

Sex and Gender: How they Influence Women's Health and Diseases

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- Sarah Temkin, M.D. (she/her), is the Associate Director for Clinical Research at ORWH. Dr. Temkin provides clinical expertise on issues related to the health of women, specifically cancer control, supportive care for cancer, therapeutics for female-specific malignancies, surgical care, and gynecologic disorders. Her clinical research team oversees the U3 Administrative Supplement Program, as well as the office's interprofessional development program.
- Dr. Temkin is a gynecologic oncologist who earned her medical doctorate from Georgetown University, completed her residency in obstetrics and gynecology with the Icahn School of Medicine at Mount Sinai and completed a fellowship in gynecologic oncology at the SUNY Downstate Medical Center.
- She has also had faculty appointments at several academic institutions. She has also served in the National Cancer Institute within the Division of Cancer Prevention.
- She has been active in clinical research throughout her career, with a recognized expertise in clinical trials. Dr. Temkin has served as an investigator for novel therapeutic and supportive care interventions for women with ovarian, endometrial, and cervical cancers.
- In addition, Dr. Temkin has thoughtfully contributed to national conversations about cancer prevention and equity in healthcare. In recent years, Dr. Temkin has provided a voice for equity in the physician workforce, specifically attuned to the unique challenges of surgeons and gynecologists who are women.



Disclosure

- Dr. Sarah M. Temkin has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the NIH, ORWH, Department of Defense, nor the U.S. Government.
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Learning Objectives

At the end of the presentation, the learners will be able to:

- 1. Explain the role of the ORWH and NIH on women's health, including clinical research and practice.
- 2. Compare the male and female genetic and physiological make-up and their contribution to health.
- 3. Differentiate sex from gender and their effects to health and diseases.
- 4. Describe how social constructs influence to health.
- 5. Identify diseases that have higher prevalence in women.



ORWH Mission

Enhance and expand women's health research

Include women and minority groups in clinical research



Promote career advancement for women in biomedical careers

NIH Vision

Ś

Sex and gender integrated into biomedical research

Every woman receives evidence-based care

Women in science careers reach their full potential



Women's Health





Sex Influences Health



"A common, recurring message emerged ... This message is that sex—that is, being male or female—is an important basic human variable that should be considered when designing and analyzing the results of studies in all areas and at all levels of biomedical and health related research.

Differences in health and illness between individuals are influenced not only by individuals' genetic and physiological constitutions but also by environmental and experiential factors, all of which interact."

Institute of Medicine, 2001



Sex vs Gender



- Every cell has a sex (XX or XY)
- Sex begins in utero
- Sex affects behavior and perception
- Sex affects health—from disease risk to treatment response



GENDER

A multidimensional psychosocial construct that integrates roles, behaviors, expressions, and identities of girls, women, boys, men, and gender-diverse people

- Influences how people perceive themselves and others, and how they act and interact
- Gender begins after birth, also affects behavior and perception, and health
- No agreed-upon definition of gender in the U.S., but new tools with which to study it



Cellular Level Sex Difference



- Exposure to stressors induces different responses depending on sex
 - Male and female cells differ in their ability to modulate the activity or expression rate of different molecular targets in response to estrogens (e.g., PARP-1, ER, RLIP76)

Sex differences in metabolic pathways

- Male cells favor carbohydrate and amino acid metabolism
- Female cells favor fatty acid metabolism
- Female mitochondria produce less reactive oxygen species (ROS) despite their higher mitochondrial activity





Sex Differences at the Level of the System

Nervous System

- Estrogen alters pain perception
- Women respond to opioids at lower doses than men

Vascular System

- Estrogen enhances induces vasorelaxation in female and male vessels
- Androgen signaling promotes vasorelaxation in in vitro studies but elevate blood pressure in vivo

Immune System

- *Toll-like receptor* (TLR) *7* and angiotensin-converting enzyme (ACE) *2* are localized to the X chromosome and escape X-chromosome inactivation in females
- Estrogen positively regulates TLR-mediated pro-inflammatory pathways
- Testosterone reduces natural killer (NK) cell activity and the secretion of pro-inflammatory cytokines





Sex Differences Influence Animal Models



- Treatment with the nNOS inhibitor (7nitroindozole, 25 mg/kg) increased infarction in female C57BI6 WT mice but protected male mice.
- Cell death pathways involving NO and ischemic neurotoxicity
 - Solely operant in male brain
 - The integrity of PARP-1 signaling is paradoxically protective in the female.



