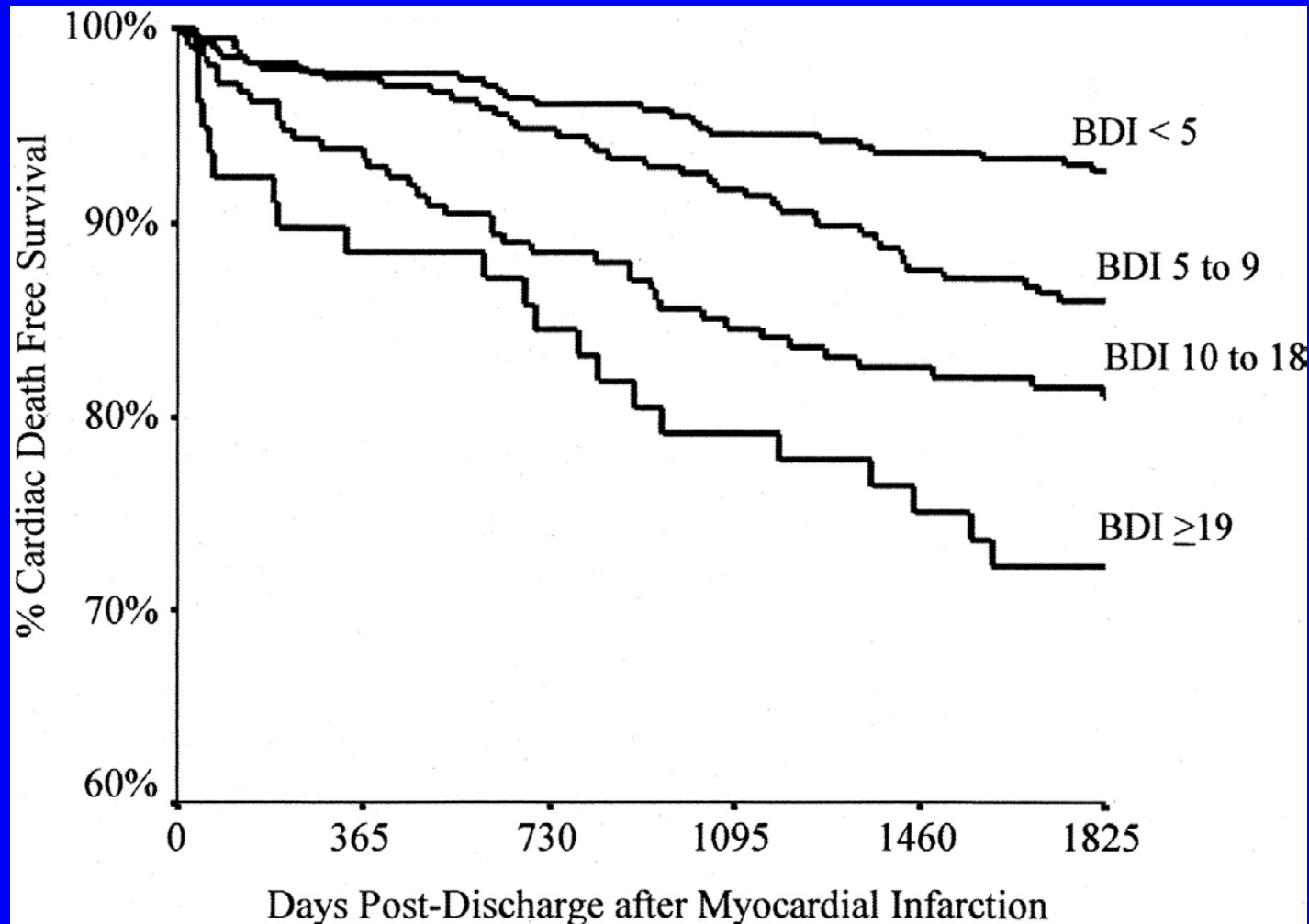


2014

American Heart Association Scientific Statement

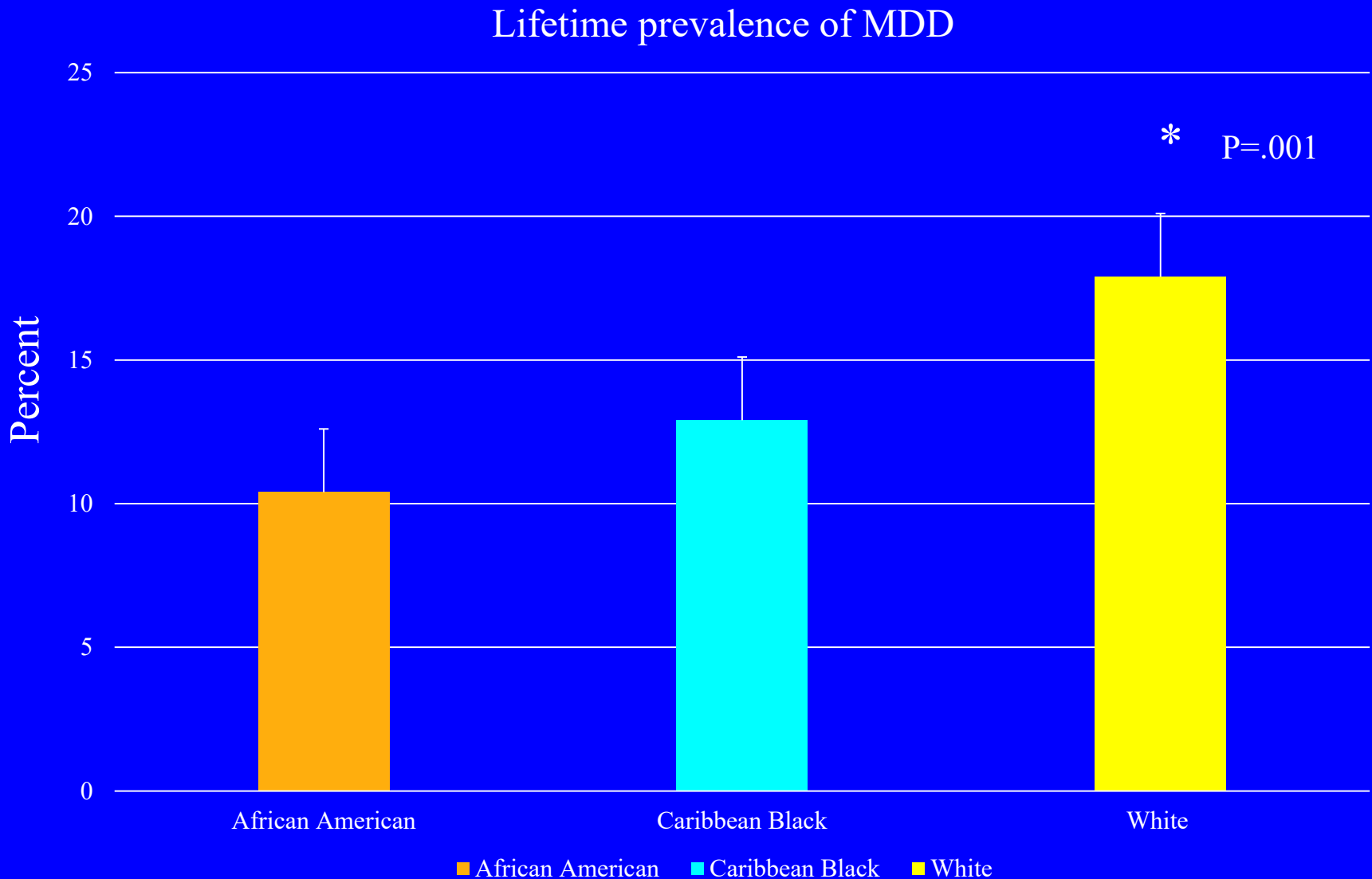
- *“The preponderance of evidence supports the recommendation that the American Heart Association should elevate depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome.”*

Higher Depression Scores following a Myocardial Infarction Predict Lower Rates of Survival from Cardiac Death Over 5 years

