

Sex and Gender Factors in Medical Studies Implications for Health and Clinical Practice

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Males and females have different patterns of illness and different life spans . . . Understanding the bases of these sex-based differences is important to developing new approaches to prevention, diagnosis, and treatment.¹

THE US CENSUS BUREAU PROJECTS that the US population will have increasing numbers of women in the next decades and a greater proportion of the population will be elderly and nonwhite persons.² Women are the major consumers of health care, the major consumers of prescription drugs, and the primary decision makers about health care for their families.³ As attention is directed to improving health of and health care for women, sex and gender differences in research design and regulatory policies interface with clinical practice. An interdisciplinary, inclusive approach to health care based on sex- and gender-specific data is sought by consumers of health care, especially women.^{4,6}

Understanding the role of sex in health and disease begins with consistency in medical literature of the terms *sex* and *gender*.⁷⁻⁹ The recent Institute of Medicine report *Exploring the Biological Contributions to Human Health: Does Sex Matter?*¹ provides clarification of these terms in its discussions of differences between men and women. The term *sex* is used when differences are primarily biological in origin and may be genetic or phenotypic (genetic or physiological characteristics of being a man or woman), and *gender* is used when referring to social and cultural influences based on sex (BOX).

There is a long history of advocacy for health care specific to women in the

United States, dating as far back as the Popular Health Movement of the 1800s.³ The efforts of women in medicine, government, and advocacy in the 1980s propelled improvement of women's health through biomedical research and were primarily based in the public policy realm, relating to the inclusion of women in clinical studies. Results of these efforts included major revisions in policies for research as well as expanding what constitutes women's health. This goes beyond reproductive health and addresses women's health across their lifespan.¹⁰ As the women's health movement focused on the inclusion of women in clinical research to provide basic fundamentals for gender-appropriate health care, there has also been realization that sex and gender comparisons are important factors in research design. Such research has valuable implications for the practicing physician in the care of both female and male patients.¹¹ Not only may physicians need to make diagnostic and treatment decisions based on the sex of the patient, but they will also need to respond to gender differences in how women and men approach their physicians, their own health, and how they communicate their health concerns.^{12,13}

Historical Gender Bias

A 1994 report¹⁴ from the Institute of Medicine, *Women and Health Research*, referred to 2 forms of historical gender bias in the design and conduct of clinical studies: male bias, which is observer error caused by adopting a male perspective and habit of thought, and the male norm, which is the tendency to use men as the standard even in studies of diseases that affect both sexes. Although there are arguments that women's health issues have not been studied less than

men's health issues,¹⁵ the prevailing lack of information about sex and gender differences or similarities in health and disease has been documented in many publications.^{16,17} This historical bias is now being redressed through policies, priorities based on gaps in knowledge, and scientific mandates for analyses by sex or gender of clinical research results.¹⁸⁻²²

It is difficult to document and assess actual numbers of women and men included in clinical research prior to the earliest data compiled by the National Institutes of Health (NIH) for fiscal year 1994.²³ However, in response to the NIH Revitalization Act of 1993,¹² policies have been implemented that require monitoring the numbers of volunteers by sex and analyses by sex or gender. There are now efforts to encourage the publication of the results of such analyses, even if no differences are found, so that the clinical implications of sex differences in responses can be incorporated into health care practices.²⁴ Now that the results of clinical research are expected to be analyzed for sex differences, sex- and gender-appropriate, or sex- and gender-specific approaches for prevention, diagnosis, treatment, and counseling of both male and female patients can be better facilitated.^{6,25-27}

The Institute of Medicine report¹ states, "An additional and more general reason for studying differences between the sexes is that these differences, like other forms of biological variation, can offer important insights into underlying

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See also Patient Page.

Box. Definitions*

Sex: The classification of living things as man or woman according to their reproductive organs and functions assigned by chromosomal complement.

Gender: A person's self-representation as man or woman, or how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology and shaped by environment and experience.