Sex Differences in our Measurements

Standard lab values can differ in women at different stages of the menstrual cycle



Statistically significant menstrual cycle-related changes were found in the following tests:

Higher during the early follicular phase: Sodium (Na), Chlorine (Cl), Creatine kinase, C-reactive protein, Serum amyloid A, Carbohydrate antigen 125, Parathyroid hormone

Higher during the luteal phase: Insulin, Total cholesterol, White blood cell count



Sex and Gender Interact to Influence Human Health

"The relevance of gender relations and sex-linked biology to a given health outcome is an empirical question, not a philosophical principle; depending on the health outcome under study, <u>both</u>, <u>neither</u> <u>one</u>, or the <u>other</u> may be relevant as sole, independent, or synergistic determinants." (Krieger, 2003, p.656)

"The sex-gender or nature-nurture accounts of difference fail to appreciate the degree to which culture is a partner in producing body systems commonly referred to as biology." (Fausto-Sterling, 2005, pg. 1516)



Temkin, 2021



Social Expectations: Gender

Gender roles: how we're expected to act, speak, dress, groom, and conduct ourselves based upon our assigned sex





Gender Influences How We Think About Sex

- Our "default" model for ovarian development was inherited from the 1950s and 1960s.
- Ovarian development has historically been described as a "default" or "passive" developmental outcome
 - Research into sex determination focused primarily on testis development
 - Active processes controlling ovarian development were largely ignored
 - The notion of a "passive" female developmental process fit with gender assumptions about women

Molecular and Genetic Events in Mammalian Sex Determination

Genes in the female pathway repress Sox9; genes in the male pathway express it



https://genderedinnovations.stanford.edu/case-studies/genetics.html#tabs-2





THE EGG AND THE SPERM: HOW SCIENCE HAS CONSTRUCTED A ROMANCE BASED ON STEREOTYPICAL MALE-FEMALE ROLES

EMILY MARTIN





The Egg and the Sperm

The egg behaves "femininely"

- The egg is seen as large and passive.
- It ... passively "is transported," "is swept," or even "drifts" along the fallopian tube.

The sperm behaves "masculinely"

- The sperm are "streamlined," and active.
- They "deliver" their genes to the egg, "activate the developmental program of the egg," and have a "velocity" that is often remarked upon.
- Their tails are "strong" and efficiently powered.



Gender Influences our Perceptions of the Health of Women



These Hysterical Women

RYING ... sobbing ... laughing! help her. How well and happy she migh She has no control of herself . . . be. the slightest thing drives her to distraction. Tired all the time . . . overwrought . . . nerves strung to the breaking point. Constant headache, backache, and dizzy spells are robbing this woman of youth, beauty and health.

ham's Vegetable Compound a chance to for other suffering women.

cine Company, 1172 Cleveland St., Lynr Massachusetts for a bottle which sell. regularly for \$1.50. Let us prove that this

Try Lydia E. Pinkham's Vegetable Compound Tablet Form

- The tablet form is so easy to take. Send fifty cents to the Lydia E. Pinkham Medi

If she would only give Lydia E. Pink- medicine can do for you what it has done

- The term hysteria is derived from the Greek word for the uterus, hysterika
- Ancient Greece: the uterus was to blame for the anxiety, insomnia, depression, irritability, fainting and other 'women's' symptoms
- Freud described hysteria as 'characteristically feminine' and recommended treating hysteria with marriage
- Removed from the Data and Safety Monitoring Board (DSMB) in 1980
- We still use this word for surgical removal of the uterus (hysterectomy)
- Dismissal of women's symptoms as "in her head" remains common http://screaminginallcaps.com/2014/04/04/words-have-meanings-hysteria/



Gender Influences How Women Receive Care

When Doctors Downplay Women's Health Concerns

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THE REPORT

Dying to be Heard

Maya Dusenbery discusses why women can have such a hard time getting the medical care they need.

By Gabrielle Levy Political Reporter April 20, 2018, at 6:00 a.m.

"They don't really take my bleeds seriously": Barriers to care fo women with inherited bleeding disorders

Sumedha Arya, Pamela Wilton, David Page, Laurence Boma-Fischer, Georgina Floros, Rochelle Winikof Jerome Teitel, Katie Dainty, Michelle Sholzberg 🔀

First published: 28 March 2021 | https://doi.org/10.1111/jth.15311 | Citations: 1

HARVARD HEALTH BLOG

Women and pain: Disparities in experience and treatment



Women are more likely to wait longer for a health diagnosis and to be told it's 'all in their heads'. That can be lethal: diagnostic errors cause 40,000-80,000 deaths in the US alone.

