

*What A Difference an X Makes:
The Role of Sex Hormones
and Sex Chromosomes in All Aspects of
Life*

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What A Difference an EX Makes:

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Males And Females Are Different?

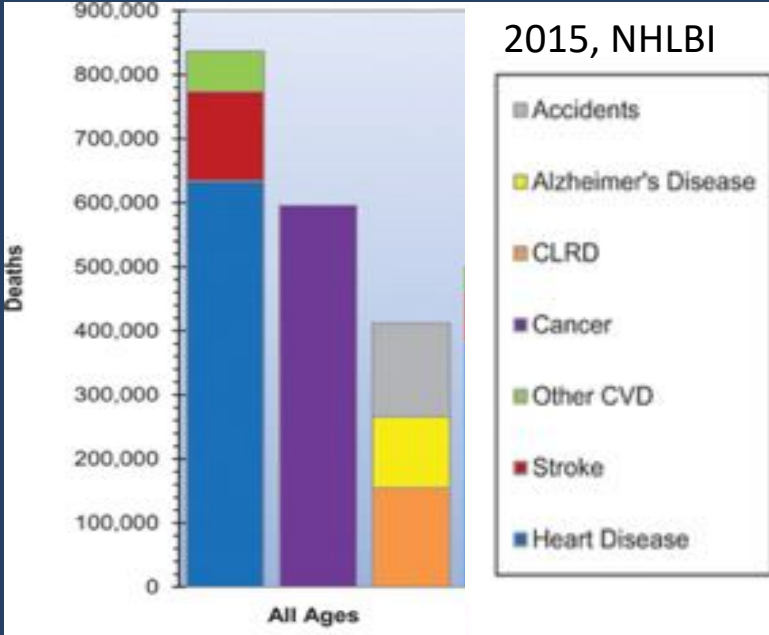
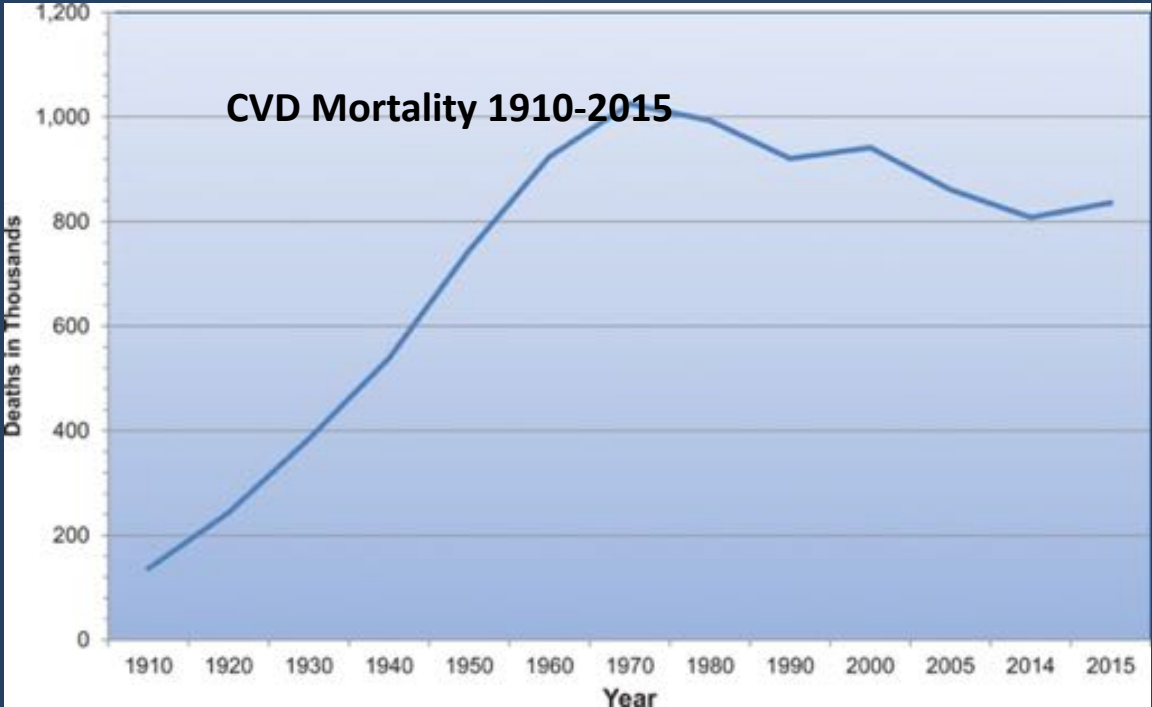
Males And Females Are Different!!!!!!



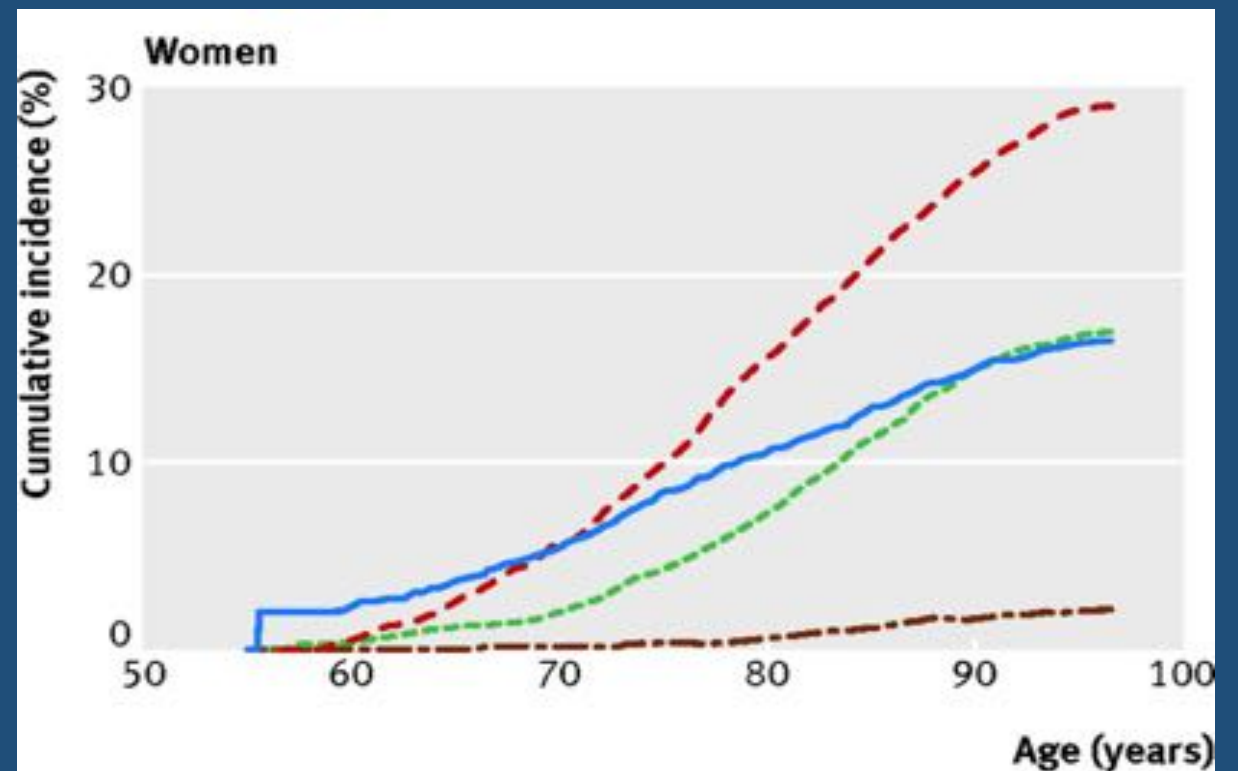
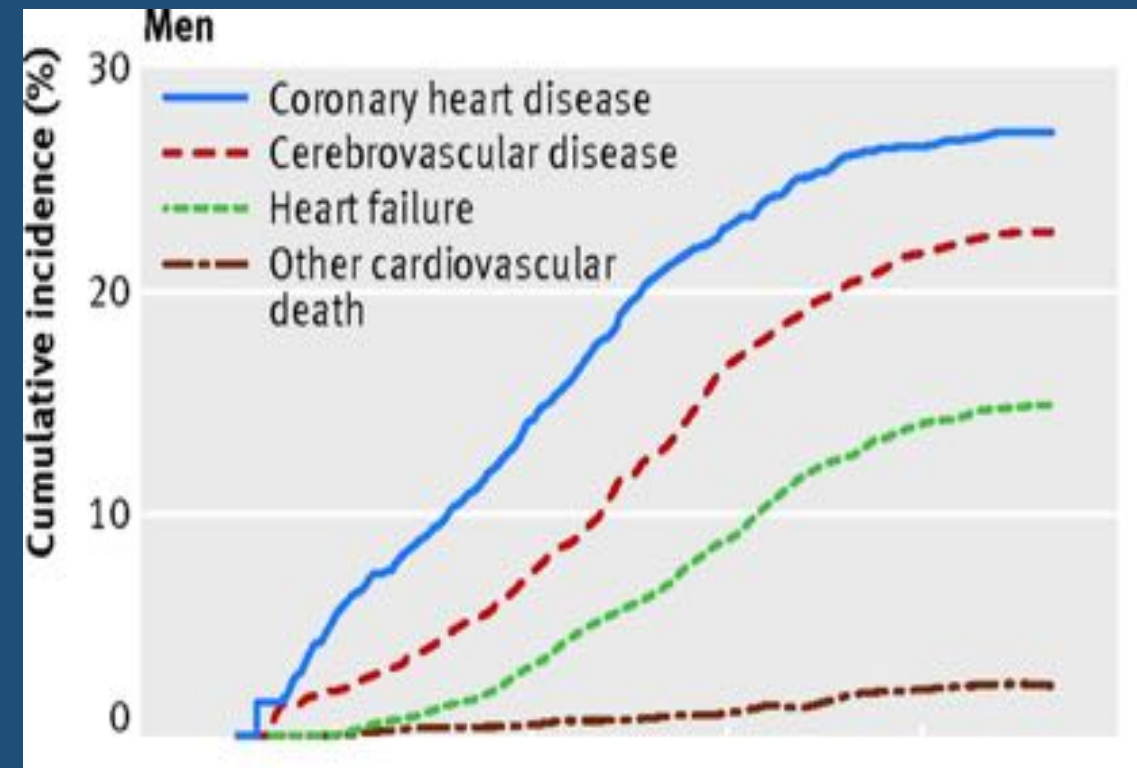
Dogma

- Outside the gonads XY and XX cells are functionally equivalent....
- NOT True!!!!
- $X \neq Y$
- In females, the majority of the cells on one of the X chromosomes are silenced
- However, some genes on the inactive X chromosome are not silenced, leading to higher levels of their products in female cells
- The Y chromosome carries genes that are involved in basic cellular functions

