Bioenergetic and Metabolic Consequences of the Menopause Transition

SCOR on Sex Differences
P50 HD073063

SCORE on Sex Differences
U54 AG062319

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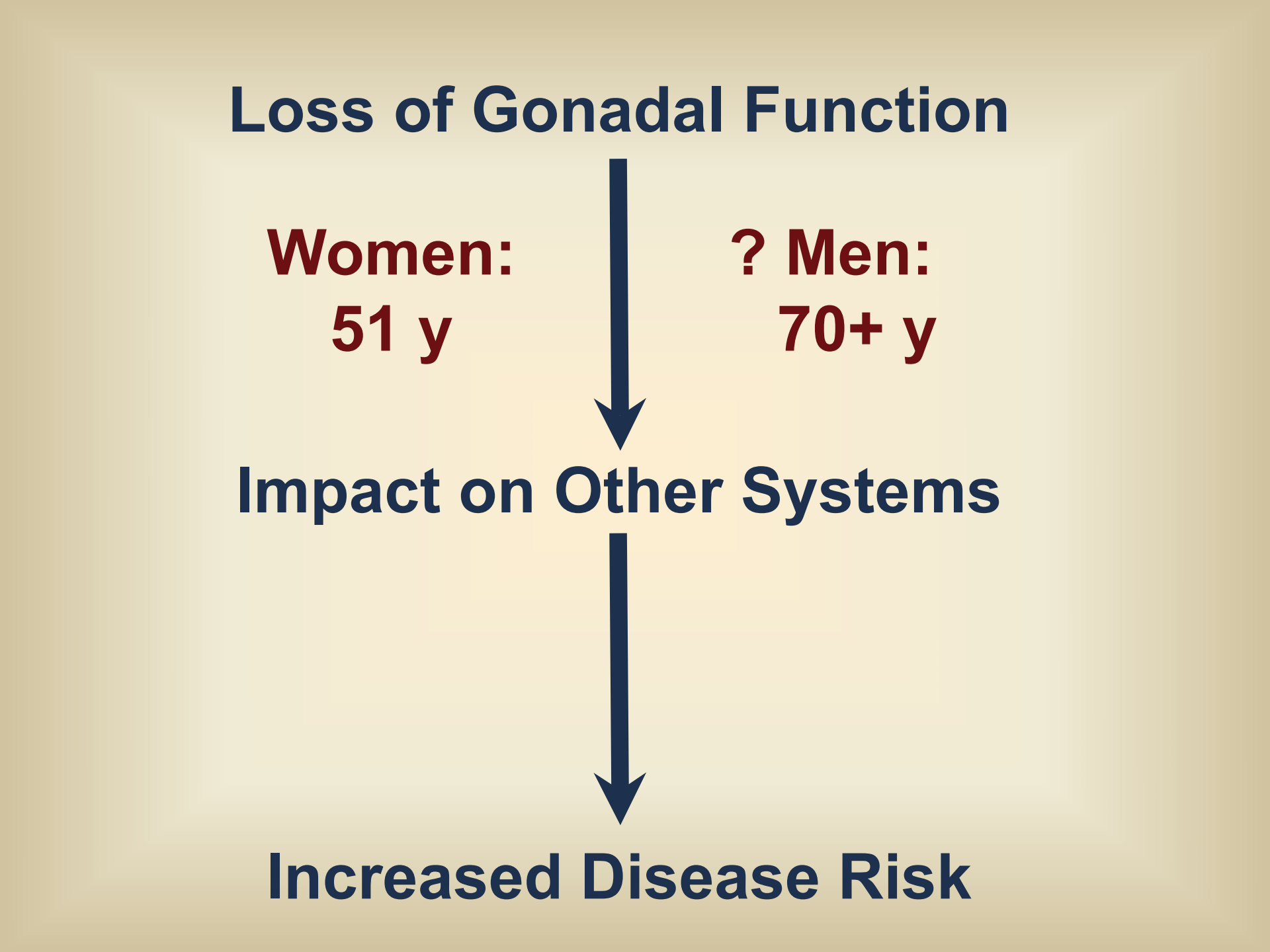
Outline

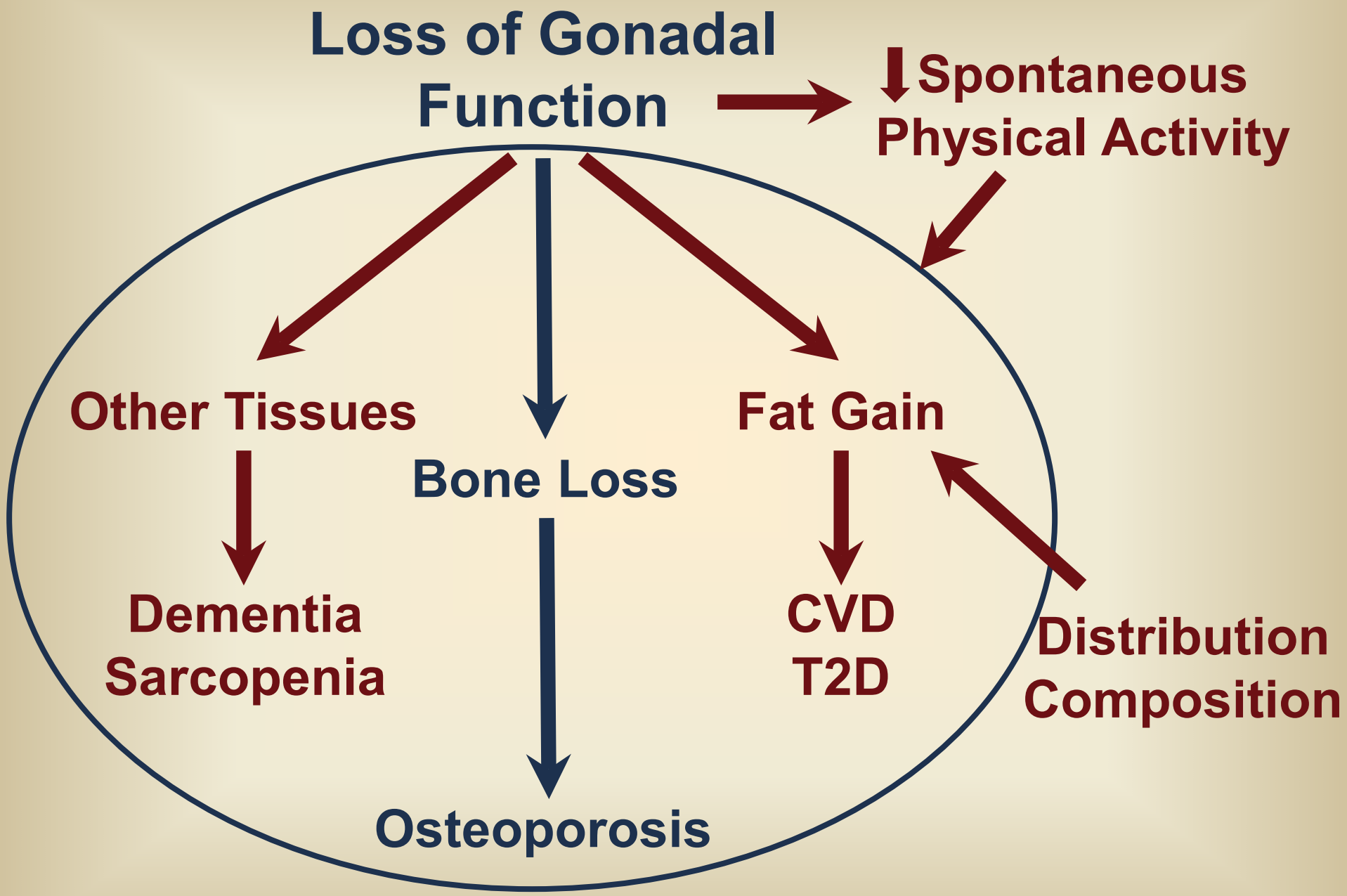
1. Potential consequences of the loss of gonadal function – working model

2. Bioenergetic and metabolic consequences of the loss of ovarian function – preclinical

3. Bioenergetic and metabolic consequences of the loss of ovarian function – clinical

4. New SCORE directions


Loss of Gonadal Function
Women:
51 y
? Men:
70+ y
Impact on Other Systems
Increased Disease Risk

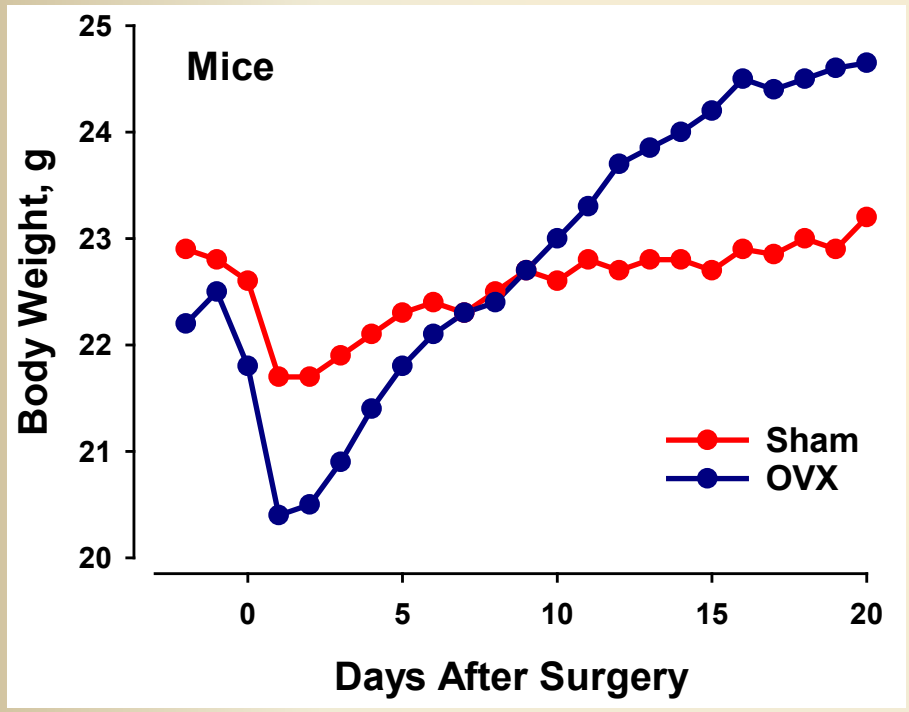

Loss of Gonadal Function
Spontaneous Physical Activity
Other Tissues
Bone Loss
Fat Gain
Dementia
Sarcopenia
Osteoporosis
CVD
T2D
Distribution
Composition