The Health Gap



National Institutes of Health Office of Research on Women's Health

Race Influences Health



A consistent body of research demonstrating significant variation when insurance status, income, age, and severity of conditions are comparable.



Differences, Disparities, and Discrimination: Populations with Equal Access to Healthcare. SOURCE: Gomes and McGuire, 2001



Race as a Social Construct Impacting Health Is Not A New Concept

- In 1899 WEB DuBois described racial differences in health as reflecting differences in "social advancements" - the "vastly different conditions" under which Black and White citizens lived
- Tuberculosis was the leading cause of death for the Black population in Philadelphia
 - Causative factors were "bad ventilation, lack of outdoor life for women and children, poor protection against dampness and cold are undoubtedly the chief causes of the excessive death rate"



Du Bois, 2007.



Our Zip Code May Be More Important Than Our Genetic Code: Social Determinants of Health, Law and Policy

DANNIE RITCHIE, MD, MPH GUEST EDITOR



Robert Wood Johnson Foundation



Life Expectancy at Birth for U.S. Census Tracts, 2010-2015



National Institutes of Health

Intersectionality



- Coined in 1989 by professor Kimberlé Crenshaw to describe how race, class, gender, and other individual characteristics "intersect" with one another and overlap
- The study of intersectionality has grown to include all of our intersections and identities.
- In 2013, The Oxford Dictionary of Social Work and Social Care broadened Crenshaw's conceptualization of the term, defining it as the combined effects of one's multiple identities, which includes identities such as race, gender, sexual orientation, religion, and employee status.



Maternal Morbidity and Mortality



²AHRQ, 2018. Trends in delivery hospitalizations involving SMM, 2006-2015.

https://www.cdc.gov/reproductive health/maternal-mortality/disparities-pregnancy-related-deaths



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Cardiovascular disease (CVD)

- CVD is the leading cause of death in women and men
 - Marked differences in the burden and outcomes associated with biologic, environmental, psychosocial, and structural factors.
- Percentages of all deaths caused heart disease, disaggregated by sex, race, and ethnicity vary widely
 - Black women have higher mortality rates from CVD than Asian men





COVID-19 sex differences

The Sex and Gender and COVID-19 Project





US COVID data

What does the sex-disaggregated data along the clinical pathway show?





Women are more vulnerable to infection from occupational risk



High risk of job loss





Geographic differences in Male: Female mortality

Mortality Rate Ratio



Male:female mortality rate ratio by pandemic waves (a–c) and cumulatively (d) across states. Orange indicates higher rates among men, blue indicates higher rates among women, and yellow indicates equal rates.



Predicted weekly mortality rate. The black trendline is the average across states at that week. Texas, New York, and Connecticut are emphasized in orange, blue, and green, respectively, to highlight trends.

National Institutes of

COVID, race, ethnicity and sex



Unadjusted and predicted COVID-19 mortality for individuals aged 18-65, per 100,000 persons, by race, ethnicity and sex, under alternative compositional, educational, and occupational distributions

Matthay et al., 2021, In press



Gender, Race and Ethnicity Influence the Healthcare Workforce

Full-Time Women Faculty by Rank and Race/Ethnicity, 2018

0.1%

FIGURE 13





0.1%

AMERICAN INDIAN OR ALASKAN NATIVE

BLACK OR AFRICAN AMERICAN

HISPANIC, LATINO, OR OF SPANISH ORIGIN

NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER

ASIAN

WHITE

HISPANIC

MULTIPLE RACE -

MULTIPLE RACE -

OTHER RACE/ETHNICITY

MISSING RACE/ETHNICITY

NON-HISPANIC

Professor Level, Race and Ethnicity



US Medical School Faculty at Professor Level - Black/African American Women



US Medical School Faculty at Professor Level - Hispanic/Latina Women

"The sheer number of inexorable zeros at the professor and chair level in aggregate at US medical schools provides evidence—especially in combination with a large body of scientific research on workforce gender and race/ethnicity disparities—that structural and institutional gender bias and racial/ethnic discrimination are influencing hiring and promotions in academic medicine."



Gender Influences Specialty Choice and Status



National Institutes of Health

Office of Research on Women's Healt

Women's health physicians are doing more for less

The more women in a specialty, the less money all physicians tended to earn.



For every 10% increase in the percentage of women there was a \$8255 decrease in mean salary for men and women p < .001.

Comparison of 2015 Medicare relative value units for gender-specific procedures: Gynecologic and gynecologic-oncologic versus urologic CPT coding. Has time healed gender-worth?

