2019 NIA RCCN Workshop on Sex and Gender Differences in Aging

What Do We Mean by Sex and Gender?

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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 → Gender Dysphoria

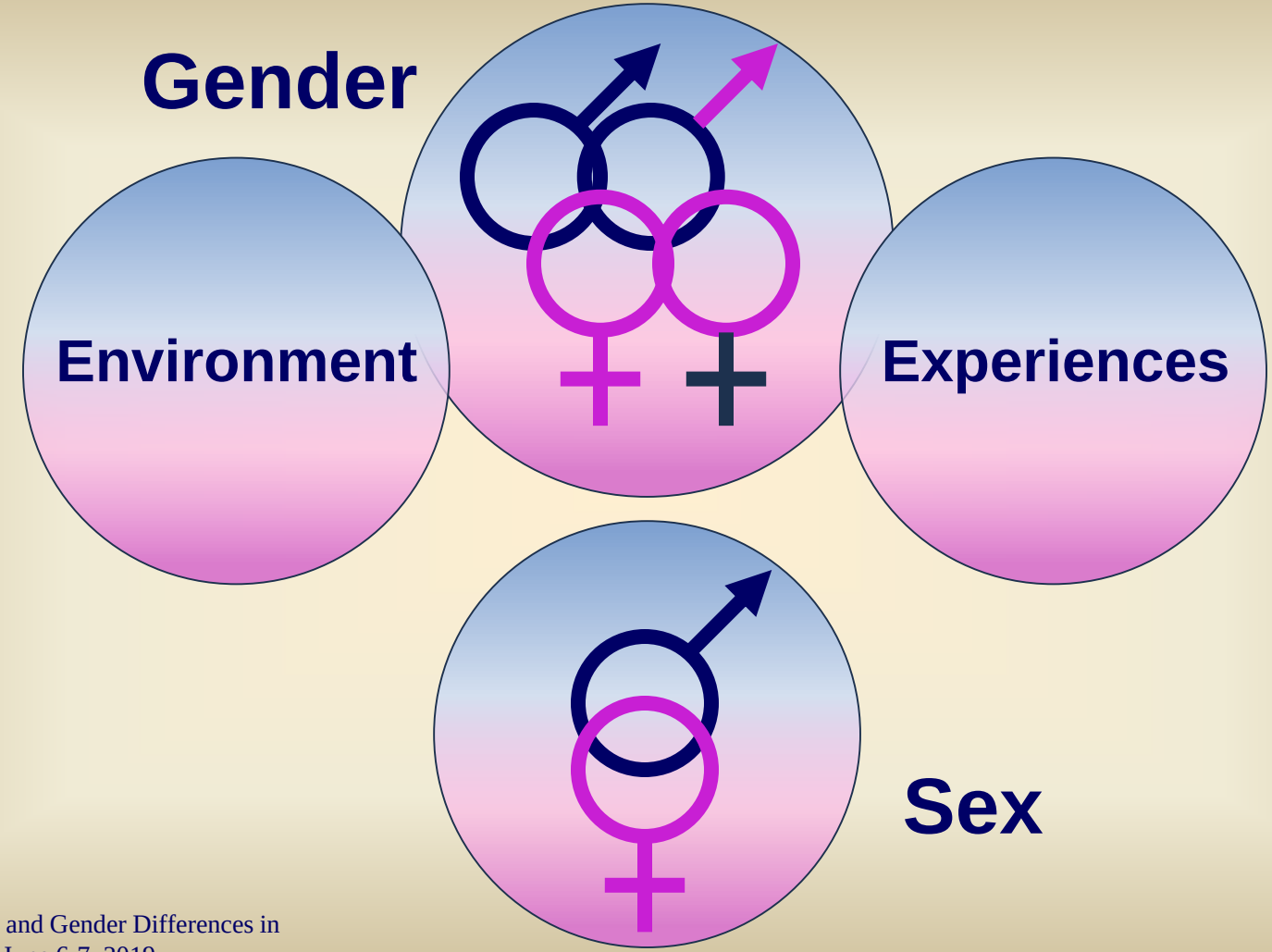
Definitions

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)


Gender
Environment
Experiences
Sex

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**

Early Success

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

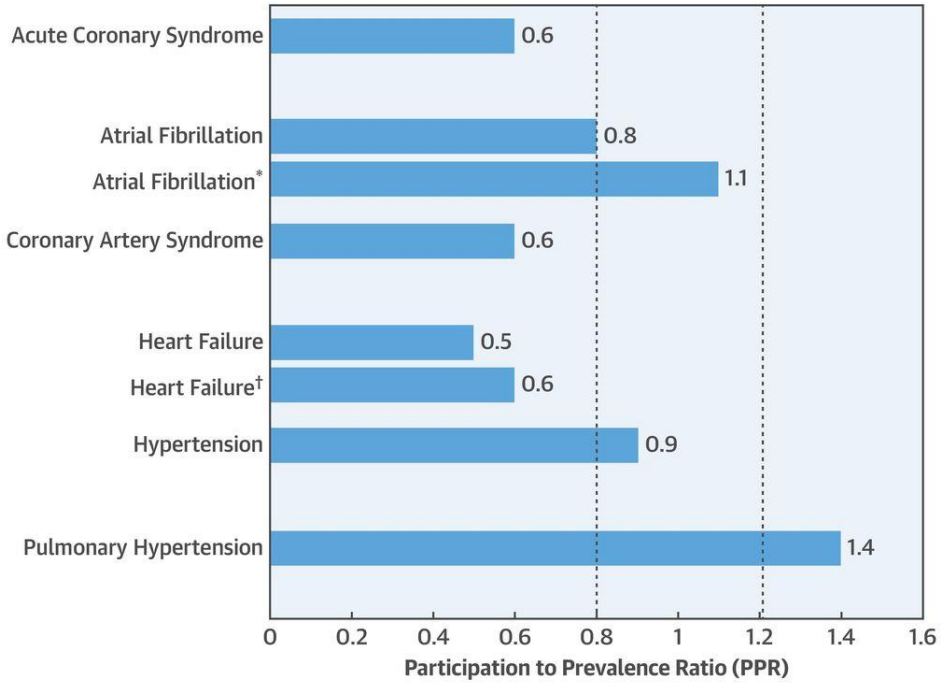
Small proportion of women in early small-scale safety studies (establish toxicity and safety doses)