Cardiovascular Disease is the Leading Killer of US Adults



Sex Differences In Cardiovascular Disease



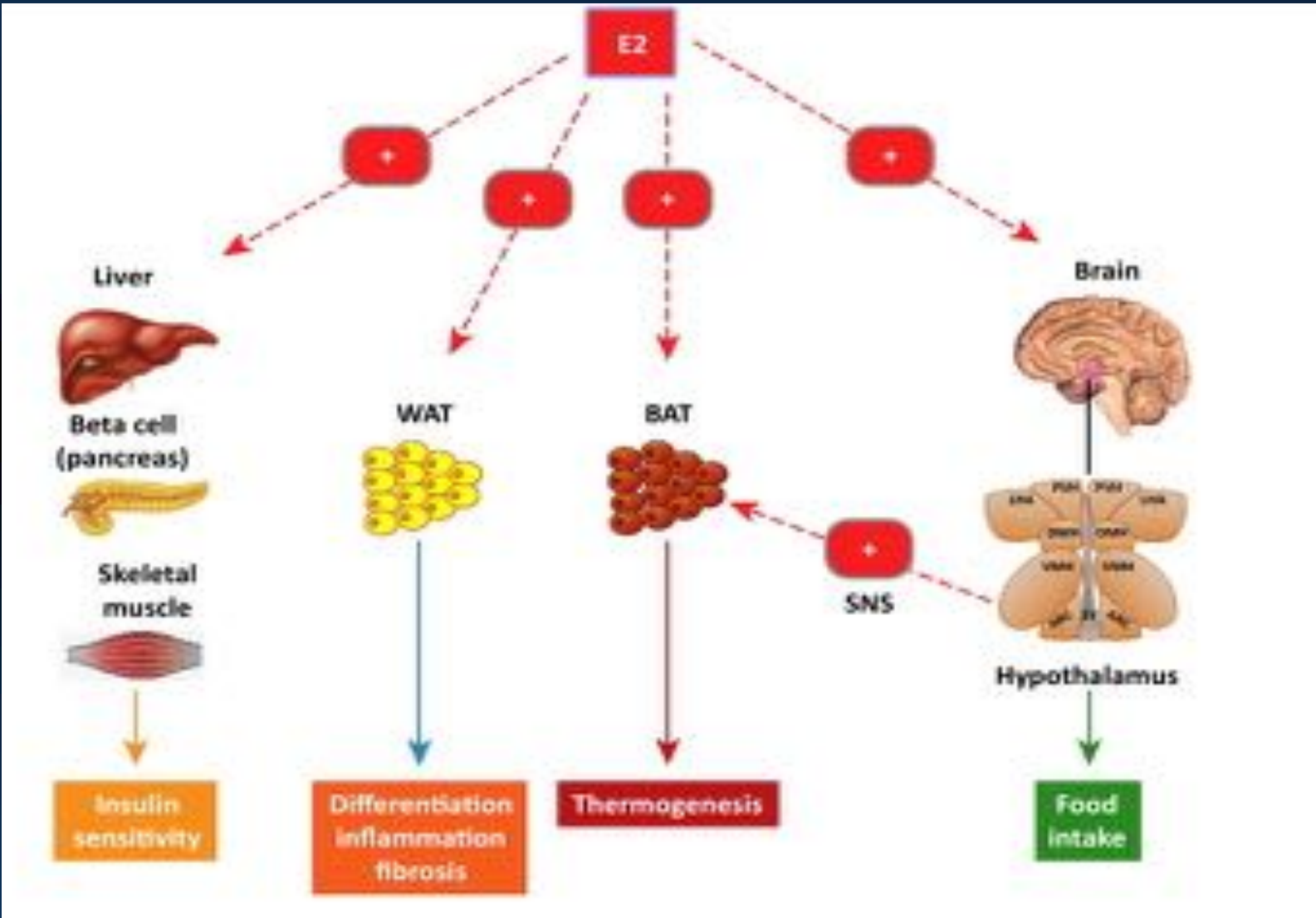
Estrogens Regulate Metabolism



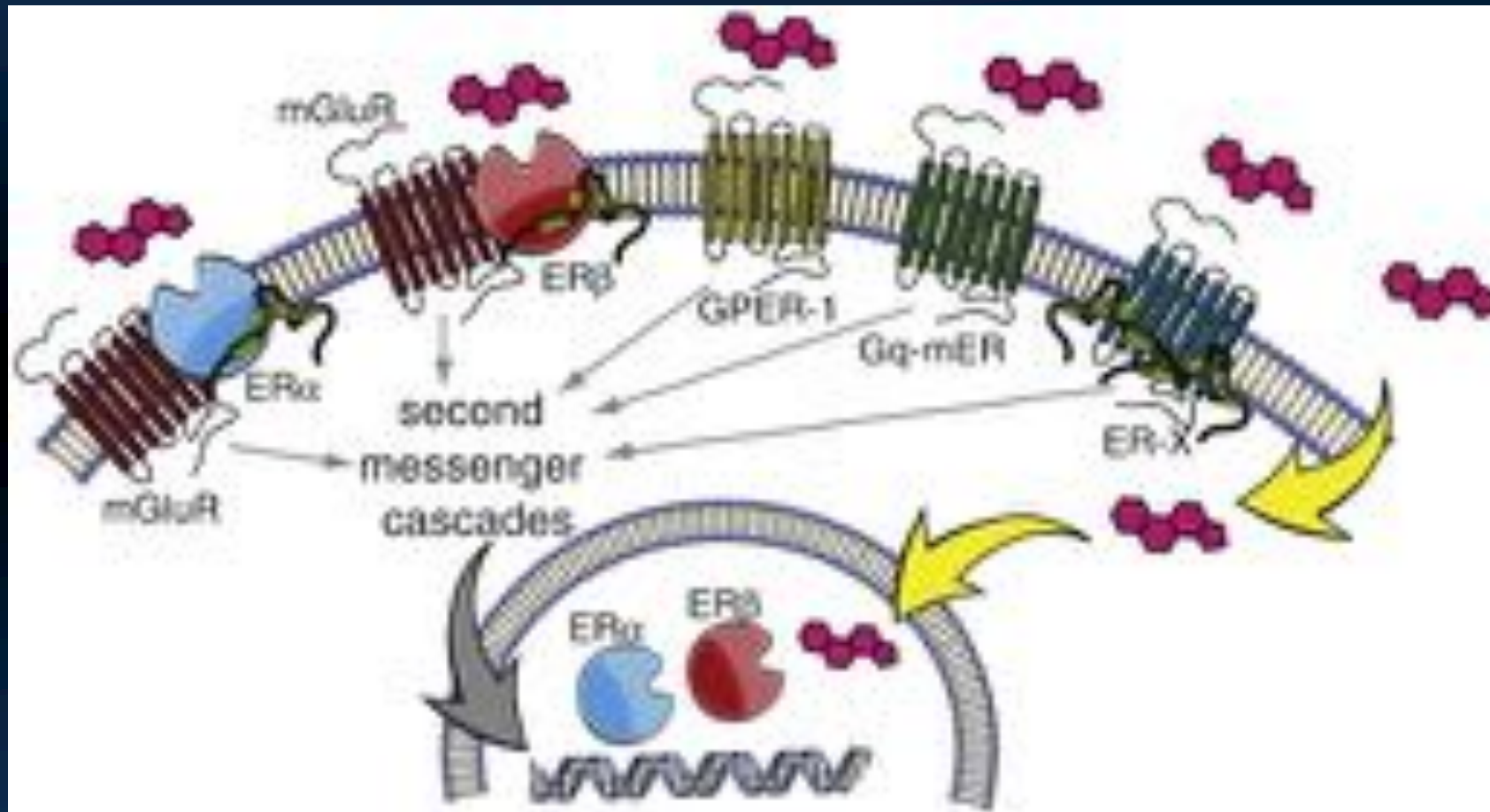
Basic Science

UTSW Medical Center

Estrogens: Critical Regulators of Metabolic Function



Estrogens Bind to One of Many Different Receptors



ER α Influences Body Weight

1056

THE NEW ENGLAND JOURNAL OF MEDICINE

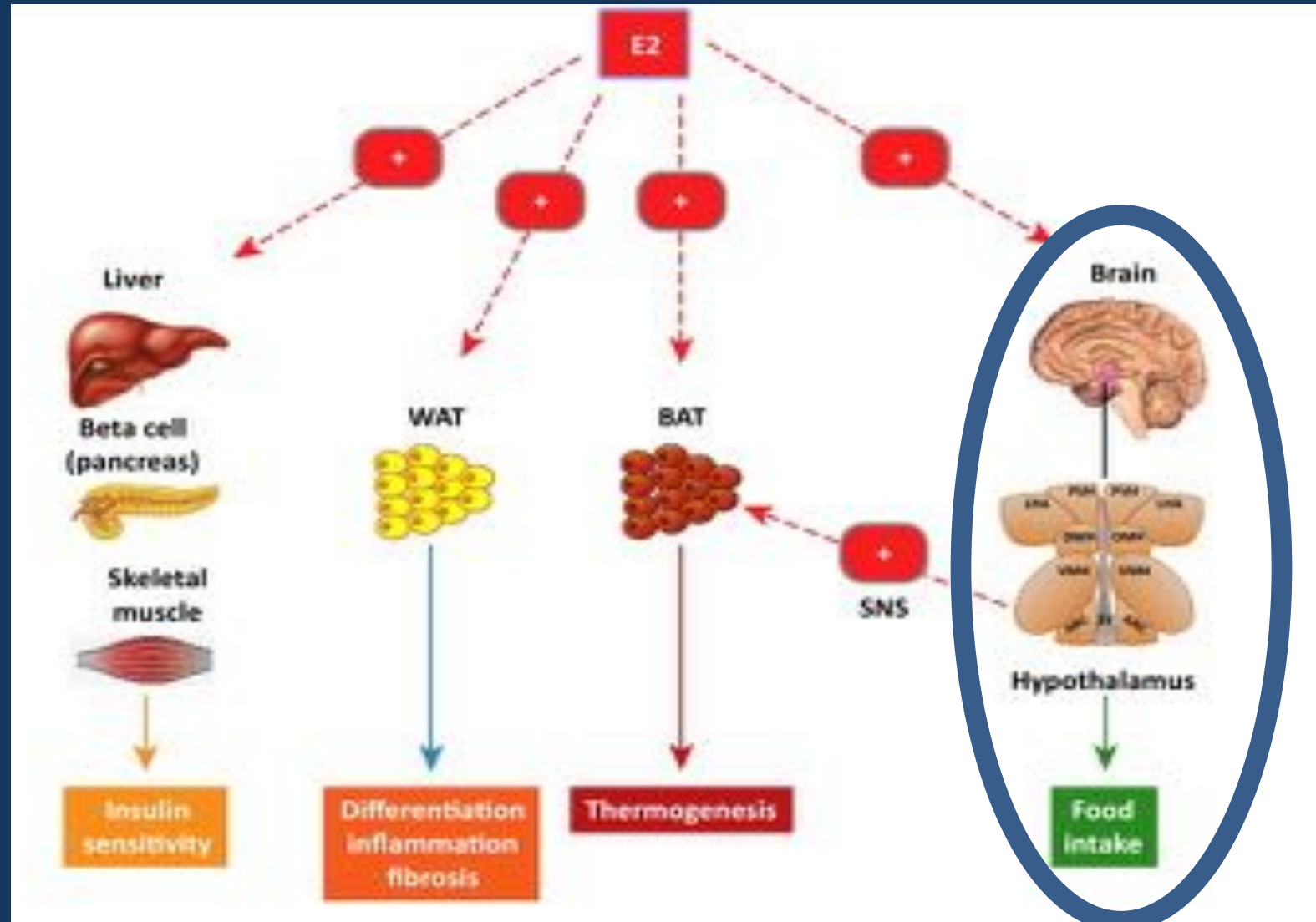
Oct. 20, 1994

ESTROGEN RESISTANCE CAUSED BY A MUTATION IN THE ESTROGEN-RECEPTOR GENE IN A MAN

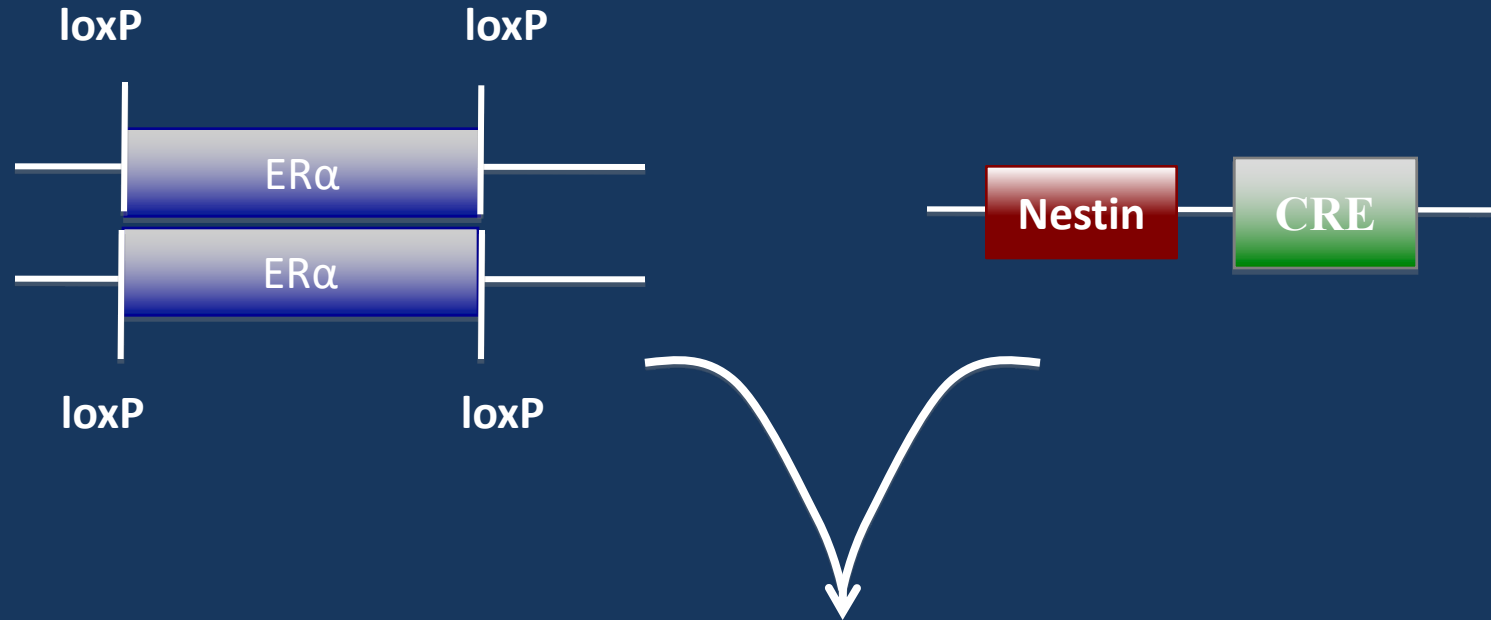
ERIC P. SMITH, M.D., JEFF BOYD, PH.D., GRAEME R. FRANK, M.D., HIROYUKI TAKAHASHI, M.D., PH.D.,
ROBERT M. COHEN, M.D., BONNY SPECKER, PH.D., TIMOTHY C. WILLIAMS, M.D., DENNIS B. LUBAHN, PH.D.,
AND KENNETH S. KORACH, PH.D.

- Obesity
(BMI: 30.5)
- Insulin Resistance
- Glucose Intolerance
- CVD

Estrogens: Critical Regulators of Metabolism



ER α ^{loxlox}/Nestin-Cre



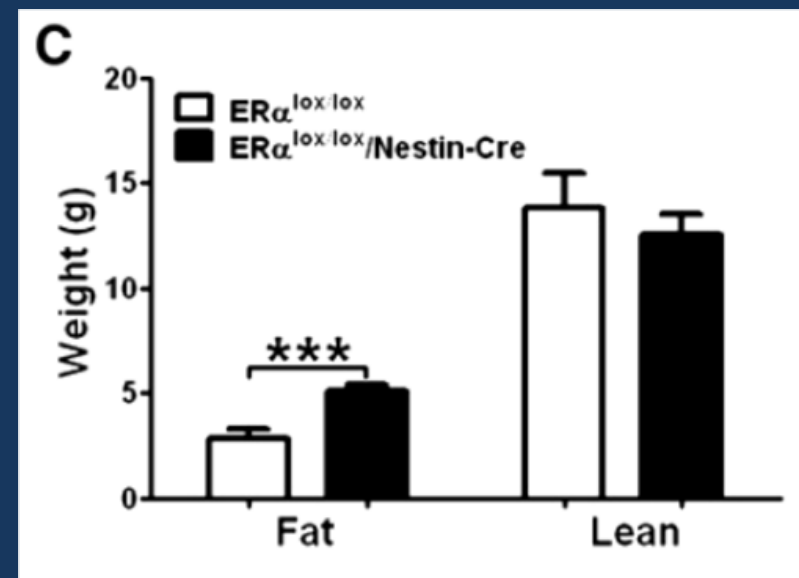
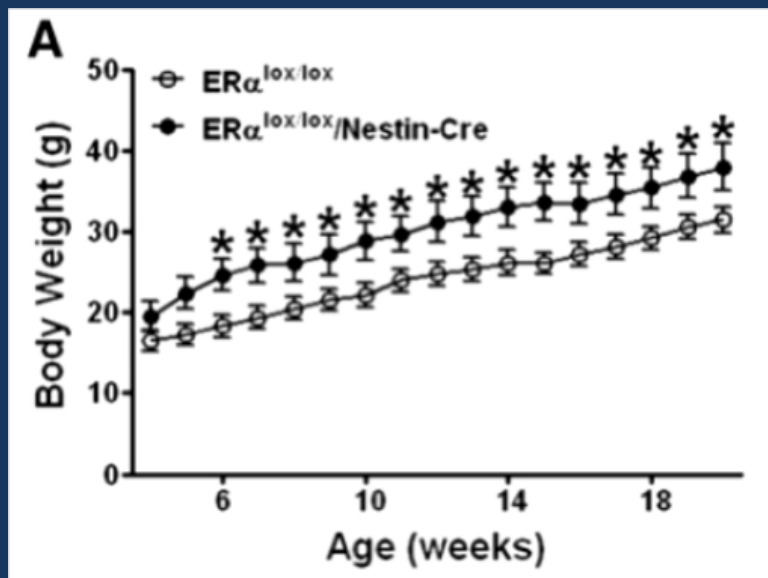
Reduction of ER α expression
in the whole brain

Hypothalamic ER α Influences Body Weight

Distinct Hypothalamic Neurons Mediate Estrogenic Effects on Energy Homeostasis and Reproduction

Yong Xu,^{1,2,5} Thekkethil P. Nedungadi,^{3,5} Liangru Zhu,¹ Nasim Sobhani,³ Boman G. Irani,³ Kathryn E. Davis,³ Xiaorui Zhang,¹ Fang Zou,¹ Lana M. Gent,³ Lisa D. Hahner,³ Sohaib A. Khan,⁴ Carol F. Elias,² Joel K. Elmquist,² and Deborah J. Clegg^{3,*}

Xu Y. et al., *Cell Metabolism*, 2012





HFD-Induced Obesity

Western diet

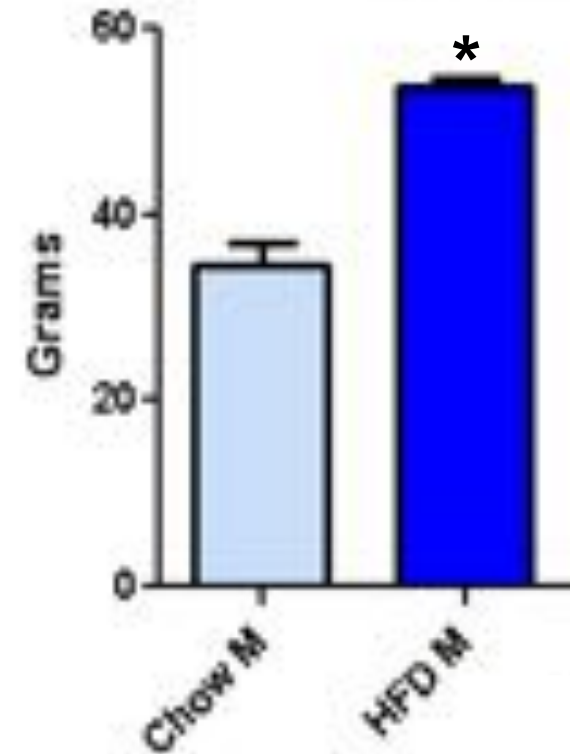
	% by weight	% kcal from
Protein	17.3	15.2
Carbohydrate	48.5	42.7
Fat	21.2	42.0

Typical Fatty Acid Profile, % of total fatty acids ¹	Mean	SD
Saturated fat	61.8	2.0
Monounsaturated fat	27.3	2.1
Polyunsaturated fat	4.7	0.8
4:0	2.1	1.1
6:0	1.5	0.7
8:0	1.1	0.3
10:0	2.6	0.5
12:0	3.3	0.5
14:0	10.6	0.9
16:0	28.9	1.3
16:1	1.5	0.2
18:0	12.5	0.8
18:1 (Oleic)	20.9	2.6
18:1 Isomers ³	4.0	1.2
18:2 (Linoleic)	2.3	1.0
18:2 Isomers ⁴	1.3	0.5
18:3 (Linolenic)	0.7	0.2