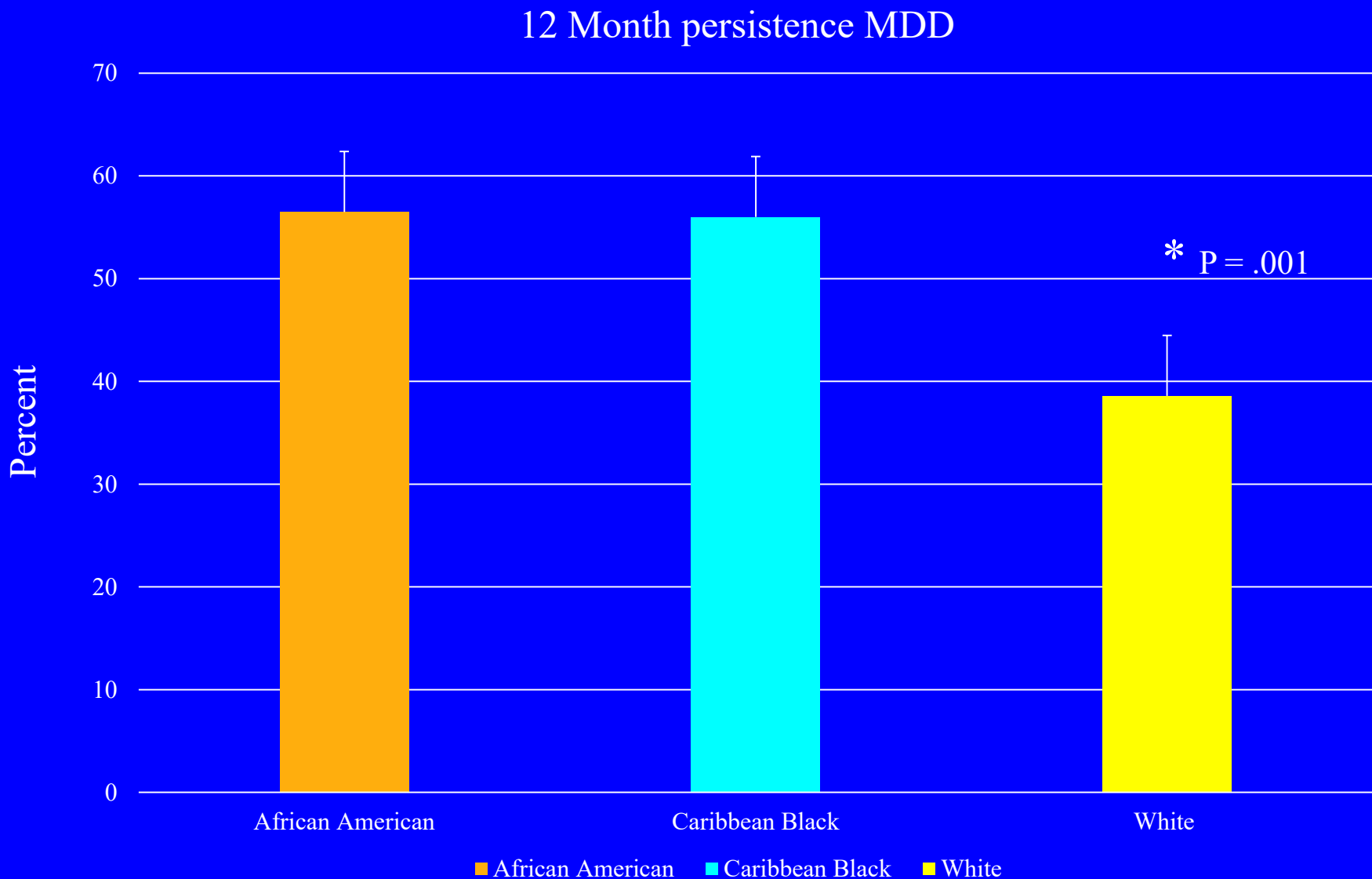


Prevalence of Major Depression in a National Sample by Race

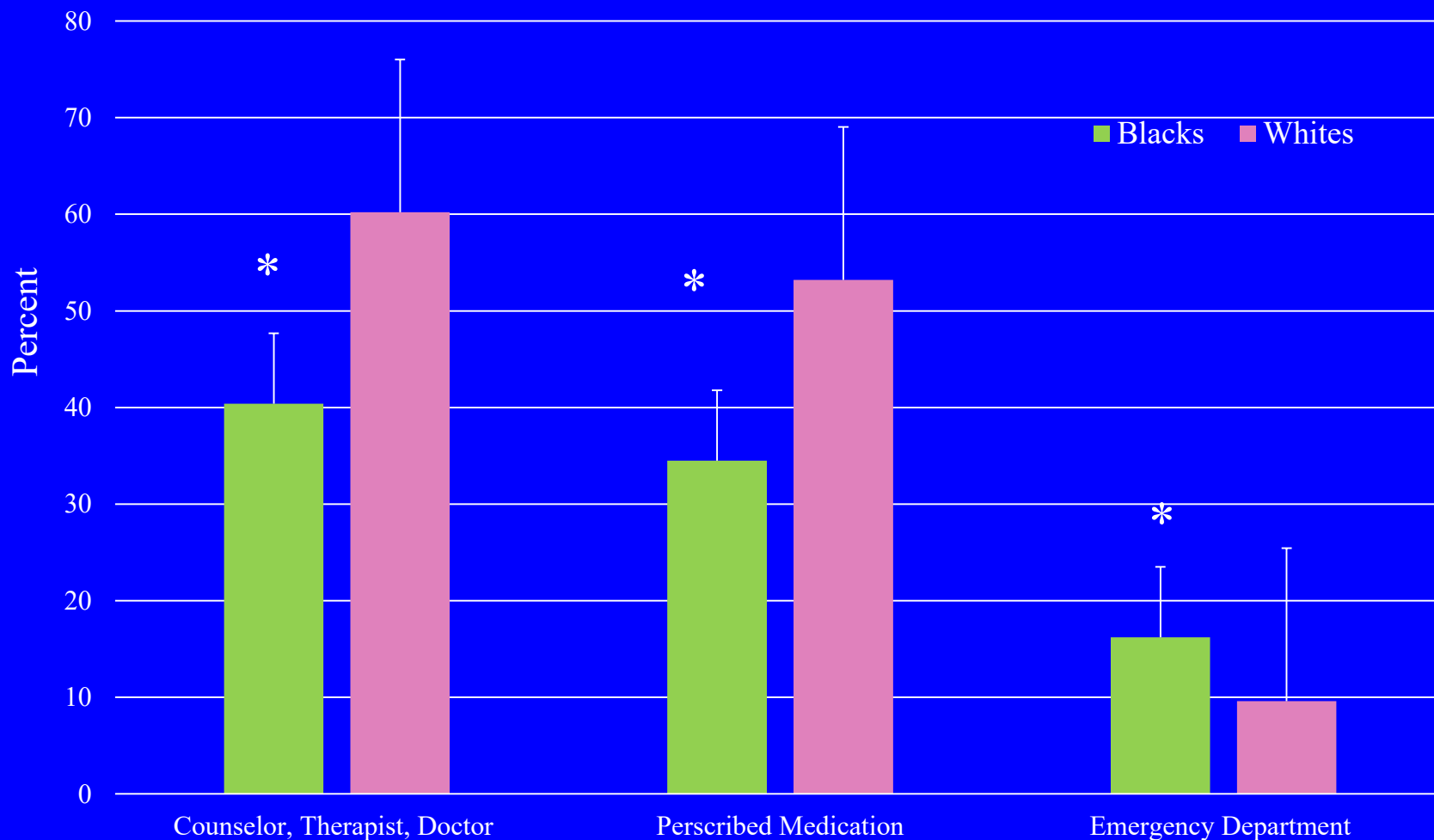
(N = 6082)