M.F. Benoit^{a,*}, J.F. Ma^b, B. A Upperman^c



- 42/50 (84%) male-based procedure compensated at a higher rate
- Male specific surgeries were reimbursed 27.67% higher
- No increase in female procedurebased work relative value units (RVUs) over 20 years



Bravender et al, 2021

Representation in NIH study sections





Bias in our Review Process



Research Conducted in Women Was Deemed More Impactful but Less Publishable than the Same Research Conducted in Men

Sohad Murrar, PhD,¹ Paula A. Johnson, MD, MPH,² You-Geon Lee, PhD,³ and Molly Carnes, MD, MS⁴⁻⁶



Workforce issues during COVID



In the United States, employment figures were down by 4.4 percentage points for women and 3.9 percentage points for men. White men's unemployment rate in the United States increased by 3.6 percentage points, but rose 4 percentage points for white women, 4.9 for Black or African-American women and 6.2 for Hispanic or Latina women



Global Gender Gap Report, 2021



The Impact of COVID-19 on the Careers of Women in Academic Sciences, Engineering, and Medicine



FIGURE 2-1 Summary of effects of COVID-19 on the work effectiveness and productivity of women in academic STEMM from the October 2020 survey.



Challenges for women healthcare workers

- Availability of correctly sized equipment and uniforms
- Accommodations for pregnant and other high risk (e.g., immunocompromised) populations
- Accommodations for breastfeeding
- Childcare reliability
- Visibility in leadership
- Pay equity

U.S. conflict or workforce	Total frontline providers, no.	Women frontline providers, no. (%)
World War I	4,734,99141	36,279 (0.8)41
World War II	16,112,56641	400,000 (2.5)41
Persian Gulf War	2,225,00041	155,750 (7.0)41
2019 health care workforce	9,684,000 ¹	7,301,736 (75.4)



Ensuring the Generalizability of Clinical Research

Subjects should be representative of the patient population for which the intervention is intended

2004

57%

43%







62%

2009

38%

2015

46%

54%

Median percentage

of subject sex across

RCTs that included

both sexes

Sex & Gender in NIH-Supported Research: Major Policies



- 1993: NIH Revitalization Act
 - Requires inclusion of women and racial/ethnic minorities in NIHfunded clinical research
 - Statutorily established ORWH (established in 1990)



- 2016: SABV Policy
 - Requires that "sex as a biological variable [SABV] will be factored into research designs, analyses, and reporting in vertebrate animal and human studies"
 - To study only one sex, application must include "[s]trong justification from the scientific literature, preliminary data, or other relevant considerations"



- 21st Century Cures Act
 - Individuals of all ages and pregnant and lactating women as important research participants
 - Requires NIH-defined applicable phase III CTs to report results disaggregated by sex and/or gender, race, and ethnicity into ClinicalTrials.gov



The Impact of SABV on Basic Science Research



 Between 2009 and 2019 the number of sex-inclusive research studies significantly increased across most biological disciplines



Consider Gender in Research

Inclusion Across the Lifespan: guidance for applying the policy

The Inclusion Across the Lifespan policy (IAL) applies to **all exempt and non-exempt human subjects research** (see <u>NOT-OD-18-116</u>), beginning with competing grant applications due **on/after January 25, 2019**, and R&D contract solicitations issued on/after this date.

For ongoing, non-competing awards, the Inclusion of Children in Research Policy continues to be in effect.



- Research involves data from pre-enrolled participants
- Laws/regulations bar inclusion of individuals in a specific age group in research
- The study poses unacceptable risk to the excluded age group

For the purposes of the policy, a <u>child</u> is an individual under the age of 18. An <u>older adult</u> is an individual 65 years of age or older. For more information, visit the <u>Inclusion Across the Lifespan website</u>.

 Inclusion policy and reporting options do not distinguish between sex and gender <u>Inclusion FAQ</u> refers to "sex/gender"

Inclusion categories in HSS limit reporting to *either* sex or gender—<u>researchers choose</u>

"consider what is most relevant to the scientific question under study (e.g., sex at birth, current gender identity, etc.)"