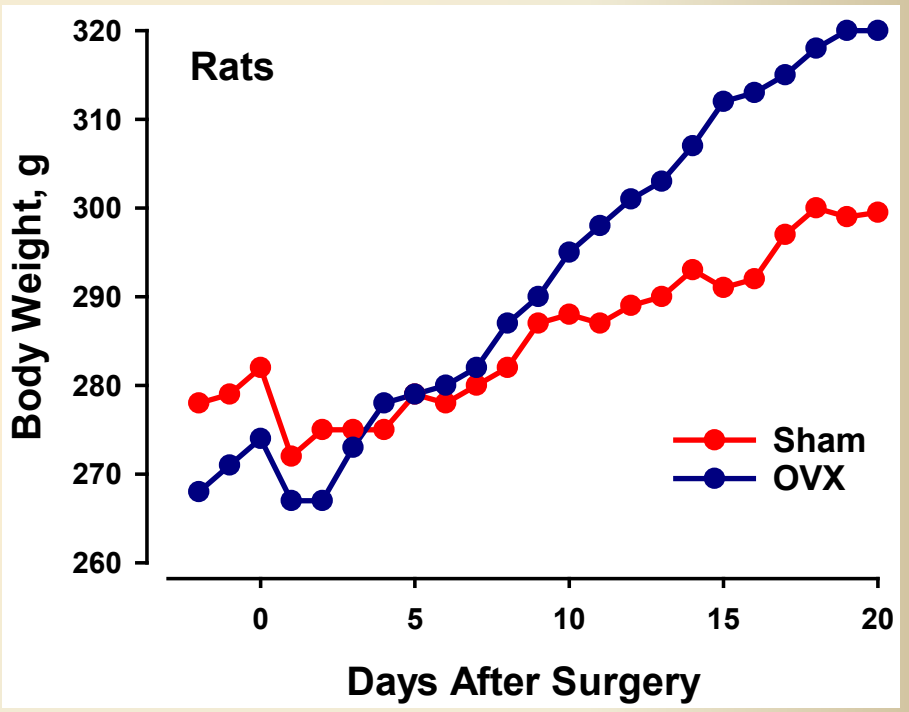
Outline

1. Potential consequences of the loss of gonadal function – working model

2. Bioenergetic and metabolic consequences of the loss of ovarian function – preclinical

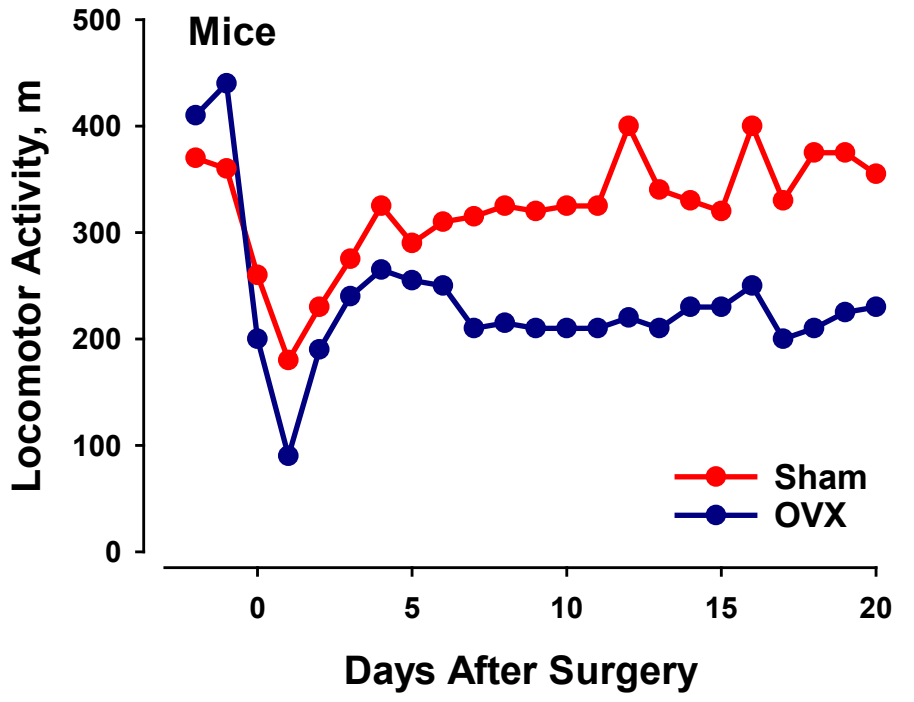
Body Weight in Mice and Rats OVX vs Sham

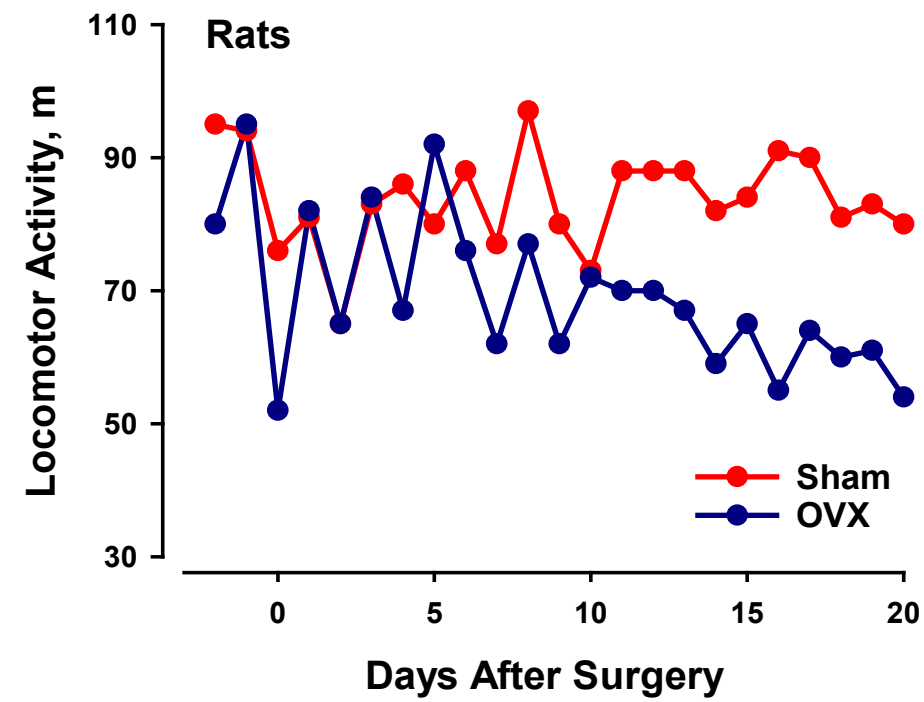




Adapted from: Witte MM et al. *General Compar Endocrinol* 166:520, 2010

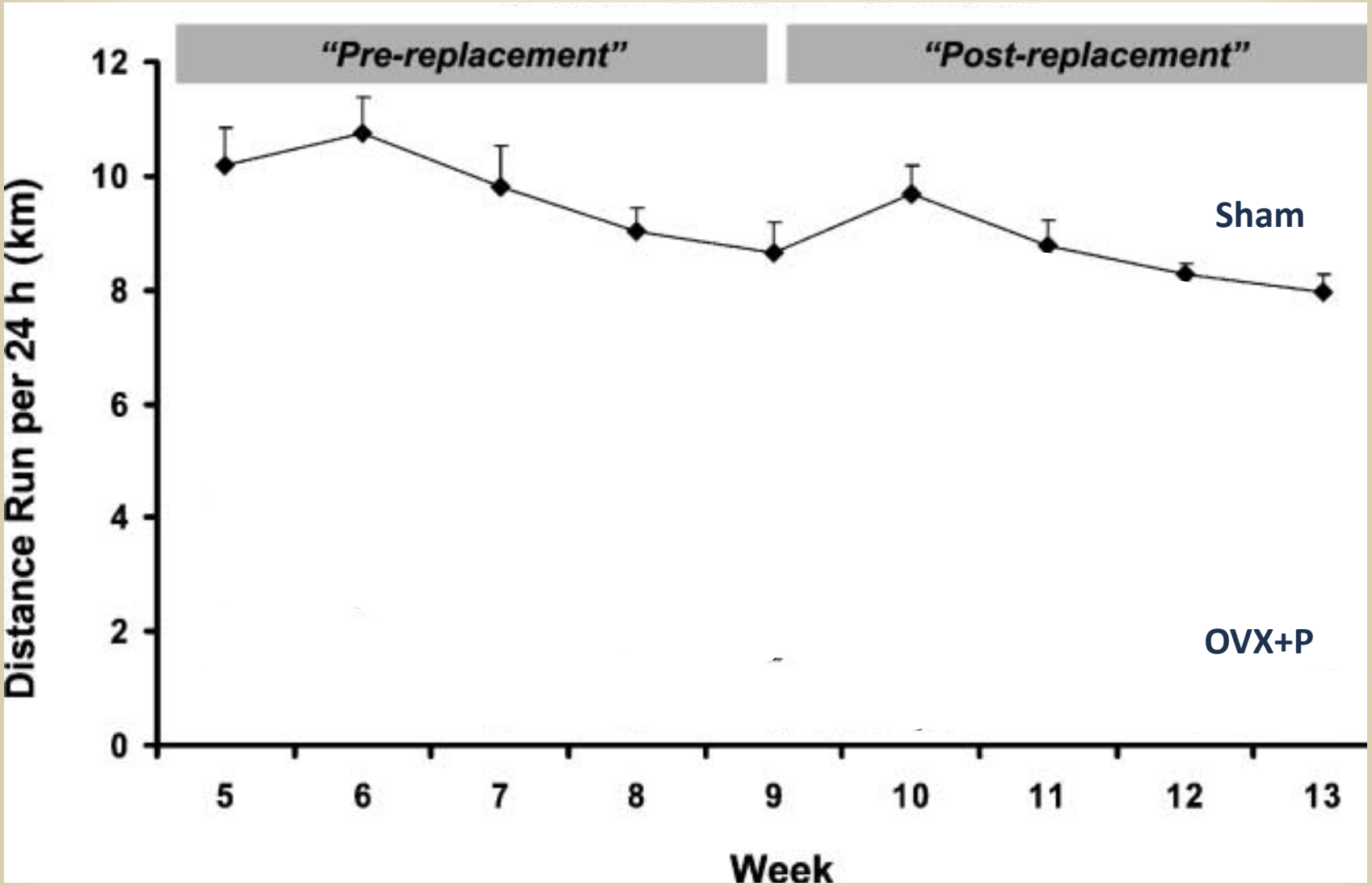
Locomotor Activity in Mice and Rats OVX vs Sham





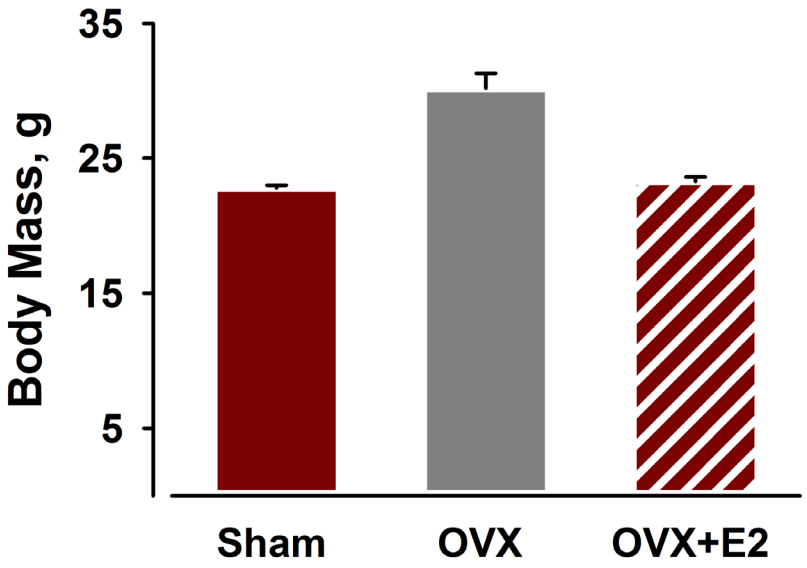
Adapted from: Witte MM et al. *General Compar Endocrinol* 166:520, 2010

