug Administration, 1977). The term “childbearing potential” included all women capable of becoming pregnant, even if they were using contraception, were abstinent, or had sterile partners. However, in 1993,

this ruling was reversed, with a guidance document called "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," which gave the decision of whether to include women of childbearing potential in early research to Institutional Review Boards (IRBs), researchers, and women themselves. This was because people began to view the 1977 guidance as "rigid and paternalistic, leaving virtually no room for the exercise of judgment by responsible research subjects, physician investigators, and IRBs" (U.S. Food and Drug Administration, 1993). The 1993 document acknowledged the fact that researchers who want to exclude pregnant women can use pregnancy tests to confirm that a woman is not pregnant or require women to use a form of contraception or to be abstinent, rather than excluding all women with the potential to become pregnant. In addition, there was concern about the 1977 guidance unintentionally causing a general underrepresentation of women in drug studies (U.S. Food and Drug Administration, 1993). In fact, some researchers believe that this is exactly what has led to the exclusion of women from many studies, despite the FDA reversing their ban and now allowing women of childbearing potential to be included in trials (Mazure & Jones, 2015).

Another reason that females have been routinely excluded from clinical trials is because of two contradictory beliefs that have both led to researchers' faulty assumptions that testing on females is unnecessary. The scientific community has held the belief that women's and men's bodies are alike in every way except for their reproductive systems (Merton, 1993) and that women will respond to the same treatments as men (Mazure & Jones, 2015), so including women in a study is superfluous (Mazure & Jones, 2015) and will waste resources and slow down research (Fields, 2014). Instead, researchers can use only male subjects and apply the results to both sexes (Lee, 2018). However, one of the flaws in this line of thinking is the fact

that researchers have used this excuse to perform studies with just males and have not performed studies that include only females and applied those results to men (Merton, 1993).

In direct contrast to this claim that women do not need to be studied because they are so similar to men, science has also recognized that women are vastly different from men physiologically, specifically related to their different hormones, and that studying both sexes will confuse results and increase expenses (Scott, 1993). This inconsistency was excellently summarized by Laurence and Weinhouse (1997) in their book, *Outrageous Practices: How Gender Bias Threatens Women's Health,* asserting that "it defies logic for researchers to acknowledge gender difference by claiming women's hormones can affect study results -- for instance, by affecting drug metabolism -- but then to ignore those differences, study only men, and extrapolate the results to women."

Others insist that not only are women different from men, but they are also different from each other, and are therefore too complicated to study (Faden & Federman, 1994). It is thought that because of females' hormonal variations throughout the month due to the stages of the estrous cycle, females need to be tested at each of the four stages in order to accurately portray the effect of a certain treatment, (Prendergast et al., 2014) a practice that would add complexity and increase costs (Mazure & Jones, 2015). Along these lines, Dr. David Palmer, Associate Professor of Human Genetics at the University of Chicago, argues that studying only males "reduces variability and makes it easier to detect the effect that you are studying" (Rabin, 2014). However, a meta-analysis of 293 articles that tested various traits in mice, including behavioral, morphological, physiological, and molecular traits, compared the variability of male mice with that of female mice at different stages of the estrous cycle. The results showed that female mice at different points in the estrous cycle showed no significantly greater variability than males did

to each other for all of the traits and that it is therefore not necessary to significantly increase the costs and labor involved by testing females at each of the four stages (Prendergast et al., 2014). Although variability among females has been shown not to be significant, the differences between the way females and males respond to specific treatments can be significant, as will be discussed later, showing how important it is to include both genders in a study. In addition, others point out that including women actually saves costs in the long run, because it prevents dangerous and costly situations, such as lawsuits and withdrawal of drugs post-marketing due to harmful effects in females (McCullough et al., 2014). Furthermore, the FDA's guidelines in March 1994 claimed that cost is not an acceptable reason to exclude groups from clinical studies (U.S. General Accounting Office, 2000).