"investigators may collect data using other categories (e.g. non-binary) as long as they can aggregate the data into the sex/gender categories listed on the form"



https://orwh.od.nih.gov/sites/orwh/files/docs/ACRWH-CorbettInclusion-Spring2019-508C.pdf

Support Multi-Dimensional Research Frameworks

National Institute on Minority Health and Health Disparities Research Framework

		Levels of Influence*				
		Individual	Interpersonal	Community	Societal	
Domains of Influence (Over the Lifecourse)	Biological	Biological Vulnerability and Mechanisms	Caregiver–Child Interaction Family Microbiome	Community Illness Exposure Herd Immunity	Sanitation Immunization Pathogen Exposure	
	Behavioral	Health Behaviors Coping Strategies	Family Functioning School/Work Functioning	Community Functioning	Policies and Laws	
	Physical/Built Environment	Personal Environment	Household Environment School/Work Environment	Community Environment Community Resources	Societal Structure	
	Sociocultural Environment	Sociodemographics Limited English Cultural Identity Response to Discrimination	Social Networks Family/Peer Norms Interpersonal Discrimination	Community Norms Local Structural Discrimination	Social Norms Societal Structural Discrimination	
	Health Care System	Insurance Coverage Health Literacy Treatment Preferences	Patient-Clinician Relationship Medical Decision-Making	Availability of Services Safety Net Services	Quality of Care Health Care Policies	
Health Outcomes		A Individual Health	Family/ Organizational Health	合 Community 合合 Health	Health	

National Institute on Minority Health and Health Disparities, 2018

*Health Disparity Populations: Race/Ethnicity, Low SES, Rural, Sexual and Gender Minority Other Fundamental Characteristics: Sex and Gender, Disability, Geographic Region



Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Administrative Supplement Program

 Purpose: To provide one-year supplemental funding to active NIH parent grants to address health disparities among populations of women in the US who are underrepresented, understudied, and underreported (U3) in biomedical research









Such as *social determinants of health* including **gender**, environment, & policies

Preconception

Interaction



Childhood

Adolescence

Adulthood

Biological Perspective – Internal Factors

such as **sex** influences at genetic, molecular, cellular, & physiological levels





Interaction

Training the next generation of women's health researchers



- Created by the Office of Research on Women's Health (ORWH), the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) is a mentored career-development program designed to connect junior faculty, known as BIRCWH Scholars, to senior faculty with shared interest in women's health and sex differences research.
- Since the program was created in 2000, 88 grants to 44 institutions supporting more than 700 junior faculty have been awarded by ORWH and its partners among the NIH institutes and centers.



https://orwh.od.nih.gov/in-the-spotlight/all-articles/day-one-dec-14-bircwh-annual-meeting-marks-20th-anniversary-opens

ORWH's e-learning

Bench to Bedside: Integrating Sex & Gender to Improve Human Health

Immunology | CVD | Pulmonary Disease | Neurology | Endocrinology | Mental Health

Sex as a Biological Variable Primer

- With support from NIH National Institute of General Medical Sciences and the NIH Office of the Director
- Introduction to the Scientific Basis of Sex- and Gender-Related
 Differences | Including facilitator's guide





bit.ly/ORWHeLearning



Connect with ORWH



30TH ANNIVERSARY ISSUES

quarterly newsletter bit.ly/ORWHInFocus



The Pulse

monthly email bit.ly/ORWHpulse



WOMEN'S HEALTH IN FOCUS AT NIH A QUARTERLY PUBLICATION OF THE NIH OFFICE OF RESEARCH ON WOMEN'S HEALTH

Key takeaways

- ORWH continues its work to ensure that women's health research is part of the scientific framework, not only at NIH, but throughout the biomedical research enterprise.
- Differences in health and illness between individuals are influenced not only by individuals' genetic and physiological constitutions but also by environmental and experiential factors, all of which interact.
- Sex is a genetic and biologic condition defined by our chromosomes; Gender is a psychosocial construct based in our social expectations that guides acceptable behaviors that is unique to humans.





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Thank you!

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Questions?



To receive CE/CME credit, you must register by 0800 on 25 FEB 2022 to qualify for the receipt of CE/CME credit or a certificate of attendance. You must complete the program posttest and evaluation before collecting your certificate. The posttest and evaluation will be available through 10 MAR 2022 at 2359 ET. Please complete the following steps to obtain CE/CME credit:

- 1. Go to URL: https://www.dhaj7-cepo.com/FEB2022CCSS
- 2. Search for your course using the Catalog, Calendar, or Find a course search tool.
- 3. Click on the REGISTER/TAKE COURSE tab.
 - a. If you have previously used the CEPO CMS, click login.
 - b. If you have not previously used the CEPO CMS click register to create a new account.
- 4. Follow the onscreen prompts to complete the post-activity assessments:
 - a. Read the Accreditation Statement
 - b. Complete the Evaluation
 - c. Take the Posttest
- 5. After completing the posttest at 80% or above, your certificate will be available for print or download.
- 6. You can return to the site at any time in the future to print your certificate and transcripts at: <u>https://www.dhaj7-cepo.com/</u>
- 7. If you require further support, please contact us at: dha.ncr.j7.mbx.cepo-cms-support@mail.mil