Wheel-running Distance in Sham and OVX Mice



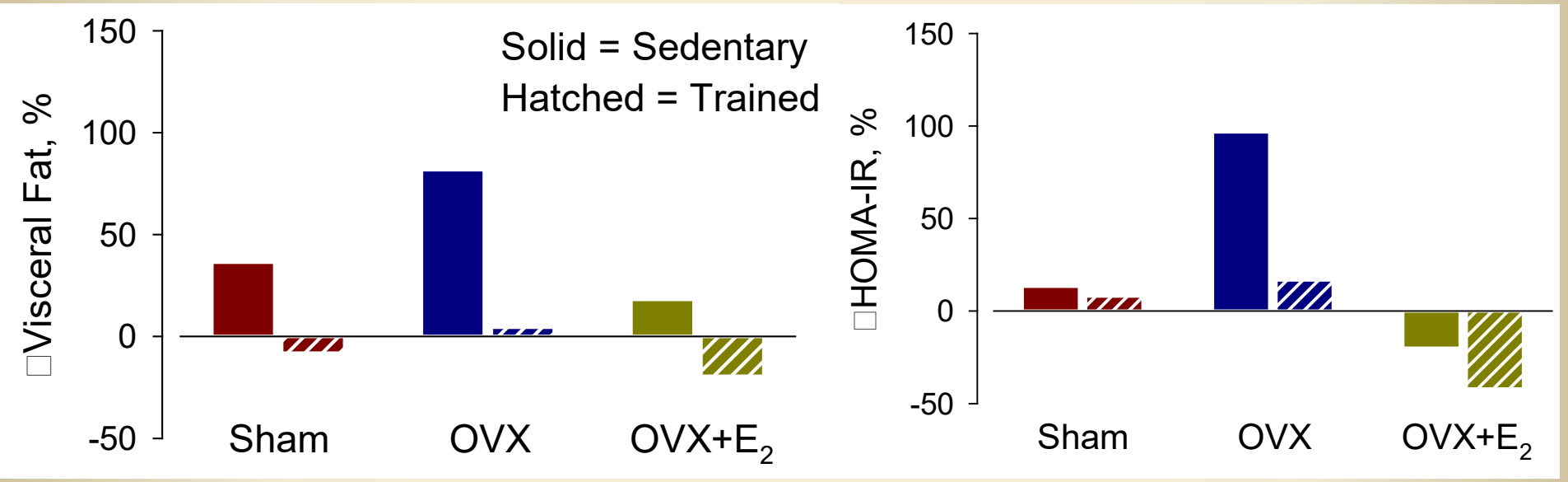
From: Gorzek JF et al. *Med Sci Sports Exerc* 39:248, 2007

Effects of OVX and E_2 Add-back in Mice



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

Effects of Programmed Exercise on Adiposity and Insulin Action



Adapted from: Pighon A et al. *Climacteric* 13:238, 2010

Effects of OVX:

- decreased physical activity
- decreased resting metabolic rate
- increased energy intake (some species)
- increased abdominal fat gain
- metabolic dysfunction

Prevented by E_2 treatment and by exercise

Outline

1. Potential consequences of the loss of gonadal function – working model

2. Bioenergetic and metabolic consequences of the loss of ovarian function – preclinical

3. Bioenergetic and metabolic consequences of the loss of ovarian function – clinical

Ovarian Hormone Suppression ($GnRH_{AG}$; 5 months) With Placebo or E_2

2-group model	$GnRH_{AG}$+PL n=35	$GnRH_{AG}$+E_2 n=35
Age, y	36 ± 2	35 ± 2
Wt, kg	74 ± 3	76 ± 3
BMI, kg/m^2	28 ± 2	28 ± 1
FM, kg	28 ± 2	28 ± 3
FFM, kg	46 ± 1	48 ± 1

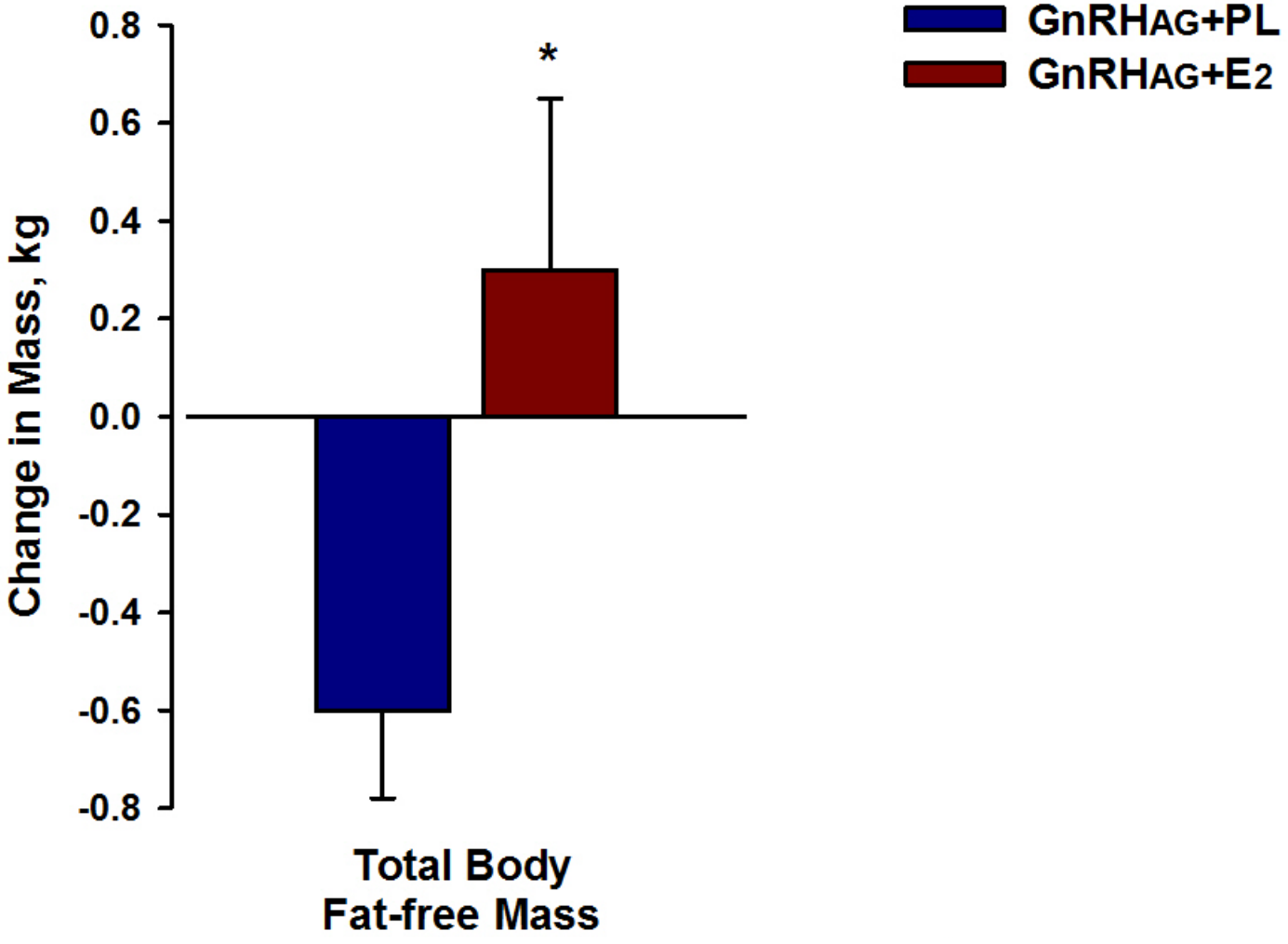
Shea K et al. *Menopause* 22:1045, 2015

Ovarian Hormone Suppression ($GnRH_{AG}$; 5 months) + Placebo or E_2, ± Resistance Exercise

4-group model	$GnRH_{AG}$+PL n=35		$GnRH_{AG}$+E_2 n=35	
	-Ex n=23	+Ex n=12	-Ex n=23	+Ex n=12
Age, y	36 ± 2	36 ±2	34 ± 2	36 ±2
Wt, kg	74 ± 4	75 ± 4	76 ± 4	78 ± 5
BMI, kg/m^2	28 ± 1	28 ± 2	28 ± 1	29 ± 2
FM, kg	27 ± 3	28 ± 3	28 ± 3	28 ± 3
FFM, kg	47 ± 1	47 ± 2	48 ± 1	50 ± 2