Persistence of Major Depression in a National Sample by Race

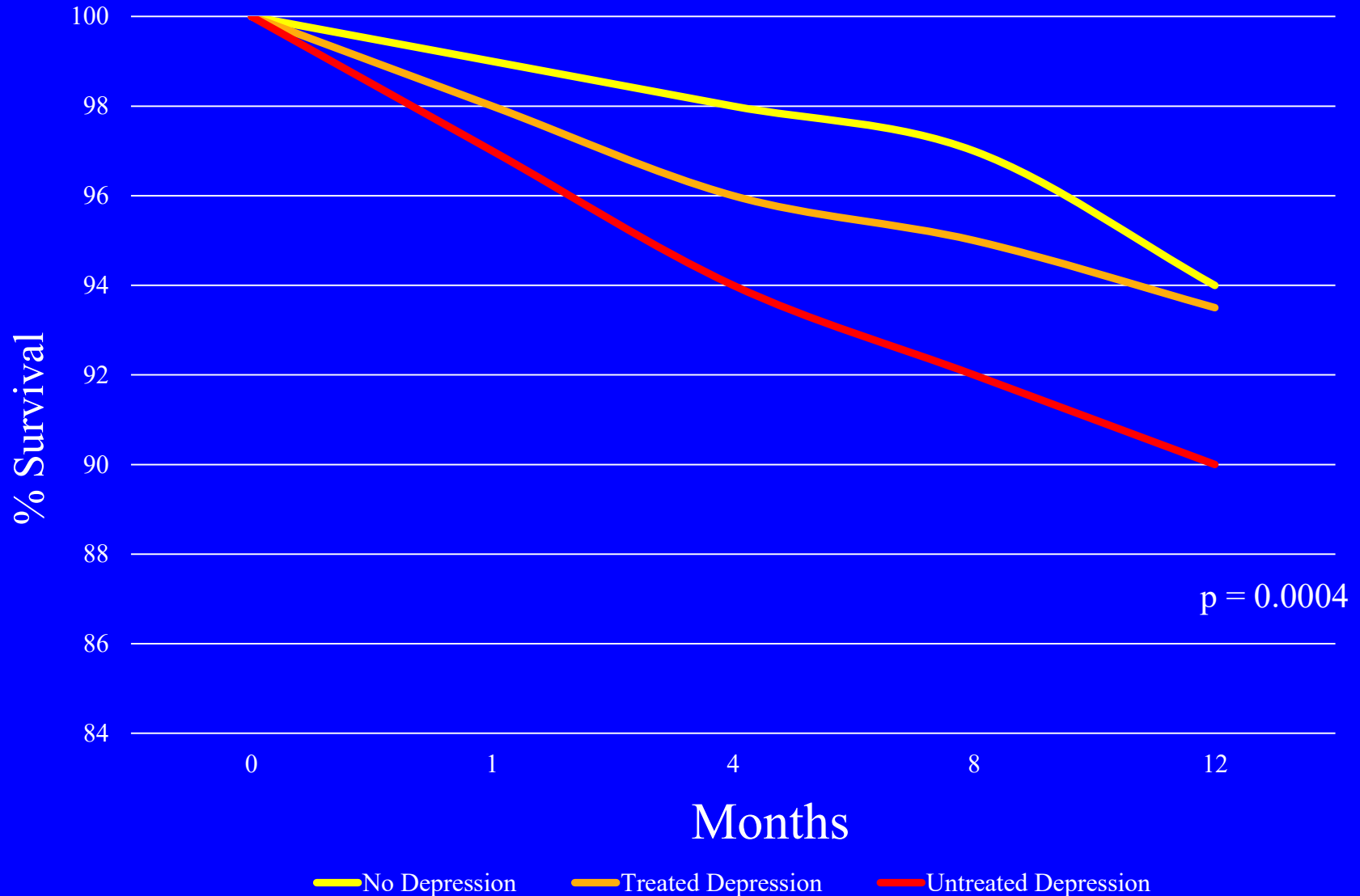


Treatment received for 12 month Major Depression among Black and White Adults (n= 1183)



Depression Treatment and 1 Year Mortality after Acute Myocardial Infarction

N = 4,062



More “Take Aways”

- Heart disease is the #1 killer of women, especially African American women
- Depression is an independent predictor of cardiac morbidity and mortality especially if untreated (and persistent?)

Menopause Risk

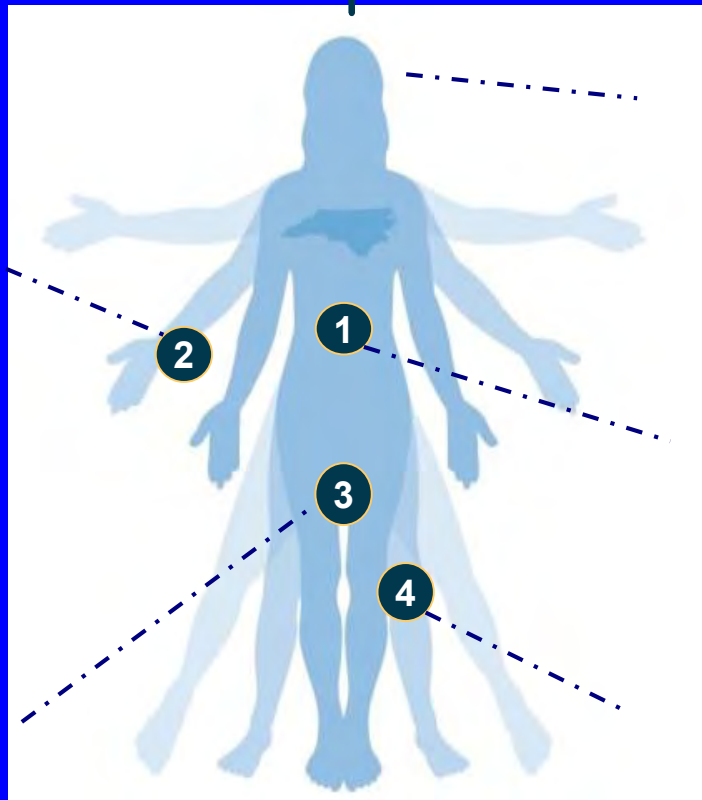
57 million mid-life women in the U.S. – every day 6,000 reach menopause

Cardiovascular Disease

Major Depressive Disorder

Rheumatoid and Osteoarthritis

- Affects 2 - 35% of mid-life adults, respectively
- Prevalence and severity are higher in mid-life women vs. men



STRESS

- Unique stressors of mid-life women

Metabolic Syndrome

- 37% of women in mid-life
- A stronger predictor of mortality in women

Osteoporosis

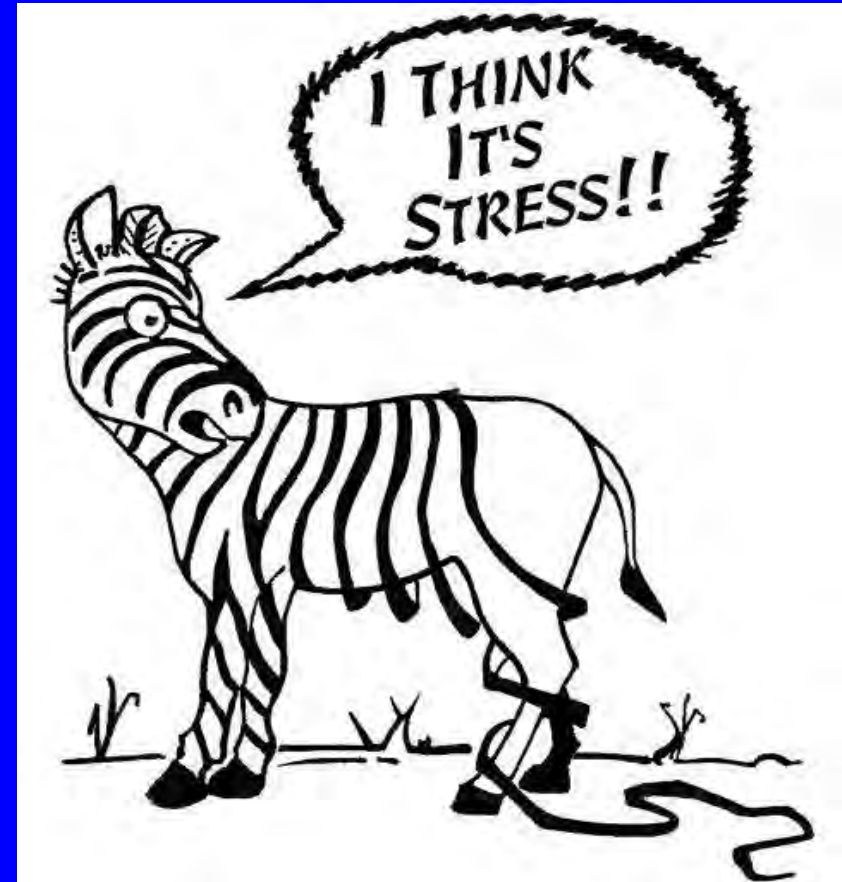
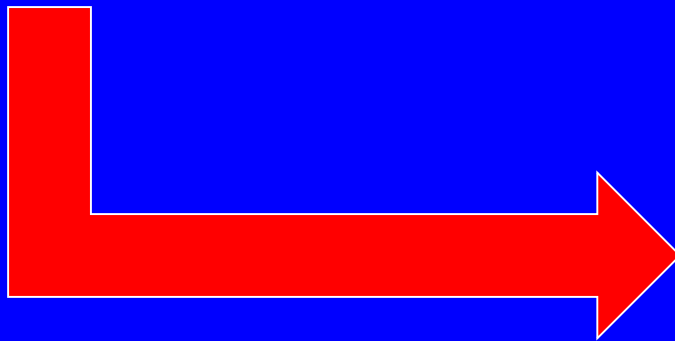
- Affects 16% mid-life women (3% mid-life men) in the U.S.

Pelvic Floor Disorders and Sexual Dysfunction

- 38 – 60% of mid-life women, respectively

How Stress Gets “Under the Skin” to Promote Illness

WHEN PHYSIOLOGIC
RESPONSES TO STRESS ARE
IN EXCESS OF OUR
METABOLIC NEEDS



Depression



Behavioral Risk Factors

Physiological Risk Factors

Smoking
Alcohol
Sedentary Lifestyle
Medical Adherence

STRESS

Inflammation
Endothelial Function
Cortisol Dysregulation
Cardiac Autonomic Imbalance
Metabolic Syndrome & Diabetes
Obesity
Hypertension

Estrogen



Estrogen
Deprivation



Cardiovascular Events



PERITI

Perimenopausal Estrogen Replacement Therapy Study

Funded by the National Institutes of Health:
NIH RO1 MH087619

Principal Investigators:

Susan Girdler, Ph.D. and David Rubinow, M.D.
Center for Women's Mood Disorders
University of North Carolina at Chapel Hill

Cohort: Medically healthy, non-depressed women, 45 – 60 years of age in the menopause transition (STRAW -1, -2 or +1)



1. Will creating a more stable hormone levels with transdermal estradiol buffer against the **emergence of depression** in initially non-depressed perimenopausal women?
2. Will there be corresponding **benefit for CVD risk**?