In discussing possible reasons why there may be fewer women in clinical trials, it is necessary to consider whether it is possible that females are less likely to enroll in a clinical trial, even when they are invited to do so. Research on the subject has been mixed, with most studies showing that women are, in fact, less likely to participate in clinical trials. In a randomized trial including 783 participants 18 years of age and older across 13 clinical centers, participants were randomly given a standardized, one-page description of a hypothetical, randomized, double-blind, placebo-controlled cardiovascular disease prevention drug trial. The side effects and their probabilities, trial duration, study sponsor, presence or absence of researcher financial conflict of interest of the researcher, and amount of monetary compensation were all randomized among the descriptions. After reading the description, participants were first asked to rate their willingness to enroll on a five-point Likert scale, after which they were asked to rate their attitudes about the harm and benefits of joining the trial and about medical researchers and the healthcare system. The results showed that women were 15% less likely to be willing to

participate in the trial, which was fully explained by the fact that women perceived fewer benefits and greater risk from participating in the trial than the men did (Ding et al., 2007). It is plausible that this can be related to the fact that in general, women are more averse to taking risks than men (Doyal, 2001). A similar study surveyed 660 patients on their willingness to consider participating in two randomized controlled trials, one of which was going to evaluate percutaneous coronary angioplasty, and one of which aimed to study coronary-artery bypass surgery. Here too, women were significantly less likely than men to participate in either trial (Peterson et al., 2004). On the other hand, Klabunde et al. (1999) conducted a study in which they evaluated factors correlating with the willingness of adult cancer patients to enroll in clinical trials sponsored by the National Cancer Institute at 15 medical facilities across southeastern United States. In this study, sex did not predict enrollment, meaning that females were not any less likely to participate in the trials. Given the mixed results, it is critical to consider women's unwillingness to participate as a possible factor in the lack of females in clinical trials, but it is certainly not the only element contributing to women's underrepresentation.

Lack of Analysis by Sex and Gender

Even when females are included in research, whether in a study involving humans or one using animals or cells, many studies fail to analyze the results by sex. In other words, a study can include both males and females, but results are analyzed only with both sexes combined, without evaluating the outcomes specifically in the context of sex. However, women and men have distinct biologic characteristics, and they often tend to have different symptom presentations,

responses to treatments, and manifestations of pain. Therefore, it is vital for data to specify outcomes by gender.

In 2000, the U.S. General Accounting Office (GAO) presented a report assessing progress since the NIH Revitalization Act issued in 1993. The report detailed that there had been improvement in including females in clinical trials, but there was limited movement in analyzing results by sex (U.S. General Accounting Office, 2000). This assertion in the report was based largely on a release by the Society for Women's Health Research that reviewed articles published in four major medical journals from 1993-1998. The release showed that only one-quarter to one-third of the non-sex-specific studies that included female subjects analyzed data by sex, with no improvement over the five years (U.S. General Accounting Office, 2000). A similar conclusion was found in a study by Weinberger et al. (2010), who presented an analysis of 150 randomized, controlled trials relating to depression that were published in 2007. This study observed that 50% of the studies did not analyze results by gender, and 15% of the articles did not even state the gender of the participants at all. In addition to looking at the already published articles, the authors looked at the 768 interventional studies for depression on the clinical trial registry that were currently listed, and found that although 89% of the studies listed planned to include both male and female subjects, fewer than 1% of them included gender as part of their study design, analysis plan, or hypothesis (Weinberger et al., 2010). Geller et al. (2011) assessed articles from nine prominent medical journals that were written in 2009 to further assess progress since the NIH Revitalization Act and found that 64% of articles did not specify their results by sex, and none of these studies provided an explanation as to why they omitted the influence of sex from their analysis (Geller et al., 2011). More recent research, related to the Covid-19 pandemic, showed that of the 4,420 studies described on ClinicalTrials.gov from 2020 through

2021, only 4% explicitly reported a plan to include sex/gender as an analytical variable (Brady et al., 2021).

According to the 2000 US GAO report mentioned above, even when researchers did interpret results by sex, many times this data had not been published. Sometimes, the reason for this omission was because the data analysis showed that there was no difference in outcome between men and women, and editors tend to discourage including "no news" results (U.S. General Accounting Office, 2000). However, as Lee (2018) clearly states, "finding no sex difference is as significant as the presence of a sex difference."

Physiological Differences Between Men and Women

In November 1999, the Institute of Medicine formed the Committee of Understanding the Biology of Sex and Gender Differences, and tasked them with evaluating sex differences at the biological level. Their report titled "Exploring the Biological Contributions to Human Health: Does Sex Matter?" was published in 2001 (Institute of Medicine Committee on Understanding the Biology of Sex and Gender Differences, 2001). This paper gave light to the fact that it is important both to include females in studies and to analyze results by sex, because women and men have entirely different biologies, and therefore can present with different symptoms for the same condition and respond differently to the same drug or treatment.

