What Do We Mean by Sex and Gender?

Wendy M Kohrt, PhD
Professor of Medicine, Division of Geriatric Medicine
Nancy Anschutz Chair in Women’s Health Research
University of Colorado – Anschutz Medical Campus
Outline

- Definitions of sex and gender

- Progress in advancing research on sex differences

- Research highlights
Definitions

Sex

Biological status as female or male, typically established (>99.9%) at birth based on anatomy

Intersex cases (0.06%) are disorders of sex development that do not fit strict criteria of female or male. Indicators of sex in addition to external genitalia include internal reproductive organs, sex chromosomes, and gonadal hormones.
Definitions

Intersex

- Chromosome combinations other than XX or XY (e.g., XXY, Klinefelter syndrome)
- Genetic mosaicism (e.g., ovotestes)
- About one-third include genital ambiguity

Intersex Traits $\rightarrow$ Gender Dysphoria
Definitions

Gender

Attitudes, feelings, and behaviors that a given culture associates with biological sex (APA)

Socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for women and men (WHO)

A person's self representation as female or male, or how that person is responded to by social institutions based on the individual's gender presentation (FDA)

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Milestones in research on sex differences

1993 NIH Revitalization Act required inclusion of women in all clinical research and analysis of results by sex for phase III trials

1993 FDA reversed 1977 policy *barring women of childbearing potential from participating in clinical research*

2001 IOM report recommended that sex be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research

2015 NIH required that research address sex as a biological variable

2016 21st Century Cures Act required applicable RCTs to submit results of valid analyses by sex/gender, race, and ethnicity to ClinicalTrials.gov

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Early Success

2001 Women made up 52% of FDA trial participants in new drug applications (NDAs); but …

Small proportion of women in early small-scale safety studies (establish toxicity and safety doses)

Sex differences reported in any NDA on any dimension (safety, efficacy, or pharmacokinetics), even when statistically significant, were not judged to be clinically relevant by either the NDA sponsors or the FDA reviewers

FDA lacked management systems to comply with regulations addressing sex-related issues

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Participation of women in trials supporting 36 CVD drug approvals from 2005 to 2015

**CENTRAL ILLUSTRATION:** Participation of Women of CVD Clinical Trial: Prevalence-Corrected Estimate

- Acute Coronary Syndrome: 0.6
- Atrial Fibrillation: 0.8
- Atrial Fibrillation: 1.1
- Coronary Artery Syndrome: 0.6
- Heart Failure: 0.5
- Heart Failure: 0.6
- Hypertension: 0.9
- Pulmonary Hypertension: 1.4

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Loss of Gonadal Function

Women: 51 y

? Men: 70+ y

Impact on Other Systems

Increased Disease Risk

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Loss of Gonadal Function

- Bone Loss
  - Fat Gain
    - CVD
    - T2D
  - Other Tissues
    - Dementia
    - Sarcopenia

Spontaneous Physical Activity

Distribution, Composition

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Effects of OVX and $E_2$ Add-back in Mice

GnRH$_{AG}$+PL vs GnRH$_{AG}$+E$_2$
5-mo Changes in FFM and Muscle CSA


Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
GnRH$_{AG}$, +/- E$_2$, +/- Resistance Exercise
5-mo Changes in FFM and Muscle CSA

5-mo Changes in Fat Mass and Abd Fat Areas

GnRH$_{AG}$, +/- E$_2$, +/- Resistance Exercise
5-mo Changes in Fat Mass and Abd Fat Areas


Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Adipogenesis – Conventional Dogma

AT-resident MSC

Preadipocyte

Hyperplasia

Mature Adipocytes

Hypertrophy
Novel Lineage of Adipocytes

Majka SM, Barak Y, Klemm DJ Stem Cells 2011

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
**BMDA exhibit increased expression of inflammatory cytokine genes**

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Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Increased Production of BMDA in OVX and ERKO Mice

Gavin KM et al *Front Endocrinol* 2018

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Donor-derived Adipocytes in Bone Marrow Transplantation Patients

0-35% of adipocytes

0-27% of adipocytes

Gavin K et al. 2016 FASEB J 30:1096
Ryden et al. 2016 Cell Metab. 22:408

Wendy Kohrt, "Sex and Gender Differences in Aging" June 6-7, 2019
Take-home Messages

- Basic (ERKO), preclinical (OVX), and clinical studies (GnRH$_{AG}$) provide consistent evidence for the role of gonadal hormones in the regulation of energy balance.

- Studying sex differences across the spectrum of translational research and across the lifespan will fill knowledge gaps regarding the biological contributions of sex to human health.

- Given the numerous non-reproductive targets of gonadal hormones and the age-discordance between women and men for the loss of gonadal hormones, it is particularly important that aging research includes a focus on sex as a contributing factor.