4166 Women Initiated Screening

350 Provided Consent and Underwent
Additional Screening

172 Randomized

86 Randomized to 12 months
Transdermal Estradiol, 100 μ g +
int. 200 mg oral micronized P4

23 withdrawals

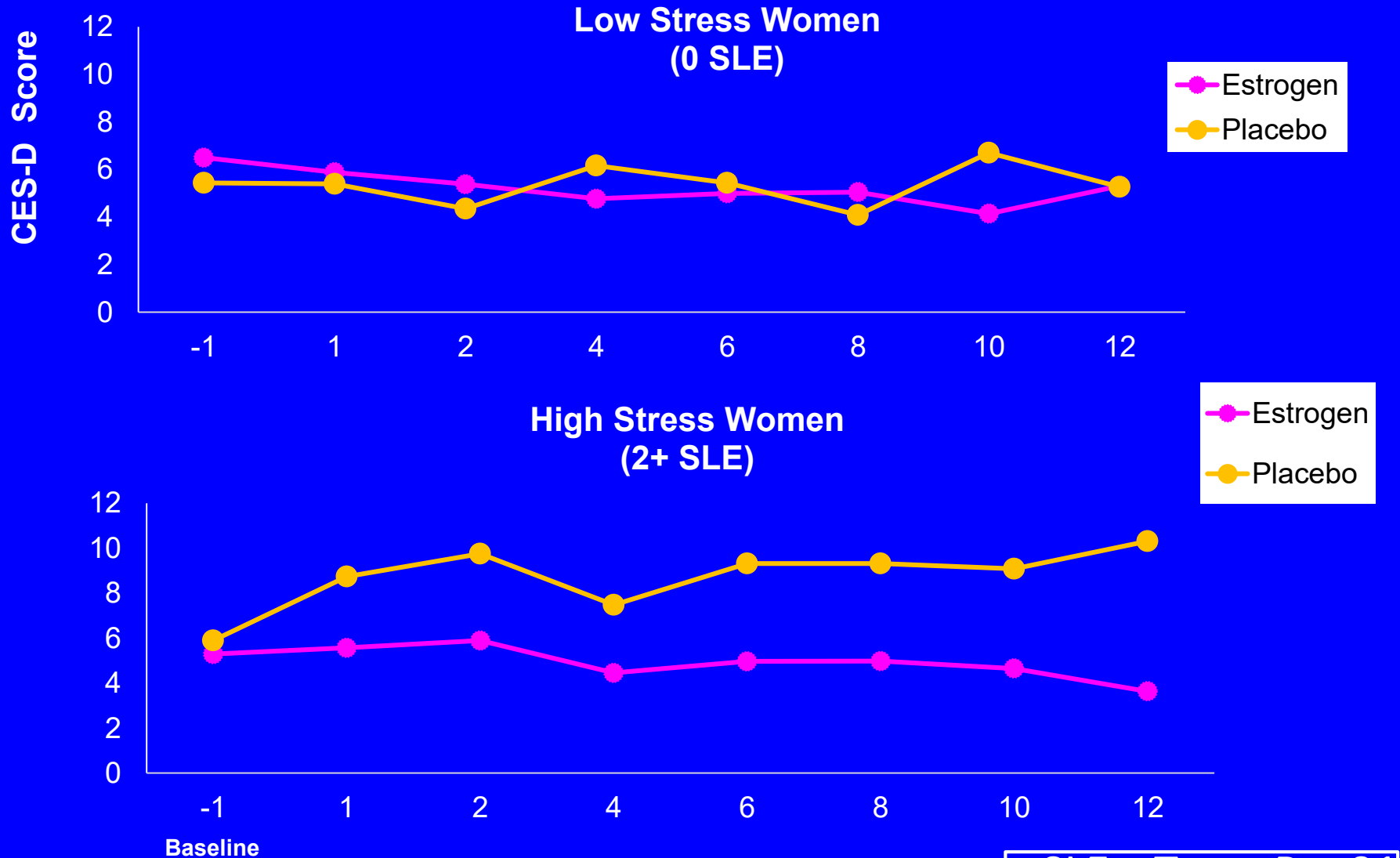
63 completed treatment

86 Randomized to 12 months
of Transdermal Placebo +
oral placebo P4

17 withdrawals

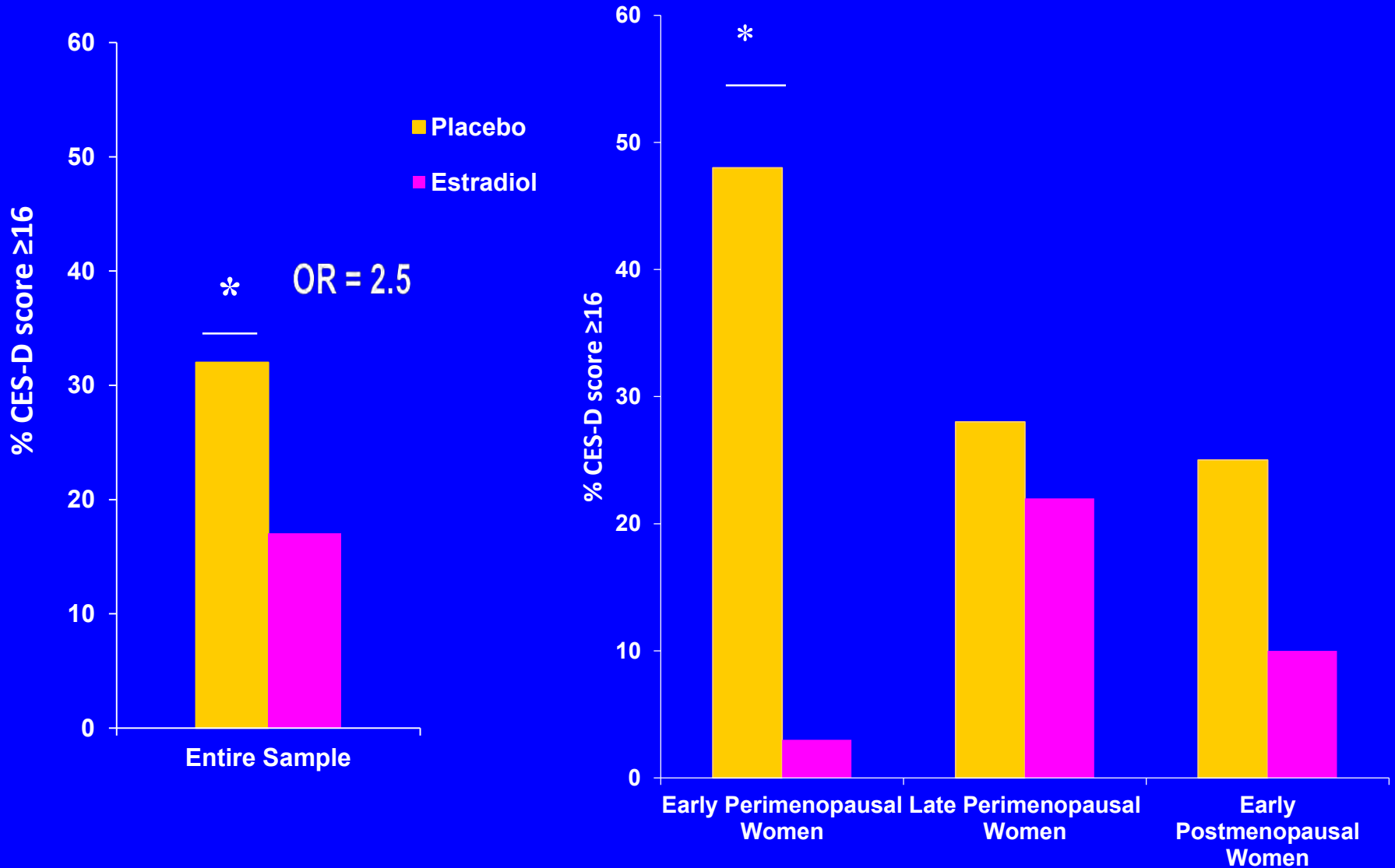
69 completed treatment

Model-Based Estimates of Condition Effect on Depression Symptoms Over Time



SLE x Trmt: P <.01

Estradiol Reduces the Odds of Clinical Depressive Episodes Over 12 Months in Initially Euthymic Women