On the most basic level, males and females differ in their chromosomal makeup, with females possessing two X chromosomes and males possessing an X and a Y chromosome (Institute of Medicine Committee on Understanding the Biology of Sex and Gender Differences, 2001). A female undergoes X-chromosome inactivation, in which one of the X chromosomes is shut off, so that females do not have too many of the genes contained on the X chromosome

(Institute of Medicine Committee on Understanding the Biology of Sex and Gender Differences, 2001). However, about 10-15% of the genes linked to the X chromosome are still expressed after X-chromosome inactivation (Carrel & Willard, 1999). This is one factor accounting for differences in biological functions between males and females. Similarly, the fact that males have a Y chromosome and females do not results in various biological differences. The Y chromosome contains some genes involved in basic cellular functions, which directly or indirectly affect activities of the body. Since females do not have a Y chromosome, some cellular functions may take place with slight differences (Institute of Medicine Committee on Understanding the Biology of Sex and Gender Differences, 2001).

Another major fundamental difference between men and women relates to sex hormones. Generally, males and females produce the same hormones, but the production sites, blood concentrations, and interactions with different organs and systems of the hormones are entirely distinct (Svechnikov & Söder, 2008). Males predominantly produce testosterone from the testes in a consistent daily amount, while the testes and adrenal glands, and sometimes the peripheral tissues, also produce small amounts of estrogen and progesterone (Tyagi et al., 2017). On the other hand, females mainly produce estrogen and progesterone from the ovaries in a cyclical pattern, with the addition of small amounts of testosterone from the ovaries and adrenal glands (Simpson, 2003).

These key differences in male and female biology lead to many differences in body composition and in body functions. For example, males have proportionally more muscle mass, more bone mass, and a lower percentage of body fat than females do, as a direct result of the different concentrations of the sex hormones (Blair, 2007). Sex hormones also play a role in the manifestation of cardiovascular disease. When experiencing a heart attack, males tend to have

acute, crushing chest pain, while females are more likely to experience shortness of breath, fatigue, and more minor chest pain. Females have a more aggressive immune response to infections, and vaccines induce higher antibody levels in females than in males, also as a direct result of sex hormones (Institute of Medicine Committee on Understanding the Biology of Sex and Gender Differences, 2001).

Other anatomical and physiological differences exist between males and females that affect various biological processes. Men have larger lungs, wider airways, and greater lung diffusion capacity, as well as significantly greater left ventricular mass and chamber size than women (Blair, 2007). Furthermore, women have a longer QT interval, meaning that the interval between heart muscle contractions is longer for females (Haverkamp, 2000).

Metabolic differences between males and females can have a significant impact on the way that each sex metabolizes drugs, which is important in determining the appropriate dosage. Women tend to metabolize some antihypertensive and cardiovascular drugs at slower rates than men do (U.S. General Accounting Office, 1992). Some antidepressant drugs are more powerful in women. For instance, for women, certain tricyclic antidepressants, when taken with other drugs, could overflow into the bloodstream and potentially cause more side effects. In addition, women have a less acidic stomach, which may cause them to feel the effects of antianxiety medication faster and more powerfully, and the drugs can be more toxic to women at standard doses. Men's kidneys filter out drug compounds faster than women's, so women may need to wait longer before taking a second dose of some drugs, such as Xanax (Jacobson, 2014). When women and men ingest the same dose of propranolol, a beta blocker used to treat hypertension, abnormal heart rhythms, and angina, a high concentration will remain in the blood levels for eight hours longer in the women than in the men (U.S. General Accounting Office, 1992). Many

women take oral contraceptives (Daniels & Abma, 2018), and taking other drugs with oral contraceptives can cause harmful interactions (U.S. General Accounting Office, 1992).