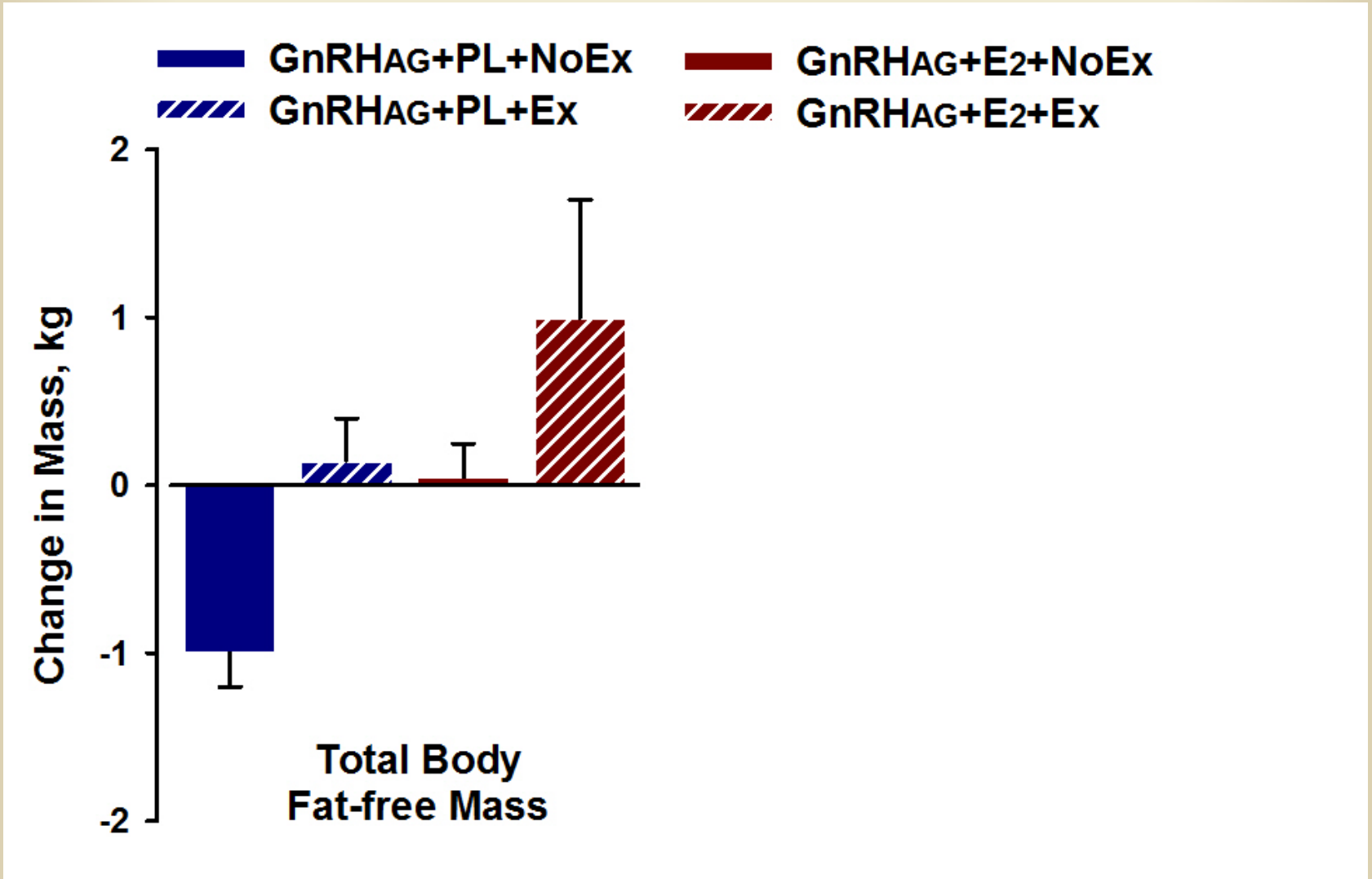
Shea K et al. *Menopause* 22:1045, 2015

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



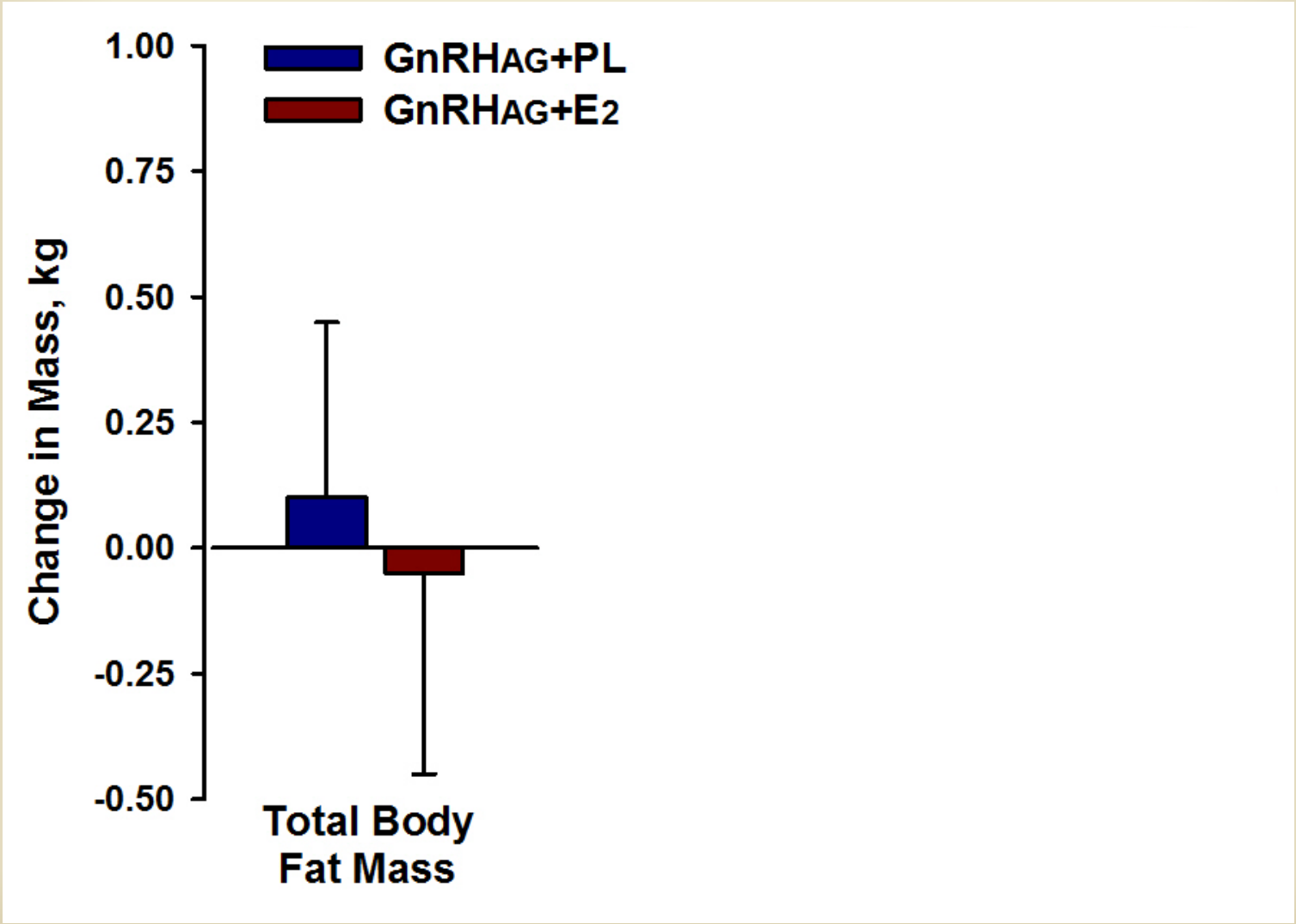
Shea K et al. *Menopause* 22:1045, 2015

$GnRH_{AG}$, +/- E_2, +/- Exercise Training
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



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

$GnRH_{AG}$+PL vs $GnRH_{AG}$+E_2
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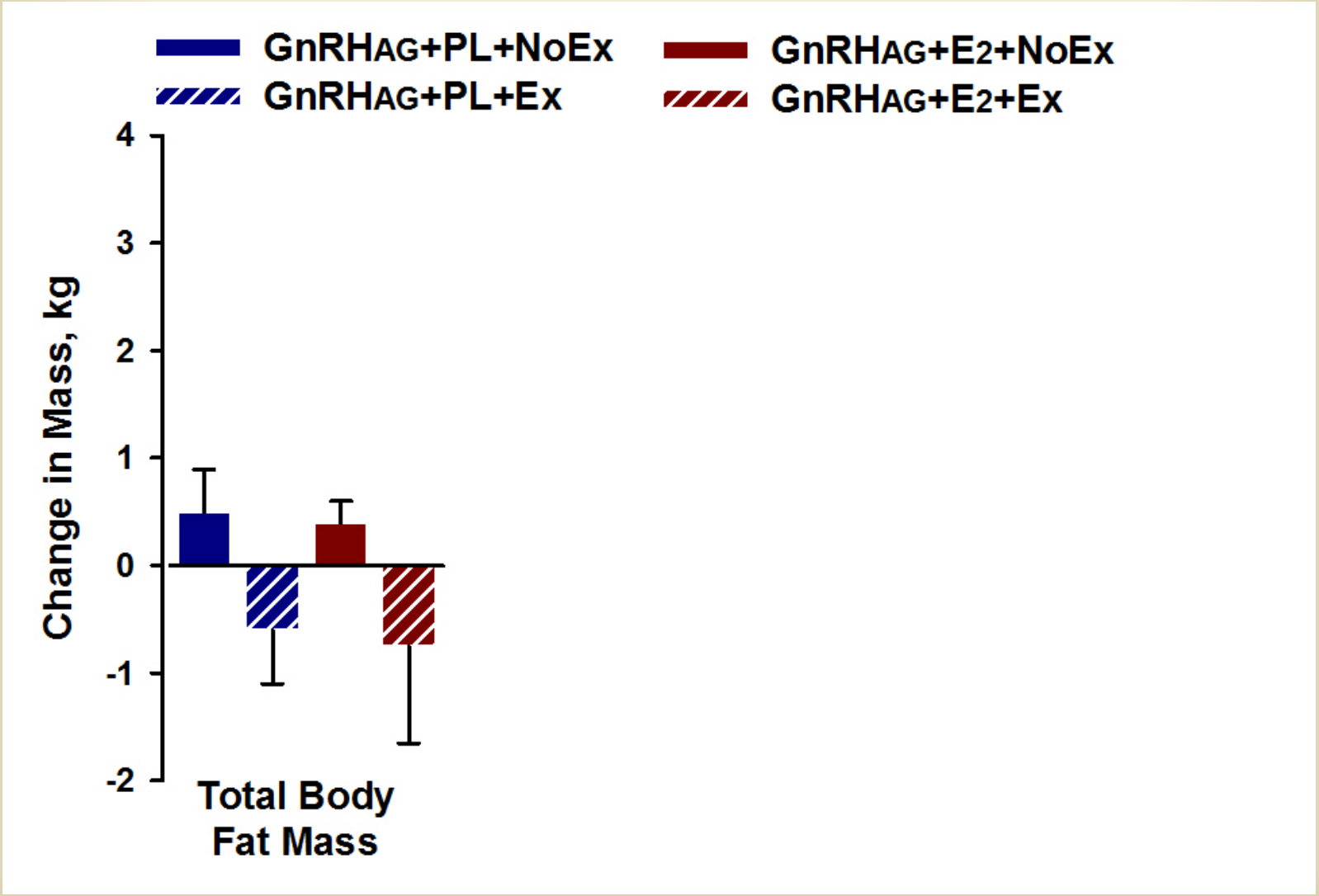
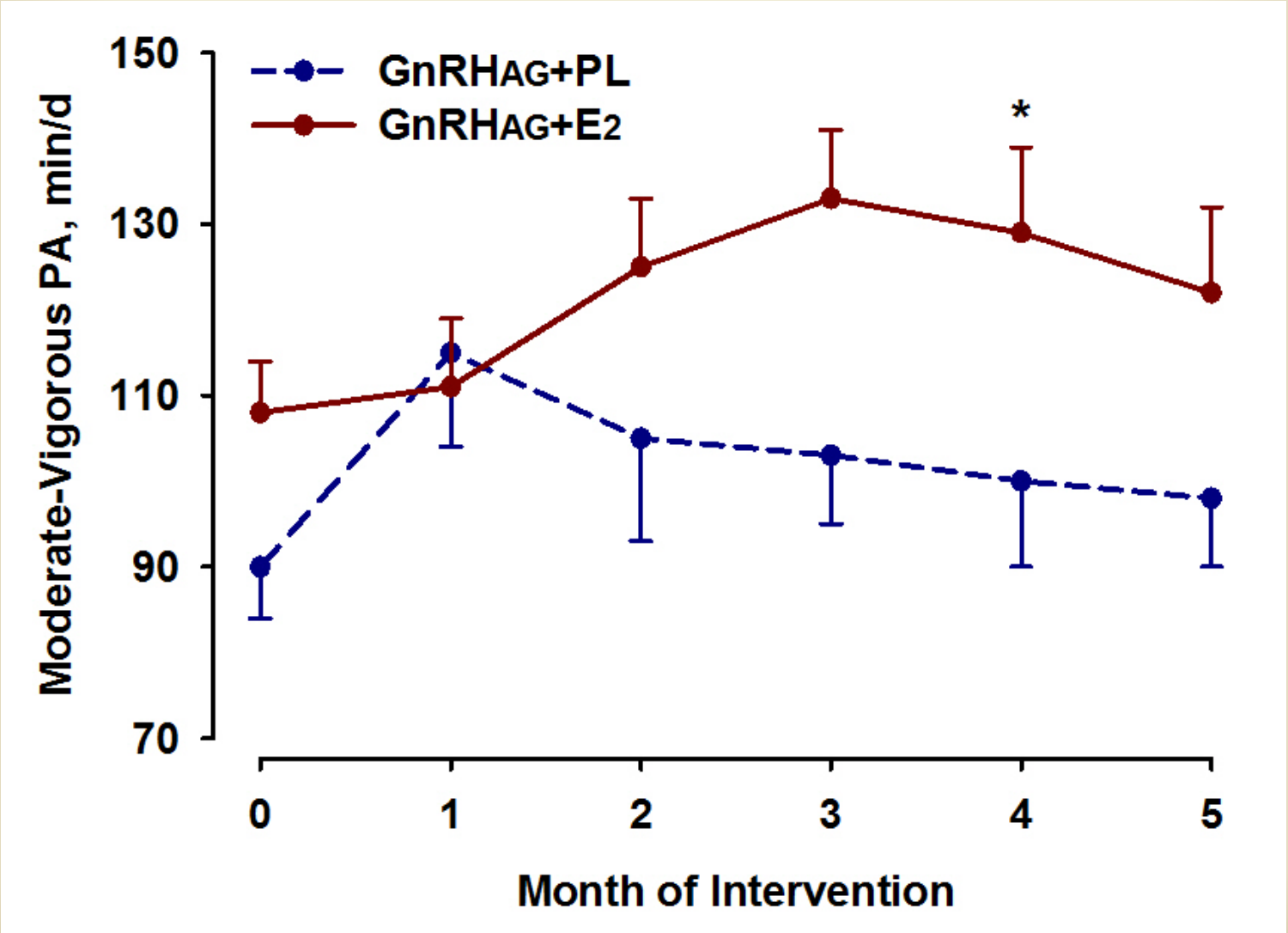