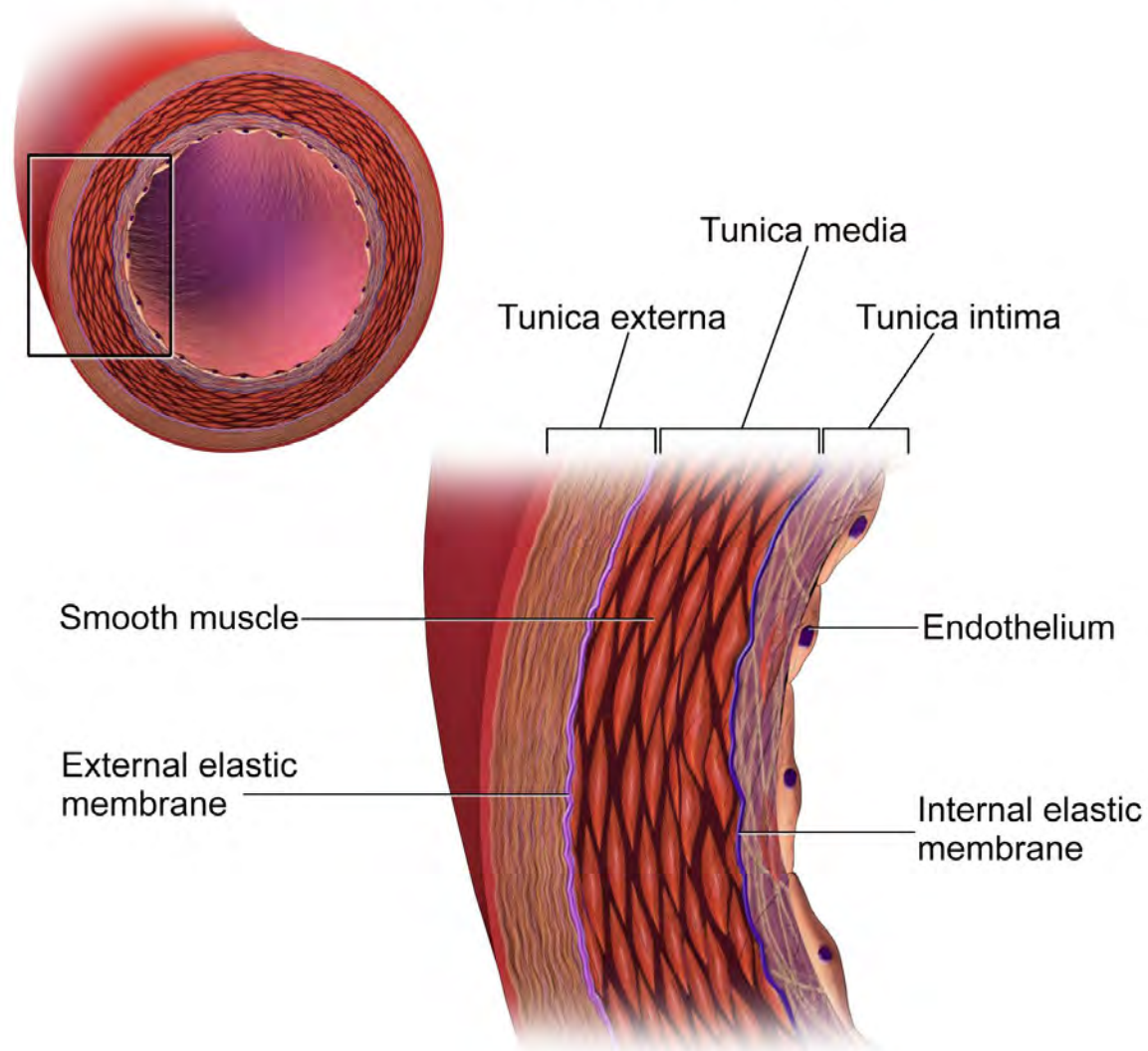
Transdermal Estradiol Improves Cardiovascular Risk Indices

Beneficial effects of estradiol vs. placebo:

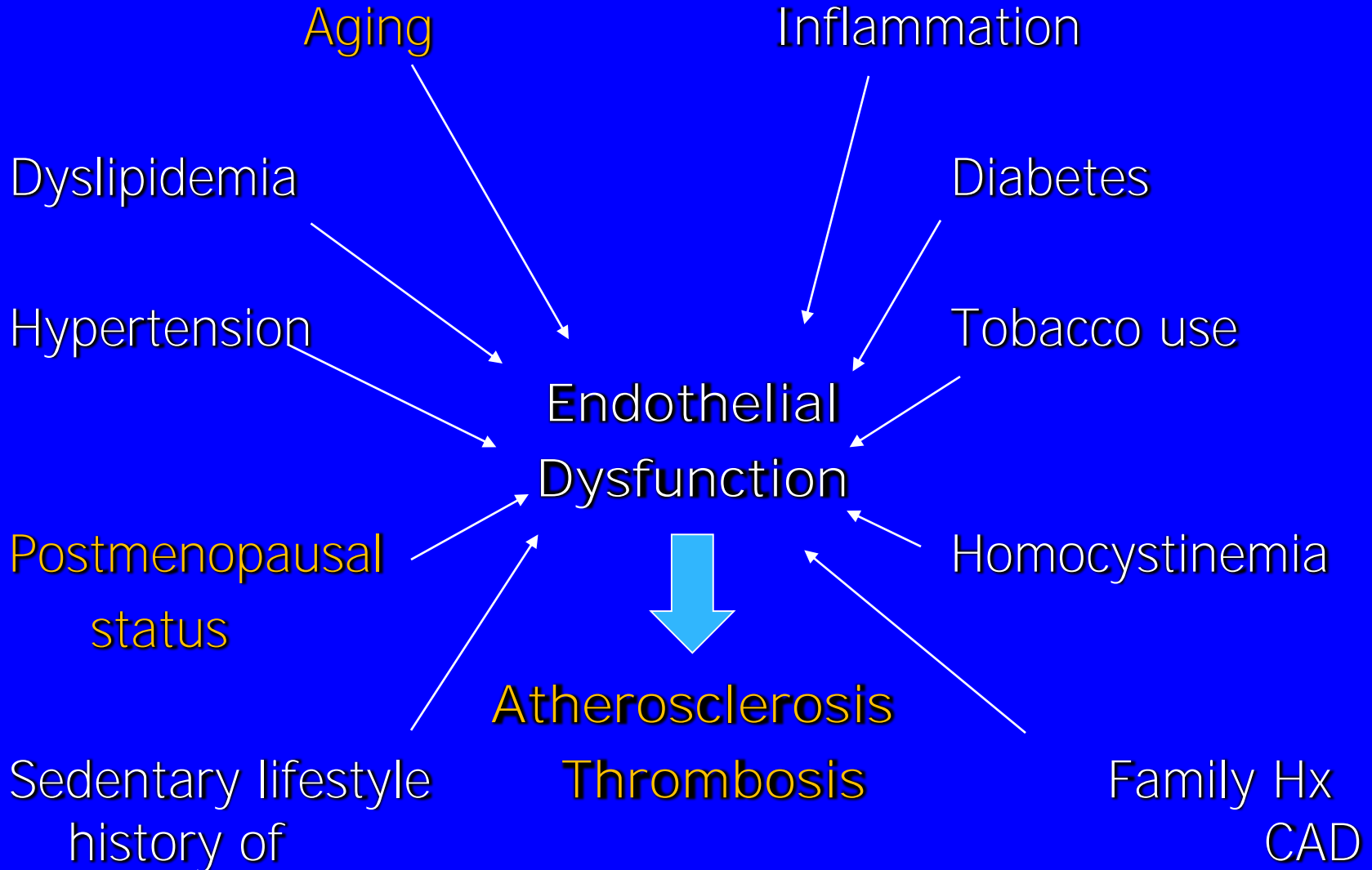
- ✓ **Diastolic blood pressure**
- ✓ **Cardiac autonomic control**
- ✓ **Fasting LDL cholesterol**
- ✓ **Fasting insulin**
- ✓ **Insulin resistance (HOMA-IR)**