Sex differences in the ways that each sex metabolizes drugs has had additional important implications. In 2001, the U.S. GAO identified the drugs that had been withdrawn from the market since January 1, 1997. They identified ten drugs that were recalled, and eight of them posed greater health risks for women than for men. While four of these drugs were prescribed more often to females, leading to more adverse effects in females, the other four drugs that were withdrawn were prescribed equally to males and females (Harkin et al., 2001). It is likely that many of these drugs were tested on men, and males were used to establish appropriate dosing, but women's different metabolism caused the same dose to be harmful to females. In 2013, the FDA recommended that the dosage for the sleeping pill Ambien, commonly known as Zolpidem, be lowered by half for women. It was discovered that the original dose, set on the basis of research in men, was more likely to leave women with next-day impairment. Since men and women metabolize the medication differently, the same dose was leaving the women with the drug still in their bodies the next morning and affecting their ability to drive (U.S. Food and Drug Administration, 2019). Consistent with the above findings, Whitley & Lindsey (2009) found that women are 50-75% more likely than men to have an adverse drug reaction.

Policies

Food and Drug Administration (FDA)

As a result of the catastrophe that occurred with the birth defects from thalidomide, the FDA issued "General Consideration for the Clinical Evaluation of Drugs" in 1977. This guideline recommended excluding women of child-bearing potential from phase I and early

phase II trials, with the exception of studies that tested drugs to treat life-threatening diseases. "Childbearing potential" referred to all women capable of becoming pregnant, including "women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomized, or whose husbands have received or are utilizing mechanical contraceptive devices" (U.S. Food and Drug Administration, 1977). Once the drugs were shown to not cause birth defects or affect fertility in animals, researchers were allowed to include these women in later phase II and phase III trials (U.S. Food and Drug Administration, 1977).

This policy was reversed in 1993, with the guidance document "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." The FDA published new guidelines due to worries that the old policies led to the lack of women in clinical trials entirely and a severe lack of information regarding the effects of drugs in women. There was a recognition of the fact that women metabolize certain substances at different rates than men, raising a need for drugs to be evaluated specifically among women. In addition, researchers realized that it was not medically necessary to exclude ALL women of childbearing potential from early clinical trials, because the risk of fetal exposure could be severely minimized by controlling patient behavior and utilizing lab testing, such as the use of contraception and pregnant tests. Therefore, the new guidelines allowed researchers and IRBs to decide whether they wanted to include female participants, and women themselves to decide whether to enroll in a trial. It was required for women to receive adequate counseling regarding the possible dangers of becoming pregnant during a study, and recommended for women to take precautions to make sure they would not become pregnant during the duration of the study. With this new guideline, women were still not required or even advised to be included in clinical trials, but they were no

longer recommended for exclusion. In addition, these guidelines suggested, but did not require, analysis of data based on sex differences (U.S. Food and Drug Administration, 1993).

In 1994, the FDA created the Office of Women's Health (OWH) to foster progression in the field of women's health through research, policies, and outreach. One of the main goals of the OWH was to "promote the inclusion of women in clinical trials and the implementation of guidelines concerning the representation of women in clinical trials and the completion of sex/gender analysis." The OWH works off of the main principle that sex as a biological variable (SABV) should be factored into research design, analysis, reporting and education (U.S. Food and Drug Administration, n.d.).

However, even with analysis by sex deemed as important in research, a further guideline was released in 1998, titled "Presentation and Effectiveness Data for Certain Subgroups of the Population in Investigational New Drug Application Reports and New Drug Applications (NDAs)," which required the presentation of data by sex, but not the analysis of it. More specifically, this guideline stated that new drug applications (NDAs) must present data regarding safety and efficacy for all subpopulations, including according to sex, age, and race, and that the FDA has the right to reject any NDA that does not comply. The document clearly stated that "the numbers of subjects enrolled to date in clinical studies need to be counted and listed in tabular form in annual reports according to age group, gender, and race. No analysis of data is required for annual reports" (U.S. Food and Drug Administration, 1998).

After no further policies regarding women in clinical research were adopted for a number of years, in 2014, the FDA published a document titled "Evaluation of Sex-Specific Data in Medical Device Clinical Studies: Guidance for Industry and Food and Drug Administration Staff." This guidance encouraged the consideration of sex during study design and

recommended sex-specific statistical analysis of the study data (U.S. Food and Drug Administration, 2014).

