GENDER IN MEDICINE

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Introduction

Increasingly, a significant amount of research calls attention to the influence of sex and gender in health and disease. For example, various studies suggest that disparities between men and women exist in the diagnoses and treatment of a variety of health conditions (IOM 2010, Kent, Patel, and Varela 2012). To some extent, health disparities may be the result of biological differences between groups, such as anatomical, physiological, hormonal, and genetic differences. Disparities may also be partly explained by differences in behaviors and lifestyle choices. However, gender also significantly affects differences in the power and control that men and women have over socioeconomic resources, their social position, their treatment in communities, their access to education and health care, and their susceptibility and exposure to particular health risks. Thus, gender health disparities can be the result of complex social factors, including discriminatory norms and practices related to health and disease within households, differential vulnerabilities to disease, and biases in health systems and health research (Sen and Ostlin 2008). Failure to be attentive to differences related to sex and gender can itself also create or exacerbate health disparities.

The purpose of this chapter is to show some of the ways in which attending to potential biological and social differences along sex and gender lines can be important for improving health outcomes in women and addressing gendered health inequalities. Using cardiovascular diseases (CVDs) as an example, we discuss how utilizing gender as a category of analysis in medicine can help uncover a variety of relevant phenomena crucial in researching, diagnosing, and treating a disease, and how failing to do so may obscure such phenomena. Differences between men and women in relation to CVD have become well known (Collins et al. 2011, Stock and Redberg 2012, Wenger 2012, Wyant and Collett 2015), thus this case provides an opportunity to examine the relevance of using sex and gender as categories of analyses in order to improve health outcomes.

Although in ordinary language use, “sex” and “gender” are often used interchangeably, feminist scholars have historically distinguished sex (being female or male) from gender (being a woman or a man) and have associated sex with biological characteristics and gender with social ones (Warnke 2011). Nonetheless, the categories of sex and gender, like that of race, are contested ones (Spelman 1988, Fausto-Sterling 2000, Butler 2004, Alcoff 2006, Warnke 2011, Witt 2011, Haslanger 2012) and should not be assumed to track simple binary categories. In this chapter we do not take a position on the sex/gender distinction (i.e., whether there is one and what, if anything, it amounts to). We do, however, take the category gender/sex to
be a relevant category of analysis in medicine, one that can be helpful in calling attention to unjust health disparities and needed in order to decrease existing health inequalities. In what follows, we use “gender” to refer to differences that can result from biological, psychological, and social aspects and from the interplay of these aspects. Thus, it captures, but is not limited to, traditional understandings of sex categories. Although here we focus on how gender affects health outcomes for women, notice that gender is not a category that applies only to women, and thus gender differences are relevant also to the health of all human beings. For example, masculinity norms can lead men to risk-taking behaviors that are likely to negatively affect their health (Fleming and Agnew-Brune 2015). Of course, one of the challenges of using gender as a category of analysis is that it does not track a monolithic group. There are significant differences, for instance, among women of different races, ages, sexual orientation, and socioeconomic classes. Despite these differences, our claim is that gender, along with other axes of difference, is often important to understanding and improving health problems.

In the first section we briefly introduce CVD and present evidence for the various ways in which inattention to gender and gender bias can influence medical research and clinical practice in this area and ultimately contribute to unjust gender health disparities: from animal studies, to the design of clinical trials, to clinical care. In the last section we point out different ways in which gender can be used as a relevant category of analysis throughout research and diagnosis so as to minimize gender biases and achieve better health outcomes for all.

**Gender Biases in Medicine**

An increasing number of studies are focusing on the effects of gender in health and disease and many have shown the existence of important gender health disparities. Gender differences in CVD in particular have received a significant amount of attention. CVDs are a class of disorders that involve the heart and blood vessels and include coronary artery disease, heart failure, stroke, and hypertension (WHO 2015). Despite significant declines in CVD mortality rates during the last decade, these diseases are currently the leading cause of death in women and men globally (WHO 2015). However, more women than men who have CVDs die from these diseases, and there has been an increase in mortality among young women with ischemic heart disease, despite a higher prevalence of this disease in men (Wyant and Collett 2015). Studies also show that a greater proportion of women with heart attacks die before hospital arrival, and a greater proportion also die within 1 year of having the disease compared with men (Stock and Redberg 2012). Similarly, women experience greater morbidity and mortality than do men after having coronary artery bypass. Additionally, although risk factors for CVD are the same in women and men, there are gender differences in the prevalence of risk factors such as high blood pressure and diabetes mellitus (Mosca, Barrett-Connor, and Wenger 2011).

