

The Power, Potential and Promise of Considering Sex and Gender to Advance Health

Chyren Hunter, Ph.D.

Associate Director for Basic and Translational Research
Office of Research on Women's Health

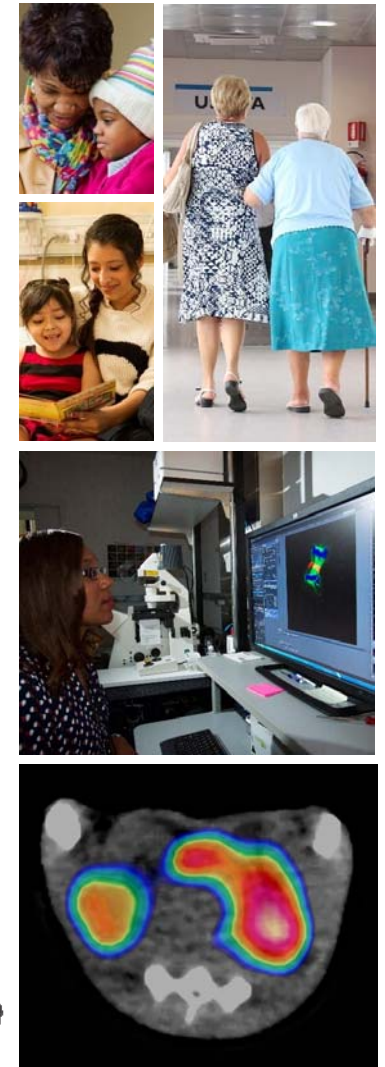
June 6-7 – RCCN 2019 SEX AND GENDER DIFFERENCES IN AGING



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

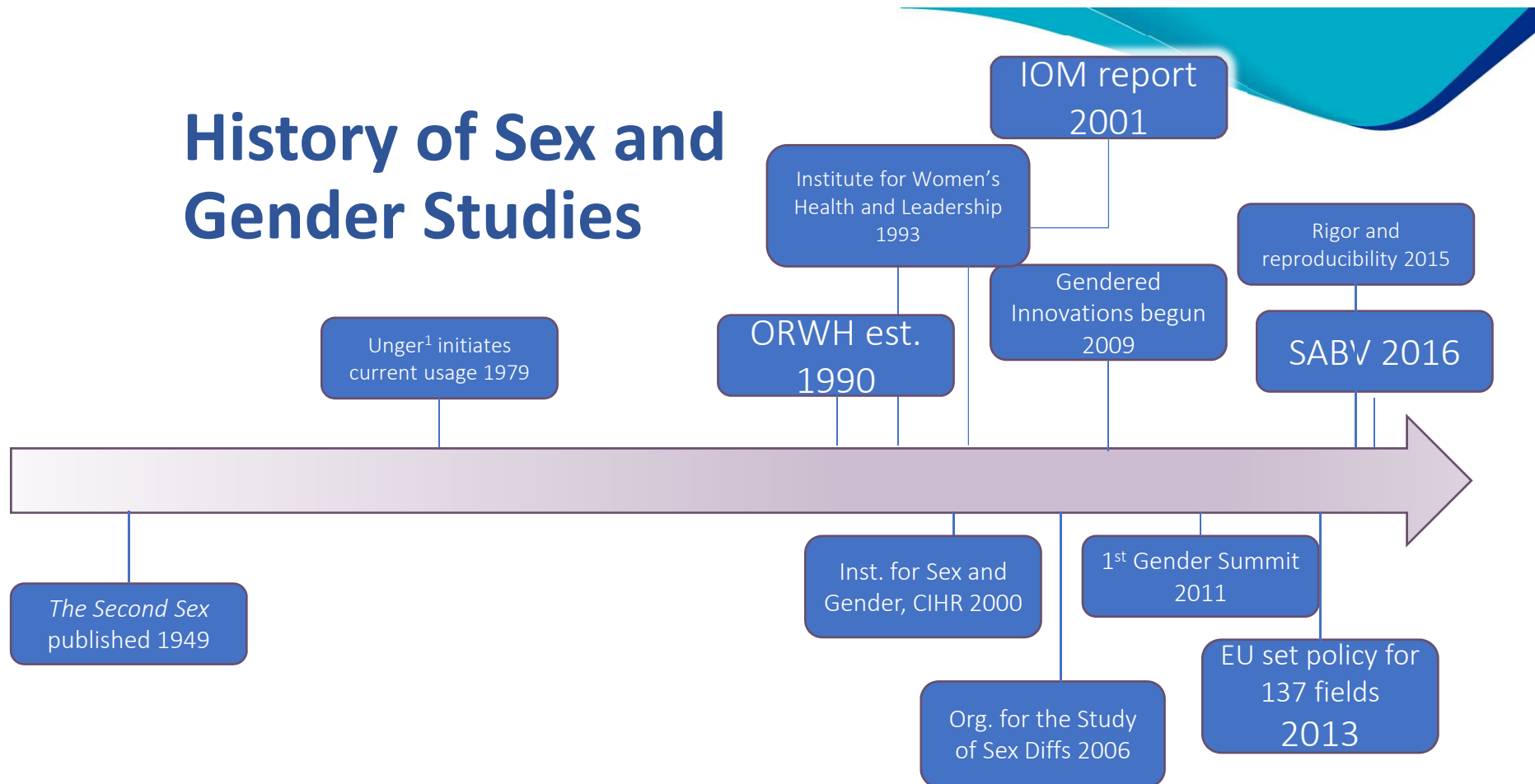
Outline

- History of Sex and Gender
- Promise: Seeing the whole picture
- Power: SABV and disaggregating by sex
- Potential: Programs to advance the health of women (and men)