In 2018, the FDA published guidance regarding the inclusion of pregnant women in clinical trials. In discussing the importance of including pregnant women in clinical trials, the document emphasized that women need safe and effective treatments during pregnancy, and failure to have appropriate dosing, safety, and efficacy during pregnancy can compromise the health of both the mother and the fetus. Additionally, in some cases, involvement in a clinical trial can offer direct benefit to a woman or fetus that is unattainable outside of the research setting. Given all these reasons to include pregnant women, this recent guidance recommended that for premarketing studies, pregnant women should be included once adequate nonclinical studies have been completed, including studies on pregnant animals. For postmarketing studies, pregnant women should be included when adequate nonclinical studies have been completed and safety data have been established in nonpregnant women, and preliminary safety data have been established regarding use in pregnant women. An additional requirement is that safety in pregnant women cannot be assessed by other study methods, and/or efficacy in pregnant women cannot be reasonably extrapolated based on the research on non-pregnant women (U.S. Food and Drug Administration, 2018).

National Institutes of Health (NIH)

In 1990, the US GAO performed a study of NIH grant applications that found that for clinical trials studying conditions affecting both men and women, 20% provided no information regarding the sex of the population utilized in the study. As a result, in September 1990, the NIH established the Office of Research on Women's Health (ORWH), which aimed to improve both

the quality and quantity of the research related to conditions that affect women, specifically by ensuring that women are appropriately represented in NIH-supported research and ensuring that all NIH-funded research accounts for SABV (U.S. Department of Health and Human Services, n.d.). A few years after this office was established, in 1993, the NIH published the NIH Revitalization Act, with the goal of ensuring that women are included as subjects in clinical trials. This policy required that trials must be designed and performed in a way that allows for valid analysis by sex (National Institutes of Health, 1993). In 1994, the NIH put out a further statement, stating that cost is not an acceptable reason for excluding women. Furthermore, the guidance stated that "women of childbearing potential should not be routinely excluded from participation in clinical research (National Institutes of Health, 1994).

In 2013, the ORWH launched a program that provided funding supplements to existing NIH grants to add subjects, tissues, or cells of the opposite sex used in the original grant, or if the sample already included males and females, to add more subjects of either sex to increase the power of the study and the ability to appropriately analyze the results for sex/gender differences (Clayton & Collins, 2014). This program was on the heels of a policy in 2014 requiring that all applicants report plans to balance male and female cells and animals in preclinical studies, unless exception is warranted (Clayton & Collins, 2014). In 2015, NIH put out a policy stating that "NIH expects that Sex as a Biological Variable will be factored into research designs, analyses, and reporting in vertebrate animals and human studies" (National Institutes of Health, 2015).

Journals

Various journals have adopted editorial guidelines regarding the reporting and analysis of sex and gender in their publications. Some journals have created their own guidelines, such as

the *Journal of the American Association* (JAMA), which requires authors to explain the methods used to obtain information on sex and gender in the methods section and the reporting and analysis of all outcomes by sex and gender in the results and discussion sections. If only one sex is reported or included in the study, authors must explain the reason for this (Instructions for Authors, n.d). Other journals have adopted the widely-used Sex and Gender Equity in Research (SAGER) guidelines. These were created by the Gender Policy Committee established by the European Association of Science Editors (EASE), with a panel of 13 experts representing nine different countries. An Internet survey was conducted to assess current sex/gender policies in journals; 716 respondents to the survey included journal editors, scientists, and others in the publishing field and represented 338 unique journals and 114 unique publishing houses. Participants indicated that only 7% of their journals had current sex/gender reporting policies. As a result, the SAGER guidelines were created, recommending that research be designed and conducted in a way that can reveal sex-related differences in the results. More specifically, the title and abstract should specify the sex and gender of the subjects, the methods section should report how sex and gender were regarded in study design and justify the reasons for any exclusion of one sex, and the results and discussion sections should include an analysis of outcomes by sex and gender and discuss implications, even if no difference was found (Heidari et al., 2016). These guidelines have been adopted by various journals, including the *Journal of Studies on Alcohol and Drugs*, *BMJ Global Health*, *Nature*, and *Reproductive Health Matters* (Sex and Gender Analysis Policies, n.d.). Other journals, such as the *Journal of Experimental Physiology*, *Journal of Physiology*, *PLoS Biology*, *PLoS Medicine*, and the *Journal of Surgical Research*, have adopted the Animal Research: Reporting In-vivo Experiments (ARRIVE) guidelines, which are specifically for studies using animal subjects. These guidelines require

authors to state the sex of the animal but do not require analysis by sex (Sex and Gender Analysis Policies, n.d.).