Biology: The study of life and living organisms (according to *Dorland's Illustrated Medical Dictionary*, 1994; *Stedman's Medical Dictionary*, 1995), including the genetic, molecular, biochemical, hormonal, cellular, physiological, behavioral, and psychosocial aspects of life.

*Adapted from Wizemann and Pardue.¹

ing biological mechanisms." Furthermore, the report argues that "... there are multiple, ubiquitous differences in the basic cellular biochemistries of males and females that can affect an individual's health... [that] are a direct result of genetic differences between the two sexes."¹

Sex and Gender Do Matter

Research conducted to date has deepened scientific understanding of sex and gender differences in the etiology, diagnosis, progression, treatment, health outcomes, and prevention of many conditions that may affect both women and men. In many well-recognized health areas, sex and gender considerations for health care have been documented or are under study.

Urinary incontinence, which has a female-to-male ratio of 2:1, most commonly results from deficits of urine storage in women associated with risk factors related to the female pelvic anatomy and physiology. This is in contrast with incontinence in men, often caused by bladder outlet obstruction.²⁸

Manifestations and progression of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are distinct in women, who represent an estimated 26% of new infections.²⁹ It has been demonstrated that although the initial viral load in women is significantly lower than in men, women develop AIDS at the same rate as men.³⁰ These sex differences are significant, because they determine HIV treatment guidelines.

Responses to pain and pain therapies differ between men and women, although determining if this difference is related to sex-based (physiological) mechanisms of the brain, gender (psychosocial) factors, or both has not been clearly defined. Women are more likely to have a lower pain threshold and lower tolerance for pain than men, but data also suggest that women are more likely to be inadequately treated.³¹ The effects of some analgesics have also been found to vary with sex, a striking example being kappa-opioids (eg, pentazocine and nalbuphine) that are much more effective as analgesics in women.³² In addition, adverse events to therapeutic drugs are more common in women.³³

The prevalence and care of type 2 diabetes differ between men and women.³⁴ Type 2 diabetes is more prevalent in women than in men, especially after 65 years, resulting in increased risks for coronary heart disease and other comorbid conditions. Physicians must consider strategies and counseling for women across their lifespan, including prevention of risk factors (eg, obesity), management of pregnancy, and possible complications of depression.

Other clinical conditions for which knowledge of sex and gender factors can and will contribute to better clinical diagnosis, management, and prevention include irritable bowel syndrome, 3 times more common in women than in men and the most common diagnosis made by US gastroenterologists³⁵; gen-

der differences in successful smoking cessation strategies³⁶; sex differences in prevalence of chronic fatigue syndrome (0.52% in women and 0.29% in men)³⁷; incidence and effects of musculoskeletal diseases, such as osteoarthritis and osteoporosis, and sports injuries, such as anterior cruciate ligament tears for which women have a higher risk than men³⁸; and autoimmune diseases, major contributors to the mortality of women younger than 65 years.³⁹

Heart disease has only recently been recognized as the most common cause of death in women, as well as in men, but may have different signs and symptoms, outcomes, and responses to interventions for women and men. Sex and gender bias in heart disease research and care is among the most debated women's health issues.^{4,40-45} Anecdotal examples of unrecognized acute myocardial infarctions are often recounted by women's health advocates and physicians; however, the Heart and Estrogen/progestin Replacement Study reported a low incidence of such missed diagnoses of myocardial infarction in women with known coronary heart disease.⁴⁶ Although women have been included in most of the major clinical trials on heart disease funded by the National Heart, Lung, and Blood Institute of the NIH, many of the early trials did not provide conclusive evidence about risk factors or manifestations of this disease in women.⁴⁷ More than 14 clinical trials have been initiated within the past 10 years to better define risk factors, prevention, and treatment of coronary and cardiovascular disease that are specific to women.