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

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



Scott, P.E. et al. J Am Coll Cardiol. 2018;71(18):1960-9.

W Kohrt, PhD
R Schwartz, MD
L Abbate, MD
D Bessesen, MD
J Blankenship, PhD
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K Gavin, PhD
K Hildreth, MD
K Jankowski, PhD
D Klemm, PhD
P MacLean, PhD
E Melanson, PhD
D Miller, PhD
K Moreau, PhD
Y-M Park, PhD
C Rynders, PhD
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S Wherry, PhD
M Wierman, MD

medschool.ucdenver.edu/image

NIH
U54 AG062319
U01 TR001082
P30 DK048520

GRECC

UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS
Center for Women's Health Research

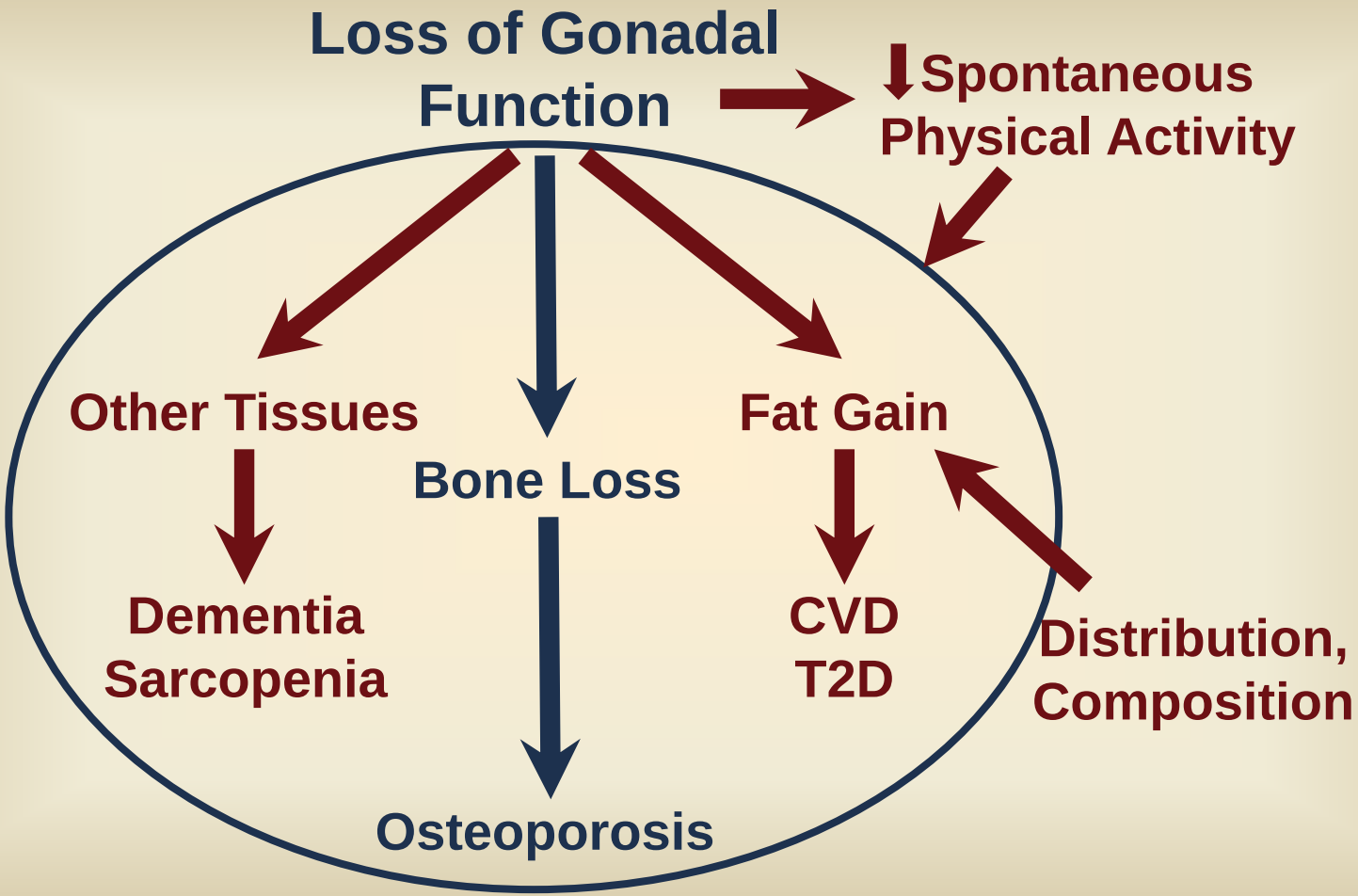
Loss of Gonadal Function

Women: 51 y

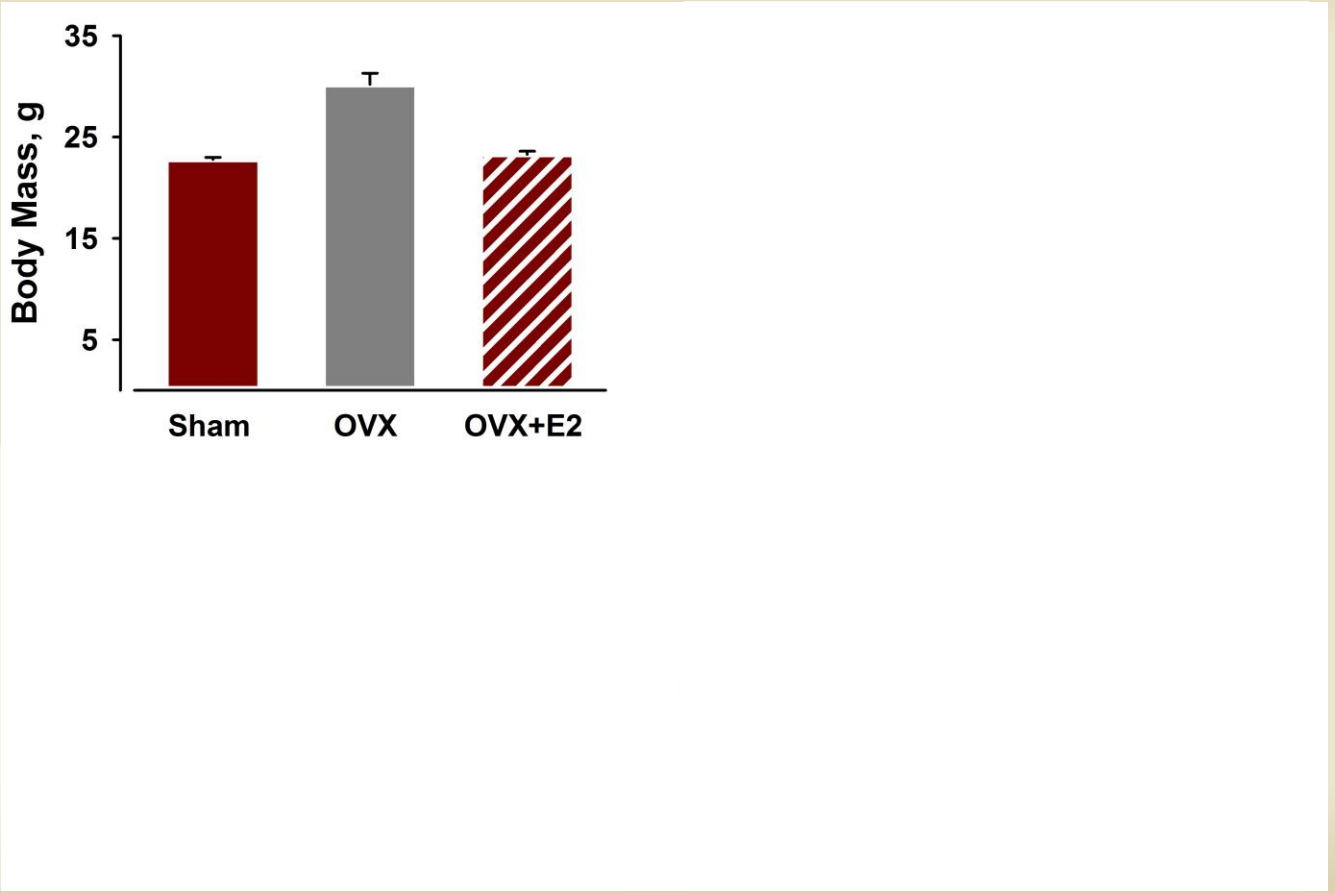