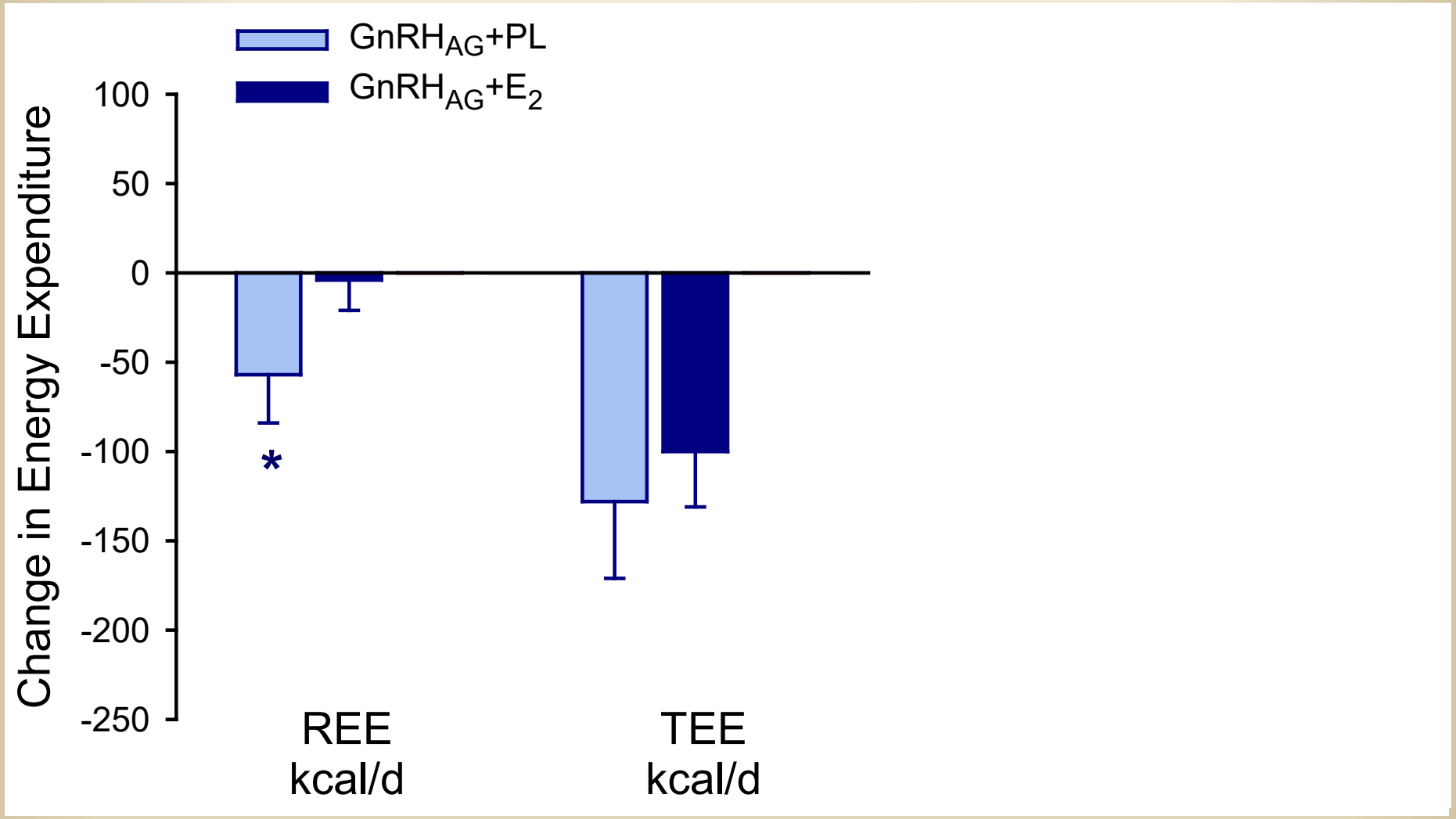
Shea K et al. *Menopause* 22:1045, 2015

$GnRH_{AG}$+PL vs $GnRH_{AG}$+E_2
Changes in Moderate-Vigorous Physical Activity



Melanson EL et al, *Med Sci Sports Exerc* 50:1704, 2018

$GnRH_{AG}$+PL vs $GnRH_{AG}$+E_2 vs $GnRH_{AG}$+PL+Ex
5-mo Changes in Energy Expenditure