The Vascular Endothelium

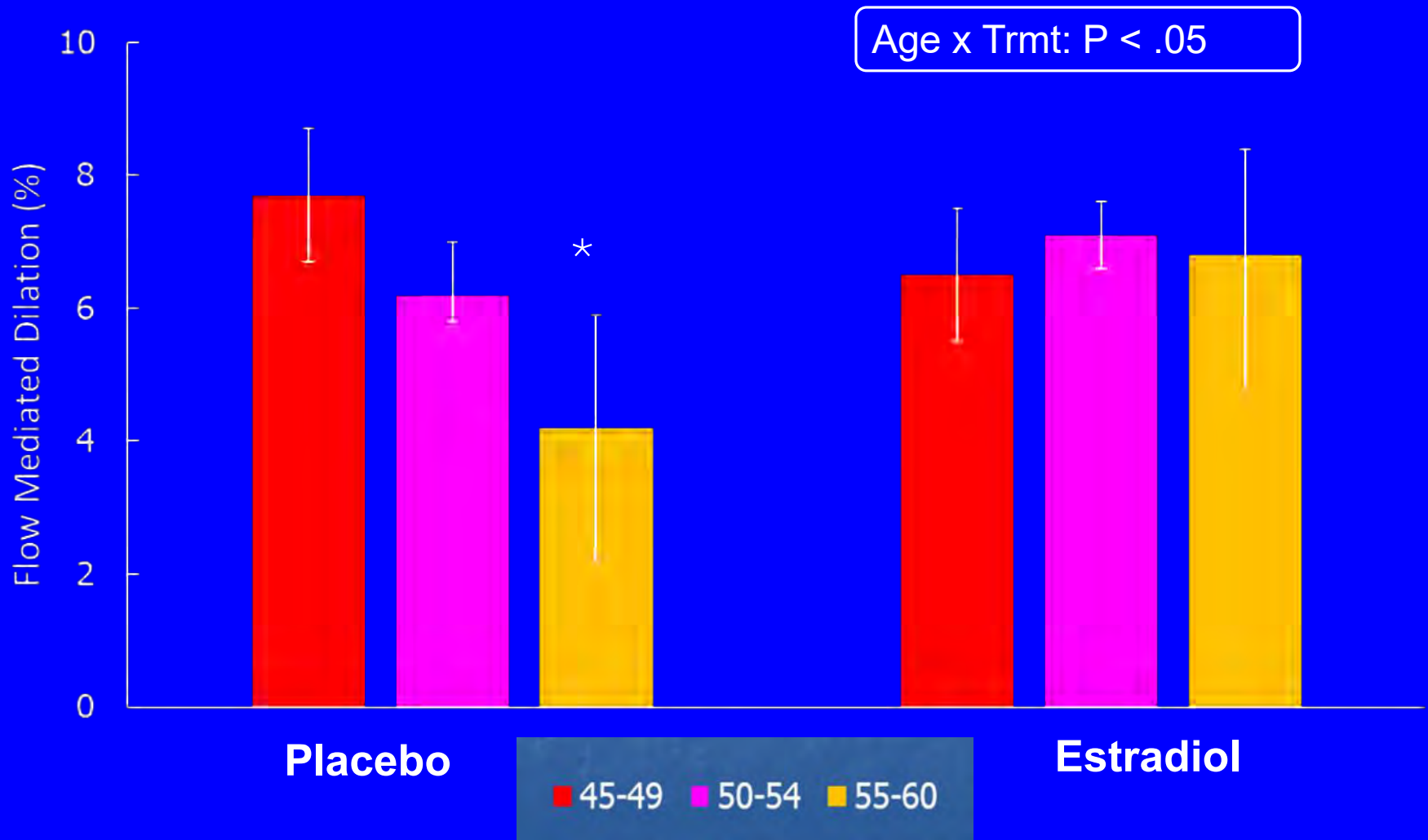
The Structure of an Artery Wall



Conditions Associated with Impaired (decreased) Endothelial Function



Estradiol Prevents Age-Related Decreases in Endothelial Function



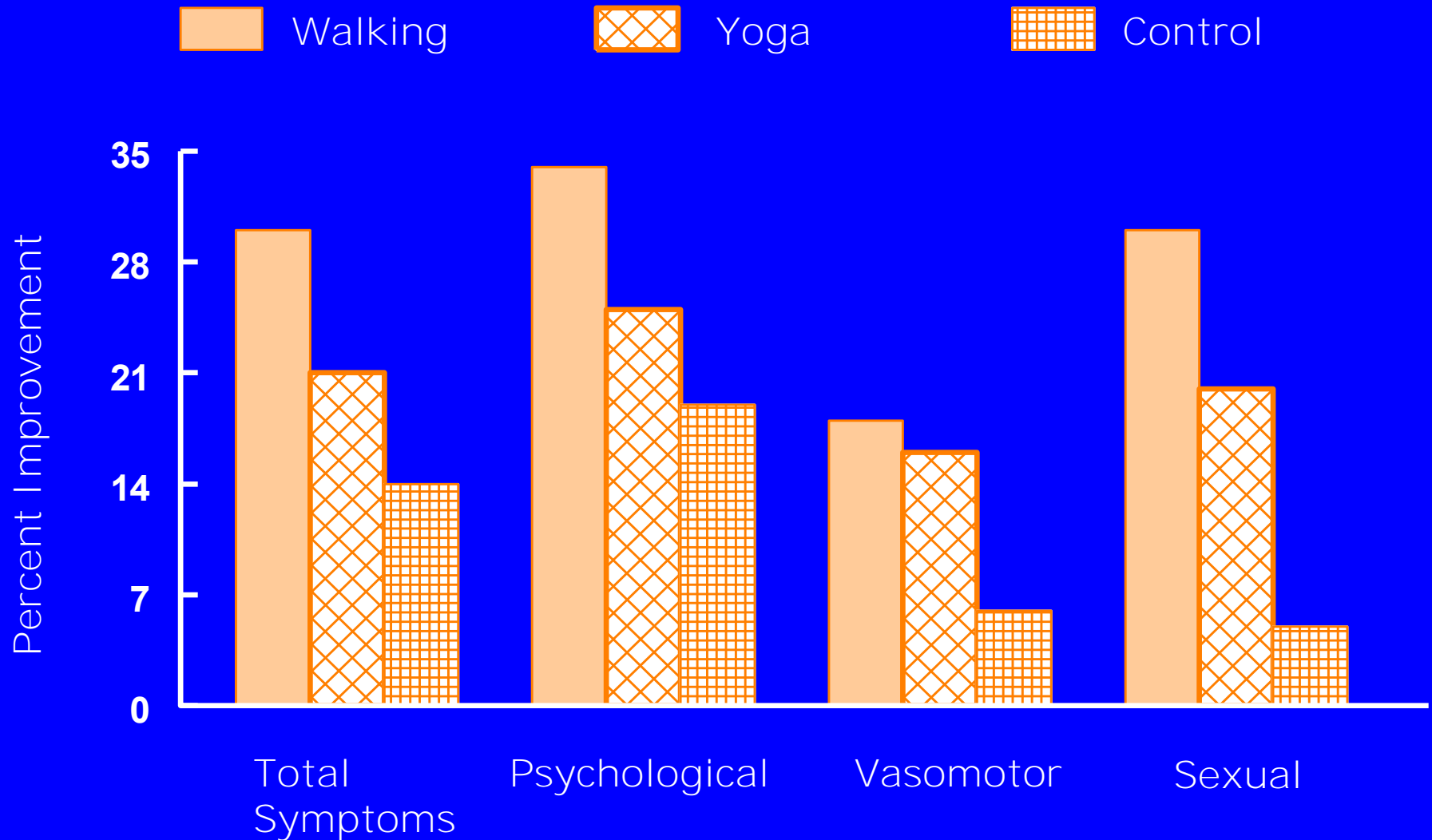
“Take Aways”

- Stress exposure and menopausal stage (estrogen variability?) predict the prophylactic antidepressant benefits of transdermal estradiol
- Transdermal estradiol has cardioprotective effects in *healthy*, perimenopausal women
- Transdermal estradiol *may* reduce age-related impairment in endothelial function (and stress reactivity, data not shown)

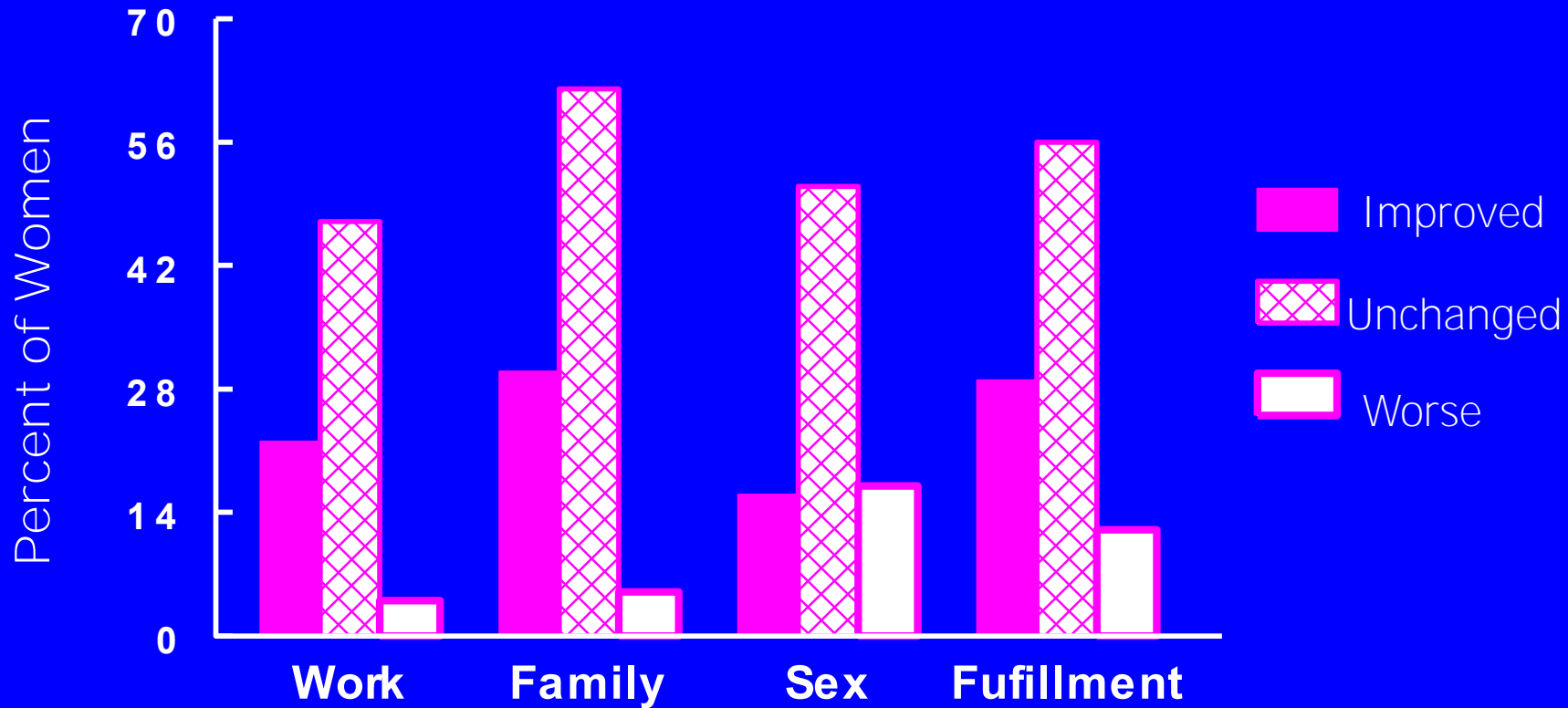


"I was on hormone replacement for two years before I realized that what I really needed was Steve replacement."