Some CVD conditions that occur in both men and women have difference prevalence rates. For example, there is a predominance of pulmonary hypertension and atrial fibrillation in females and a predominance of systemic hypertension in males (Miller and Best 2011). Gender differences also exist in disease presentation (Collins et al. 2011, Stock and Redberg 2012). For instance, chest pressure spreading to the left arm is usually thought to be the distinctive symptom of coronary heart disease, but women tend to present more often with neck, jaw, or back pain, shortness of breath, nausea, indigestion, and fatigue (Collins et al. 2011). Evidence suggests that gender-specific genetic, anatomic, and physiological differences also contribute to CVD (Mercuro et al. 2010).

A variety of factors likely contribute to the observed gender differences in cardiovascular and other diseases and disorders, from physiological, anatomic, and genetic factors to delays in recognizing symptoms, to lack of knowledge of underlying pathologic processes,
to underutilization of diagnostic tests and treatments (Collins et al. 2011, Mosca, Barrett-Connor, and Wenger 2011, Stock and Redberg 2012). As we show below, some of these health disparities are the result of gender biases that fail to recognize salient differences between men and women. Thus, taking gender into account as a relevant category of analysis in medical research and practice can contribute to reducing gender health disparities. That is, attention to gender can influence how research is done when trying to understand CVD and develop potential interventions to treat those diseases. It can also impact how CVD is diagnosed and treated in ways that may contribute to improved health outcomes in women. In what follows, we discuss how this is the case at different research and clinical stages.

Animal studies are usually the first step in the acquisition of knowledge about disease mechanisms and drug or medical intervention effects. Often, however, what are clearly encouraging results encountered in preclinical investigations fail to translate into efficacy in clinical studies with humans. Indeed, evidence shows that this is the case for around 90% of preclinical studies showing safety and efficacy (van der Worp and Macleod 2011). Clearly, the biology of human beings shares commonalities with rodents and nonhuman primates, but inferences from animal models to humans are fraught with difficulties. Reasons for this disconnect between preclinical and clinical outcomes include problems with the animal models used, poor methodological quality of animal studies, and publication bias (de Jong and Maina 2010, Jucker 2010, Berton, Hahn, and Thase 2012, van der Worp and Macleod 2011, Mergenthaler and Meisel 2012). Of importance for gender disparities is the fact that researchers often use exclusively male animals in preclinical research (Beery and Zucker 2011, Rice 2012, Kokras and Dalla 2014, Yoon et al. 2014, Franconi, Rosano, and Campesi 2015). Rodent studies used to evaluate the effects of drugs on behavior use males nearly exclusively, despite the evidence showing sex differences in drug metabolism (Hughes 2007). The underrepresentation of females in animal models exists even in studies for diseases that predominantly affect women. For instance, although diagnoses for depressive and anxiety disorders, stroke, and thyroid diseases are significantly more common in women than in men, the majority of research with animals to study these disorders actually used male animals (Zucker and Beery 2010). Similarly, the majority of basic and preclinical studies conducted on experimental animals studying physiological, pharmacological, and endocrinological aspects of cardiovascular disease mostly use male animals (Beery and Zucker 2011).