Melanson EL et al. *J Appl Physiol* 119:975, 2015

Ovarian Suppression – Body Composition

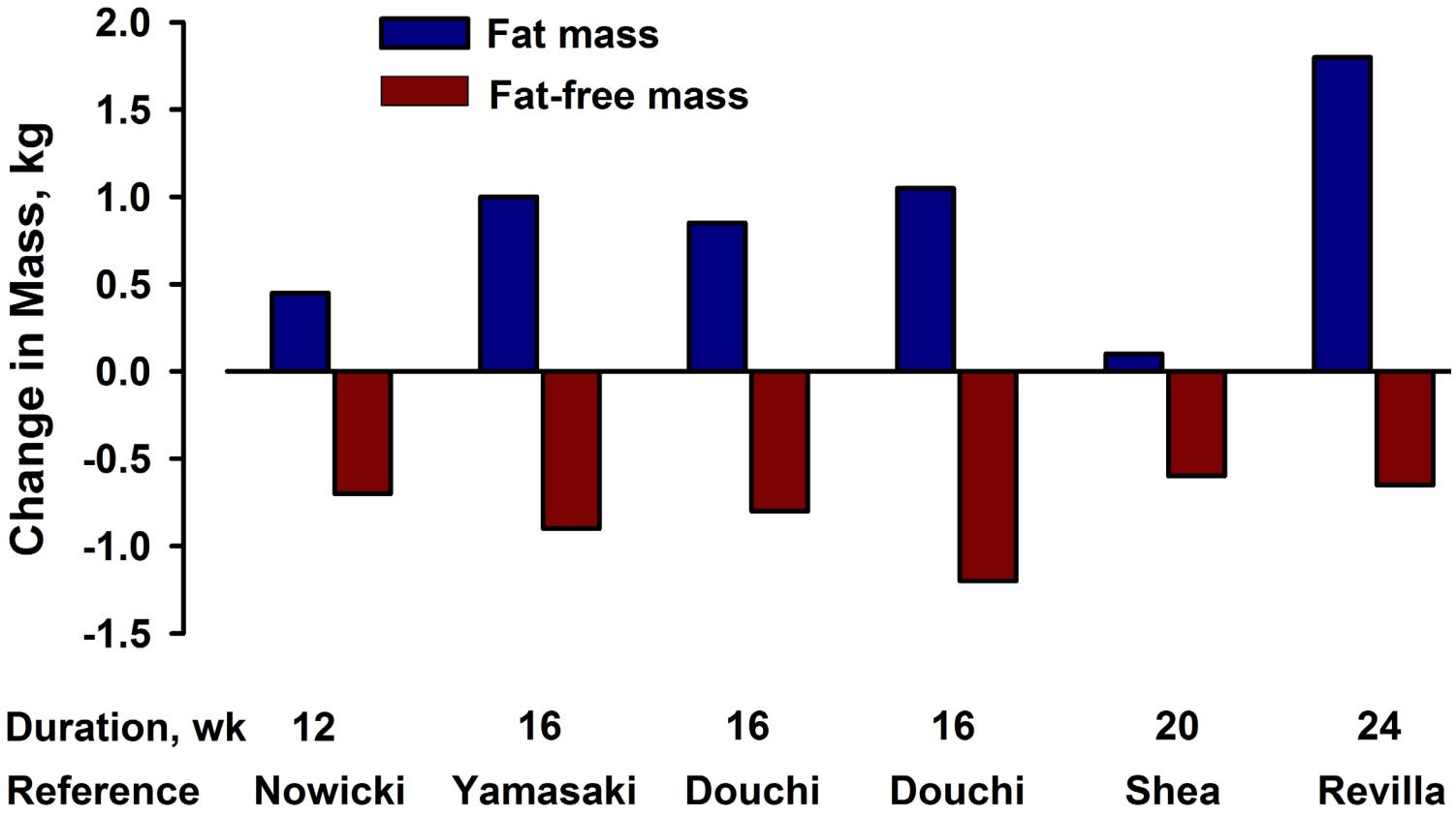


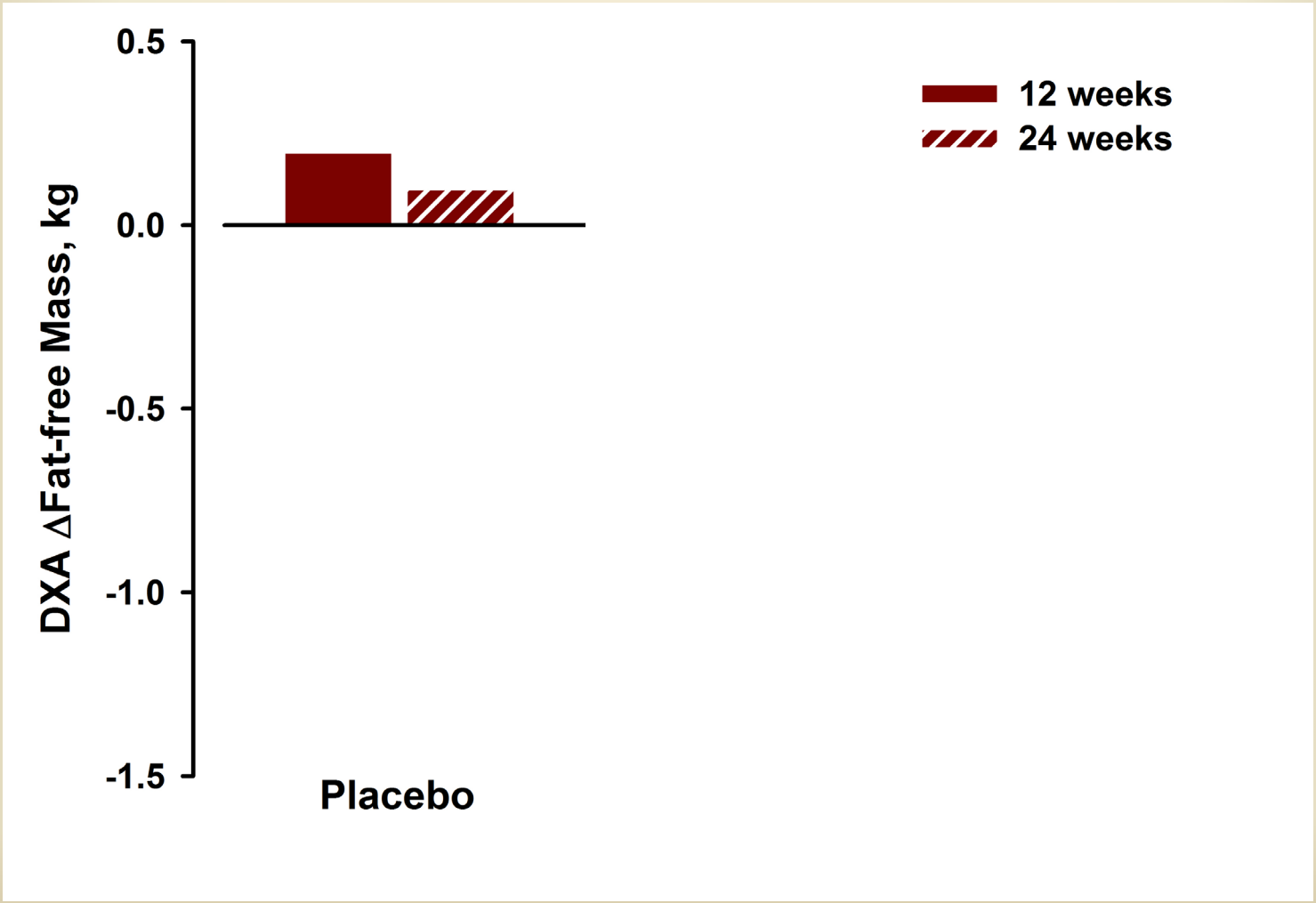
Figure 4. Changes in fat mass and fat-free mass in response to 12 to 24 weeks of gonadotropin releasing hormone therapy.

6 Months of Placebo vs GnRH Agonist Therapy ± Endurance Exercise

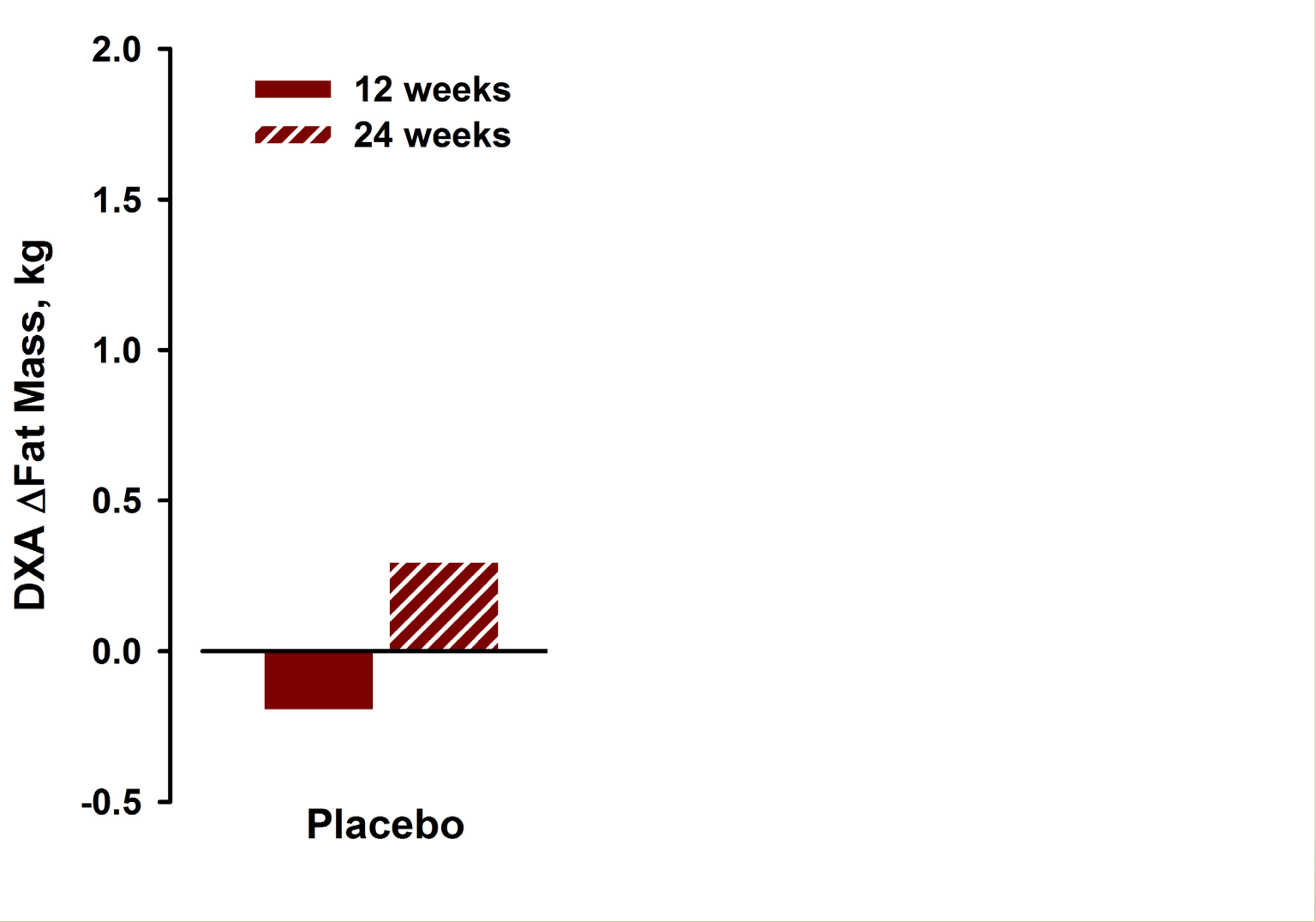
6-month intervention	Placebo	$GnRH_{AG}$ + Exercise	$GnRH_{AG}$
n	8	14	11
Age, y	46 ± 2	45 ± 3	47 ± 3
Wt, kg	72 ± 13	70 ± 13	74 ± 12
FM, kg	26 ± 12	23 ± 7	27 ± 7
FFM, kg	46 ± 5	47 ± 5	47 ± 5

Gavin KM et al *preliminary data*

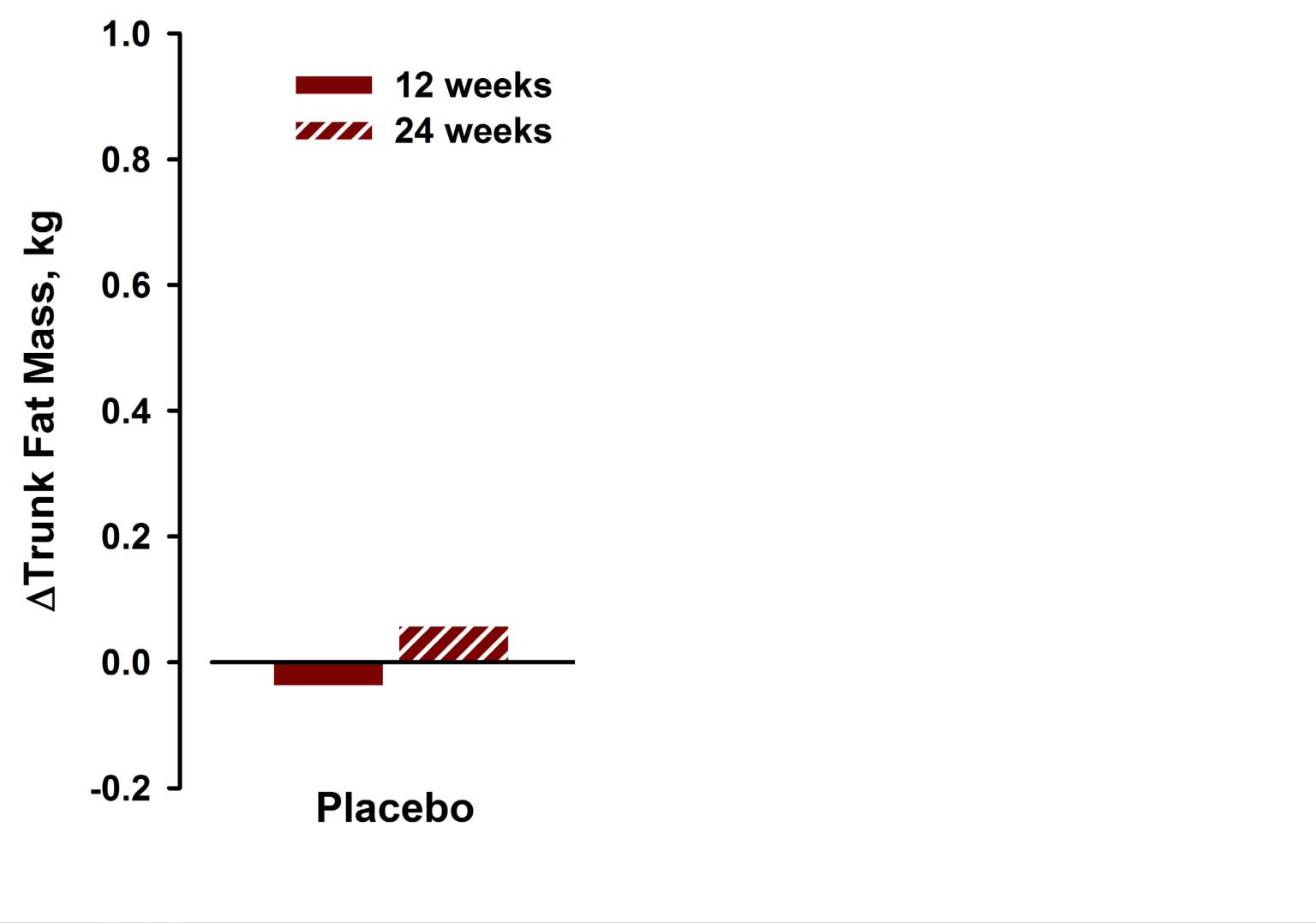
Ovarian Suppression and Endurance Exercise Change in Fat-free Mass