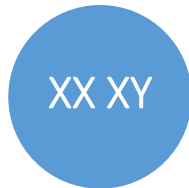
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History of Sex and Gender Studies



Unger, R. K. (1979). Toward a redefinition of sex and gender. *American Psychologist*, 34, 1085–1094.

Sex Is NOT the Same as Gender



Every cell has a sex.



Sex begins in utero.



Sex affects behavior and perception.



Gender also affects behavior and perception.

Female : Male



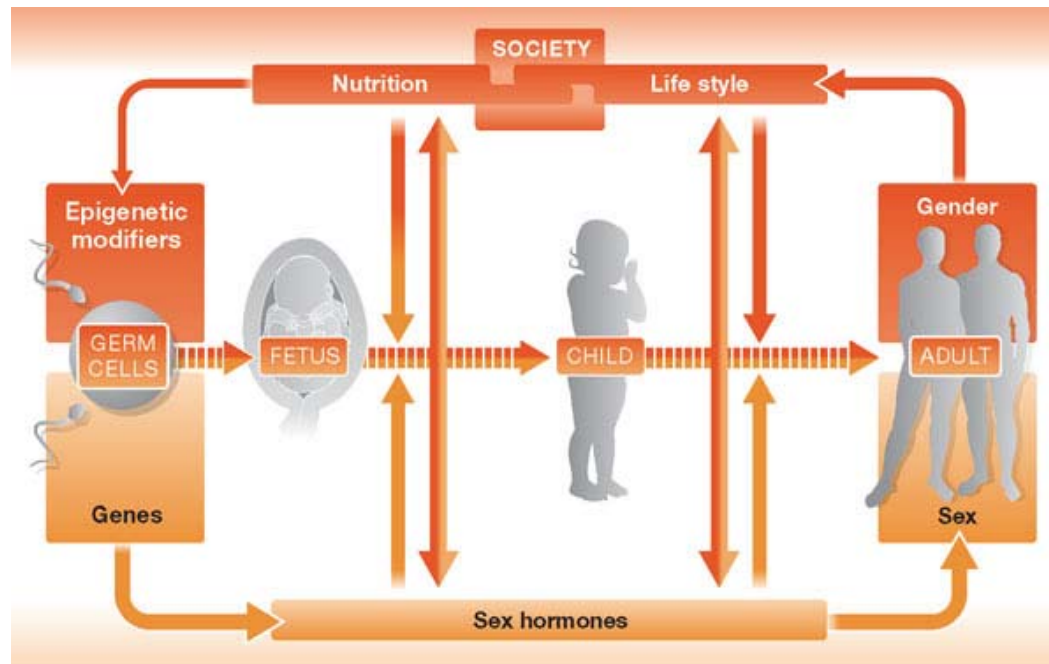
Sex: genetic, molecular, cellular, physiological

Feminine – Masculine



Gender: behavioral, environmental, social, cultural

Sex interacts with gender to influence health and disease



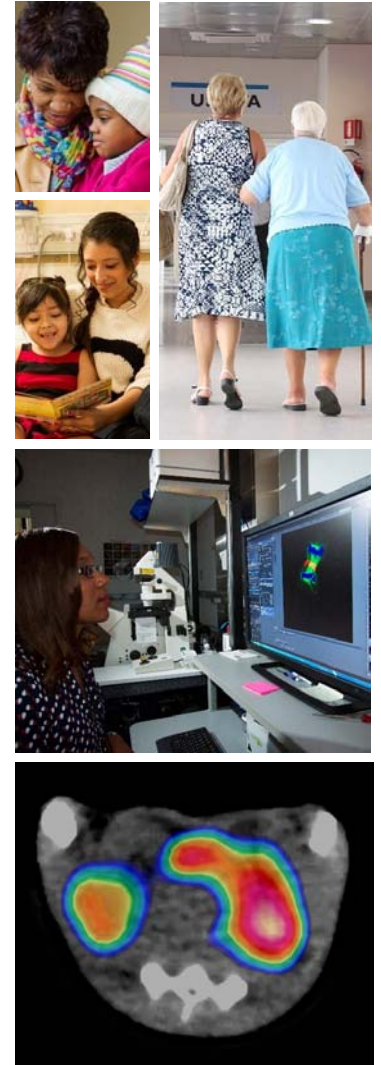
Sex and Gender influences in many clinical disciplines.

- Cardiology
- Rheumatology
- Immunology
- Neurology
- Oncology
- Endocrinology
- Hematology

Sex and gender differences in health, Volume: 13, Issue: 7, Pages: 596-603, First published: 15 June 2012, DOI: (10.1038/embor.2012.87)

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The PROMISE of Studying Sex AND Gender: Seeing the Whole Picture



Consideration of Sex is Essential to Rigor

- NIH is clarifying and revising application instructions and existing review criteria, in order to enhance reproducibility of research findings through increased scientific rigor and transparency.