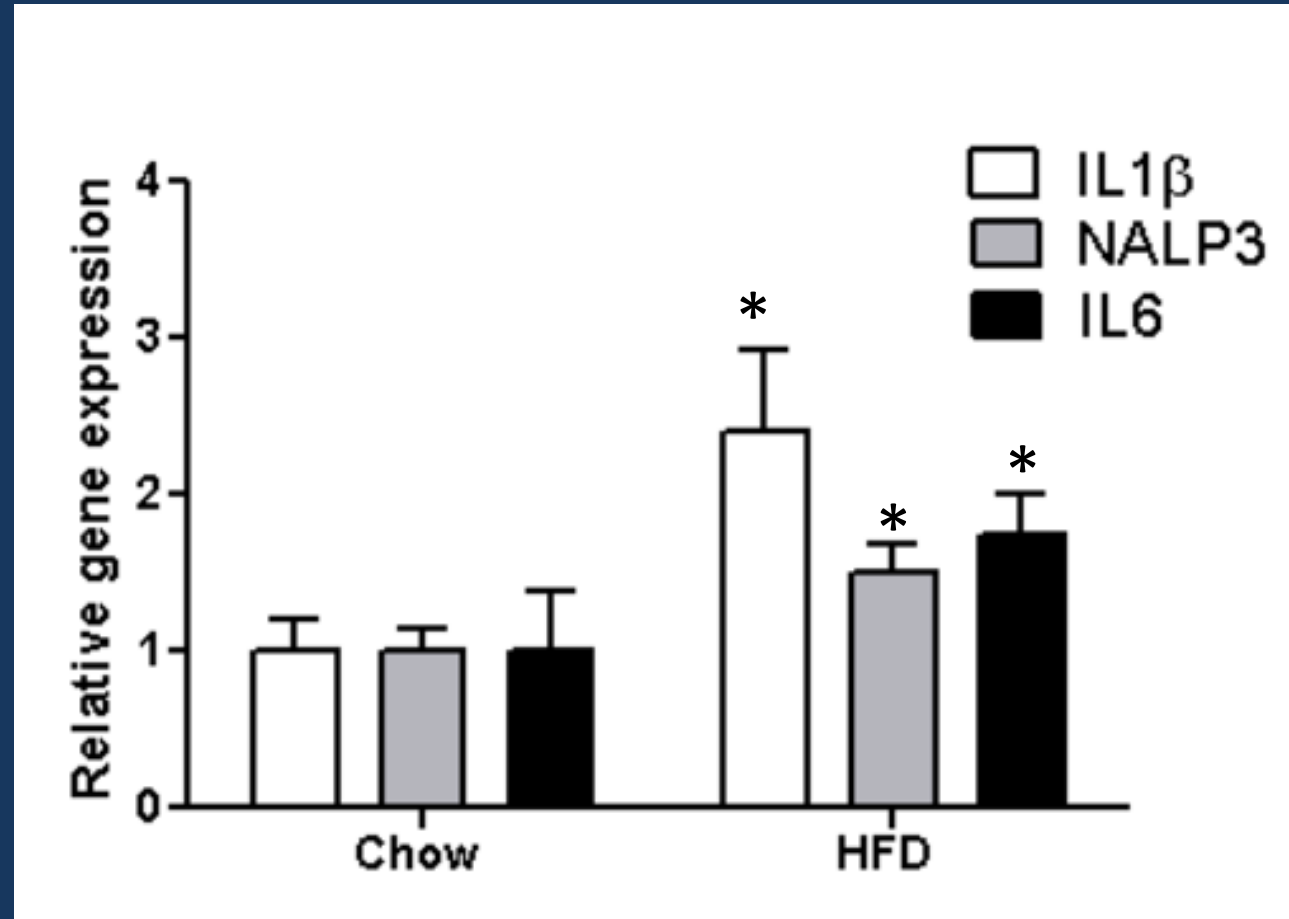


TD. 88137 Harlan

Body weight



HFD-Induces Inflammation in the Hypothalamus



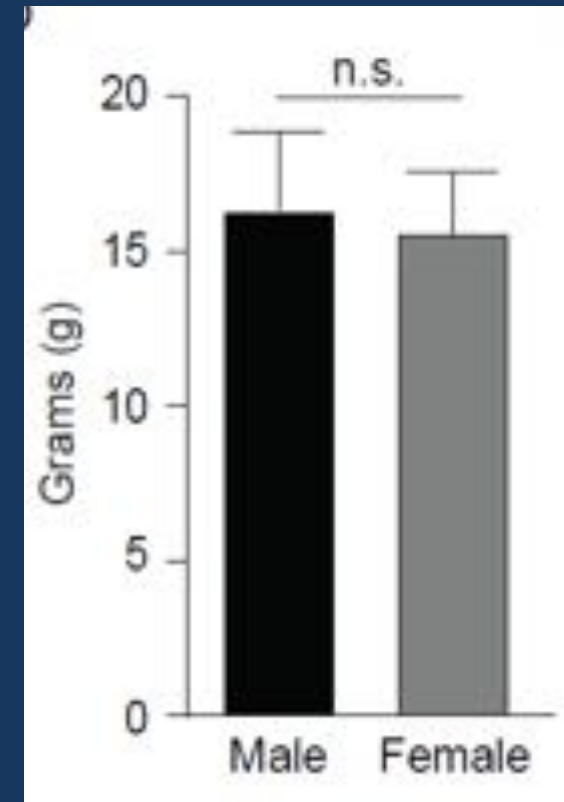
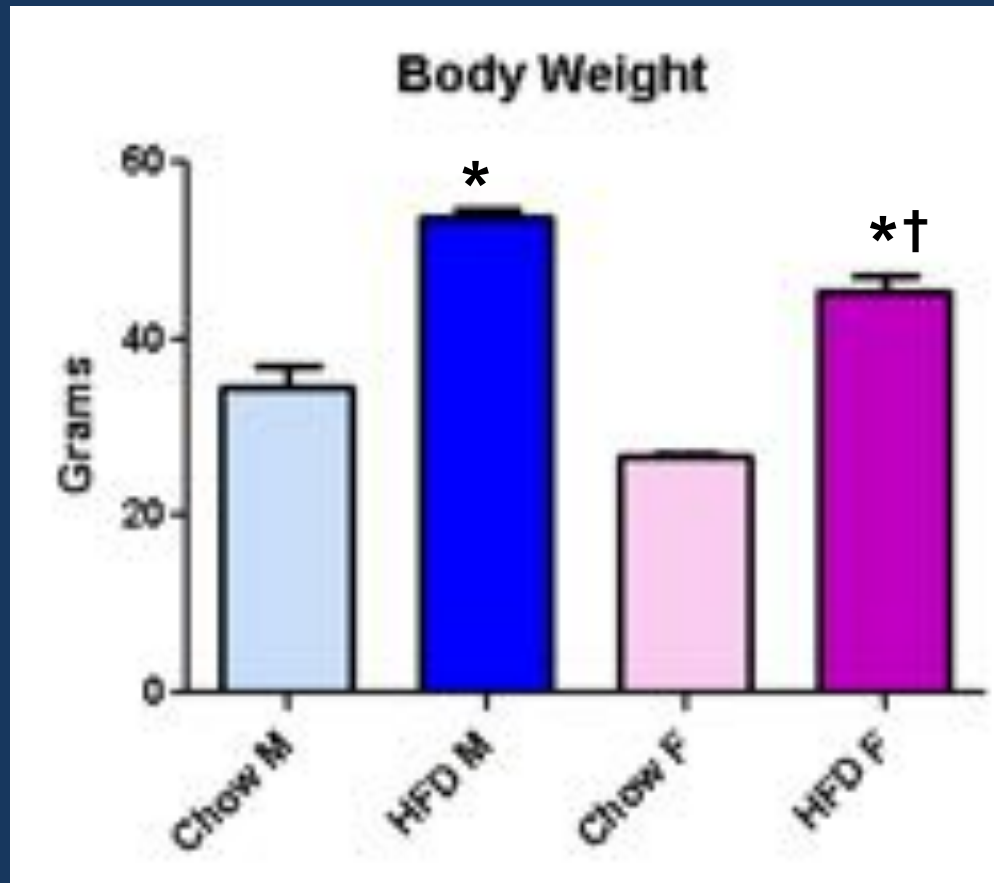
*: $p < 0.005$ (chow to HFD)

†: $p < 0.005$ (chow M to chow F)

#: $p < 0.005$ (HFD M to HFD F)

Morselli E, *Cell Reports*, 2014

Does the HFD-Induced Inflammation Occur in Females??



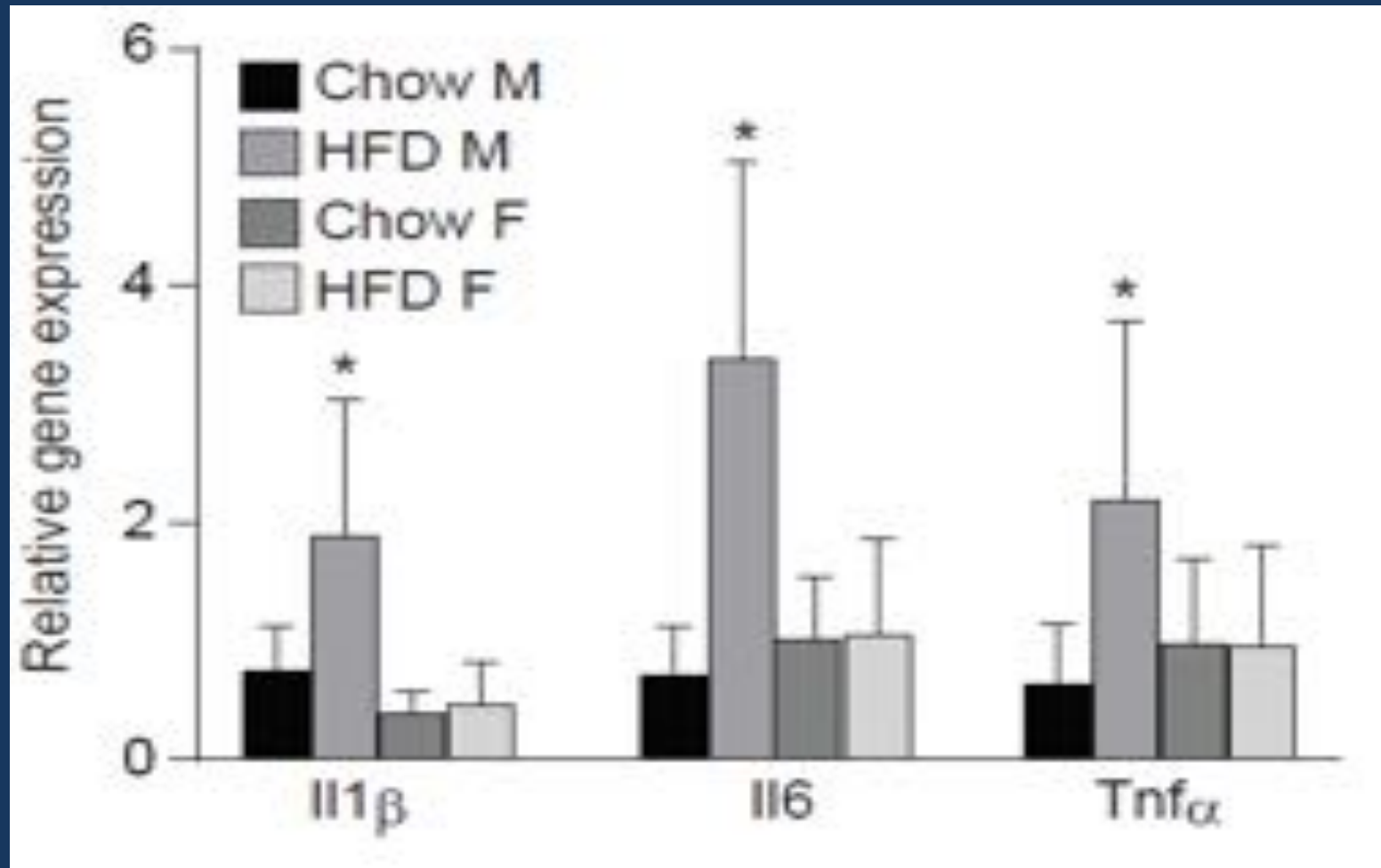
*: $p < 0.005$ (chow to HFD)

†: $p < 0.005$ (chow M to chow F)

#: $p < 0.005$ (HFD M to HFD F)

Morselli E, *Cell Reports*, 2014

Females Do Not Have HFD-Induced Hypothalamic Inflammation



In Vitro: N43 cells, Hypothalamic Neurons

Typical Fatty Acid Profile, % of total fatty acids ¹	Mean	SD
Saturated fat	61.8	2.0
Monounsaturated fat	27.3	2.1
Polyunsaturated fat	4.7	0.8
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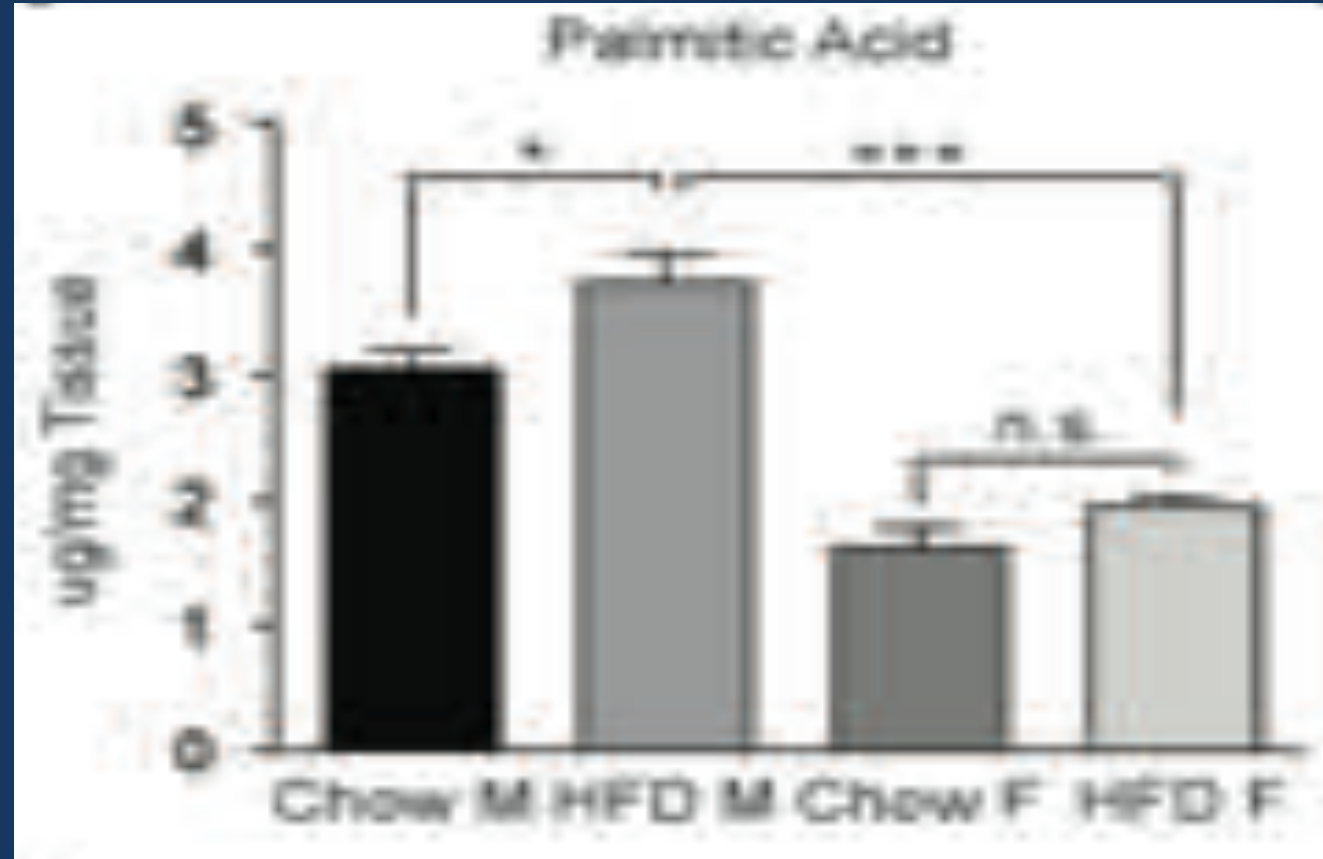
Palmitic Acid (PA)

Most common fatty acid found in animals

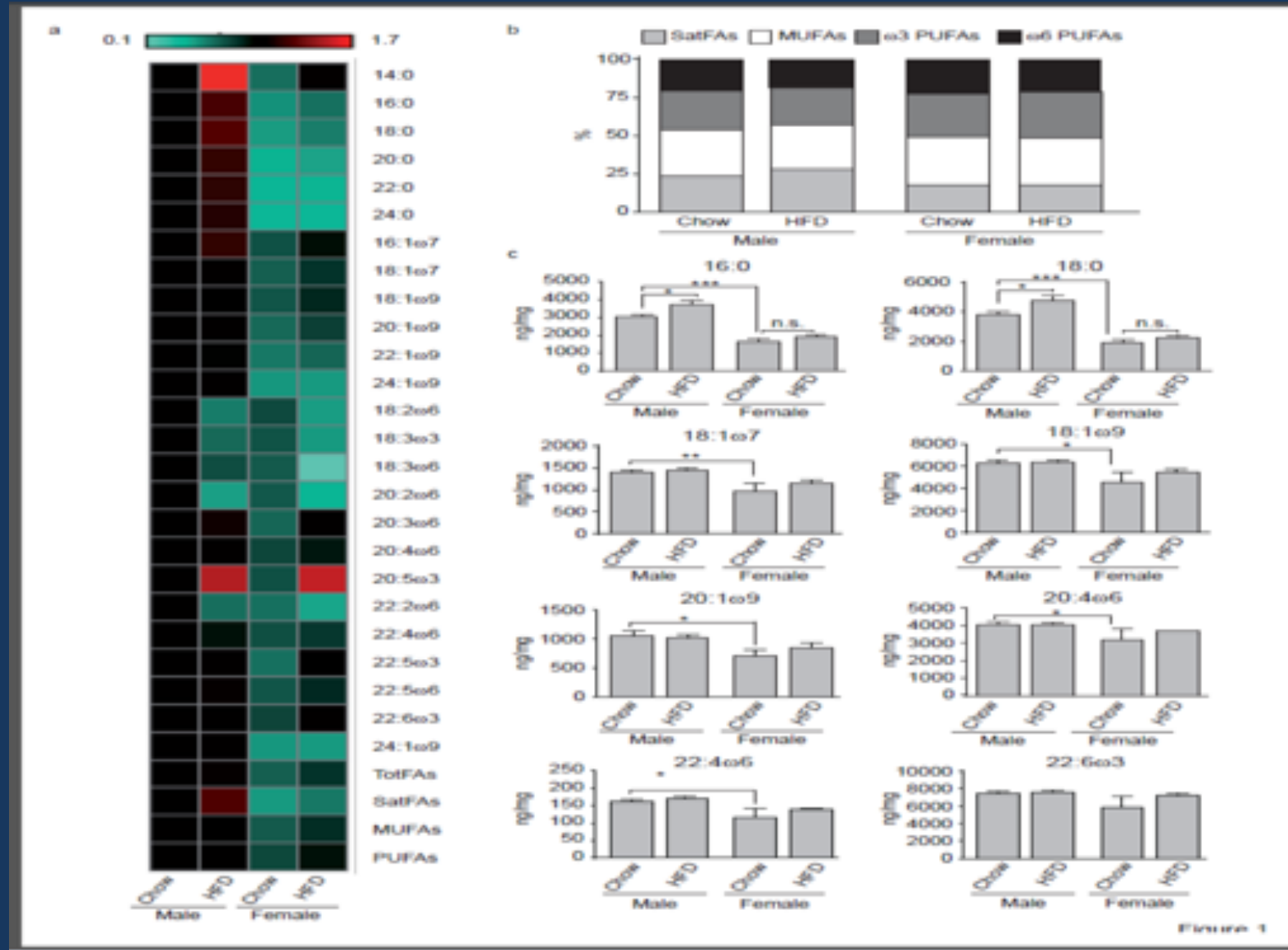
Palmitoyl-CoA is accumulated in the hypo of animals fed on HFD