? Men: 70+ y

Impact on Other Systems

Increased Disease Risk

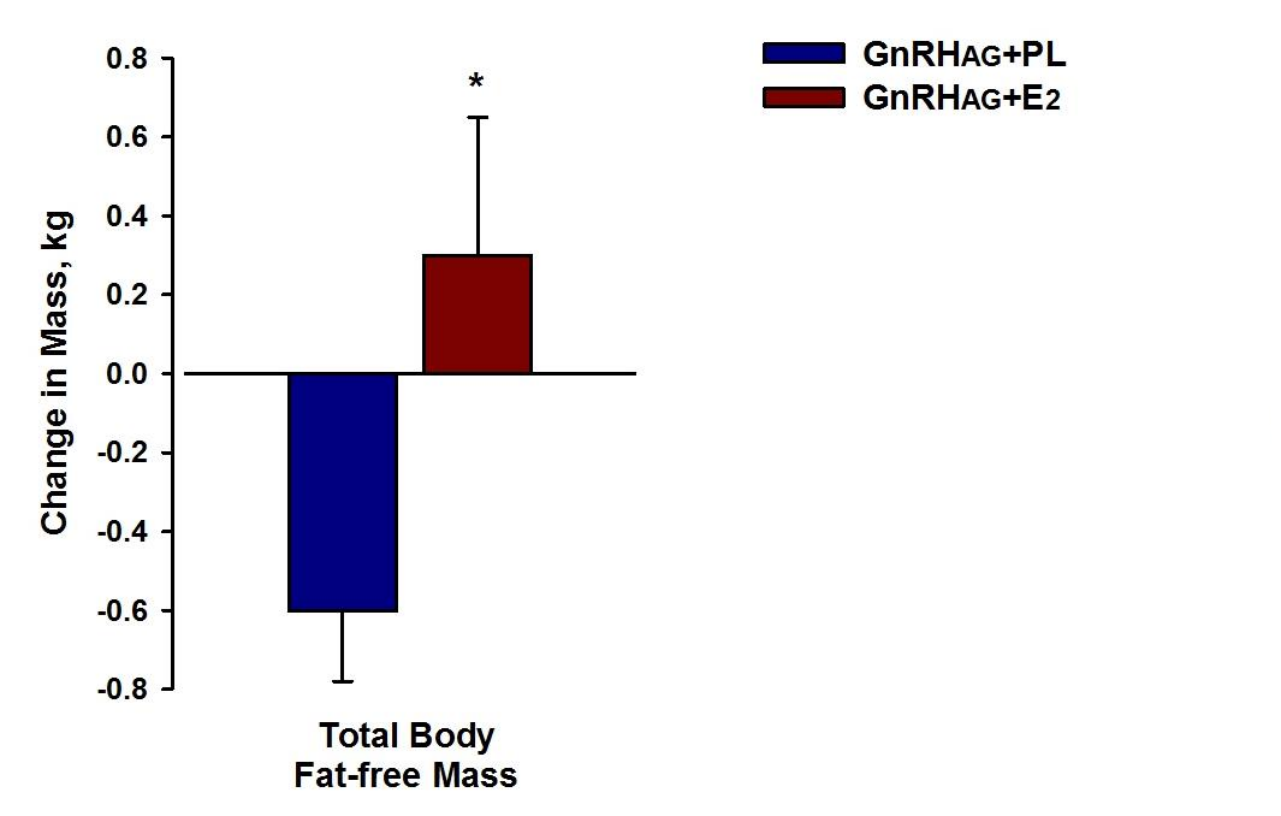

Loss of Gonadal Function
Spontaneous Physical Activity
Other Tissues
Bone Loss
Fat Gain
Dementia
Sarcopenia
CVD
T2D
Distribution, Composition
Osteoporosis

Effects of OVX and E_2 Add-back in Mice



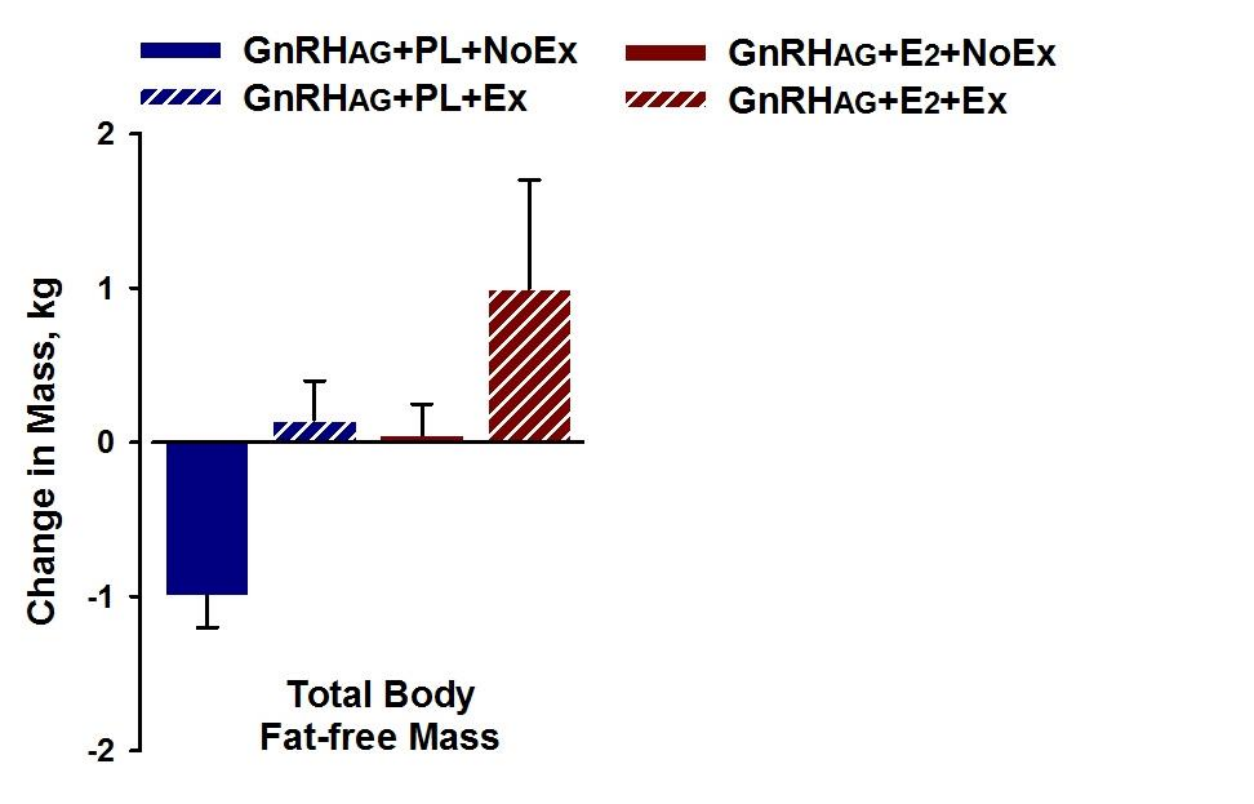
Adapted from: Camporez JP et al. *Endocrinol* 154:1021, 2013