<http://www.nih.gov/science/reproducibility/>

RIGOR AND REPRODUCIBILITY

- Rigor and Reproducibility**
- Principles and Guidelines
- Publications
- Training
- Meetings and Workshops
- Expanded Guidelines
- Application Instructions

Updated Application Instructions to Enhance Rigor and Reproducibility

The National Institutes of Health (NIH) Office of Extramural Research (OER) plans to clarify and revise application instructions and review criteria to enhance reproducibility of research findings through increased scientific rigor and transparency. These updates, pending approval by the White House Office of Management and Budget (OMB), will take effect for applications submitted for the January 25, 2016 due date and beyond.

Newly revised grant application instructions will: clarify long-standing expectations to ensure that NIH is funding the best and most rigorous science; highlight the need for applicants to describe details that may have been previously overlooked; highlight the need for reviewers to consider such details in their reviews through revised review criteria; and minimize additional burden. These new instructions and revised review criteria will focus on four areas deemed important for enhancing rigor and transparency:

[Expand All]

Consideration of Sex and Other Relevant Biological Variables

- Variables
- Authentication of Key Biological and/or Chemical Resources

Sex As a Biological Variable (SABV) Policy

“NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.”

<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102>

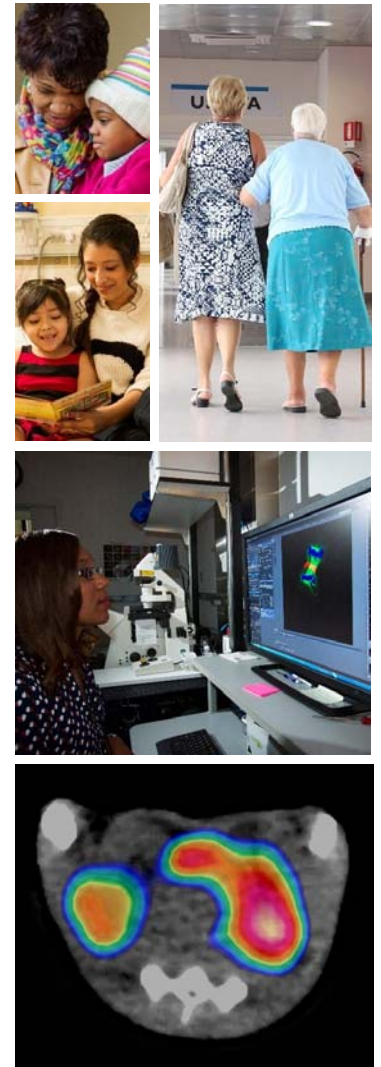
NOT-OD-15-102*: Consideration of Sex as a Biological Variable in NIH-funded Research

*Effective date: January 25, 2016



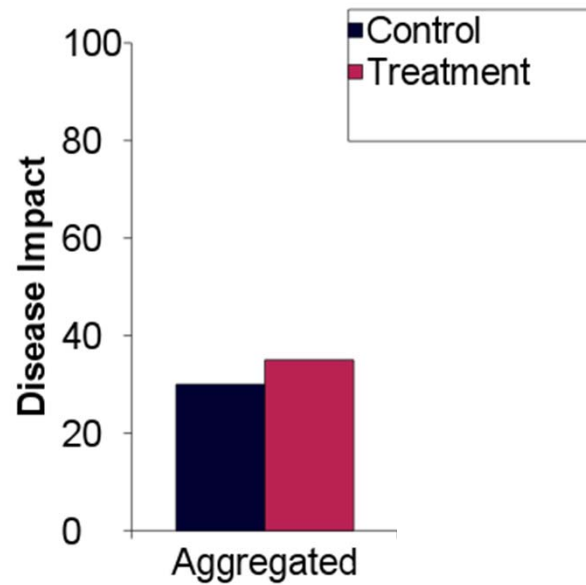
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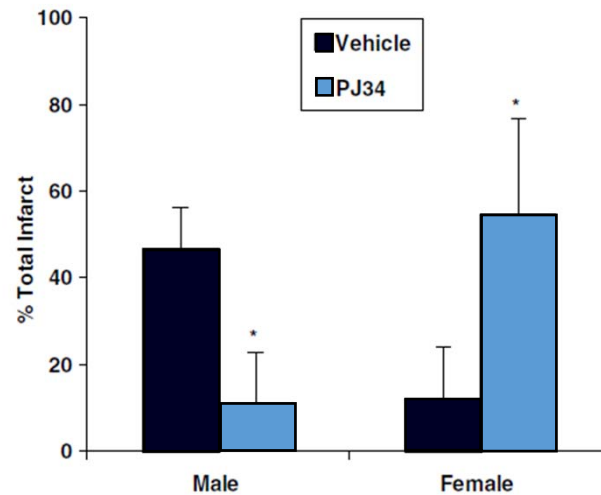
(Images from bottom: Pixabay, public domain; NCI / Wash. U., Liu & Achilefu, 2017; NCI, Daniel Sone, 2014; NCI, Sone, 2013; Pixabay, public domain; NCI, Sone,

The POWER of disaggregated data



Real-life example

Reduced
Infarction
in Males



Increased
Damage
in
Females

The effects of the selective poly-ADP ribose polymerase (PARP-1) inhibitor PJ-34 in wild-type (WT) mice of both sexes. Treatment with PJ-34 at ischemic onset reduced total infarction in male mice compared with saline-treated controls (* $P < 0.001$). A significant increase in ischemic damage was seen in PJ-34-treated females compared with control (* $P < 0.001$).