The predominant use of males in animal models has occurred in part because it has been assumed that hormonal variability during the estrous cycle of females presented confounding variables that made it difficult to establish clear causal relationships necessary for understanding the mechanisms of disease and for testing the efficacy of interventions. This assumption has nonetheless come under critical scrutiny (Prendergast, Onishi, and Zucker 2014). Moreover, it seems that to the extent that the hormonal cycles of females present confounding variables, it is not clear that this should count as a reason to prefer male-only animal models for diseases that affect both sexes and much less for those that predominantly affect women. After all, if differences in hormones play a role in the etiology of a disease, excluding females is likely to result in incomplete or inadequate knowledge of the mechanisms of disease. Similarly, if hormone cycles affect drug metabolism, excluding females can produce interventions that might be unsafe or ineffective when used by women. Indeed, to the extent that females are relevantly different, studying these differences will be crucial to understanding disease mechanisms, recognizing symptom presentation, and ensuring the efficacy and safety of medical interventions.

But underrepresentation of females in animal models is not the only problem in basic research that can affect gender disparities. Some studies have also shown that cells from male and female mice have different properties. For example, muscle stem cells taken from female mice regenerate new muscle faster than those taken from males (Deasy et al. 2007). Cells from
male and female have likewise been found to respond differently to stress and exhibit different concentrations of many metabolites (Penaloza et al. 2009). These differences in cell characteristics have potential implications for the development of effective treatments for both men and women for conditions such as muscular dystrophy. Nonetheless, even when female animals are included, sex is not often used as a category of analysis, and thus researchers fail to track it. In fact, publications of preclinical studies rarely include sex-based analyses (Beery and Zucker 2011). This lack of attention to gender in basic research and animal studies led the National Institutes of Health (NIH) in October 2014 to implement new policies. Such policies now require NIH grant applicants to report plans for the balance of male and female cells and animals in preclinical studies or to justify that sex-specific inclusion is unwarranted (Clayton and Collins 2014).

Clinical trials, biomedical or behavioral research studies involving human participants that evaluate the efficacy and safety of medical interventions, are now ahead of animal studies with respect to female inclusion. A reason for this progress was the NIH Revitalization Act passed by Congress in 1993 in order to increase the representation of women and minorities in clinical trials. Subsequently, the NIH issued guidelines that required the inclusion and evaluation of gender/sex differences in clinical trials so as to ensure that results about safety and efficacy of drugs and other interventions will be generalizable. As a consequence of this requirement, the number of women participating in clinical research has increased significantly. In fact, evidence indicates that since 1993 more women than men have been enrolled in NIH-sponsored phase 3 trials (Kim, Tingen, and Woodruff 2010). Nonetheless, this increase in women's participation seems to be primarily the result of a few large single-sex studies of reproductive cancer trials (Kim, Tingen, and Woodruff 2010). Thus, despite the improvement in women's participation, clinical trial research often also fails to be sufficiently attentive to gender (IOM 2012). Today, women are still generally underrepresented in clinical trials, even in those studying conditions that have higher prevalence in women (Blauwet et al. 2007, Hoel et al. 2009, Jagsi et al. 2009, Weinberger, McKee, and Mazure 2010). Recent evidence shows that a significant number of clinical trials for depression, for instance, fail to report the gender composition of their sample, do not analyze outcomes by gender, or do not analyze for gender differences (Weinberger, McKee, and Mazure 2010).

Inadequate attention to gender in clinical trials can have devastating effects on women’s health. This can be observed when assessing interventions for CVD approved by the FDA despite the lack of sex-specific analysis (Dhruva, Bero, and Redberg 2011). One of such interventions, the implantable cardioverter-defibrillator, was approved despite very low enrollment of women in the major trials, but a meta-analysis has shown a lack of device efficacy in primary prevention trials in women with heart failure (Ghanbari et al. 2009). Similarly, between 1997 and 2001, the FDA withdrew ten prescription drugs, eight of which were more dangerous to women than to men, and in 2000 the FDA decided to remove a component of many over-the-counter medications, phenylpropanolamine, because of a reported increased risk of bleeding into the brain in women but not in men (Pollitzer 2013).