$GnRH_{AG}$+PL vs $GnRH_{AG}$+E_2
5-mo Changes in FFM and Muscle CSA



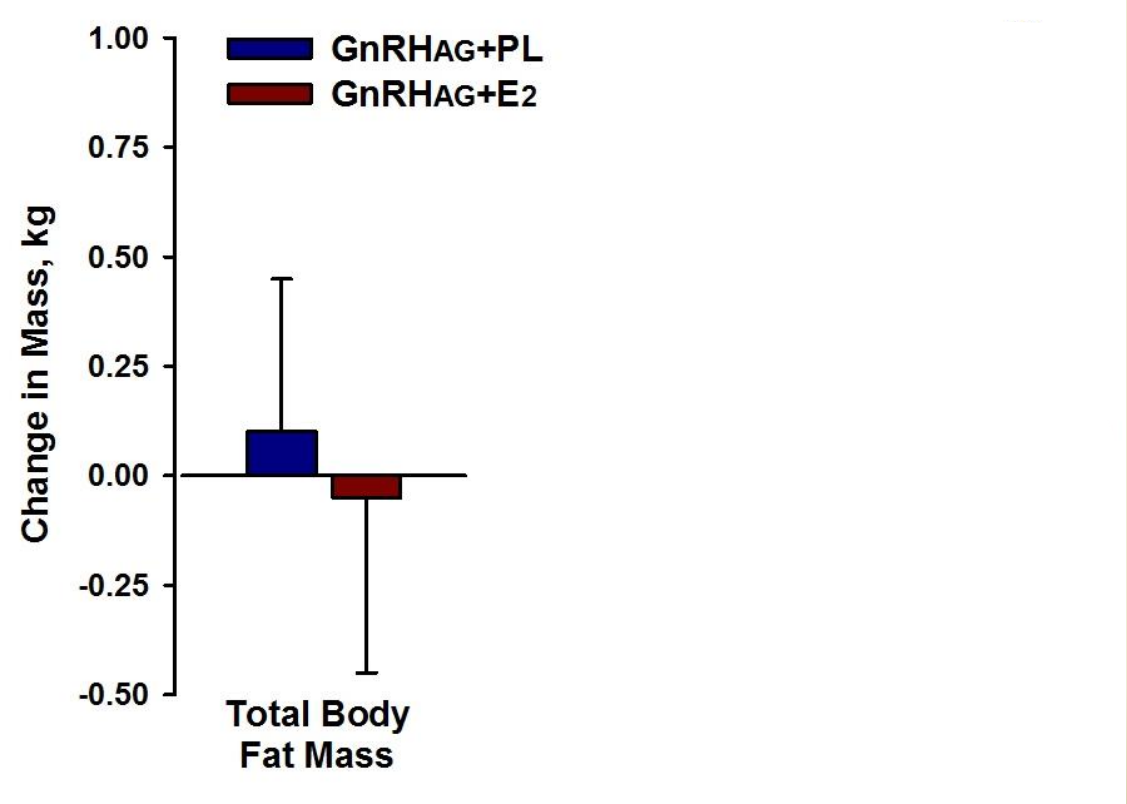
Shea K et al. *Menopause* 22:1045, 2015

$GnRH_{AG}$, +/- E_2, +/- Resistance Exercise 5-mo Changes in FFM and Muscle CSA



Shea K et al. *Menopause* 22:1045, 2015

$GnRH_{AG}$+PL vs $GnRH_{AG}$+E_2
5-mo Changes in Fat Mass and Abd Fat Areas



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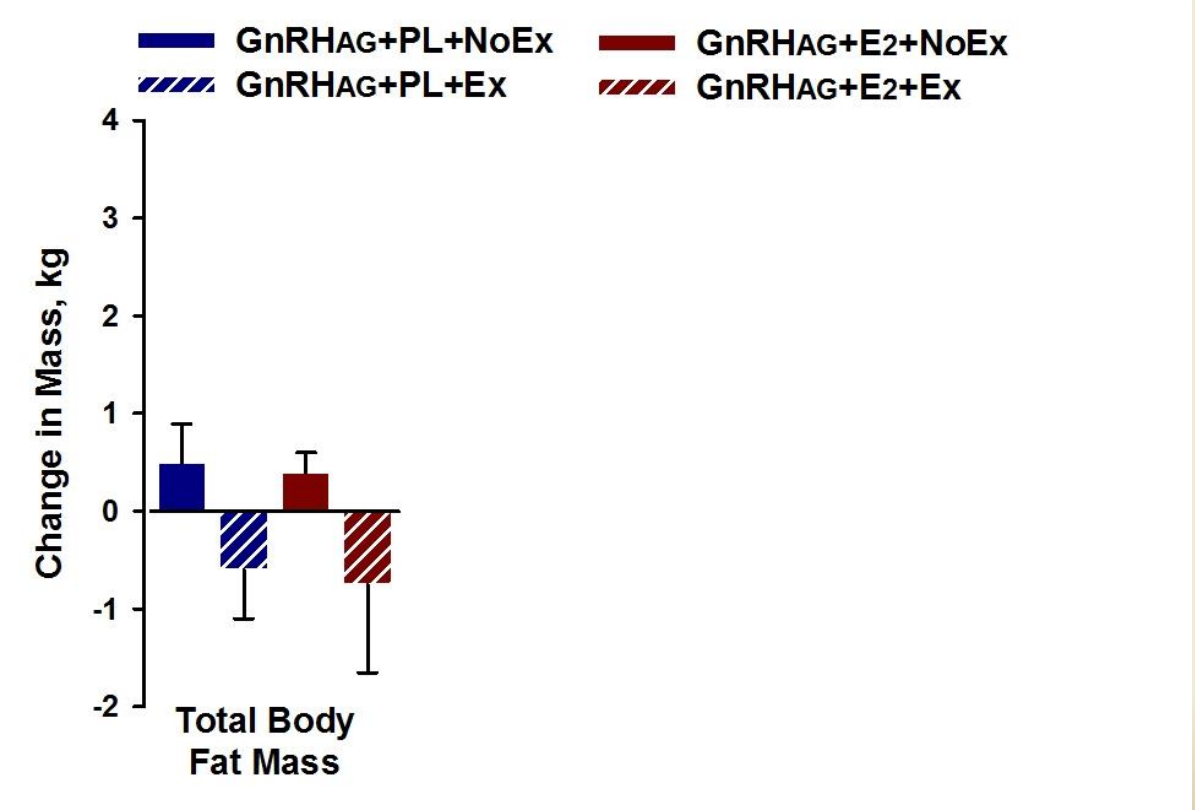