What can we do to strengthen science?

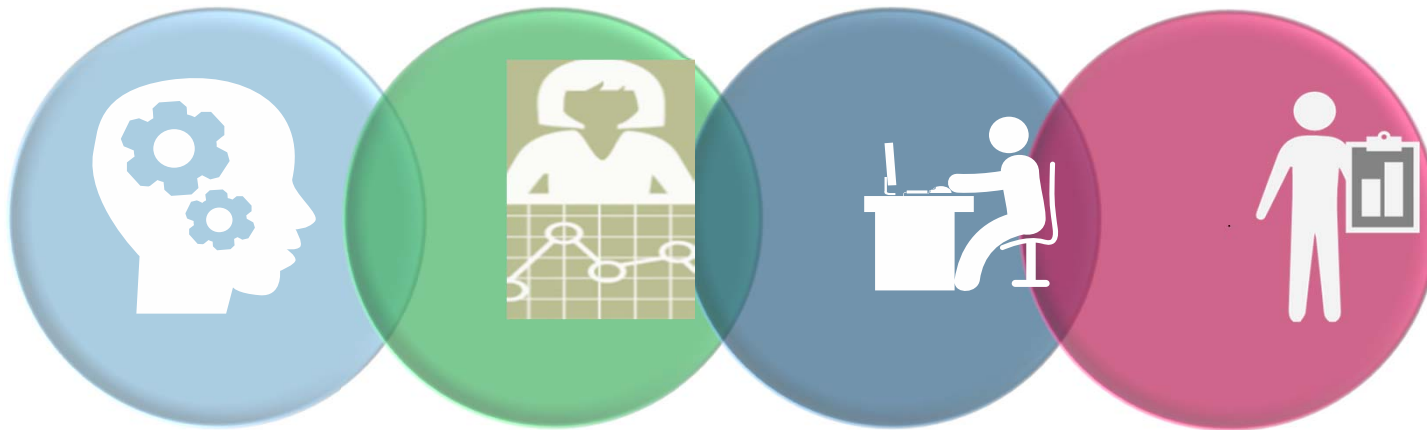
SABV

Checklist

- 1. Consider the influence of sex when formulating research questions
- 2. Review available literature for the influence of sex
- 3. Account for the influence of sex in study design
- 4. Incorporate both males and females
- 5. Alternatively, articulate a strong justification for a single-sex study
- 6. Collect, analyze data and report data disaggregated by sex
- 7. Characterize the influence of sex in the interpretation of results
- 8. Communicate appropriately generalized research findings

What can we do to strengthen science?

The 4 Cs of Studying Sex



Consider

Design studies that take sex into account, or explain why it isn't incorporated

Collect

Tabulate sex-based data

Characterize

Analyze sex-based data

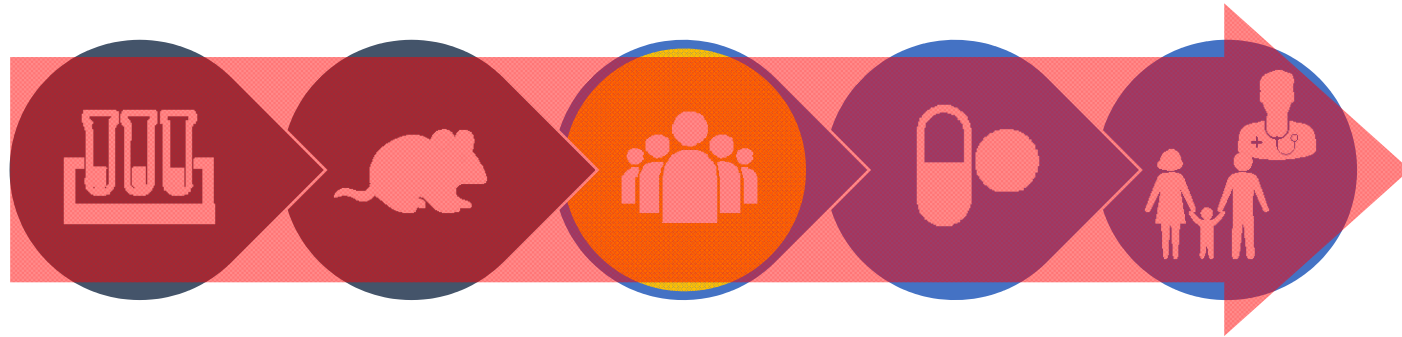
Communicate

Report and publish sex-based data



Connecting the Dots: The Research Continuum

SABV



Cell studies, samples of human or animal tissues, computer-assisted models, animal models