Pharmacologic agents used to treat cardiovascular disease may also evoke different responses in women than men, with women having a heightened sensitivity to developing cardiac rhythm disorders after exposure.⁴⁸ Women are more likely than men to develop torsades de pointes, a potentially fatal arrhythmia, in response to some of these medications, several of which have since been removed from the market because of adverse effects.^{49,50} It has also been demonstrated that both sex differ-

ences and hormonal variations during the menstrual cycle may contribute to the greater tendency of women than men to develop ibutilide-induced torsades de pointes.⁵¹ Although there has been progress in identifying and understanding the role of various metabolic enzymes in causing sex differences in pharmacodynamics, these cardiovascular drug findings typify the need for more research and a better understanding of the need for sex-based analyses of responses to drugs and other pharmacologic interventions, with closer clinical attention to detect sex-based adverse effects.

Another example of the results of sex and gender determinations is depression.^{52,53} Major depression has been identified as second only to hypertension as reasons for primary care patient encounters.⁵⁴ Major depression and dysthymia affect approximately twice as many women as men, and other mental disorders, such as anxiety disorders, anorexia nervosa, and bulimia nervosa, are more common in women. The prevalence of schizophrenia and bipolar disorders is not different for women and men, but there are gender differences in age of onset, pattern of symptoms, and treatment response.⁵⁴ Women with a history of bipolar disorder are at increased risk for postpartum recurrence.⁵⁴ Conversely, autism, learning disabilities, and attention-deficit disorder are more common in men.⁵⁴

Understanding the interactions of biological factors (eg, genetic and hormonal influences) and environmental factors (eg, poverty, stress, and victimization) in mental illness and health will not only increase medical knowledge about etiology, but may also result in more effective interventions.⁵⁵ Sex differences in drug pharmacokinetics, such as effects on cytochrome P450 isoenzymes, can influence required antidepressant dosages in women, as do other factors such as age and pregnancy; biopsychosocial gender issues must also be considered in the clinical approach to the management of depression and other mental illnesses.

Conclusion

As the research agenda for women's health has expanded from the historical concept that women's health relates to reproductive hormones and organs, expectations of health care are increasingly based on an understanding of sex and gender factors.^{46,56} Issues that will be of importance in research, policy, and health care include wellness care and prevention of chronic disorders with consideration of sex and gender differences in weight patterns, injuries, and behaviors; more specific and individually tailored drug interventions with considerations of sex differences at the genetic, cellular, and functional levels; caregiving and effects on the caregiver; interdisciplinary and comprehensive approaches to multisystemic diseases, such as autoimmune diseases and hormone-based conditions; and sex and endocrine differences in manifestations of brain health and disorders such as epilepsy and Alzheimer disease.^{12,57} Women and men will both benefit from new approaches to health care that are based on education on the role of sex and the gender influences of social, economic, cultural, geographic, and behavioral factors.^{6,58,59}