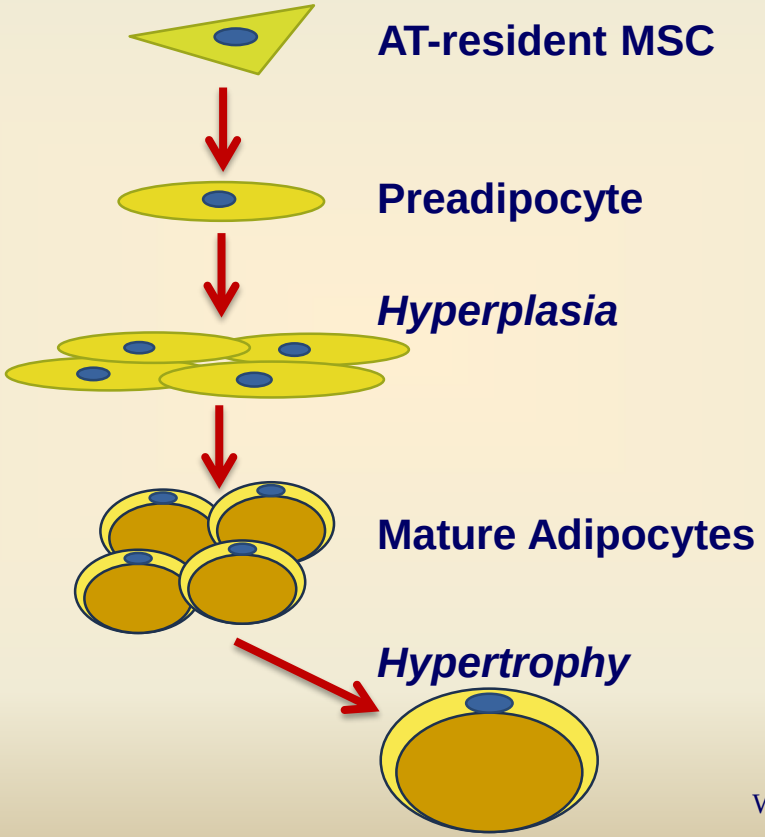
Shea K et al. *Menopause* 22:1045, 2015

Bone Marrow-derived Adipocytes

Dwight Klemm, PhD

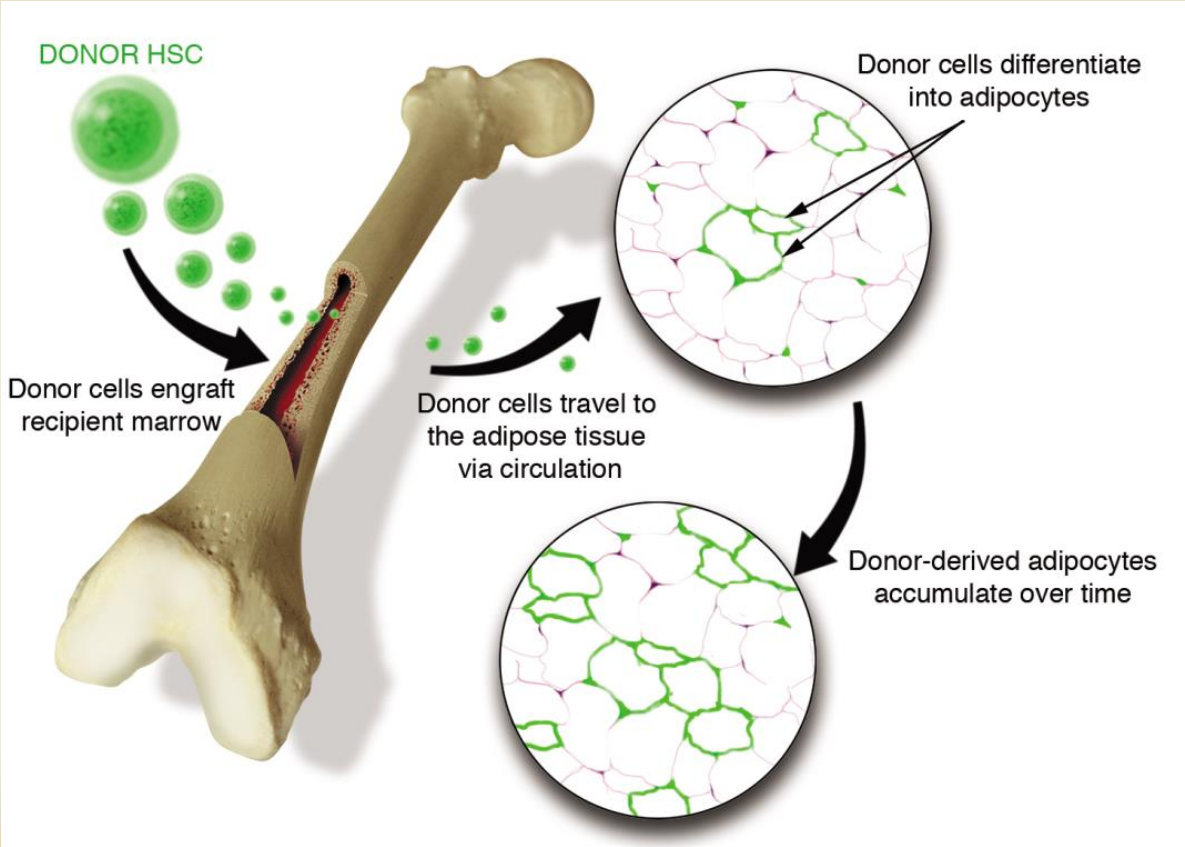
Kathleen Gavin, PhD

Adipogenesis – Conventional Dogma



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

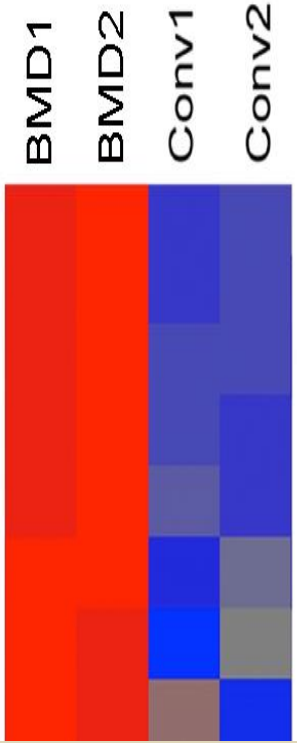
Novel Lineage of Adipocytes

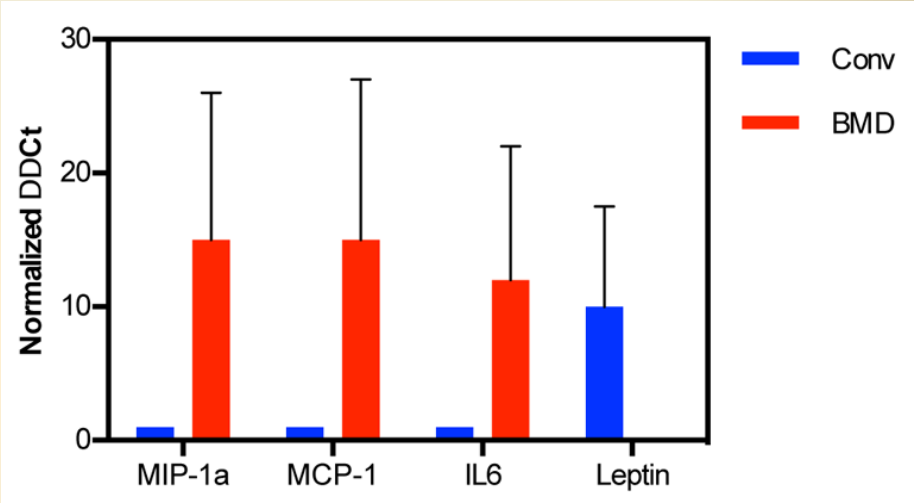