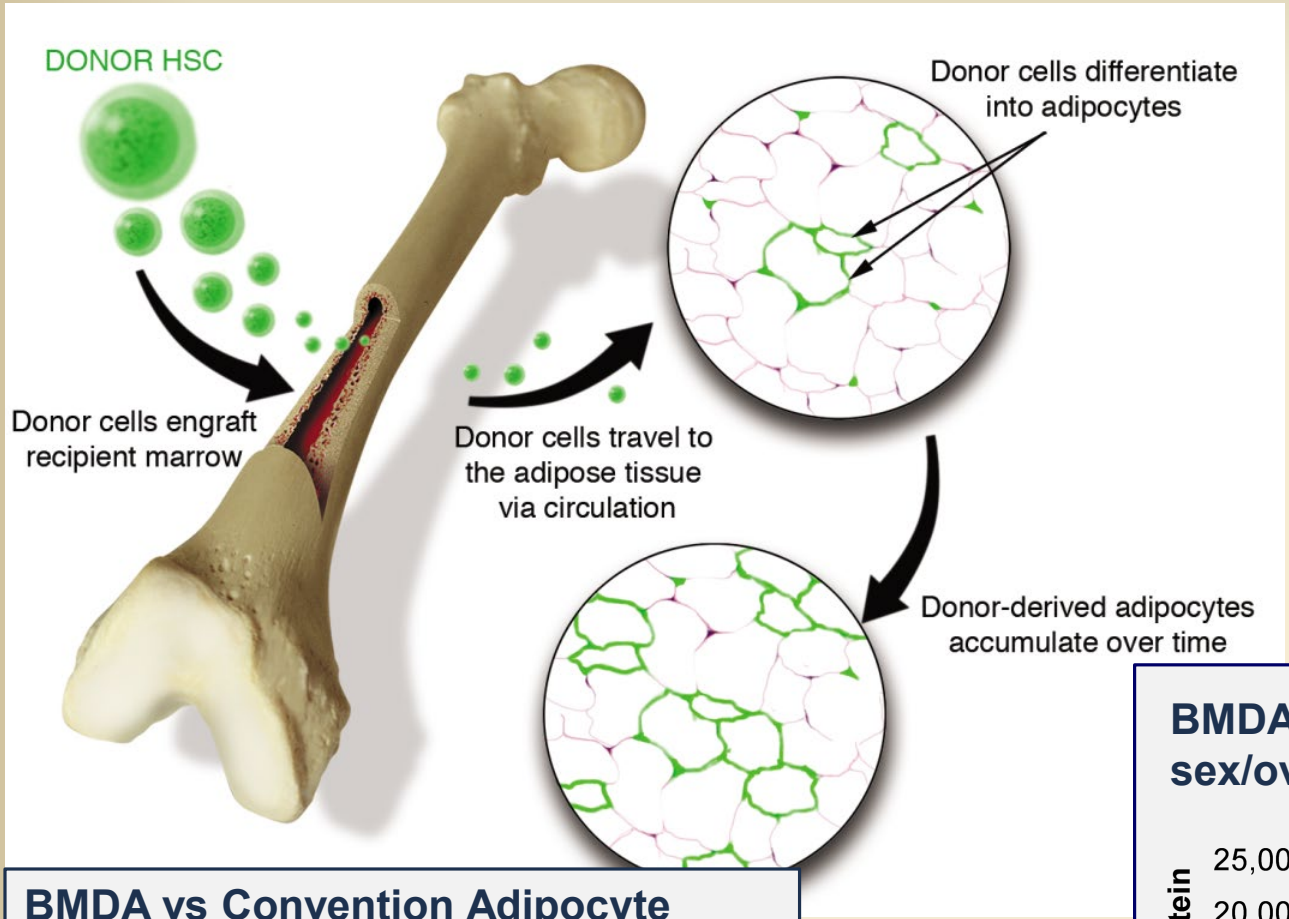
Ovarian Suppression and Endurance Exercise Change in Fat Mass



Ovarian Suppression and Endurance Exercise Change in Trunk Fat Mass



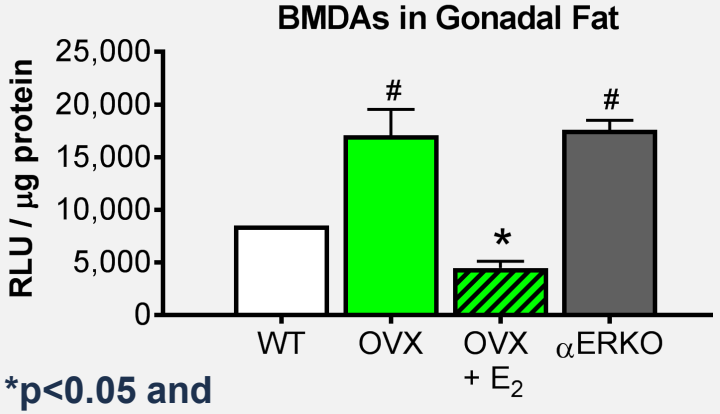
E_2 Regulation of Adipose Cellular Composition



BMDA vs Convention Adipocyte Gene Expression Signature:

- **Highly inflammatory**
- **Lower mitochondrial enzymes**
- **Lower leptin**

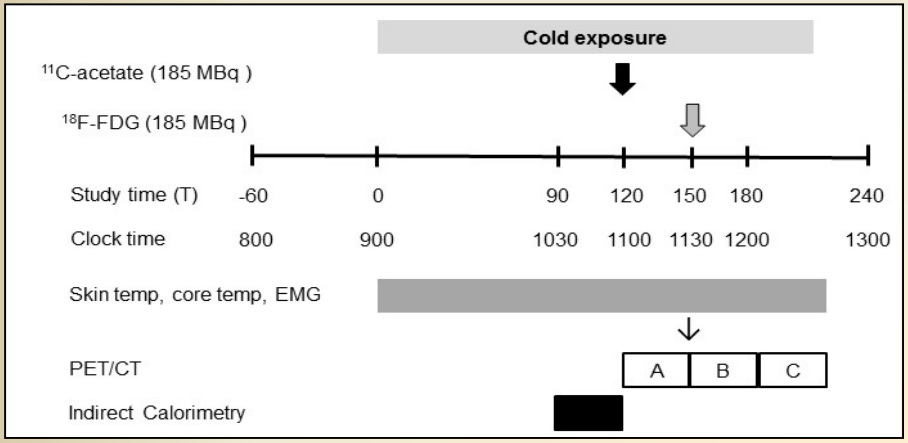
BMDA production is regulated by sex/ovarian hormone status:

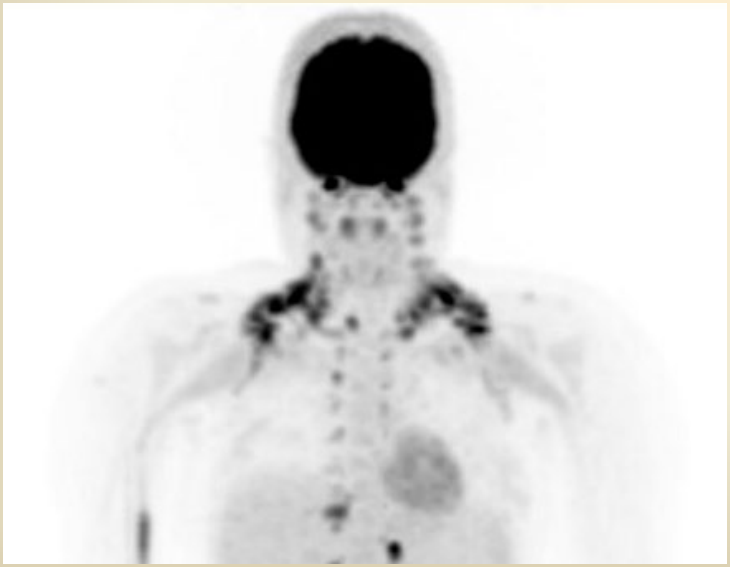


*p<0.05 and
#p=0.0001 vs WT

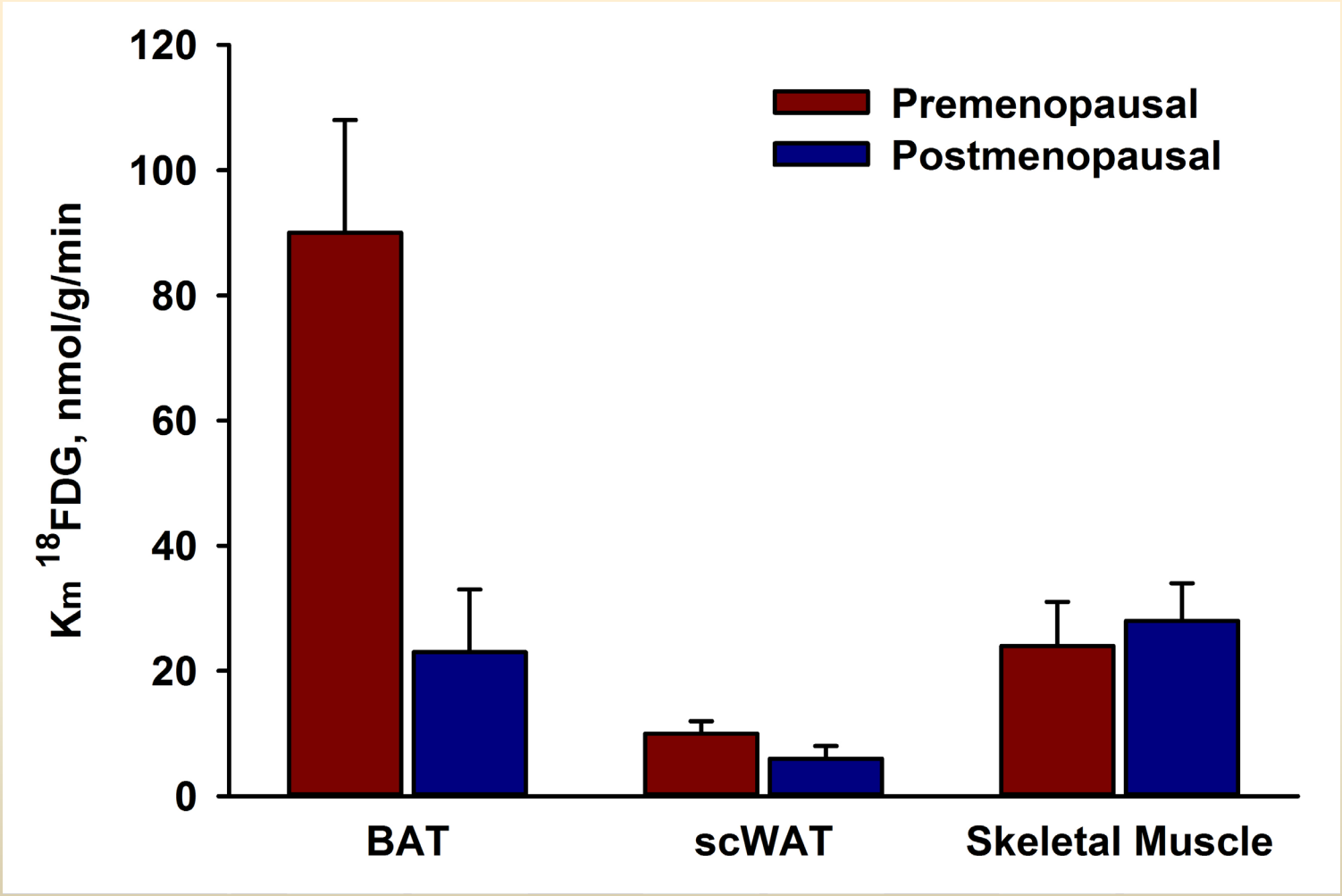
Gavin KM et al *Front Endocrinol* 2018
Majka SM, Barak Y, Klemm DJ *Stem Cells* 2011