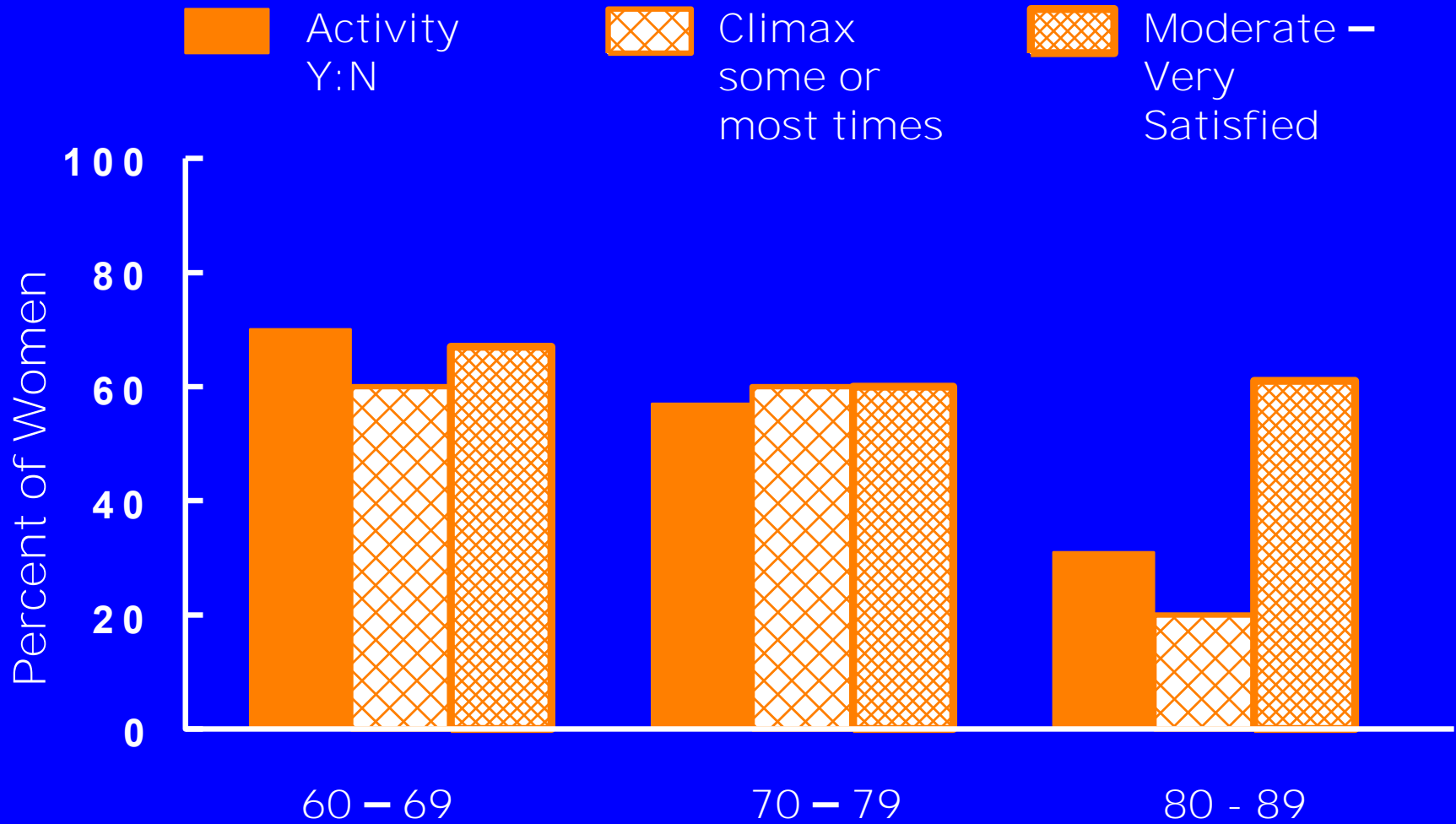
Improvement in Perimenopausal Symptoms With Regular Physical Activity



Change in Satisfaction Since Becoming Postmenopausal



Sexual Function and Satisfaction in Women 60 – 89 years of age





SHARRP

Stress, Health, and Reproduction Research Program UNC Center for Women's Mood Disorders

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Jennifer Gordon, PhD
Alan Hinderliter, MD
Lana Watkins, PhD

Postdocs:

Elizabeth Andersen, PhD
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Justin Riddle, PhD

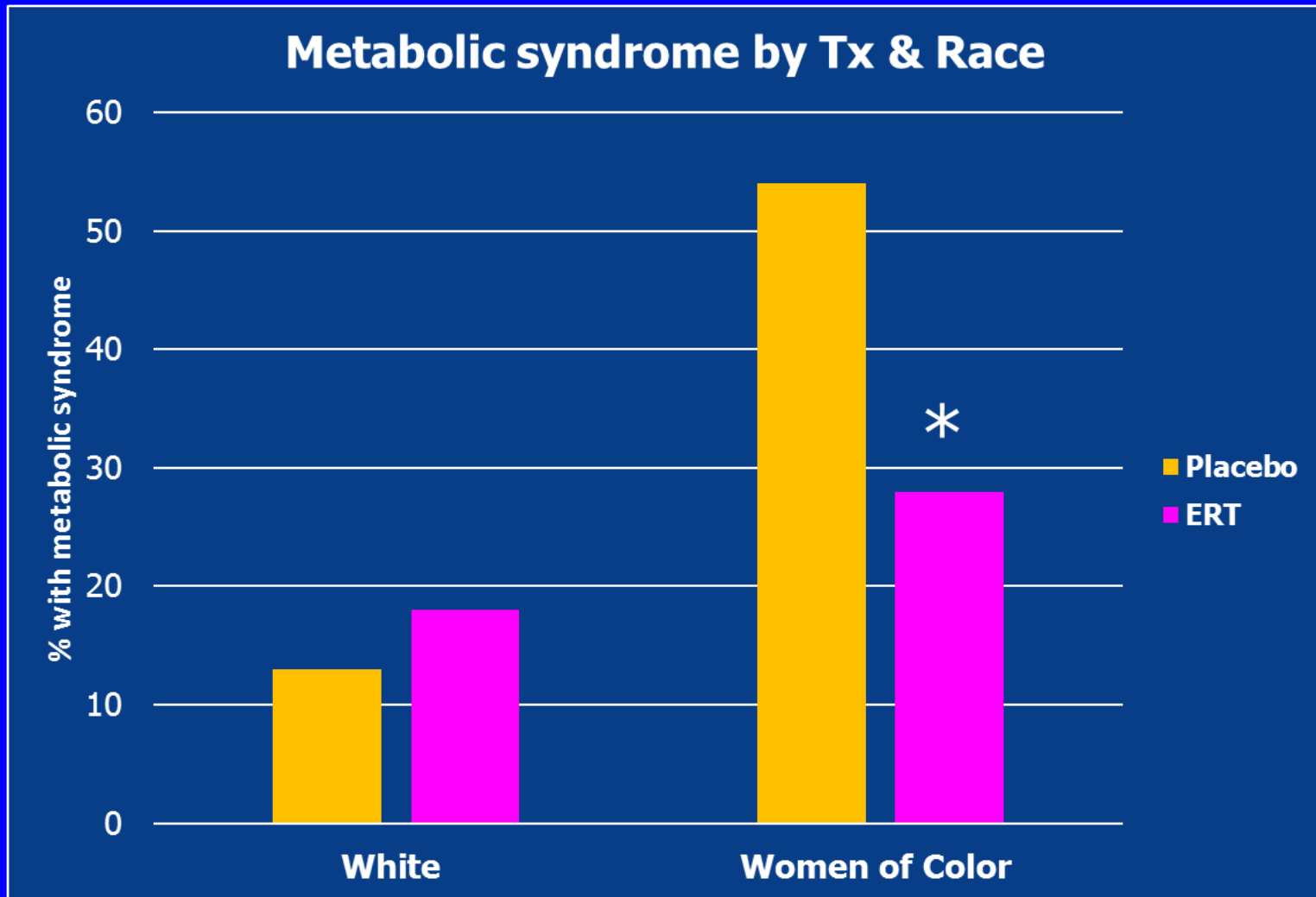
Research Team:

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Megan Gooding, BS
Tara Rana, BA



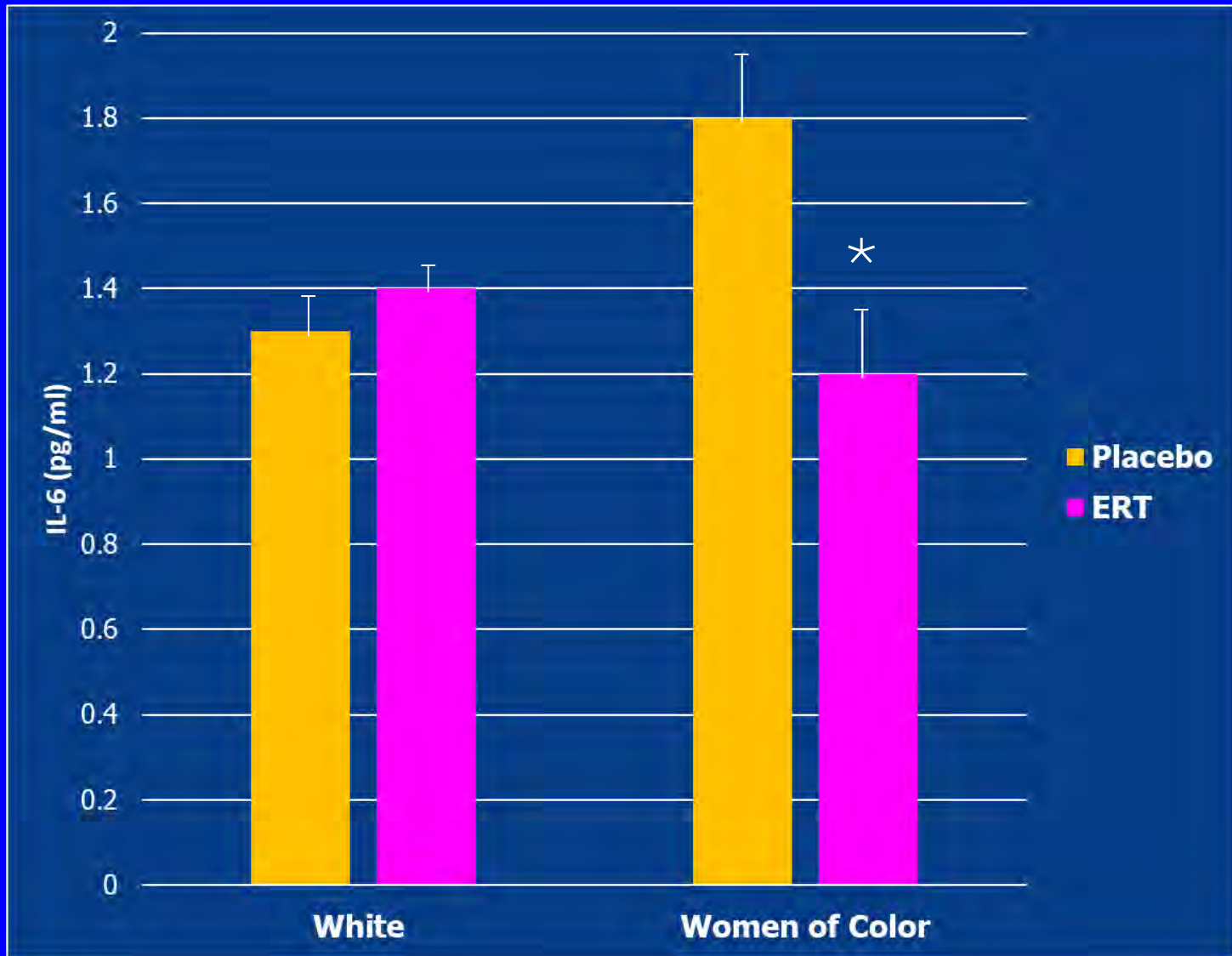
UNC
SCHOOL OF MEDICINE

Race predicts the Beneficial Effects of Transdermal Estradiol on Metabolic Syndrome in Perimenopausal Women



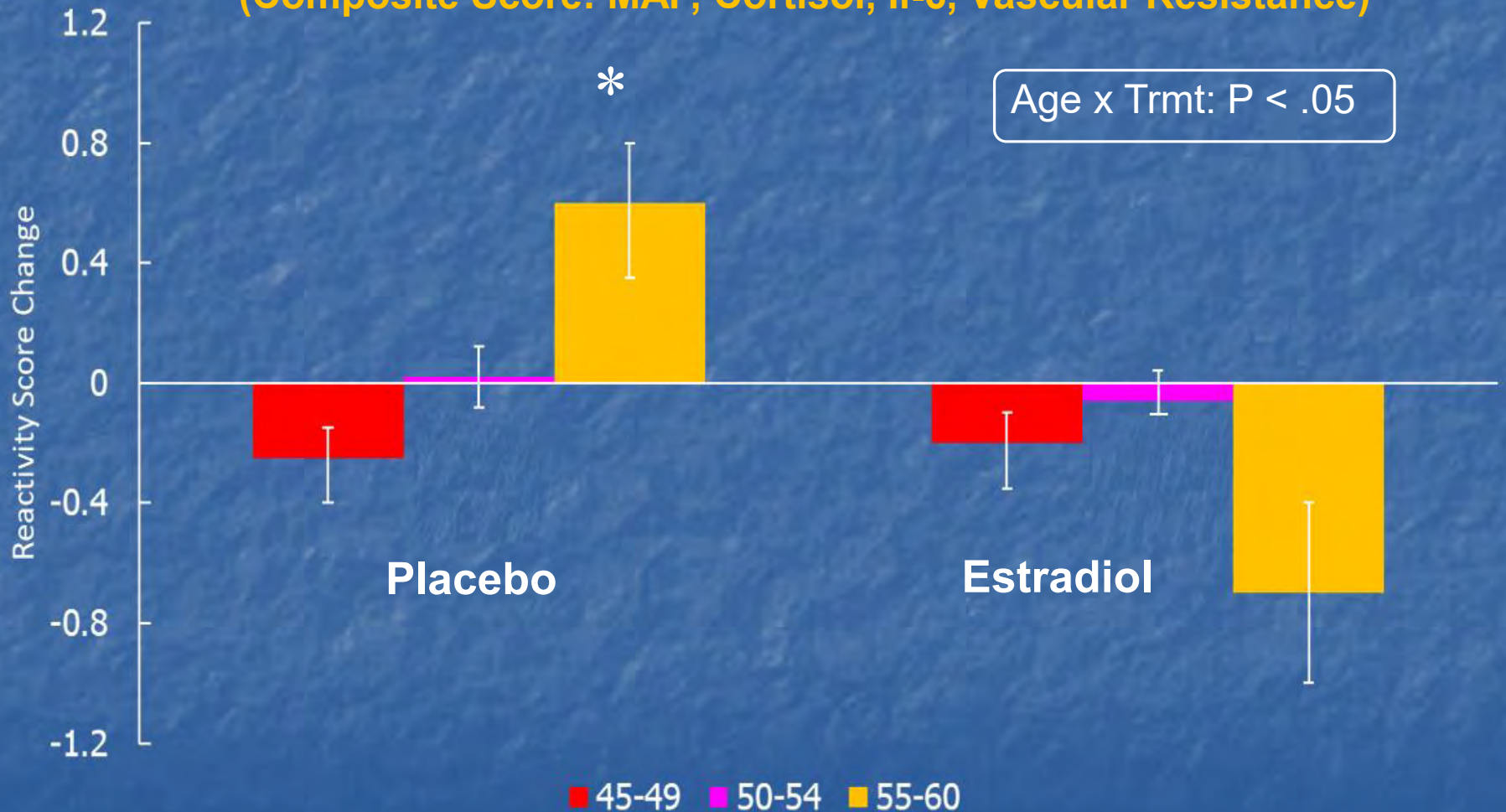
*Trmt x Race: $P < .01$

Race Predicts the Beneficial Effects of Transdermal Estradiol on pro-Inflammatory cytokines (IL-6) in Perimenopausal Women



Estradiol Prevents Age-Related Increases in Physiologic Stress Reactivity

(Composite Score: MAP, Cortisol, Il-6, Vascular Resistance)



With strong evidence of association with menopause transition (estrogen withdrawal)

- Vasomotor Symptoms (hot flashes, night sweats) – occurs with greater frequency and severity in younger women with sudden surgical onset of menopause
- Vaginal Dryness and Painful Intercourse – the percent of women experiencing this increases across the transition and persists indefinitely in some
- Sleep Disturbance
- Clinically Significant Depression