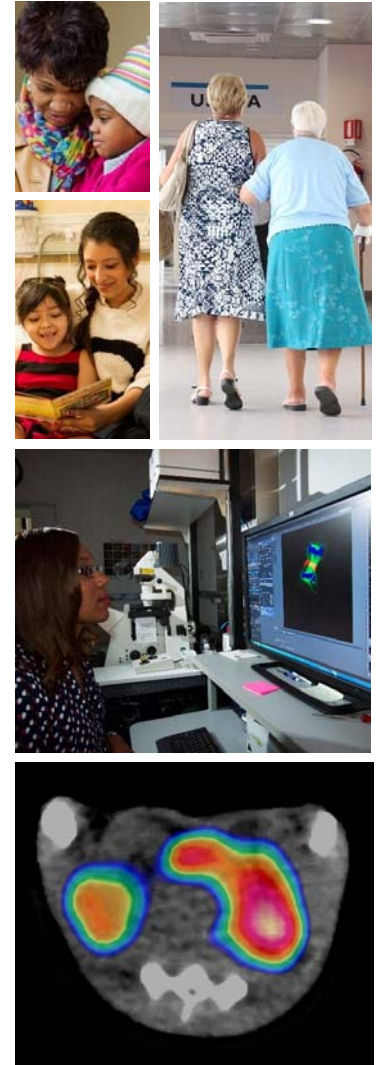


Optimal health for everyone at every age and every stage



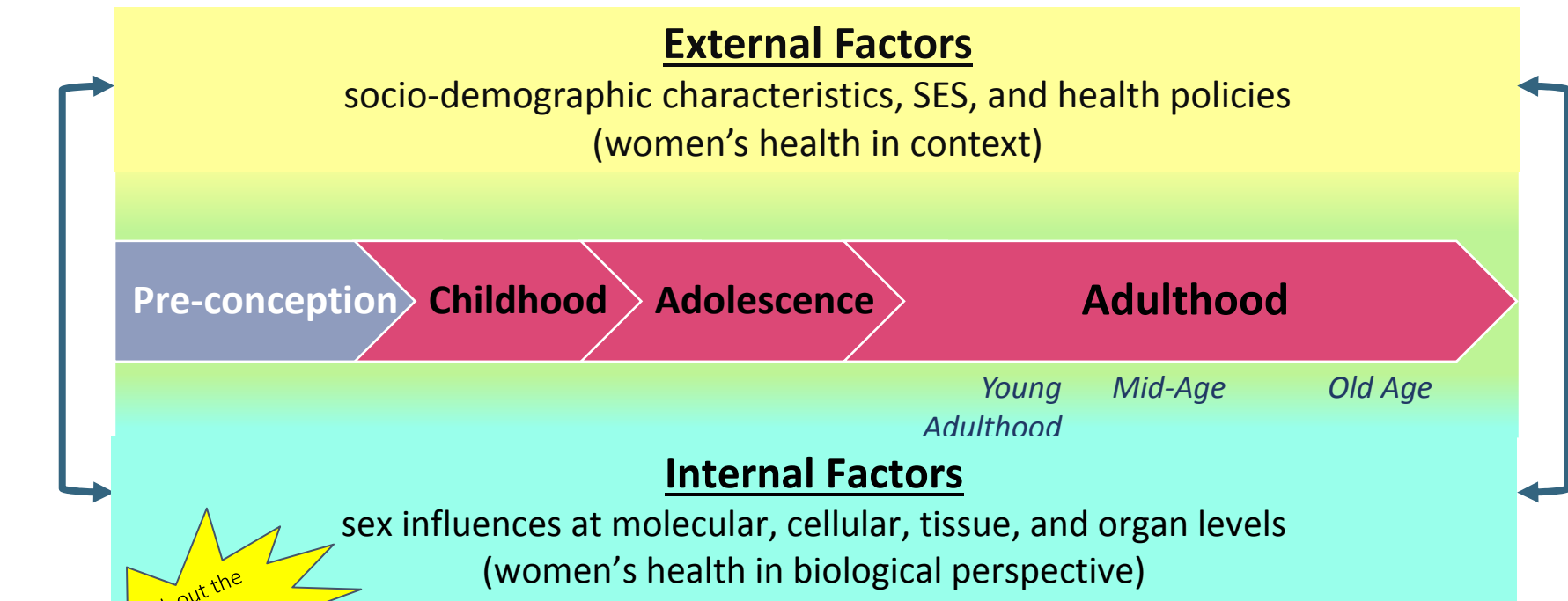
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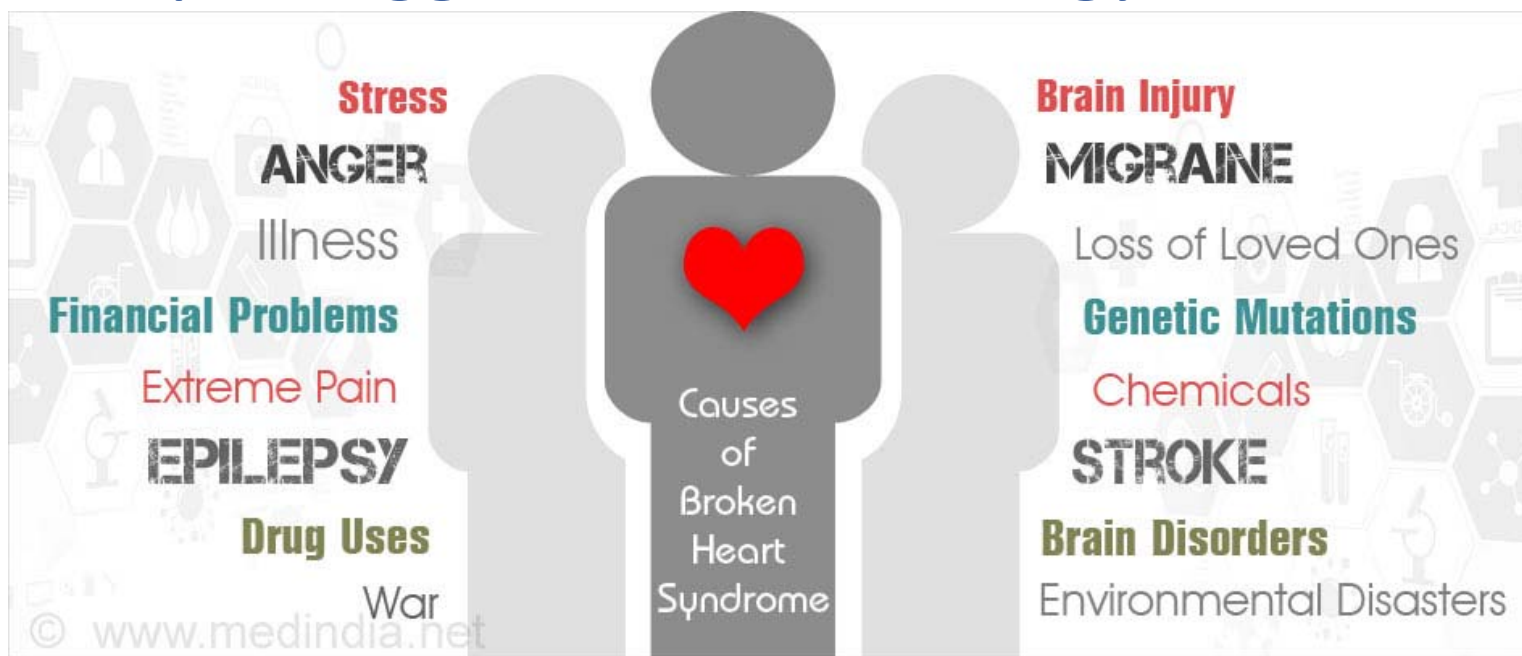
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Multi-level Model of Women's Health across the Life Course