E_2 Regulation of BAT Thermogenesis



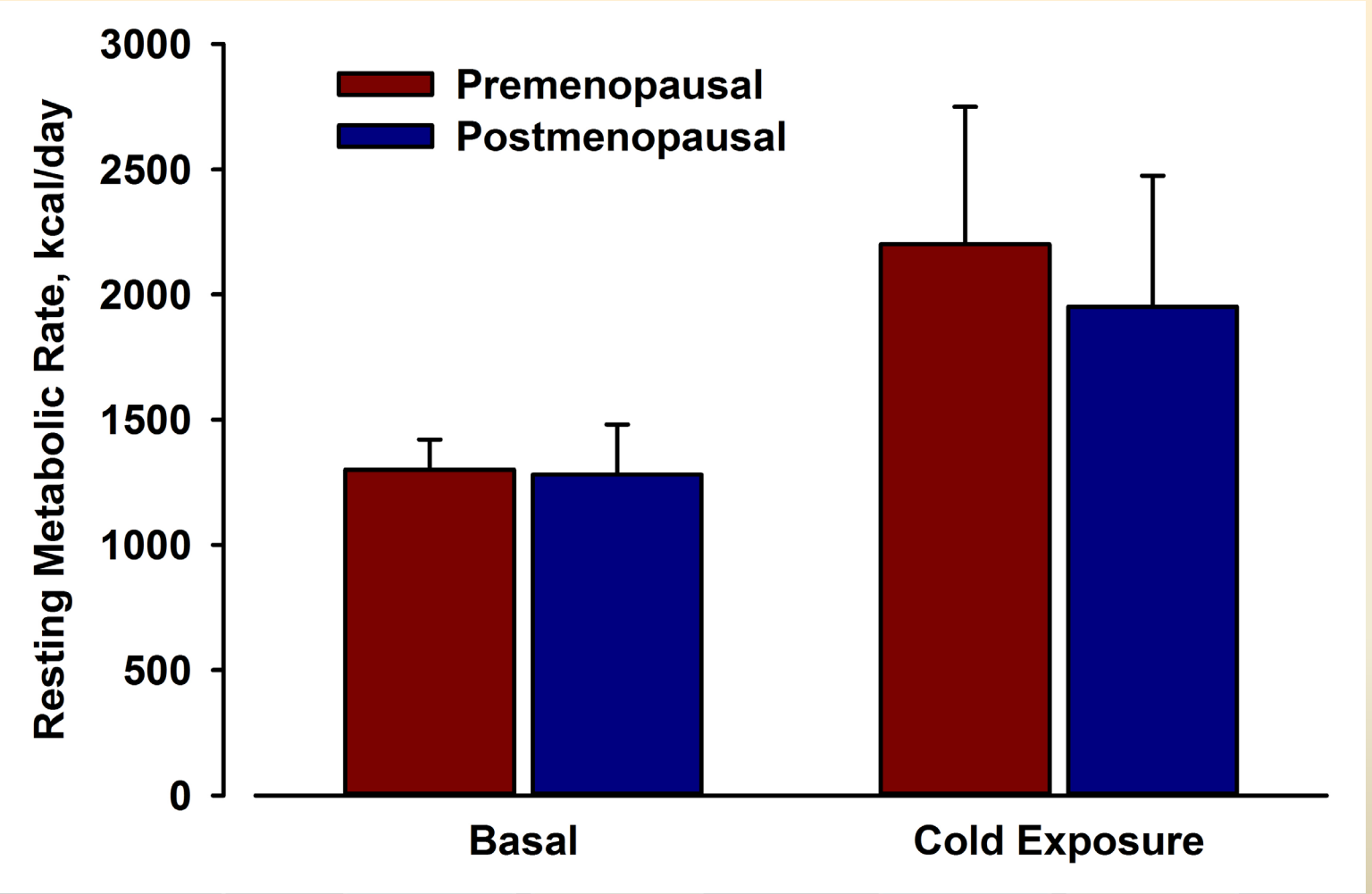


^{18}FDG Tissue Uptake
Pre- vs Postmenopausal Women



Melanson et al preliminary data

Cold-induced Thermogenesis in Pre- vs Postmenopausal Women



Melanson et al preliminary data

Estrogen Status and Energy Homeostasis

- Preclinical (OVX) and clinical studies ($GnRH_{AG}$) provide consistent evidence for the role of estrogens in the regulation of energy balance
- The loss of estrogens (OVX, $GnRH_{AG}$) may promote fat gain through multiple system-level mechanisms
  - decreased resting metabolic rate
  - decreased physical activity
  - increased energy intake (some species)
  - decreased BAT thermogenesis

Estrogen Status and Energy Homeostasis

- Mitigation by Exercise -

- In animals, exercise prevents the effects of OVX to increase abdominal adiposity and metabolic dysfunction
- Preliminary studies of women suggest *resistance* exercise may attenuate the loss of lean mass in response to ovarian aging, but not the increase in abdominal adiposity or decrease in resting metabolic rate. *Endurance* exercise may attenuate fat gain, but not central body fat.

Outline

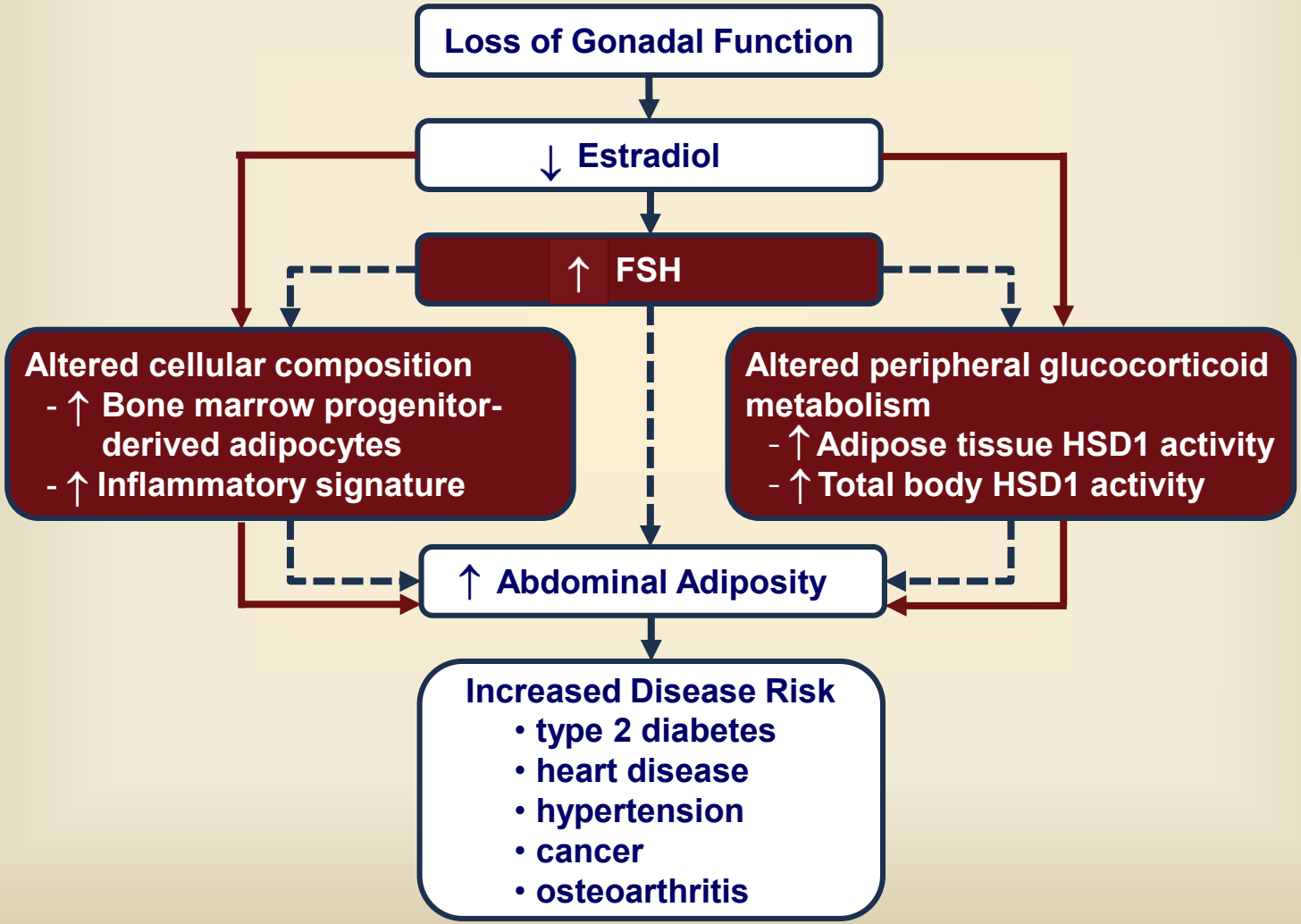
1. Potential consequences of the loss of gonadal function – working model

2. Bioenergetic and metabolic consequences of the loss of ovarian function – preclinical

3. Bioenergetic and metabolic consequences of the loss of ovarian function – SCOR results

4. New SCORE directions

Colorado SCORE - Scientific Focus



Blocking FSH induces thermogenic adipose tissue and reduces body fat

Peng Liu[1]*, Yaoting Ji[1,2]*, Tony Yuen[1], Elizabeth Rendina-Ruedy[3], Victoria E. DeMambro[3], Samarth Dhawan[1], Wahid Abu-Amer[1], Sudeh Izadmehr[1], Bin Zhou[4], Andrew C. Shin[1], Rauf Latif[1], Priyanthan Thangeswaran[1], Animesh Gupta[1], Jianhua Li[1], Valeria Shnayder[1], Samuel T. Robinson[4], Yue Eric Yu[4], Xingjian Zhang[4], Feiran Yang[4], Ping Lu[1], Yu Zhou[1], Ling-Ling Zhu[1], Douglas J. Oberlin[1], Terry F. Davies[1], Michaela R. Reagan[3], Aaron Brown[3], T. Rajendra Kumar[5], Solomon Epstein[1], Jameel Iqbal[6], Narayan G. Avadhani[7], Maria I. New[1], Henrik Molina[8], Jan B. van Klinken[9], Edward X. Guo[4], Christoph Buettner[1], Shozeb Haider[10], Zhuan Bian[2], Li Sun[1]§, Clifford J. Rosen[3]§ & Mone Zaidi[1]§

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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Preventing Fat Gain by Blocking Follicle-Stimulating Hormone

Wendy M. Kohrt, Ph.D., and Margaret E. Wierman, M.D.

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Investigations in Metabolism, Aging, Gender, and Exercise

IMAGE

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P30 DK048520

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