Induces inflammasome activation

Palmitic Acid (PA) is Elevated ONLY in the Male Brain Following HFD Exposure



Lipidomics: Males and Females Differ

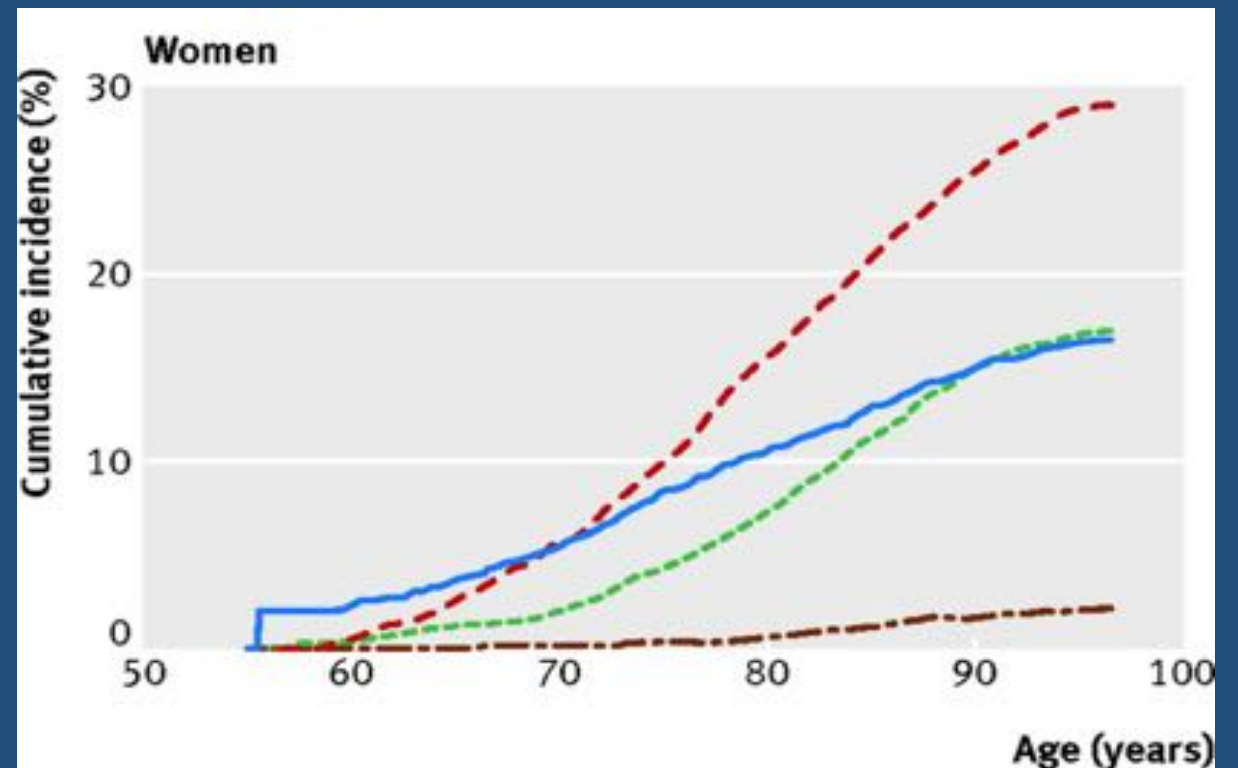
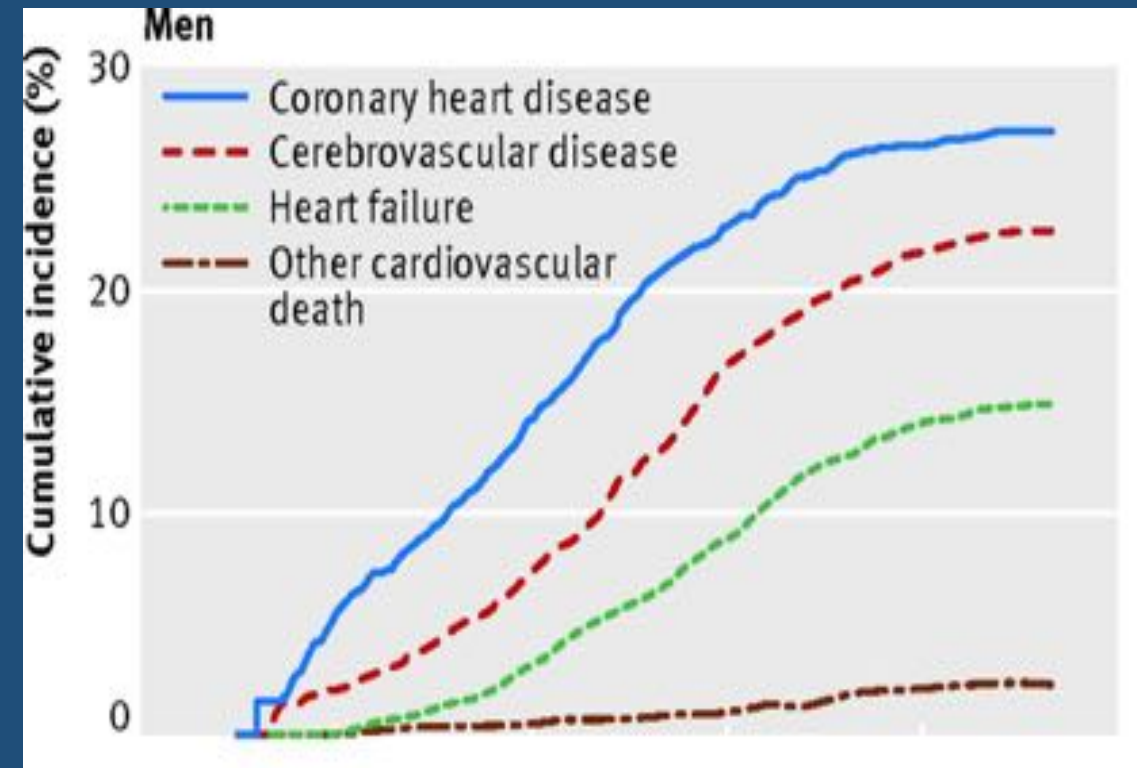


Sex As a Biological Variable Policy



NIH Mandate: January 25, 2016

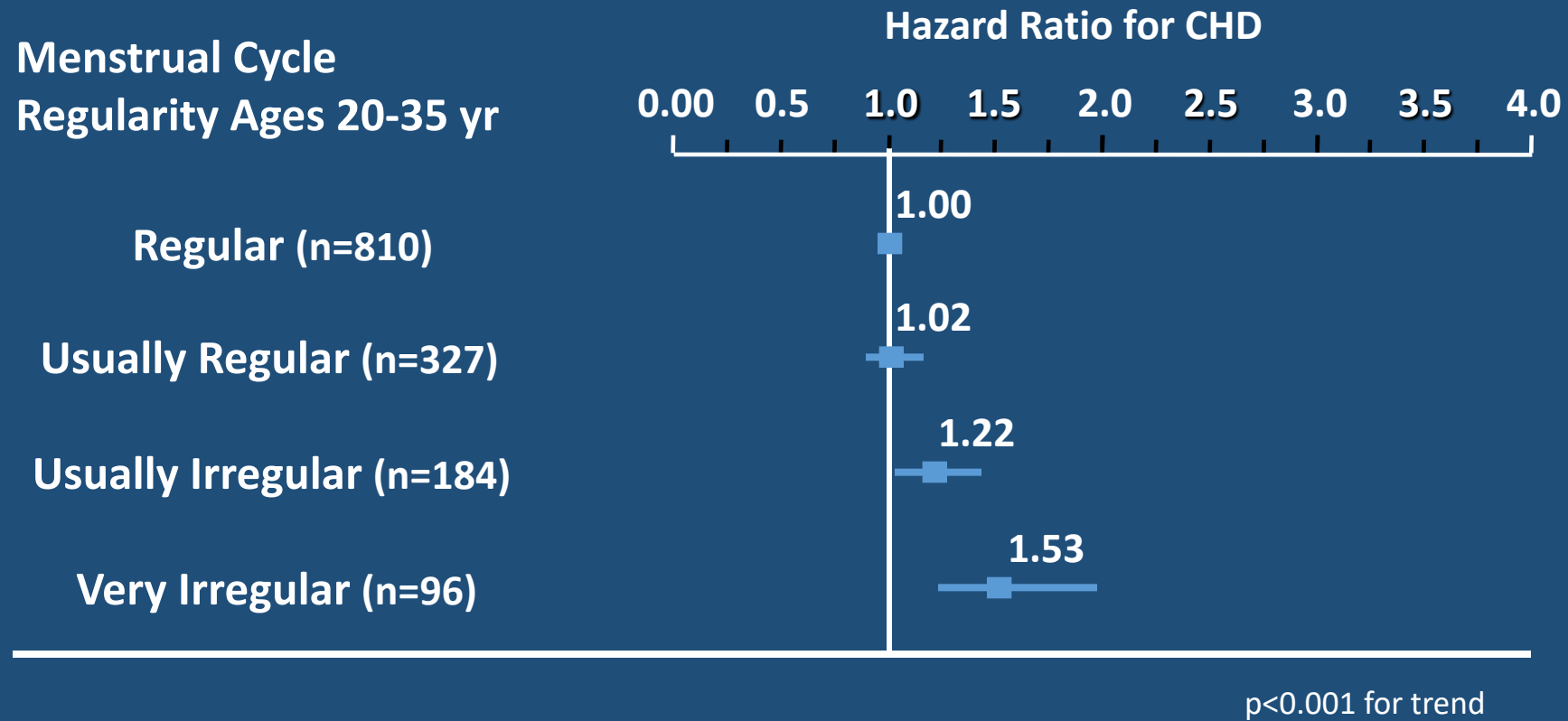
Sex Differences In Cardiovascular Disease



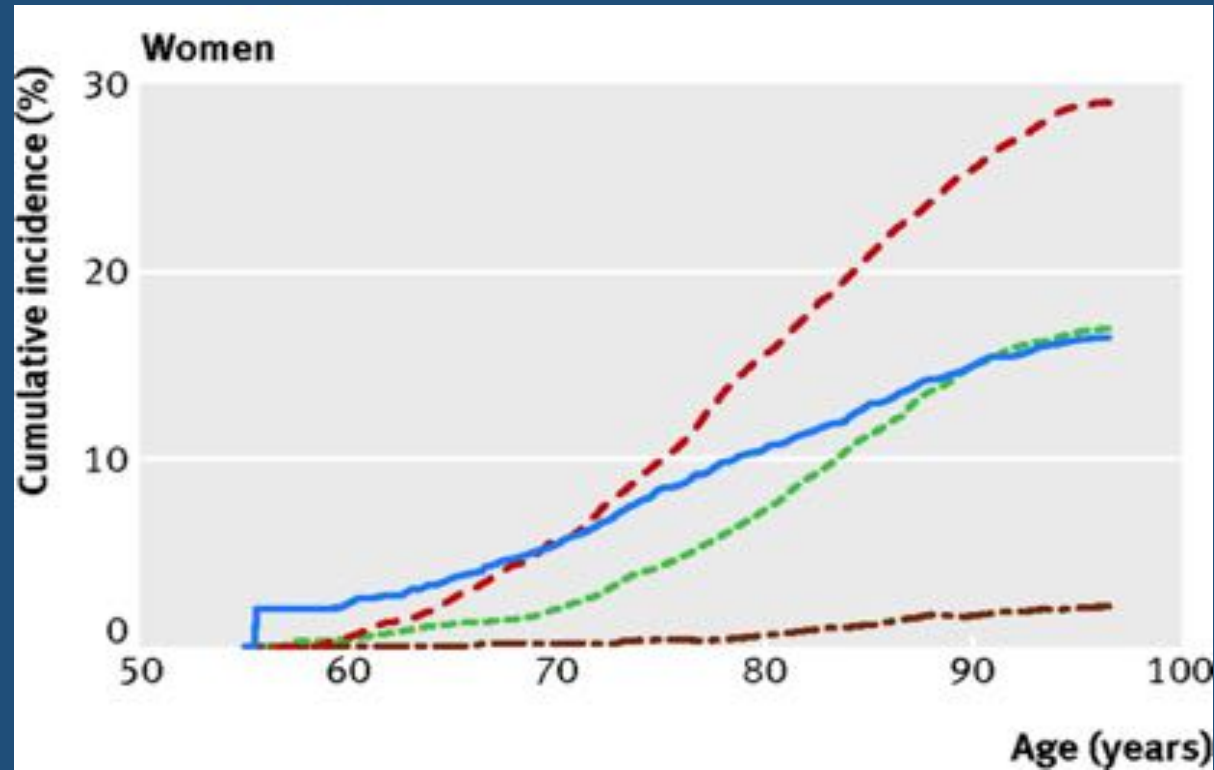
'Estrogens' and CVD Risk

- The incidence of CVD and resultant morbidity and mortality is lower in premenopausal women compared to age-matched men.
- Female protection from CVD disappears after menopause, implicating both *age* and *estrogens* as the primary sources of cardioprotection.
- Hypoestrogenemia (HypoE), such as Turner's syndrome and primary ovarian insufficiency, increases CVD risk
- Early menopause is associated with accelerated atherosclerosis, a 2.6 fold increase in CVD risk, and increased risk of CVD mortality.

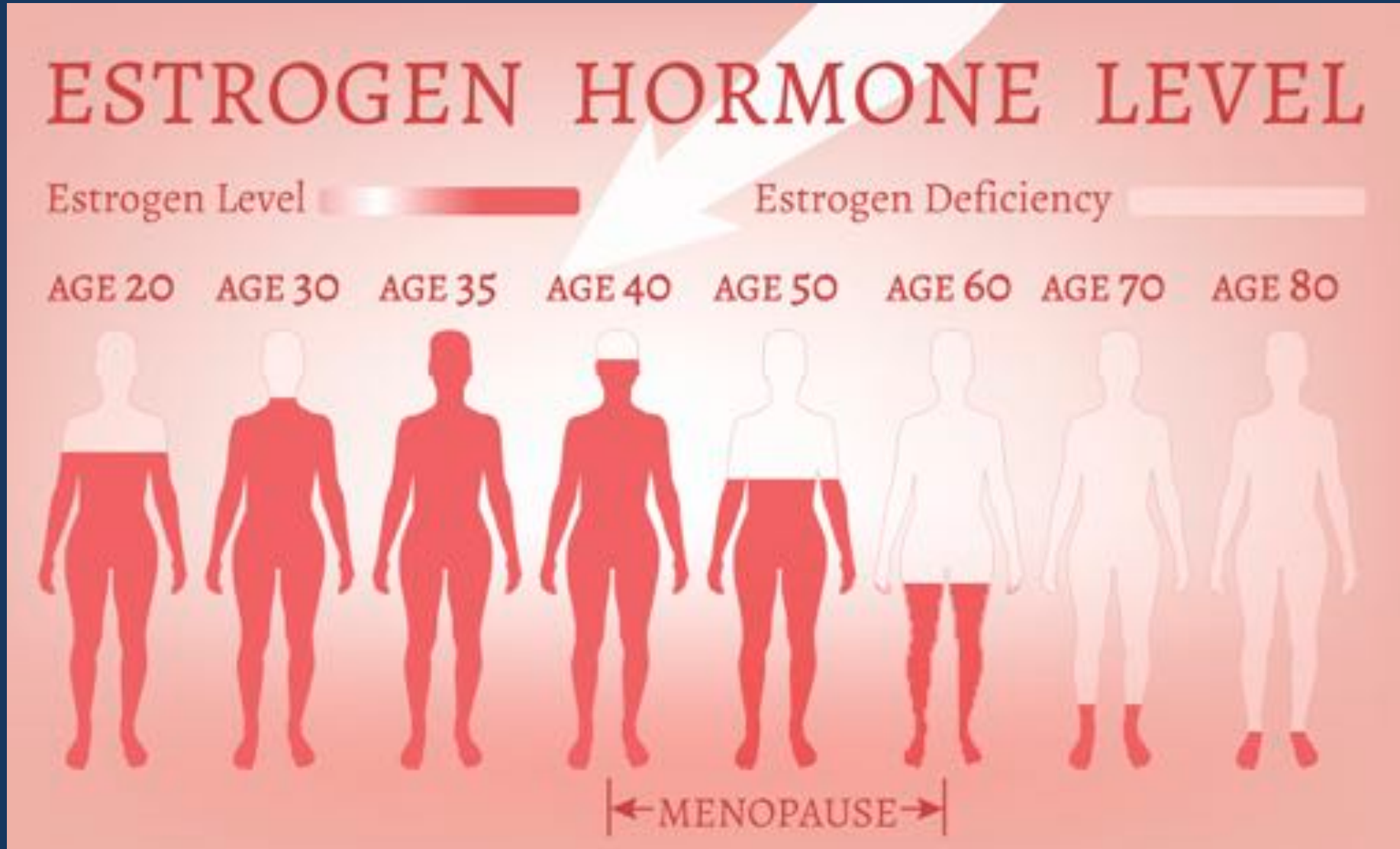
Menstrual Cycle and Risk of CHD in the Nurses Health Study



Increased Cardiovascular Disease in Women as They Age

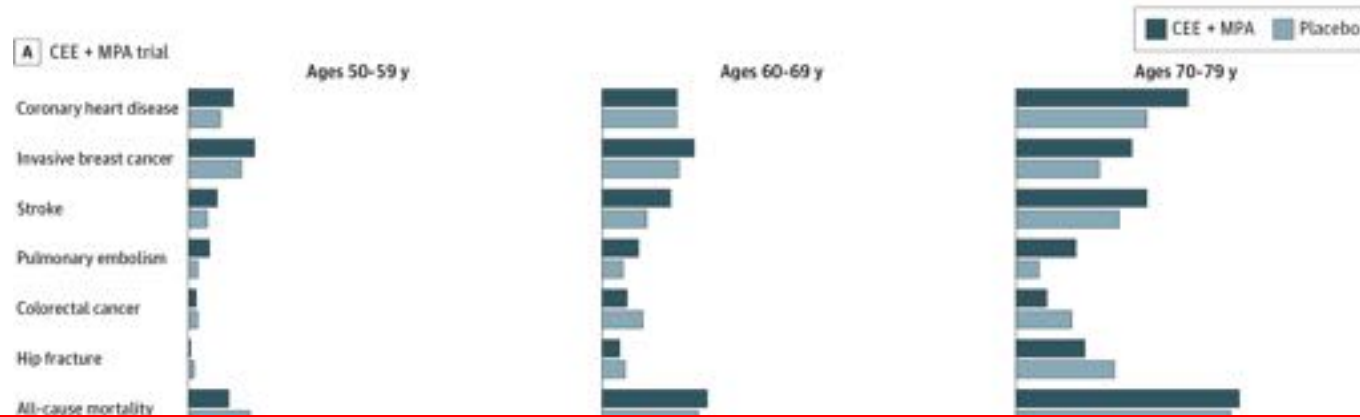


Estrogen Levels in Women Across the Lifespan

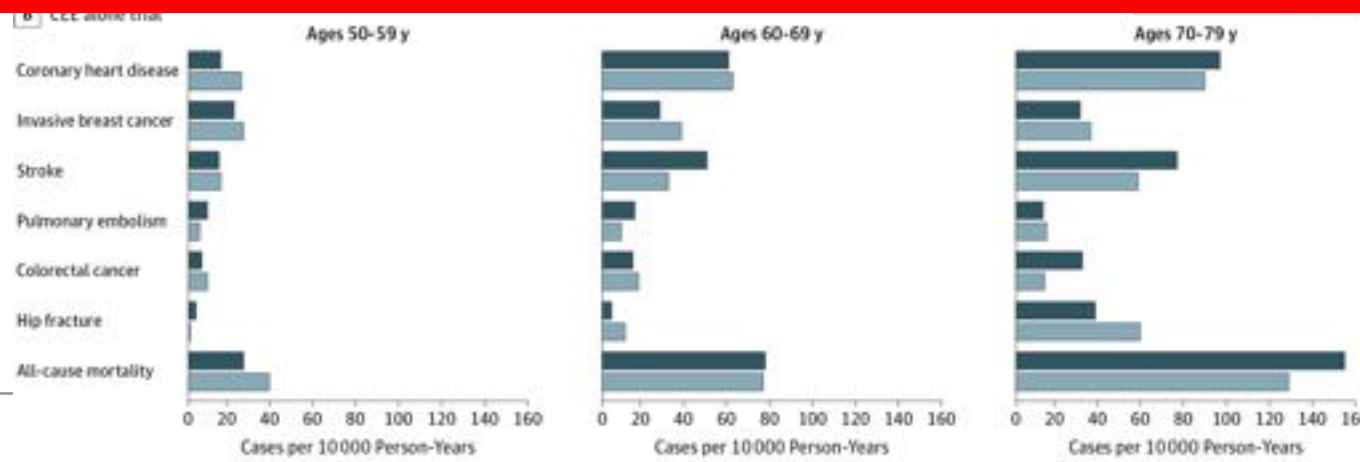


From: **Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women’s Health Initiative Randomized Trials**