Check out the Workshop videos!

Multiple triggers – Exact Etiology Unclear



Occurs more often in women than men, over 90% of the women are postmenopausal.

Bio-Social Interactions with Sex Influences on Heart Disease

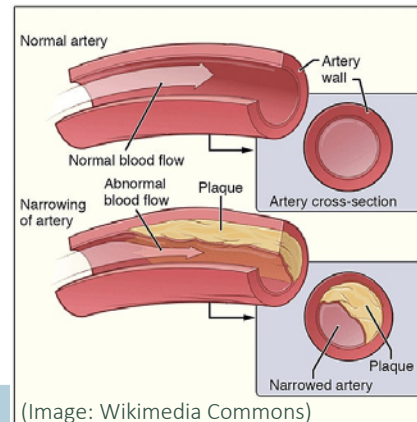


(Images: Pixabay, released under Creative Commons CC0)

social /
environmental
context

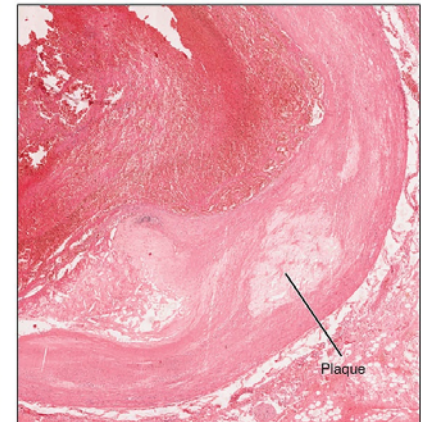
the individual

biology



(Image: Wikimedia Commons)