Conclusion

Even with all the progress that has been made and the policies that have been enacted, gaps still exist in the way women are cared for in medicine, and there is room for further improvement. While legislation has been enacted at a national level, one must wonder whether the persistence of these disparities is due to the prevailing unconscious biases that physicians harbor based on their training, leading them to continue the divide between males and females. It is noteworthy that the current literature contains data regarding how women's health is presented in medical school lectures (ABC7, 2011; Campbell, 1973; Howell, 1974) and how women are addressed in medical school textbooks (Dijkstra et al., 2008; Mendelsohn et al., 1994), though many of these studies are not current. Similarly, there are many clear findings regarding the historical lack of females, both humans and non-humans, in clinical trials. However, no studies to date have addressed whether these factors have actually correlated with a bias among physicians against women. If it were to be discovered through a quantitative study that a bias against women does exist, it would be important for the medical community to take steps to rid this bias. If physicians' attitudes towards women would change so that they are recognized as equal beings deserving of competent care, physicians may be more likely to include them in clinical trials, believe their reports of pain, and ensure that they are given adequate treatments.

Research Proposal

A proposed study to address this would aim to quantitatively measure the degree of unconscious bias against females in physicians. A popular tool to measure unconscious bias is the Implicit Association Test (IAT) (Greenwald et al., 1998), which measures the strength of association between concepts and evaluations. The IAT includes various trials. At first, participants are given concepts, such as a flower and insect, on opposite sides of the screen. Then, types of flowers and insects, such as tulips and wasps, as presented in the middle of the screen. Participants are supposed to correctly categorize these words into their respective concept, such as matching tulip with flower, by pressing the specific right-hand or left-hand key given by the computer program. In the second trial, two attributes, such as pleasant and unpleasant, are presented on opposite sides of the screen. Pleasant and unpleasant words, such as happy and sad, are then presented, and participants are supposed to correctly match the words with their overarching category.

After these two trials, two of the concepts are combined, such as flower and pleasant and insect and unpleasant, and these combinations are presented on opposite sides of the screen. Words from all the categories are presented in the middle of the screen, and participants have to match the words to the corresponding categories, just as in the previous tasks. Afterwards, the concepts are combined in the opposite formation, with flower and unpleasant being paired on one side and insect and pleasant being paired on the other side, words from all of the categories being presented again.

The theory behind the IAT is that when presented with two concepts that are associated with each other, such as “flower” and “pleasant,” the response of appropriate categorization will be faster than when two concepts that are not associated are presented together, such as “insect” and “pleasant.” In evaluating the time differences between the pairings, it can be reasonably

determined whether the participant associates concepts with positive or negative words (Greenwald et al., 1998).

Methods/Measures

For the current study, the IAT could be adapted to measure physicians' implicit associations regarding females. The concepts of "male" and "female" can be paired with both positive words, such as "trustworthy," "reliable," "honest," "admirable," and "sincere," and negative words, such as "dishonest," "untrustworthy," "detestable," "faker," and "moody," to assess whether physicians are more likely to associate "female" with the negative adjectives. Possible associations between a higher degree of bias and factors such as physician gender, specialty, and medical school will be examined. To recruit participants, an announcement with a link to the study will be sent to memberships of professional and student medical organizations.

Importance of Results

If the results show that there is no bias among physicians against females, other explanations and courses of action must be considered to explain the endurance of the disparities in clinical care for females. However, if the finding confirms that there does exist a bias of physicians against female patients, steps must be taken to address this bias. Medical school professors must make a more conscious effort to limit the passage of biased messages through their lectures, such as always using females to portray a patient who is faking symptoms. Textbooks must be revised to include a reasonable number or percent of female diagrams and pictures, and to contain specific information regarding the typical symptom presentation in both males and females as well as the appropriate treatments and dosages that are effective for both

genders. Once doctors are no longer exposed to constant expressions of bias through their training, they may be more likely to view females as equally trustworthy and deserving of competent medical care, both through the use of appropriate treatments and through the inclusion in clinical trials to develop more treatments.

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