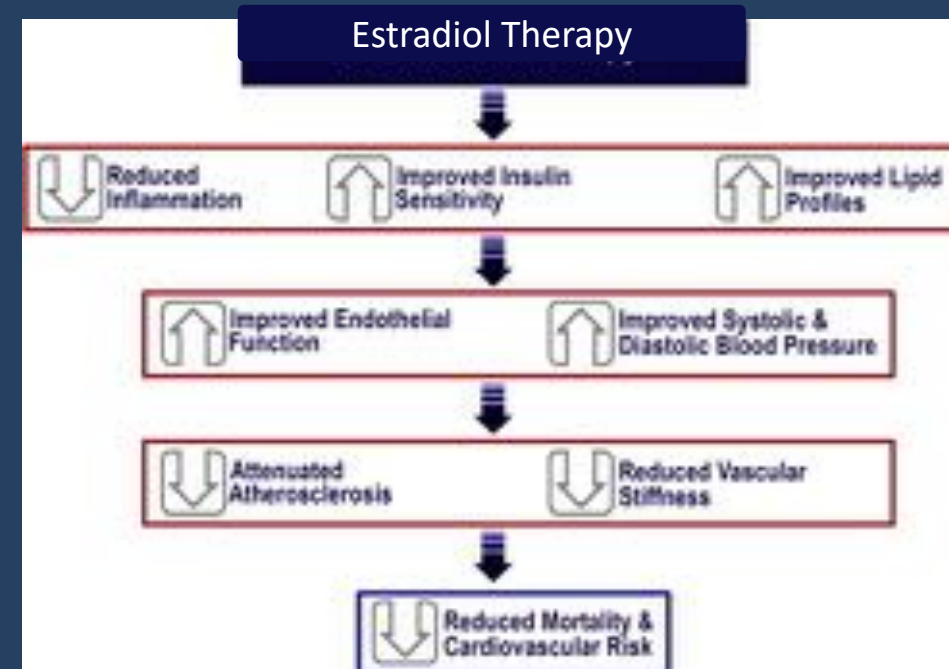
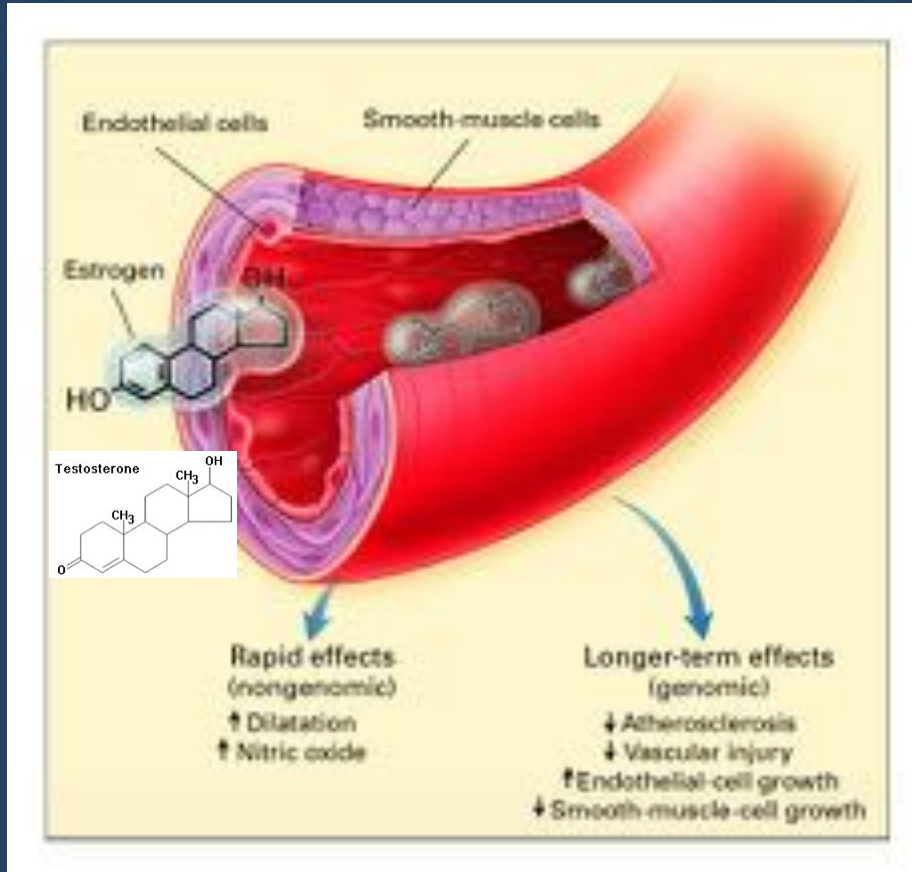
JAMA. 2013;310(13):1353-1368. doi:10.1001/jama.2013.278040



Trend for ↓ risk of heart disease when hormone therapy initiated w/in 10yr compared to ↑ risk in women > 20yr past menopause



Cardiometabolic Effects of Estradiol



Bench To Bedside



Clinical Medicine

Cedars-Sinai Medical Center

A Basic Science Approach for Determining the Mechanisms for Sexual Dimorphisms In Humans

JCI The Journal of Clinical Investigation See us JCI Inside

TECHNICAL ADVANCE The Journal of Clinical Investigation

Differentiation of hypothalamic-like neurons from human pluripotent stem cells

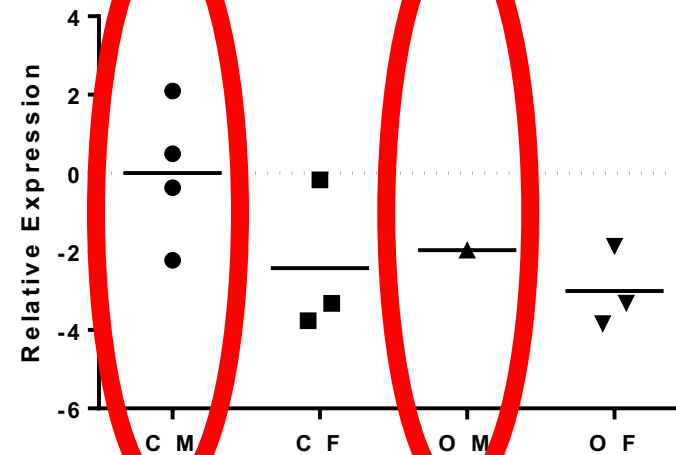
Lihong Wang,^{1,2} Karla Meece,² Damian J. Williams,⁴ Kingui Alice Lu,¹ Matthew Zimmern,³ Garrett Heinrich,³ Jayne Martin-Ladd,² Charles B. Leduc,^{2,5} Lei Sun,^{2,6} Lori M. Zeltzer,^{2,6} Matthew Freeby,⁷ Robin Coland,⁸ Stephen H. Tsang,^{2,9} Sharon L. Wardlaw,³ Dieter Egli,^{1,10} and Rudolph L. Leibel^{1,11}

¹Division of Molecular Genetics, Department of Pediatrics and Naomi Berke Davis Center, Columbia University College of Physicians and Surgeons, New York, New York, USA; ²Institute of Human Nutrition, Columbia University, New York, New York, USA; ³Department of Medicine and Naomi Berke Davis Center, Columbia University College of Physicians and Surgeons, New York, New York, USA; ⁴Department of Pathology and Cell Biology, Columbia University, New York, New York, USA; ⁵Institute of Molecular and Cell Biology, Prince George's, Singapore; ⁶New York Stem Cell Foundation Research Institute, New York, New York, USA; ⁷Cardiovascular and Metabolic Swedish Program, Umeå UMC, Umeå, Sweden; ⁸Barbara and Donald Green Laboratory of Stem Cells and Regenerative Medicine, and ⁹Genetic and Stem Cell Science Laboratory, Department of Obstetrics and Gynecology, Columbia University, New York, New York, USA.

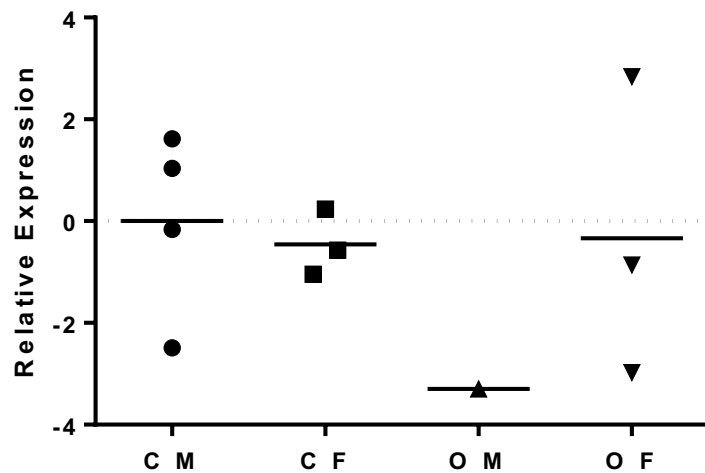
Scatter Plots

(negative value indicates downregulation)

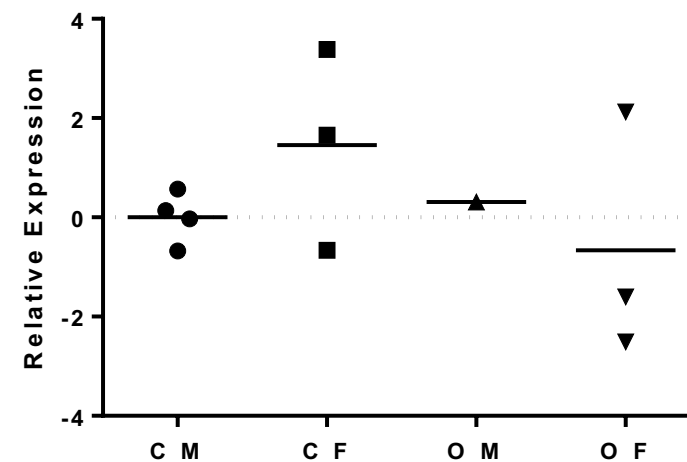
Sareen Lab - iPHSC hypo-like neurons - Esr1



Sareen Lab - iPHSC hypo-like neurons - Il6



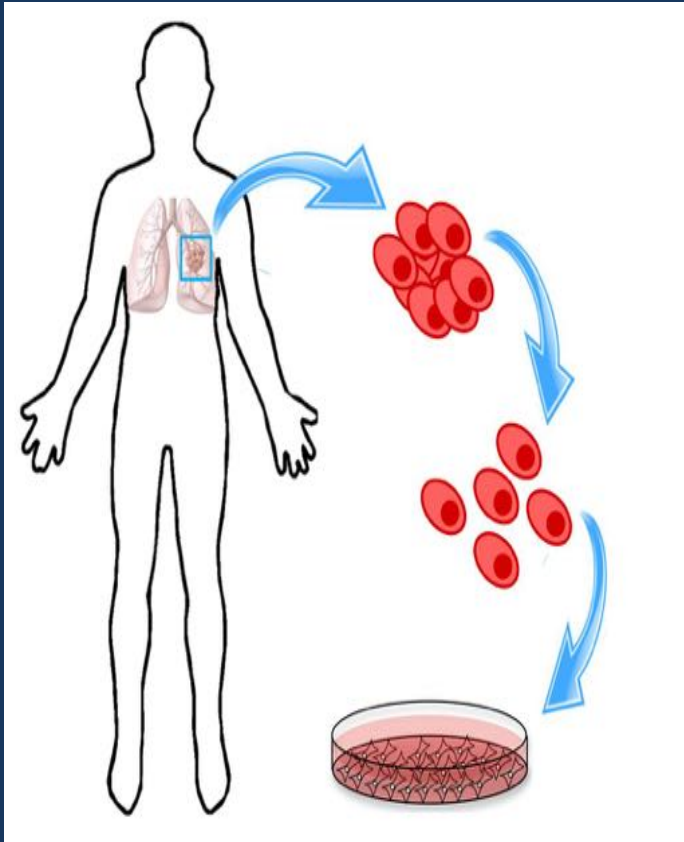
Sareen Lab - iPHSC hypo-like neurons - Tnfalpha



What??

- These data are opposite from our pre-clinical observations because:
 - Humans aren't mice?
 - Is there something that happens during the culturing of cells which augments results????
 - Does the cell culture media influence the results?

Cell Culture And Cell Sex



- Cell culture medium is the most important component of the culture environment because it provides:
 - Nutrients
 - Growth Factors
 - Hormones for cell growth
 - Factors to facilitate regulating the pH of the culture



Sex Chromosomes And Sex Hormones

Estrogen > Testosterone

Testosterone > Estrogen

Cis Female

Cis Male



VANITY FAIR

“Call me Caitlyn”

by BUZZ BISSINGER Photos by ANNIE LEIBOVITZ

© Supplied by WENN.com

Transgender Individuals



Testosterone > Estrogen

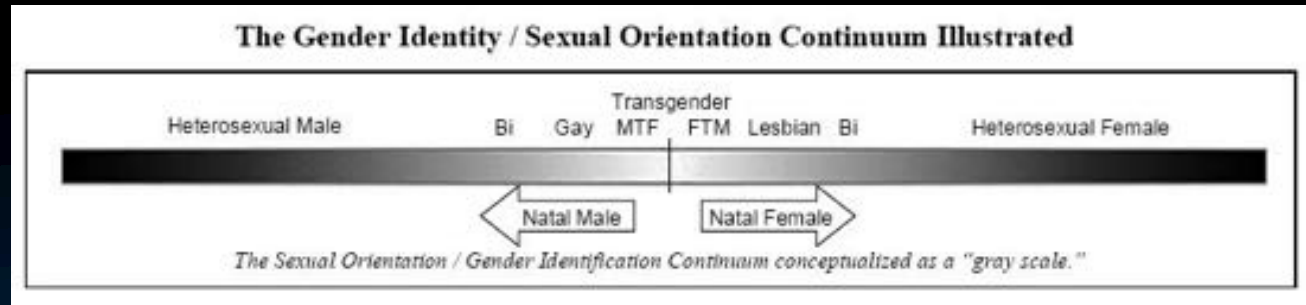
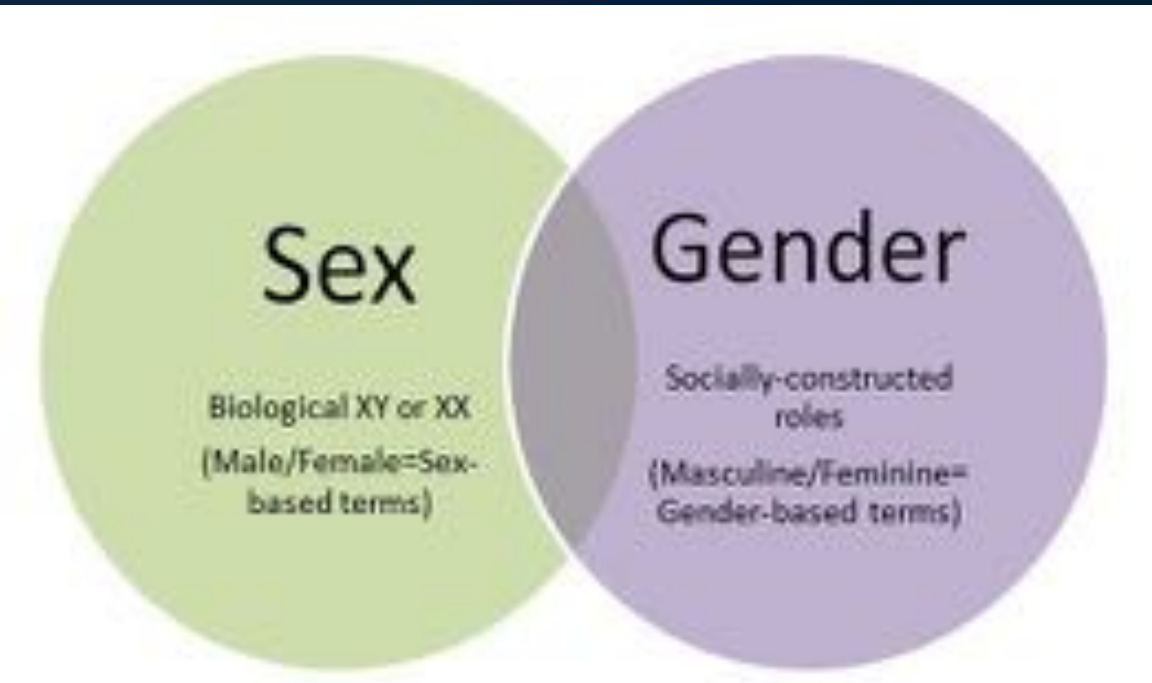
Transgender men

Estrogen > Testosterone

Transgender woman

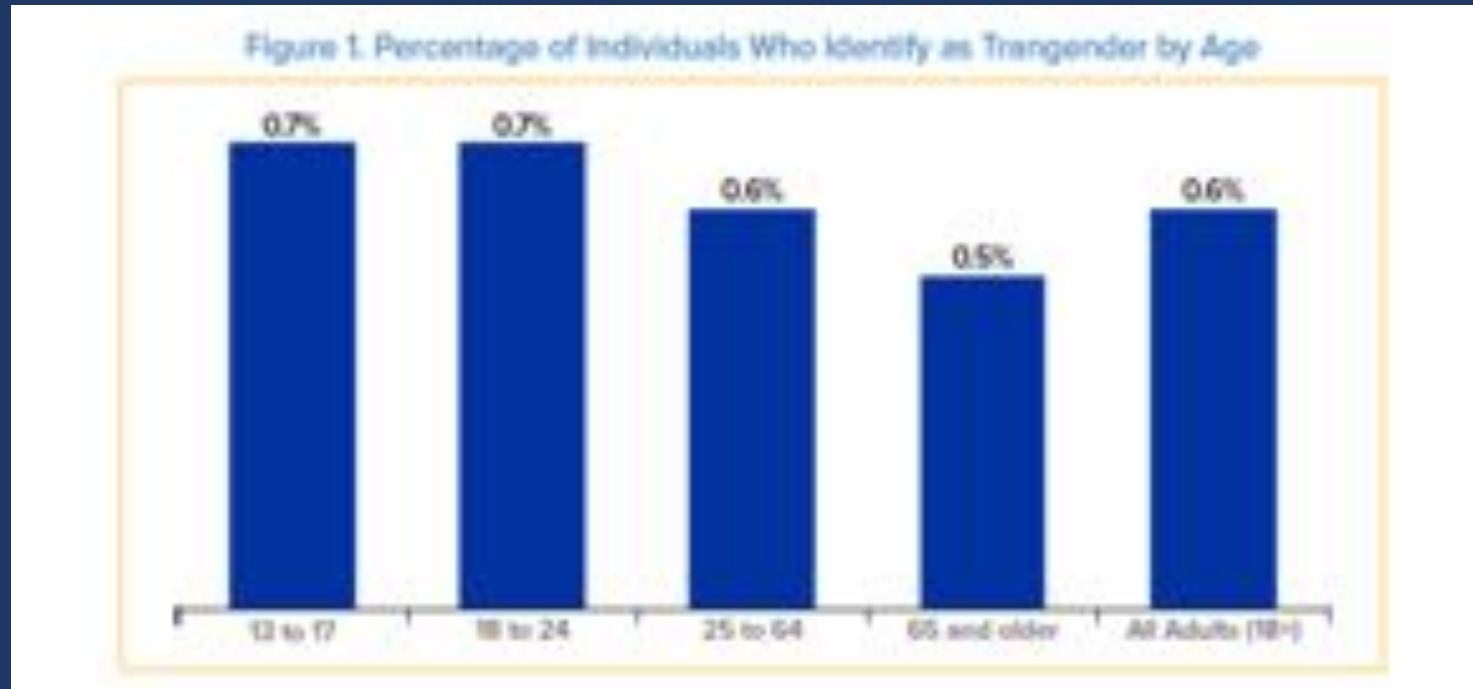


Sex and Gender



Gender Identity

- In the United States, there is an estimated 1.4 million people living with gender identity disorder