Majka SM, Barak Y, Klemm DJ *Stem Cells* 2011

BMDA exhibit increased expression of inflammatory cytokine genes

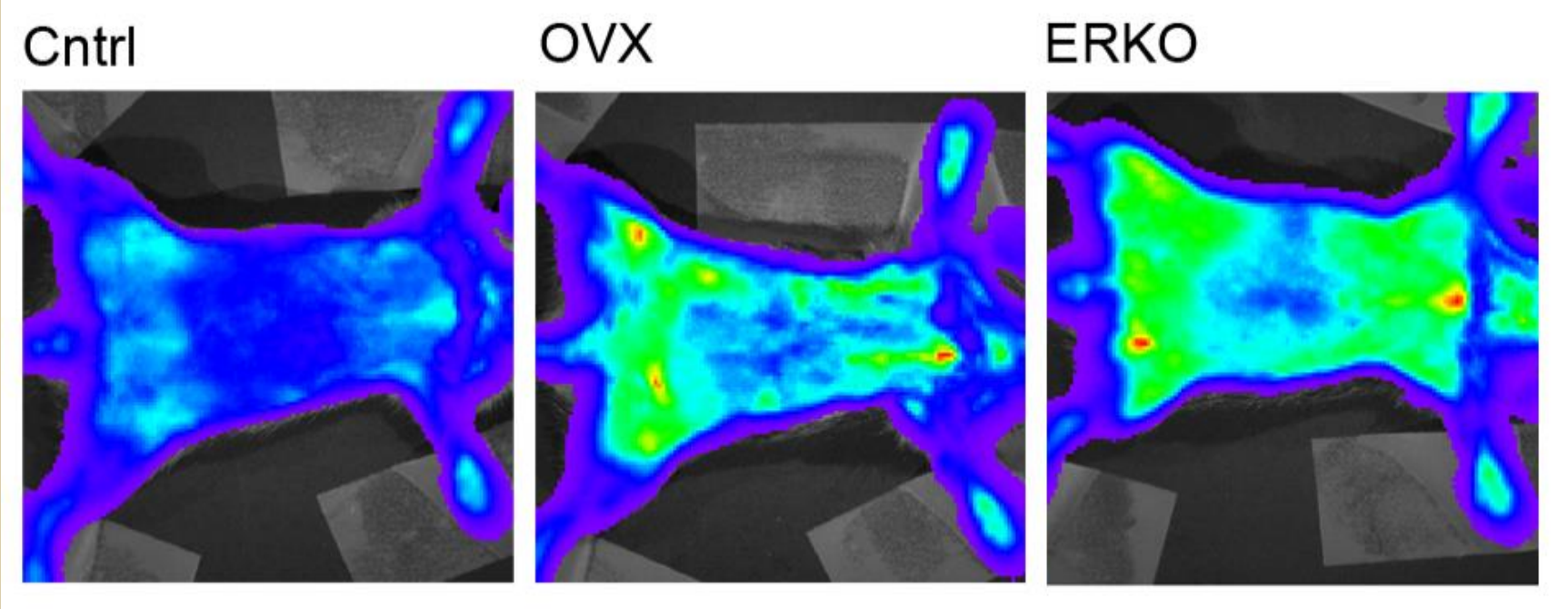
ene ode	Fold Difference[1]	p Value
xcl10	50.08	0.0012
P-1a	27.10	0.0059
CP1	15.32	0.0032
Il1r1	10.50	0.0000
CP3	8.17	0.0018
Il6	7.71	0.1001
Fgfr1	5.53	0.0014
Cse1l	4.05	0.0280





Majka, et al. 2010. Proc Nat Acad Sci USA 107:14781