Artherosclerosis



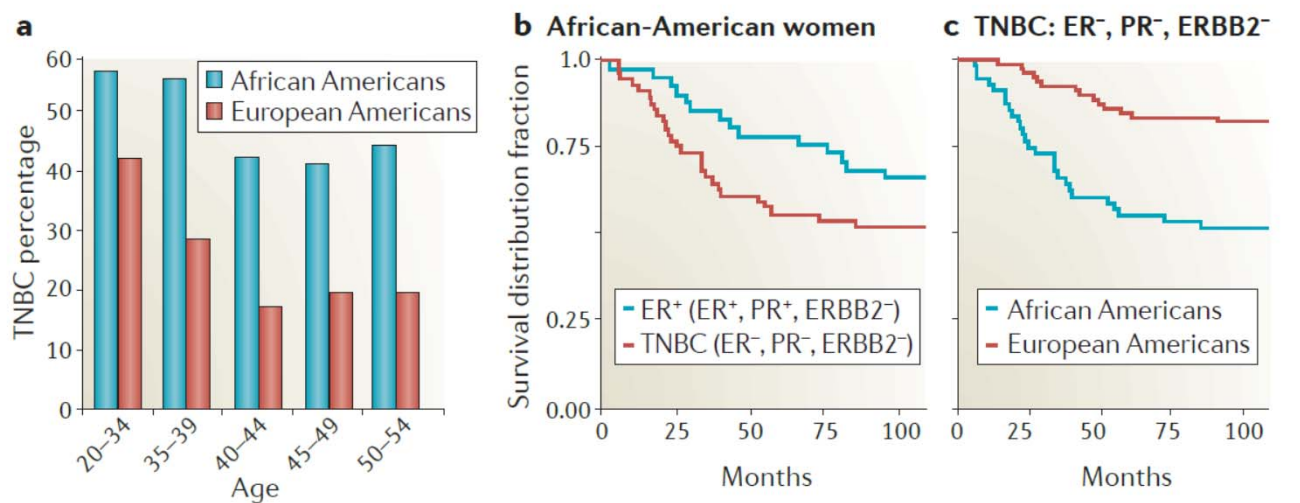
Joakimsen, O. et al., 1999. *Arterioscler. Thromb. Vasc. Biol.* **19**: 3007-3013.
 Bairey Merz, C.N. et al., 2006. *J. Am. Coll. Cardiol.* **47**: S21-S29.
 Zhang, Z., Hayward, M.D. 2006. *Journal of Marriage and Family* **68**: 639-657.
 McFarland, M.J., Hayward, M.D., Brown, D. 2013. *Journal of Marriage and the Family* **75**: 363-380.
 Mathur, P. et al., 2015. *Cardiovasc. Drugs Ther.* **29**: 319-327.
 Bots, S.H., Peters, S.A.E., Woodward, M. 2017. *BMJ Glob Health* **2**: e00258.

A Diversity of Perspectives increases the POTENTIAL for finding Answers



The leading causes of death in U.S. women vary by race and ethnicity

- Black women
 - heart disease > cancer > stroke > diabetes
- White women
 - heart disease > cancer > CLRD > stroke



Dietze et al. 2015. Triple-negative breast cancer in African-American women: disparities versus biology. *Nature Rev. Cancer* 15: 248-254.

Cervical cancer rates vary among communities of women

- Virtually all cervical cancer is caused by 15 HPV types
- New approaches for cervical cancer prevention:
 - HPV vaccination
 - carcinogenic HPV DNA testing
- Women at high risk do not have access to preventive services, or choose not to use them



Women in Cần Thơ



International District, Seattle

(Photos: Wikimedia Commons)

Do et al. 2007. Knowledge about cervical cancer risk factors, traditional health beliefs, and Pap testing among Vietnamese American women. *J. Immigrant Health* **9**:109–114.

Saslow et al. 2007. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin.* **57**: 7-28.

Wang et al. 2008. Disparities in cervical cancer screening between Asian American and non-Hispanic White women. *Cancer Epidemiol. Biomarkers Prev.* **17**: 1968-1973.

Scarinci et al. 2010. Cervical cancer prevention: new tools and old barriers. *Cancer* **116**: 2531-2542.

Nuño et al. 2011. Breast and cervical cancer screening utilization among Hispanic women living near the United States-Mexico border. *J. Womens Health (Larchmt)* **20**: 685-693.

Research on Understudied, Underreported, or Underrepresented Women (U3) Admin. Supp.

- **An ORWH Administrative Supplement Program, first FOA issued in FY'17**
- **Research on influences of sex/gender at intersection of race/ethnicity and other social determinants of health & disease**
- **Focus on health disparities in populations of women who are understudied, underreported, or underrepresented (U3) in biomedical research**



Examples of FY 18 U3 Projects by Research Category

- Clinical Research
 - *A Novel Wireless Ingestible Sensor System - Measurement of Medication Adherence*
- Prevention
 - *Risk-based Breast Cancer Screening and Surveillance in Community Practice*
- Behavioral and Social Sciences
 - *Development of Co-Morbid PTSD and Chronic Pain Among Inner-City Women*
- Mental Health
 - *The role of cultural risk and resiliency factors and the built neighborhood on maternal depressive symptoms in pregnant Mexican American women*
- Clinical Trials
 - *A Cluster-Randomized Trial of Pharmacist-Coordinated Implementation of the DPP*
- Pediatric
 - *Building Evidence for Effective Palliative/End of Life Care for Teens with Cancer*
- Minority Health/Health Disparities
 - *Demographic and Health Disparities in Recovery from Hurricane Katrina: KATRINA@10*
- Infectious Disease
 - *Primary Infection Resource Consortium (PIRC) – Barriers to HIV testing for Native American women in Urban Settings*



Administrative Supplements for Research on Sex/Gender Influences (Admin Supp)



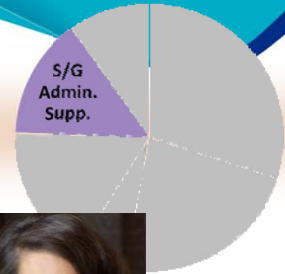
- In FY 2013, ORWH initiated a trans-NIH program to catalyze exploratory research on sex/gender differences by providing “[Administrative Supplements \(Admin. Supp.\)](#)” to ongoing peer-reviewed NIH-funded grants.
- The initiative provided one year supplements of ~ \$100,000 total cost.
- The new proposal and approaches were required to fall within the scope of parent award: preclinical, preclinical and clinical, or clinical research.
- The Admin. Supp. program supported following types of Research Approaches:
 - Add the Opposite Sex/Gender
 - Increase Sample Size (N)
 - Analyze Existing Data
- The proposed research must address at least one of the objectives from Goals 1 through 3 of the [NIH Strategic Plan for Women's Health Research](#).