Inattention to gender can also affect diagnosis and treatment of diseases. A variety of studies have shown gender differences in the use of diagnostic procedures to evaluate CVD and in the treatment of these diseases. These studies indicate that women are less likely to receive both invasive and noninvasive testing when they present to an emergency department with chest pain (Miracle 2010). Some research has shown that men presenting with chest pain are usually treated more aggressively than women with similar complaints and are more likely to be admitted to the intensive care unit, receive cardiac catheterization, and initial electrocardiogram. Women, however, are more likely to receive drugs, including anxiolytics (Kent, Patel, and Varela 2012). Some studies have also shown that women suffering from certain coronary
problems are less likely to receive recommended prescription of beta-blockers when discharged from the hospital (Birkemeyer et al. 2014). Furthermore, some diagnostic tests have been found to be less able to correctly identify CVD in women, such as exercise electrocardiography and radionuclide myocardial perfusion imaging used to diagnose coronary artery disease (Kim, Tingen, and Woodruff 2010). All of these factors may contribute toward women having higher morbidity and mortality rates from CVD.

Gender differences in treatment side effects also exist (Mosca, Barrett-Connor, and Wenger 2011). For instance, women with acute coronary syndromes receiving antiplatelet pharmacotherapy are more likely than men to have bleeding problems, although they have similar benefits from these medications. Low-dose aspirin to prevent CVD seems to also have less beneficial effects on women than men. Although statin therapies reduce global cardiovascular risk in women as in men, evidence indicates that the absolute benefit in women who do not have established coronary disease is small (Miller and Best 2011). Thus, ignoring gender as a category of analysis can obscure the fact that the risks and benefits of various interventions can be different for men and women.

Some evidence indicates that these gender disparities in diagnosis and treatment of CVD might be the result of physicians’ misinterpretations or neglect of women’s symptoms because such symptoms do not fit with those that men have and because of the belief that CVDs are primarily male diseases. Other studies indicate that disparities in diagnosis and treatment intervention might result from other gender biases. In particular, because women with CVDs present with stress and anxiety, these symptoms mislead physicians toward mental health alternative diagnoses (Chiaramonte and Friend 2006). In any case, gender stereotypes can affect how physicians interpret patients’ symptoms, and thus ignoring gender can conceal unintentional biases.

**Making Gender Visible in Medicine**

We have aimed to show that gender matters in a variety of ways to our understanding of health and disease. When researchers or physicians are not attentive to potential relevant gender differences, it can lead to unconscious biases in experimental designs, the kinds of interventions developed, the interpretation of clinical trial results, and diagnostic and treatment decisions. As we have seen, these biases can lead to incorrect diagnoses, unequal access to experimental interventions, an inattention to differences in the effectiveness of resulting treatments, and in the frequency or severity of side effects. Ultimately, a failure to take gender into account can contribute to poor health outcomes for women.

Addressing these problems, however, is not easy, particularly as it is not always possible to know a priori whether gender differences exist in a particular case or to what extent they matter for the condition studied. In addition, gender biases are generally unconscious, such that, even when they might be well-intentioned and conscientious, it is difficult for individual researchers or physicians to prevent such biases from happening. However, a variety of practices may help improve medical research and practice in ways that can contribute to reducing health disparities and improving health outcomes for both women and men. In particular, addressing the problems discussed here requires using gender as a category of analysis in both biomedical research and patient care so as to make gender and its effects more visible.

What does it mean to “use gender as a category of analysis”? In general, this means that medical researchers and practitioners ought to consider how gender differences may or may not be relevant to the decisions they make. This can be done in a variety of ways throughout the research process and in medical practice.
First, gender should be used as a category of analysis in the framing of research questions, selection of methodology, or development of interventions. In investigating a particular health problem, researchers should seek to examine similarities and differences between males and females in a variety of aspects, such as disease causes, risk factors, likely age of onset, and symptoms. In developing interventions, investigators should determine whether, and if so which, biological and social differences exist that might make specific treatments more or less effective for one sex or another. For example, as we have seen, it is important for biomedical researchers and physicians to consider questions such as whether CVD operates differently in men and women, whether risk factors are the same, and whether there are differences in the presentation of symptoms. Similarly, researchers should consider whether there are social, political, economic, or biological differences among men and women that might be relevant to understanding the epidemiology of a disease, or whether there are differences in social conditions that present challenges or require trade-offs in addressing the disease burden. For example, nearly six in ten poor adults are women, and nearly six in ten poor children live in families headed by women (DeNavas-Walt and Proctor 2015). Poverty rates are especially high for single mothers, women of color, and elderly women living alone. Socioeconomic status can affect disease risks, health outcomes, and morbidity and mortality. Being attentive to these differences makes it more likely that the framing of research problems, choice of methodologies, selection of data, and development of interventions will result in more effective treatments for both men and women.