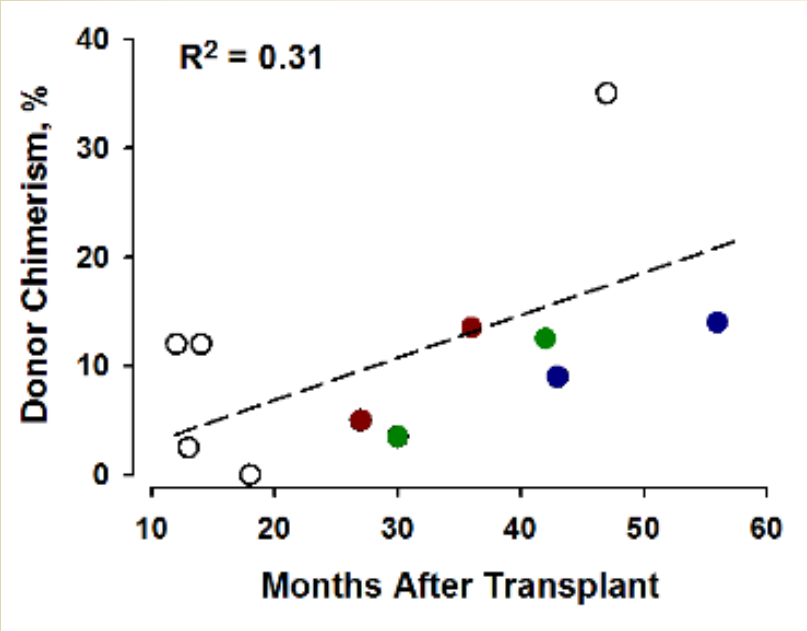
Increased Production of BMDA in OVX and ERKO Mice



Gavin KM et al *Front Endocrinol* 2018

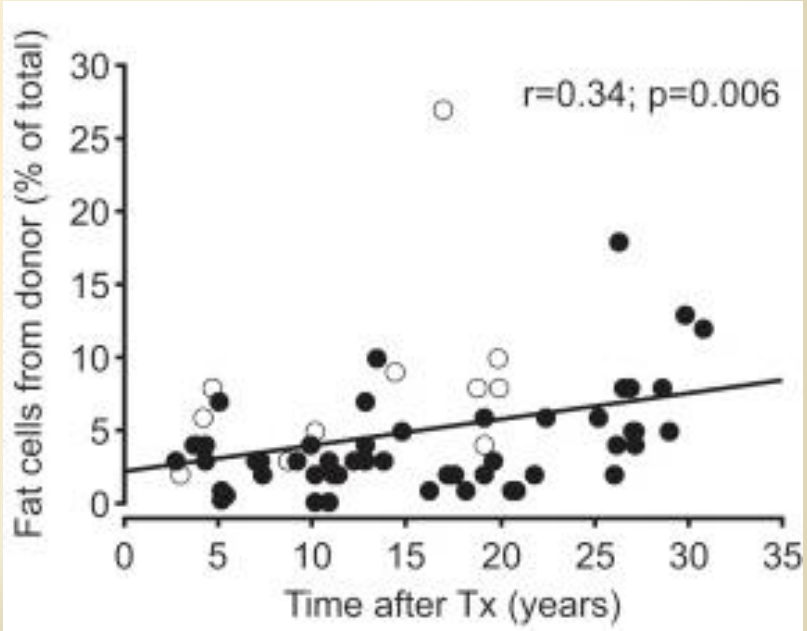
Donor-derived Adipocytes in Bone Marrow Transplantation Patients

0-35% of adipocytes



Gavin K et al. 2016 FASEB J 30:1096

0-27% of adipocytes



Ryden et al. 2016 Cell Metab. 22:408

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