- Transgender individuals opt for interventions and procedures aimed at alleviating the incongruence between their gender identity and their biological chromosomal and gonadal sex

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree,¹ Peggy T. Cohen-Kettenis,² Louis Gooren,³ Sabine E. Hannema,⁴
Walter J. Meyer,⁵ M. Hassan Murad,⁶ Stephen M. Rosenthal,⁷ Joshua D. Safer,⁸
Vin Tangpricha,⁹ and Guy G. T'Sjoen¹⁰

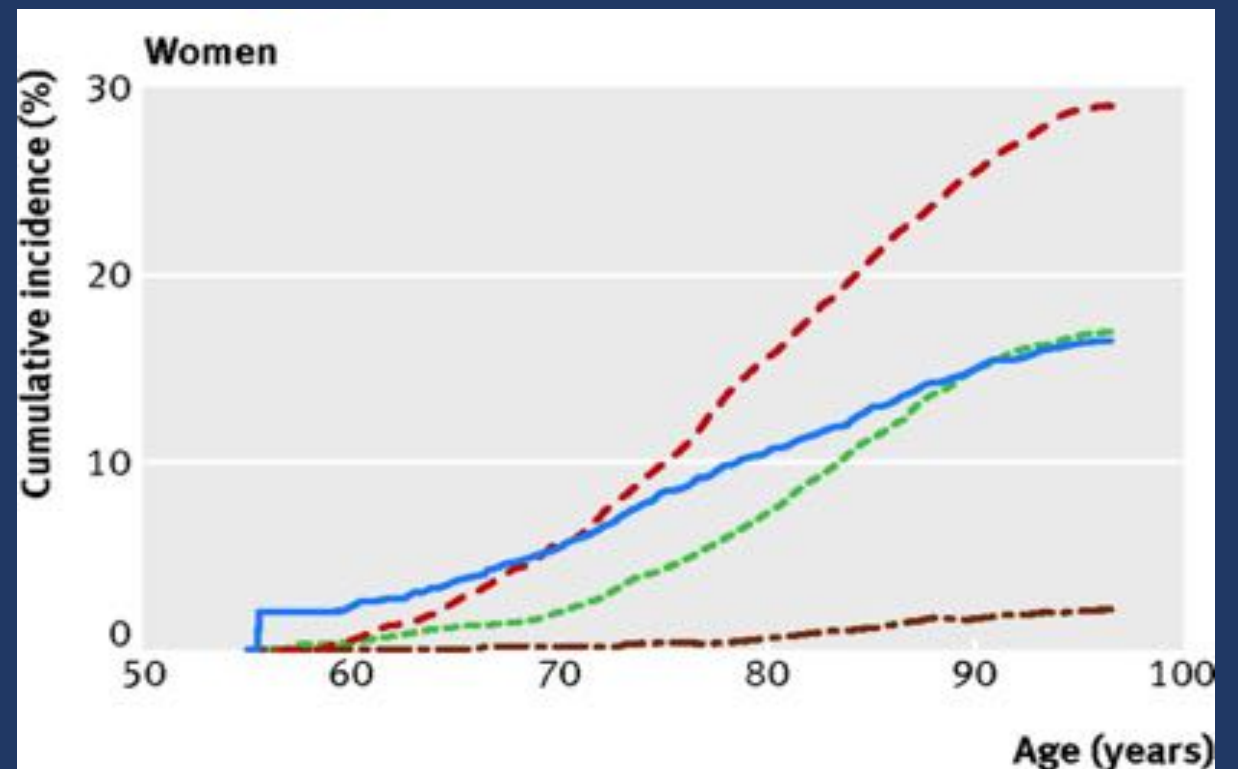
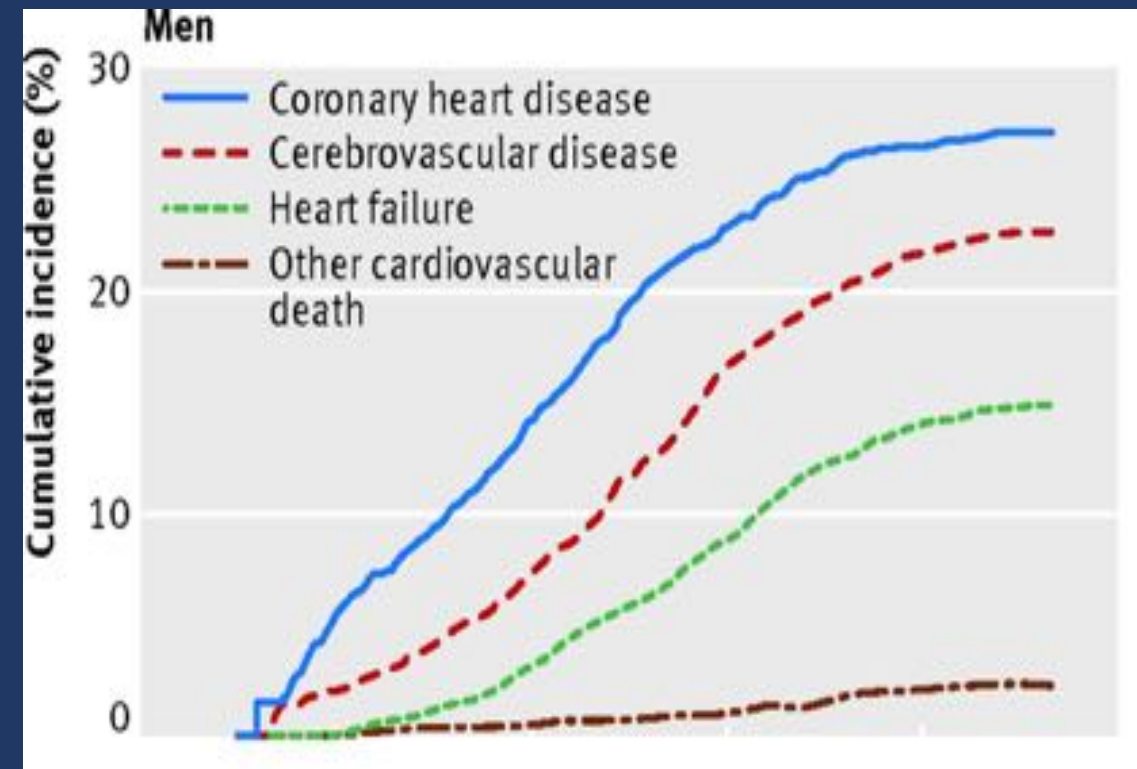
Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Table 11. Hormone Regimens in Transgender Persons

Transgender females ^a	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate ^b	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate ^c	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6% ^d	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

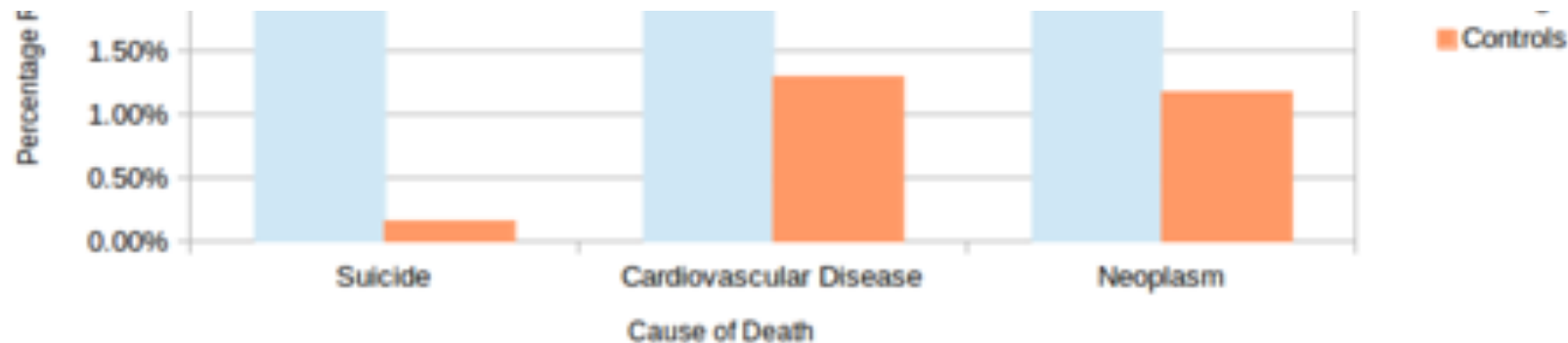
Sex Differences In Cardiovascular Disease



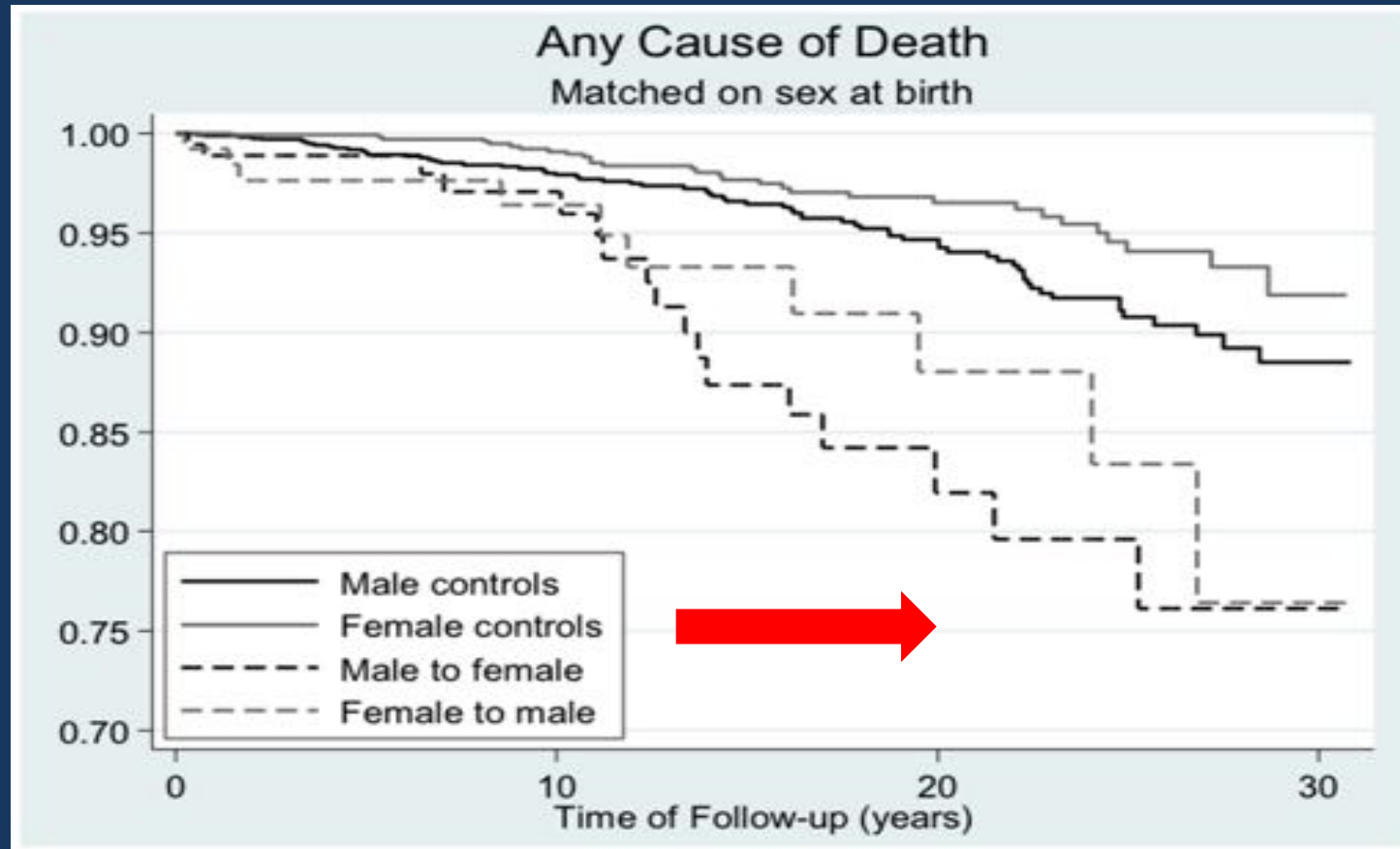
Increased Cardiovascular Morbidity/Mortality In Transgender Women

Percentage of Reported Causes of Deaths in Transgender Patients vs. 10:1 Matched Controls

Remarkably, the second leading cause of death in transgender women is CVD

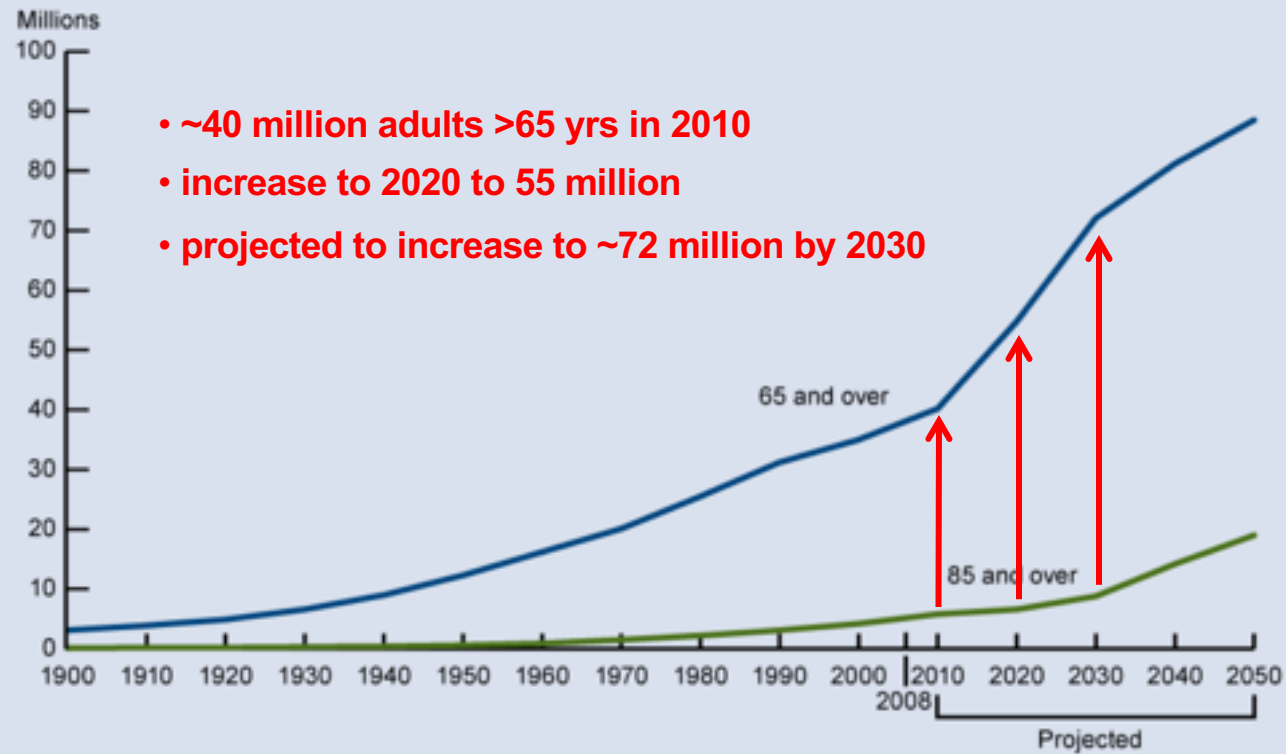


Death Rates in Transgender Individuals



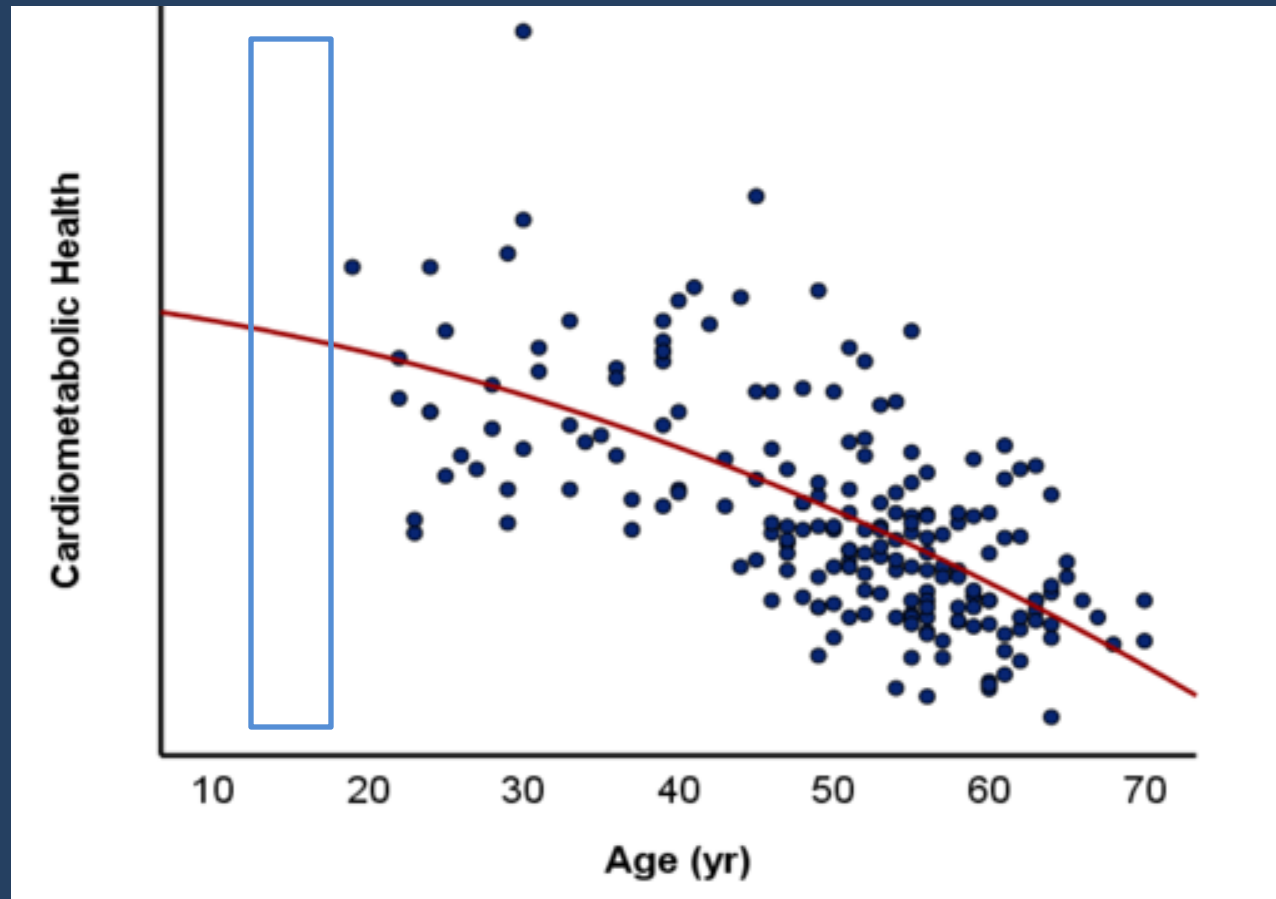
Aging Population in the US: Is CVD a Future Epidemic

Population age 65 and over and age 85 and over, selected years
1900–2008 and projected 2010–2050



NOTE: Data for 2010–2050 are projections of the population.
Reference population: These data refer to the resident population.
SOURCE: U.S. Census Bureau, Decennial Census, Population Estimates and Projections.