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REFERENCES

1. Wizemann TM, Pardue M-L, eds. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Washington, DC: National Academy Press; 2001.
2. Hobbs FB. US Census Bureau. The elderly population. Available at: <http://www.census.gov/population/www/pop-profile/elderpop.html>. Accessed March 22, 2001.
3. Hoffman E, Maraldo P, Coons HL, Johnson K. The women-centered health care team: integrating perspectives from managed care, women's health, and the health professional workforce. *Women's Health Issues*. 1997;7:362-374.
4. Hoffman E, Johnson K. Women's health and managed care: implications for the training of the primary care physicians. *J Am Med Womens Assoc*. 1995; 50:17-19.
5. Phelan EA, Burke W, Deyo RA, et al. Delivery of primary care to women: do women's health centers do it better? *J Gen Intern Med*. 2000;15:8-15.
6. Kasper AS. Understanding women's health: an overview. In: Wallis L, ed. *Textbook of Women's Health*. New York, NY: Lippincott-Raven; 1997:3-5.
7. Fishman JR, Wick JG, Koenig BA. The use of "sex" and "gender" to define and characterize meaningful differences between men and women. In: *Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century*. Vol 2. Bethesda, Md: National Institutes of Health; 1999. NIH publication 99-4386.
8. Pinn VW. Women's health research: progress and future directions. *Acad Med*. 1999;74:1104-1105.
9. LaRosa JH, Pinn VW. Gender bias in biomedical research. *J Am Med Womens Assoc*. 1993;48:145-151.
10. Healy B. The Yentl syndrome. *N Engl J Med*. 1991; 325:274-276.
11. Doyal L. Sex, gender, and health: the need for a new approach. *BMJ*. 2001;323:1061-1063.
12. Gesensway D. Reasons for sex-specific and gender-specific study of health topics. *Ann Intern Med*. 2001; 135:935-938.
13. Carlson KJ, Skochelak SE. What do women want in a doctor? communication issues between women and physicians. In: Wallis L, ed. *Textbook of Women's Health*. New York, NY: Lippincott-Raven; 1997: 33-38.
14. Mastroianni AC, Faden R, Federman D, eds. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*. Washington, DC: National Academy Press; 1994.
15. Meinert CL, Gilpin AK, Unalp A, Dawson C. Gender representation in trials. *Control Clin Trials*. 2000; 21:462-475.
16. Brandt EN Jr. Some thoughts about women's health and its evolution. *J Gen Specif Med*. 1998;1: 48-49.
17. Pinn VW. An affirmation of research and health care for women in the 21st century. *J Gen Specif Med*. 1998;1:50-53.
18. National Institutes of Health, Office of Research on Women's Health. *Report of the National Institutes of Health: Opportunities for Research in Women's Health*. Washington, DC: US Government Printing Office; 1992. NIH publication 92-3457.
19. Pinn VW. Women's health research at the National Institutes of Health: historical inequities, present priorities, future directions. In: Wallis L, ed. *Textbook of Women's Health*. New York, NY: Lippincott-Raven; 1997:971-986.
20. Prout MN, Fish SS. Participation of women in clinical trials of drug therapies: a context for the controversies. *Medscape Womens Health*. 2001;6:1.
21. National Institutes of Health, Office of Research on Women's Health. *An Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH: Women's Health Research Agenda for the 21st Century*. Vol 2. Bethesda, Md: National Institutes of Health; 1999. NIH publication 99-4386.
22. *National Institutes of Health Revitalization Act*, 42 USC §289a1 (1993).
23. Pinn VW, Roth CA, Bates AC, Fanning L. *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: Tracking Committee Report*. Bethesda, Md: National Institutes of Health; 2002. Available at: <http://www4.od.nih.gov/orwh/bluerpt.pdf>. Accessibility verified January 3, 2003.
24. Arnold K. Journal to encourage analysis by sex/ethnicity. *J Natl Cancer Inst*. 2000;92:1561.
25. Legato MJ. Is there a role for gender-specific medicine in today's health care system? *J Gen Specif Med*. 2000;3:12, 15-21.
26. Weisman CS. Advocating for gender-specific health care: a historical perspective. *J Gen Specif Med*. 2000;3:22-24.
27. US General Accounting Office. *Women's Health: NIH Has Increased Its Efforts to Include Women in Research*. Washington, DC: US Government Printing Office; 2000.
28. Romanzi LJ. Urinary incontinence in women and men. *J Gen Specif Med*. 2001;4:14-20.