Second, studying similarities and differences along gender lines obviously calls for increasing the participation of females in preclinical and clinical research. As noted earlier, the NIH has now developed new requirements to ensure increased inclusion of female animals. Grant applicants are obligated to present plans to appropriately balance the use of male and female cells and of animals in preclinical studies or justify that such balance is unwarranted (Clayton and Collins 2014). NIH's Office of Research on Women's Health now has supplemental funding for existing grants to incorporate animals, tissue, cells, or subjects of an underrepresented sex in order to allow for sex-based comparisons.

In human subject testing, medical researchers and practitioners should be particularly attentive to possible obstacles that might hinder the participation of women in clinical trials. For example, not uncommonly, pregnancy is an exclusion criterion in clinical trials. Such a criterion will obviously result in the exclusion of women but not men. Also, older patients are often excluded from clinical trials because of comorbid conditions, but this might result in a problematic underrepresentation of women, who develop some diseases, such as heart ones, later in life when they are more likely to have comorbid conditions (Bucholz and Krumholz 2015). Moreover, even when researchers may seek to include more women in clinical trials, social barriers may make achieving this goal difficult. For instance, because women are more likely to take care of their children, schedules chosen for clinical interventions in trials can unintentionally limit the participation of many women. Similarly, the costs often incurred in clinical trial participation (e.g., transportation, child care, etc.) might present significant burdens for many women.

Furthermore, physicians' biases might affect their beliefs about patients' preferences, anticipated logistical problems, patients' ability to understand or comply with study requirements, or the benefits of participation, and such beliefs might lead physicians to offer study participation to some patients but not to others (Howerton et al. 2007, Denson and Mahipal 2014). Thus, understanding the different barriers that can discourage the participation of women in clinical trials will also be important in achieving the goal of increasing women's participation in clinical trials.
Researchers, physicians, and health care organizations should also adopt strategies that actively encourage such participation. The creation of health registry programs that inquire about health and lifestyle and that then can serve as bases for clinical trial recommendations might be helpful in this respect. But, as we have indicated, these measures are unlikely to end the underrepresentation of women in clinical trials. More attention needs to be given to both investigating and trying to address institutional obstacles that make the participation of women difficult. Not only should inclusion criteria be scrutinized for its differential effects on women, but care should also be given to social factors that limit women’s participation.

Yet, while it is clearly important to increase the participation of females in preclinical and clinical studies, this is not sufficient to reduce gender health disparities. As noted earlier, even in animal and human studies that include females, gender analyses are often not conducted. Some studies rely on cells coming from both males and females, but they do not track origin and thus gender comparisons cannot be made. Therefore, it is not just ensuring an appropriate participation of female animals and women that is important but also making sex and gender visible in experimental design and selection of methodologies. Doing so obviously calls for the tracking of sex of cells, animals, and humans used in research so as to make comparative investigations possible. Failing to do so might also contribute to the long-standing, well-known, and prevalent difficulty to reproduce research findings (Begley and Ioannidis 2015). Replicability failures and lack of predictability from animal to human studies might in some cases be exacerbated by inattention to gender differences that lead researchers to fail to track sex or to include appropriate numbers of females in both preclinical and clinical studies. Using models that allow for gendered analyses and comparisons would thus be helpful.