Is the Trajectory of Cardiometabolic Health Different in Transgender vs Cisgender Individuals Across the Lifespan?



Transgender Women Dying Faster Than General Population — Biggest drivers were HIV, suicide, and CVD



In a retrospective, observational study spanning from 1972 to 2018, a total of **10.8% (317 of 2,927) of transgender women using hormonal therapy included in the analysis died during follow-up.**

This number was starkly higher than the number of cisgender men and women in the general population that died over the same period

[*The Lancet Diabetes & Endocrinology*](#) September 2, 2021

Acute CV Events in Transgender Individuals Using Hormone Therapy

Table. Standardized Incidence Ratios for Acute Cardiovascular Events in Transwomen and Transmen Receiving Hormone Therapy

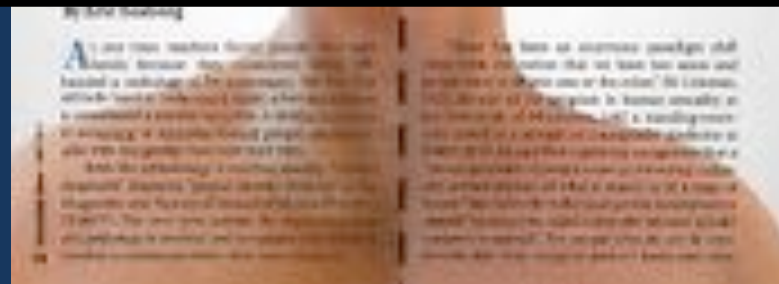
Acute Cardiovascular Events	ECs (IR)*	Using Women as Reference		Using Men as Reference	
		ECs	SIR (95% CI)	ECs	SIR (95% CI)
Transwomen					
Stroke	29 (127) [†]	12.01	2.42 (1.65-3.42) [†]	16.08	1.80 (1.23-2.56) [†]
Myocardial infarction	30 (131)	11.38	2.64 (1.81-3.72) [†]	38.03	0.79 (0.54-1.11)
Venous thromboembolism	73 (310)	13.22	5.52 (4.36-6.90) [†]	16.04	4.55 (3.58-5.86) [†]
Transmen					
Stroke	6 (55)	3.49	1.72 (0.70-3.58)	4.10	1.46 (0.59-3.64)
Myocardial infarction	11 (100)	2.98	3.69 (1.94-6.42) [†]	10.99	1.00 (0.53-1.74)
Venous thromboembolism	2 (18)	4.84	0.41 (0.07-1.37)	5.58	0.36 (0.06-1.19)

ECs indicates expected cases; IR, incidence rate; OCs, observed cases; and SIR, standardized incidence ratio.
 *Per 100,000 person-years.
 †Significant finding.

Cardiometabolic Health in Transgender Women



Cardiometabolic Health/Risk in Transgender Individuals With Gender Affirming Surgery???



Study Design

12 MtoF:

8 testes(+)

4 testes(-)

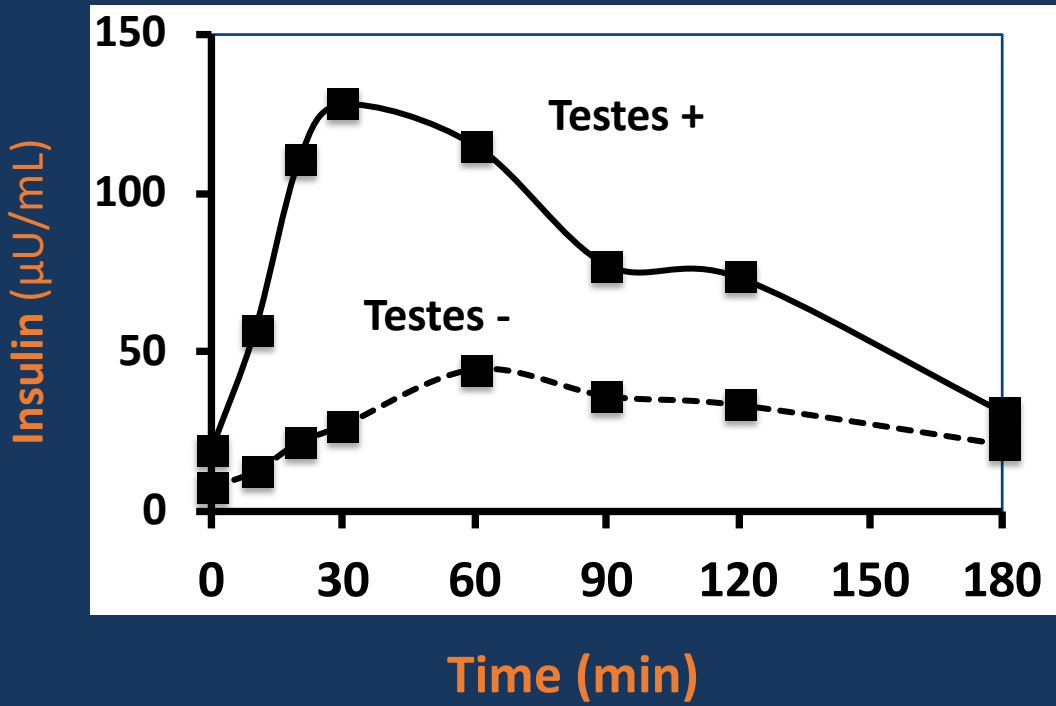
Two visits:

1) Oral glucose tolerance testing

Blood Chemistry

2) MRS - Liver

Insulin Sensitivity



	Testes +	Testes -
Total Glycated Hgb	5.9 ± 0.7	5.3 ± 0.6#
Hgb A _{1c}	5.2 ± 0.4	4.8 ± 0.3
Fasting glucose, mg/dL	91.5 ± 7.5	87.9 ± 4.1
Fasting Insulin, µU/mL	19.4 ± 15.6	7.7 ± 7.7*
HOMA - IR	4.6 ± 3.7	1.7 ± 1.8*

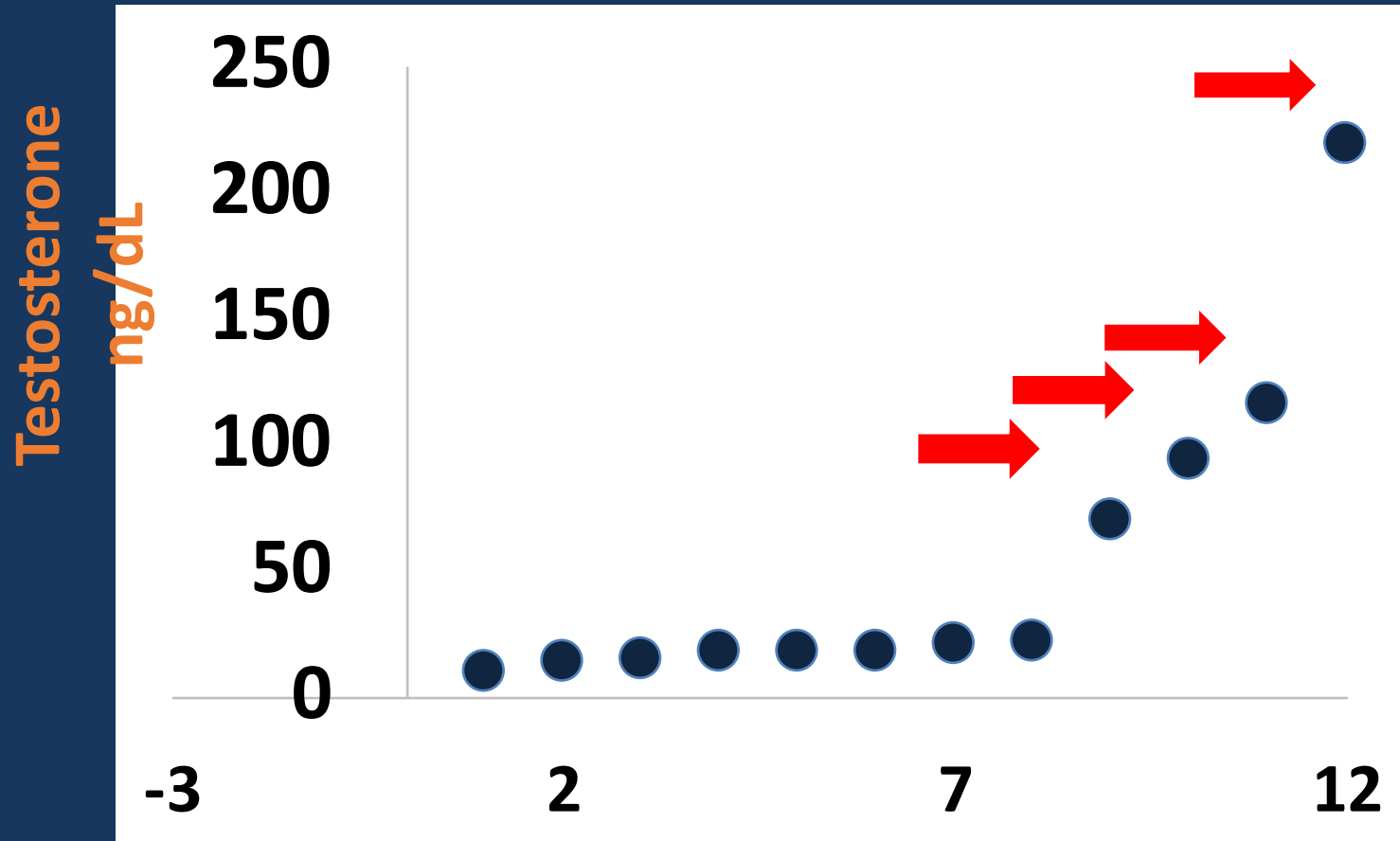


CLINICAL STUDY

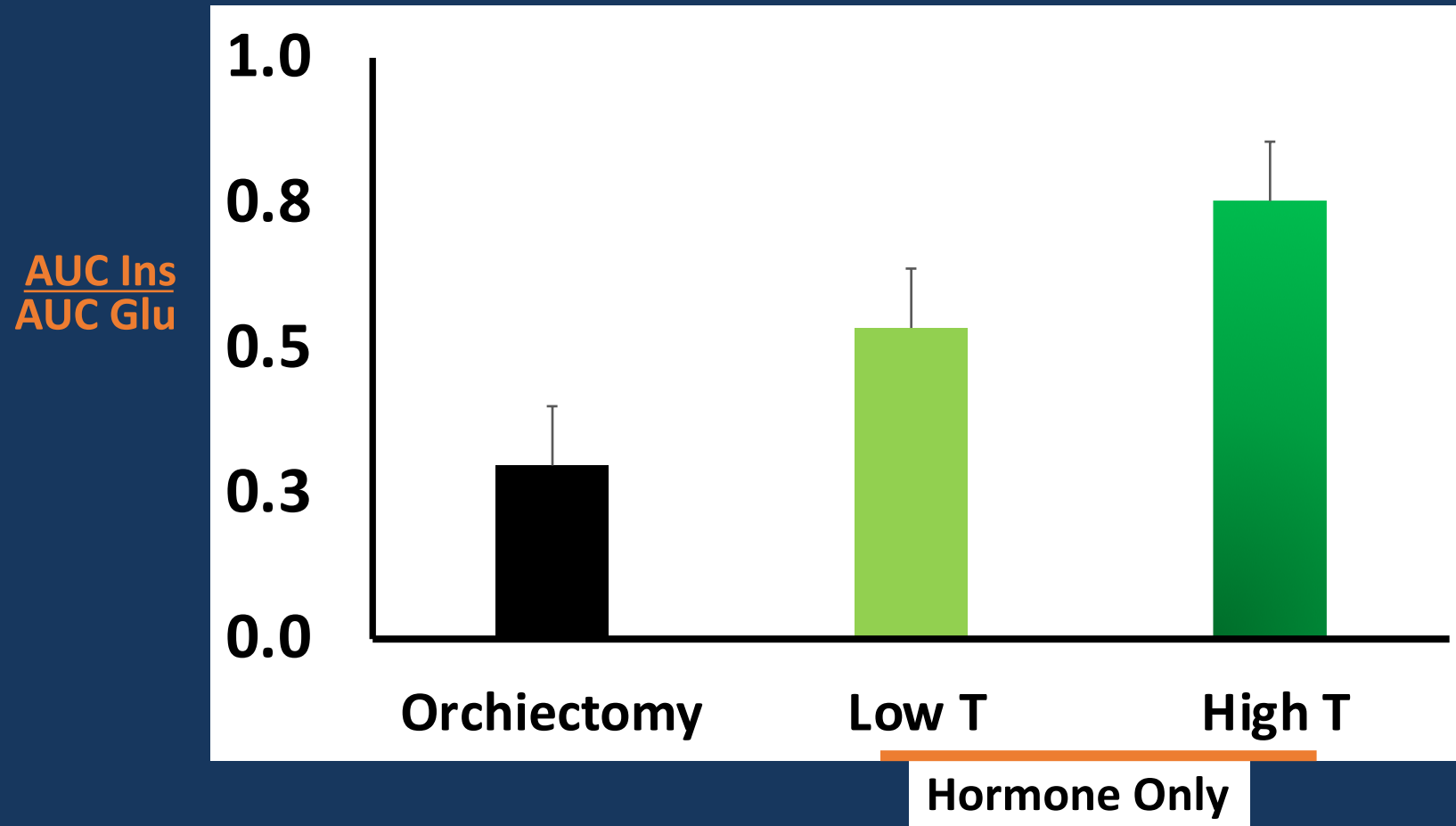
Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health In Men Study

Bu B Yeap^{1,2}, S A Paul Chubb^{1,3}, Zoë Hyde⁴, Konrad Jamrozik⁵, Graeme J Hankey¹, Leon Flicker^{1,4} and Paul E Norman⁶

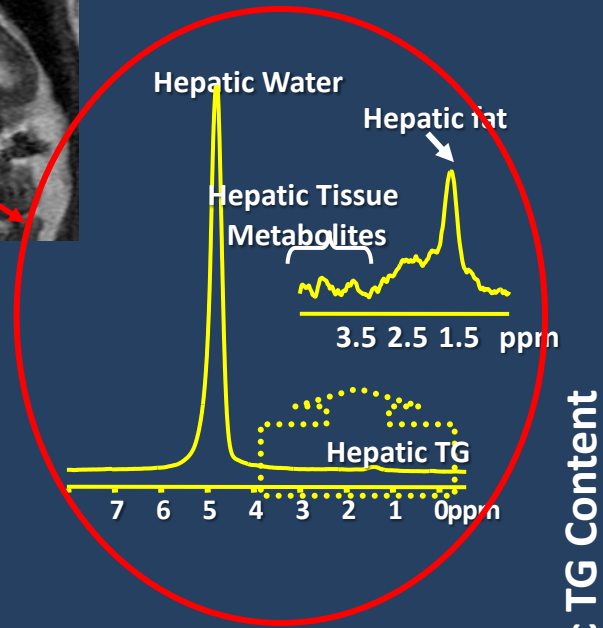
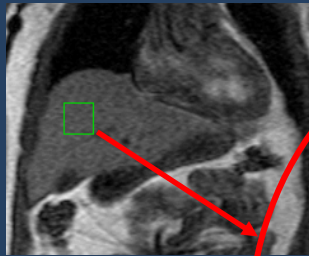
Testosterone Levels