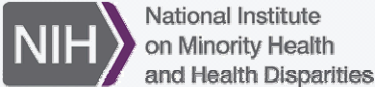




ORWH has supported 341 S/G Admin Supps since FY13 and renewed the program for FY19

Spotlight on Sex/Gender Admin. Supp.



PI & Institution	 Esther Dupont-Versteegden, Ph.D. 	 Forest White, Ph.D. 	 Monica Uddin, Ph.D. 
Parent Grant	 R01 AT009268-01 Mechanisms underlying anabolic effects of cyclic compressive loading in muscle	 U54 CA210180-02 Glioblastoma cell invasion profiles & implications for therapeutic response	 R01 MD011728-01 Epigenomic predictors of PTSD & traumatic stress in an African American cohort
Admin Supp Study Type Main Approach	Preclinical Addition of subjects to existing study to increase power for testing sex diffs.	Preclinical + Clinical Addition of new sex/gender to single sex/gender research	Clinical Sex/gender-based comparative analysis of existing samples/data sets

SABV expertise and knowhow in sex & gender analysis considered for peer review: ODP efforts

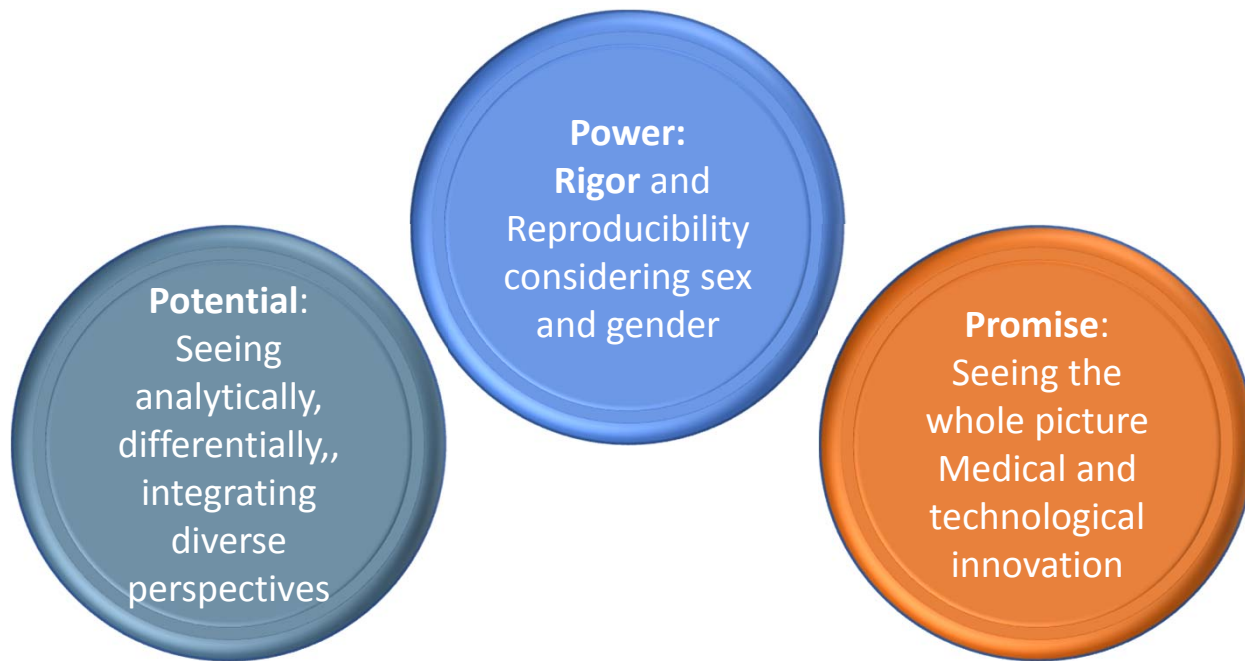


Prevention Research Expertise Survey
OMB# 0925-0728
Expiration Date: 11/30/2020

ODP enhanced their database of peer reviewers, which is populated via the Prevention Research Expertise Survey (PRES). They added:

Research Methods	None	Basic	Skilled	Expert
Agent-Based Modeling	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alternative/Authentic Assessment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Analysis of High-Dimensional Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Analysis of Small Sample Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bayesian Methods	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Arthritis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Asthma and Other Respiratory Diseases	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Propensity Score Methods (Matching, Weighting, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psychometric Methods	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sex and Gender Analysis New	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Simulation Methods	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Structural Equation Models	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Structured Observations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Subgroup Analysis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Integrating all these perspectives through a sex and gender lens



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Hunterc@nih.gov