Fourth, gender should be used as a category of analysis in diagnosis and treatment decisions. Health care professionals involved in diagnosing and treating CVD, for example, should be attentive to their patients’ gender and the ways in which gender and gender bias play a role in disease diagnosis and treatment recommendations. Physicians must be aware of the ways in which CVD presents differently for women and men and must adopt similarly aggressive testing and intervention strategies when appropriate. When relevant, treatments should be justified not only in relation to being the right course of action for a particular disease, but also for a particular disease in a patient of a particular gender. Likewise, there must be greater awareness of any differences along gender lines in terms of what side effects might result from a particular treatment. Patients should be counseled not only about what treatments are effective for a particular disease in general but also the risks and likelihoods of benefits given their sex, age, and other relevant categories. This would require medical education and training that includes a more attentive gender-specific curriculum. Although the desirability of such curriculum has been recognized for quite some time, few U.S. medical schools have fully achieved this goal (Kim, Tingen, and Woodruff 2010). The U.S. Food and Drug Administration could also help by mandating that sex-specific drug reactions be made clear to both physicians and patients.

Of course, ensuring that gender is properly used as a category of analysis throughout the research process is not only the responsibility of individual investigators and practitioners but of the health care community as a whole, including journal editors, reviewers, granting agencies, and medical educators. It should be given consideration and weight in the peer review process. Reviewers and editors should evaluate the extent to which gender analysis may be relevant and whether the presence or absence of such analysis has been appropriately accounted for in methodological choices, experimental design, and interpretation of results.
As noted earlier, one of the challenges of being attentive to gender and preventing bias is that such biases are often unintentional. As many have argued, it is very difficult for individuals to catch their own biases when they have failed to take into account potentially relevant gender differences (Longino 1990). One strategy for addressing this problem is increasing diversity among health care practitioners and within research communities. Our background assumptions and interests are significantly shaped by our experiences, and such experiences can be influenced in greater or lesser degree by a variety of factors such as our gender, race, class, or nationality. Having a diverse research community can increase the likelihood that implicit assumptions and biases of individual researchers will be identified and critically evaluated (Solomon 2001, Longino 2002, Wylie and Nelson 2007, Harding 2008, Intemann 2009, de Melo-Martín and Intemann 2011).

Given the still common underrepresentation of women in biomedical research, a call for diversity is particularly relevant. Recent statistics indicate that although in the U.S. during the last decade nearly half of all MD degrees have been awarded to women, they still constitute only about one-third of all actively practicing physicians (Lautenberger et al. 2014). Likewise, women make up just over one-third of full-time academic medicine faculty, and they constitute 34% of associate and 21% of full professors (Lautenberger et al. 2014). Moreover, the percentage of permanent women department chairs (15%) and deans (16%) remains alarmingly low (Lautenberger et al. 2014). Similarly, although more than half of the doctorates in the life sciences are currently awarded to women, they hold only 18% of full professorships (Sheltzer and Smith 2014). Encouraging strategies that would bring more women to biomedical research and medical practice, particularly in some specialties, is important because it would increase diversity in research labs, physicians’ offices, faculty at medical schools, and leadership positions.

This is not to say that female researchers or female physicians are necessarily more attentive to the issues and interests of women or less susceptible to gender biases. However, insofar as background assumptions often reflect shared experiences or convention, having a research community with diverse backgrounds, experiences, values, and interests makes it more likely that erroneous assumptions will be corrected. It might also increase the possibility that new research directions, explanations, models, methods, or interventions will be explored (Longino 2002, Solomon 2006, Intemann and de Melo-Martín 2014).

**Conclusion**

In this chapter we have aimed to examine some of the ways in which inattention to gender can play a role in researching, diagnosing, and treating certain diseases, and ultimately in causing or exacerbating health disparities along gender lines. It is a truism that no two patients are the same, and clearly a variety of biological and social factors affect disease presentation, diagnosis, and treatment. When researchers and health care professionals are not attentive to these differences, it can lead to poorer health outcomes for certain groups, even though such disparities are not intended. We have seen how this has occurred in the use of predominantly male-only animal studies, the underrepresentation of females in clinical trials, and inattention to physician biases in the diagnosis and treatment of particular diseases. A significant effort has been devoted to trying to increase the participation of females in biomedical research, and such efforts are certainly a necessary and important step toward addressing gender health disparities. Nonetheless, this is unlikely to be sufficient for addressing these health inequities. Researchers must use gender as a category of analysis in more robust ways that attend to research questions and methodologies, as well as the effects of gender biases in diagnosing and treating diseases.
References


**Further Reading**