29. Centers for Disease Control and Prevention. HIV/AIDS surveillance in women. Available at: <http://www.cdc.gov/hiv/graphics/images/1264/1264-1.htm>. Accessibility verified January 2, 2003.
30. Sterling TR, Vlahov D, Astemborski J, et al. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med*. 2001;344:720-725.
31. Hoffman DE, Tarzian AJ. The girl who cried pain: a bias against women in the treatment of pain. *J Law Med Ethics*. 2001;29:13-27.
32. Gear RW, Miaskowski C, Gordon NC, et al. Kappa- μ opioids produce significantly greater analgesia in women than in men. *Nat Med*. 1996;2:1248-1250.
33. Anthony M, Berg MJ. Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: part I. *J Womens Health Gender Based Med*. 2002;11:601-615.
34. Campaigne BN, Wishner KL. Gender-specific health care in diabetes mellitus. *J Gen Specif Med*. 2000;3:51-58.
35. Horwitz BJ, Fisher RS. The irritable bowel syndrome. *N Engl J Med*. 2001;344:1846-1850.
36. Perkins KA. Smoking cessation in women: special considerations. *CNS Drugs*. 2001;15:391-411.
37. Natelson BH. Chronic fatigue syndrome. *JAMA*. 2001;285:2557-2559.
38. Gwinn DE, Wilckens JH, McDevitt ER, et al. The relative incidence of anterior cruciate ligament injury in men and women at the United States Naval Academy. *Am J Sports Med*. 2000;28:98-102.
39. Walsh SJ, Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *Am J Public Health*. 2000;90:1463-1466.
40. Mehilli J, Kastrati A, Dirschinger J, et al. Sex-based analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention. *JAMA*. 2002;287:210-215.
41. Buring JE. Women in clinical trials: a portfolio for success. *N Engl J Med*. 2000;343:505-506.
42. Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med*. 2000;343:475-480.
43. Lawler DA, Ebrahim S, Smith GD. Sex matters: secular and geographical trends in sex differences in coronary heart disease mortality. *BMJ*. 2001;323:541-545.
44. Krummel DA, Koffman DM, Bronner Y, et al. Cardiovascular health interventions in women: what works. *J Womens Health Gender Based Med*. 2001;10:117-136.
45. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001;286:708-713.
46. Shlipak MG, Elmouchi DA, Herrington DM, et al. The incidence of unrecognized myocardial infarction in women with coronary heart disease. *Ann Intern Med*. 2001;134:1043-1047.
47. Lenfant C. Heart disease research in women: a look back and a view to the future. In: National Institutes of Health, Office of Research on Women's Health. *An Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century*. Vol 2. Bethesda, Md: National Institutes of Health; 1999. NIH publication 99-4386.
48. Berg MJ, Ketley JN, Merkatz R. Pharmacologic issues. In: National Institutes of Health, Office of Research on Women's Health. *An Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century*. Vol 2. Bethesda, Md: National Institutes of Health; 1999. NIH publication 99-4386.
49. Benton RE, Sale M, Glockhart DA, Woosley RL. Greater quinidine-induced QTc interval prolongation in women. *Clin Pharmacol Ther*. 2000;67:413-418.
50. US General Accounting Office. *Women's Health: Women in Clinical Drug Trials*. Washington, DC: US Government Printing Office; 2001.
51. Rodriguez I, Kilborn MJ, Liu XK, et al. Drug-induced QT prolongation in women during the menstrual cycle. *JAMA*. 2001;285:1322-1326.
52. Desai HD, Jann MW. Major depression in women: a review of the literature. *J Am Pharm Assoc*. 2000;40:525-537.
53. American Psychological Association. *Summit on Women and Depression: Proceedings and Recommendations*. Washington, DC: American Psychological Association; 2002. Available at: <http://www.nimh.gov/wmhc/summit.cfm>. Accessibility verified December 10, 2002.
54. Blehar MC. The NIMH women's mental health program: establishing the public health context for women's mental health. *Trends Evidence Based Neuropsychiatry*. 2001;3:42-43.
55. Kendler KS. Gender differences in the genetic epidemiology of major depression. *J Gen Specif Med*. 1998;1:28-31.
56. DeAngelis DC, Winker MA. Women's health: filling the gaps. *JAMA*. 2001;285:1508-1509.
57. Women's health in the next millennium. *Harv Womens Health Watch*. 2000;7:4-6.
58. Weisman CS. The trends in health care delivery for women: challenges for medical education. *Acad Med*. 2000;75:1107-1113.
59. Weisman CS. Women's primary care [comment]. *Health Aff (Millwood)*. 1997;16:276-277.

To think is to differ.
—Clarence S. Darrow (1857-1938)