Insulin Resistance and Testosterone Concentration

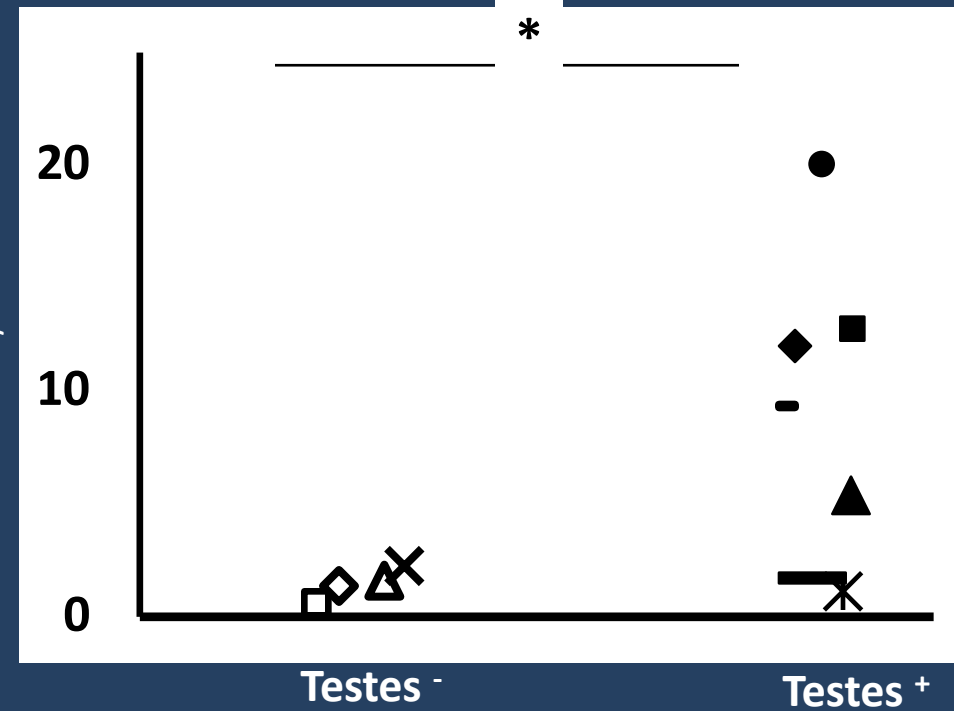


Hepatic Steatosis

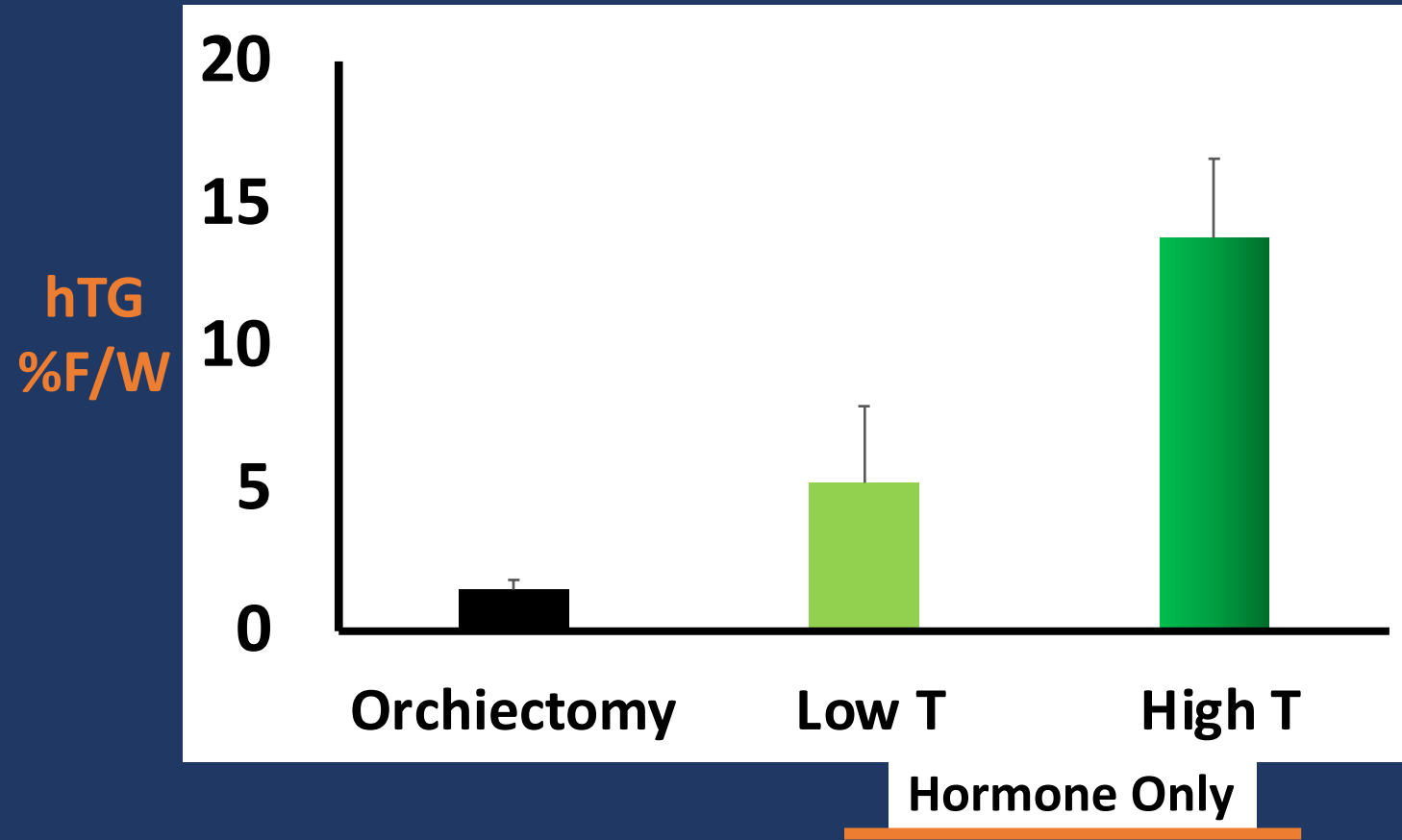


Hepatic TG Content

% F/W

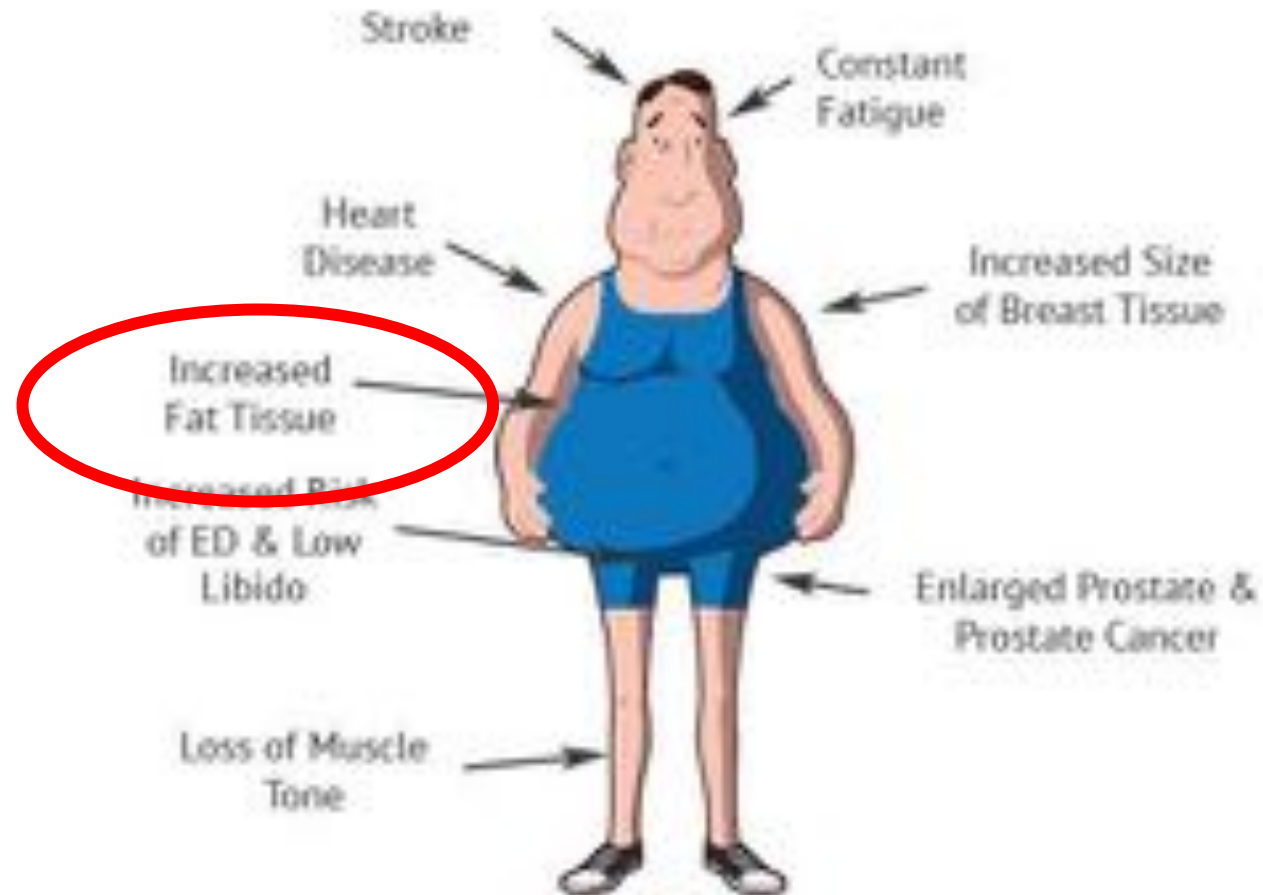


Hepatic Steatosis and Testosterone Concentration

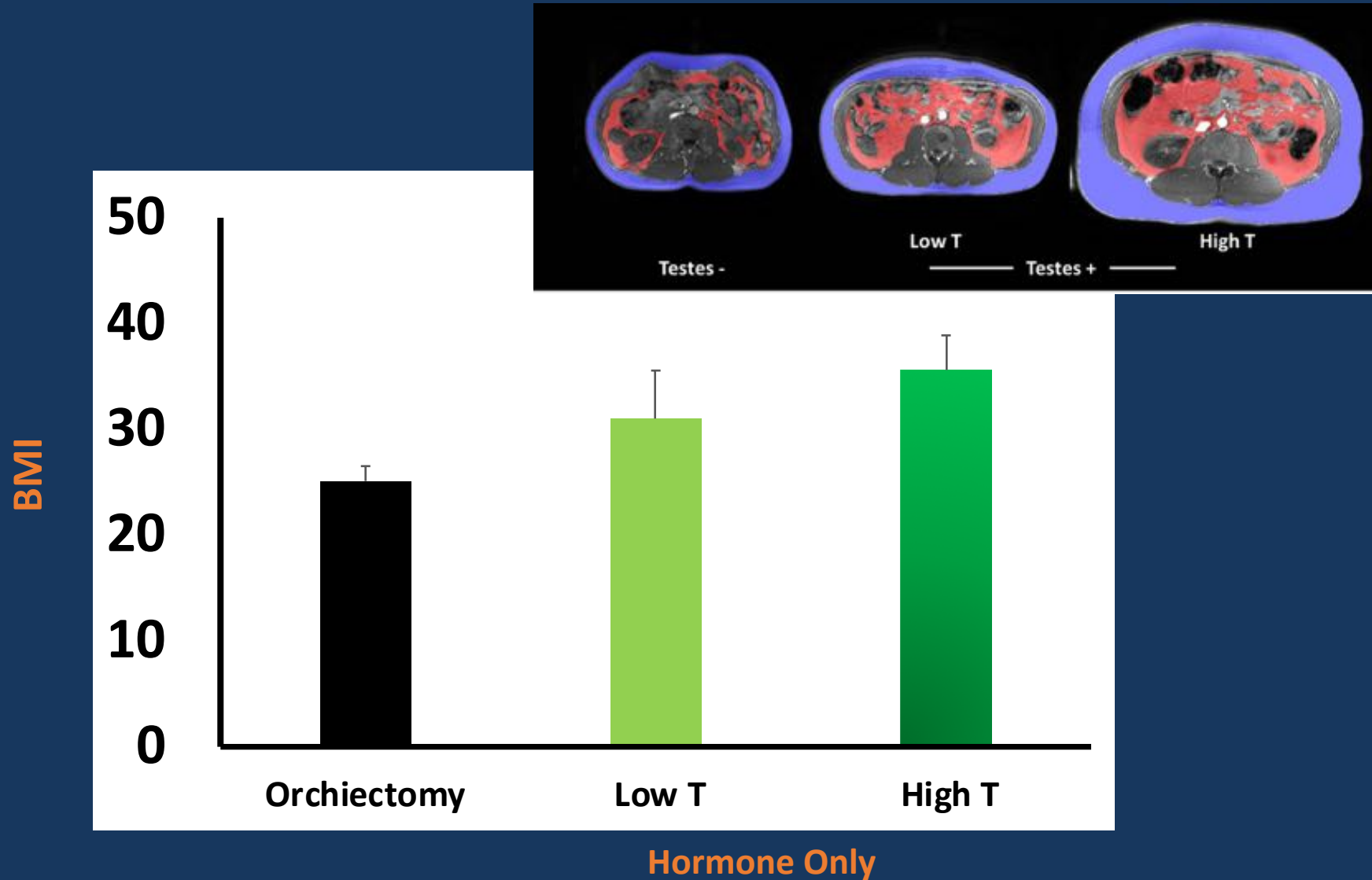


Estrogens in Men

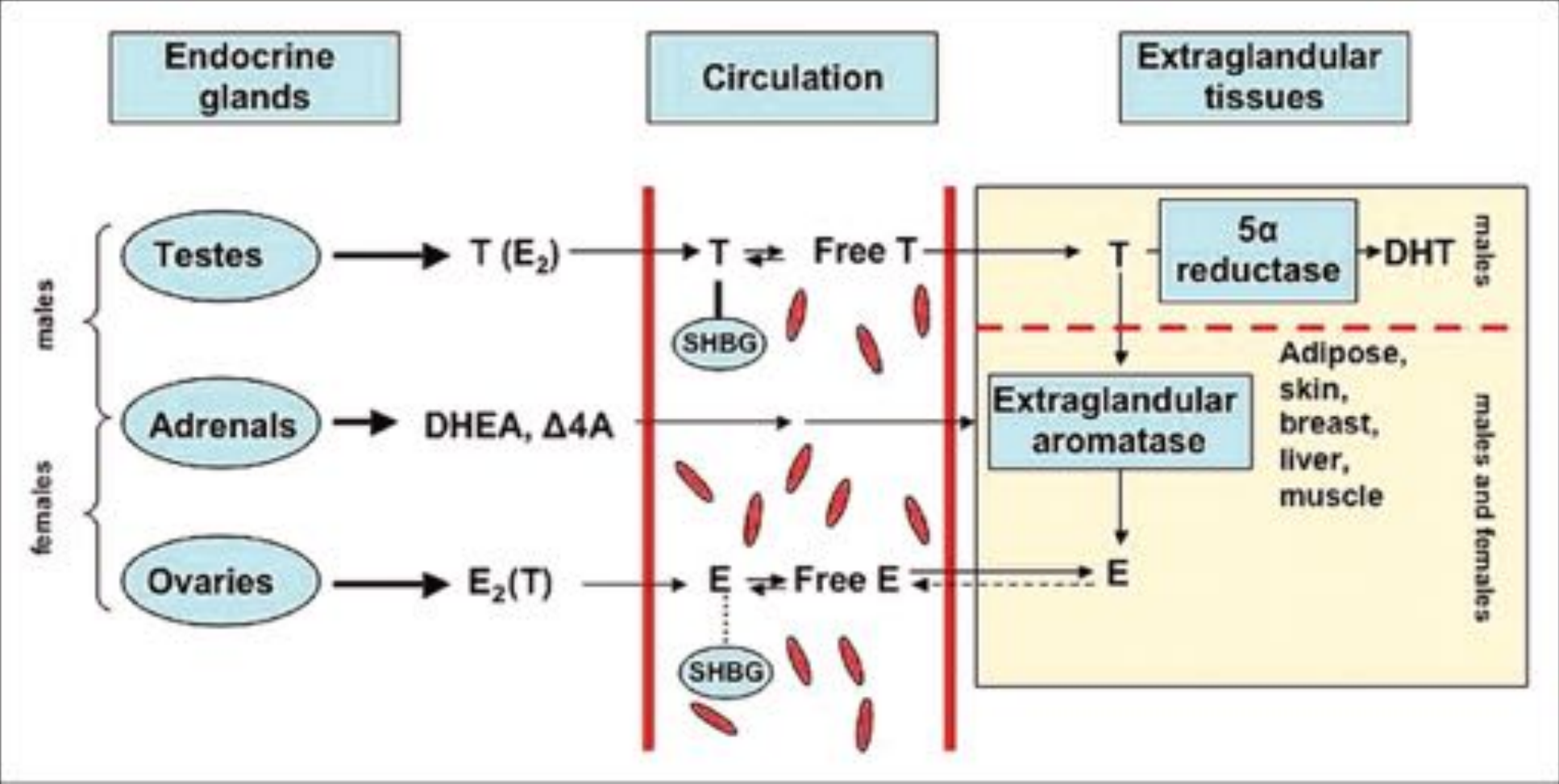
High Estrogen in Men



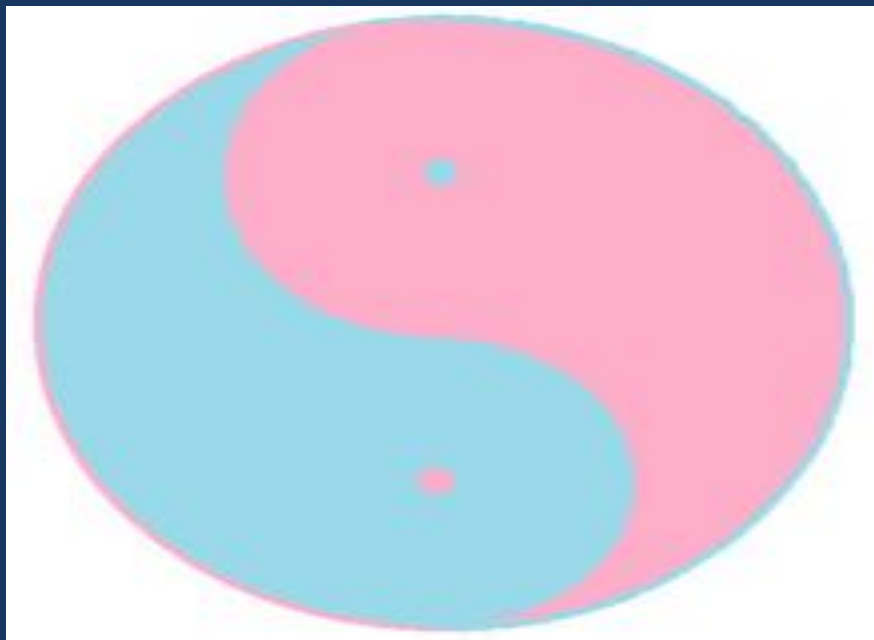
High Testosterone Levels Associated with Obesity



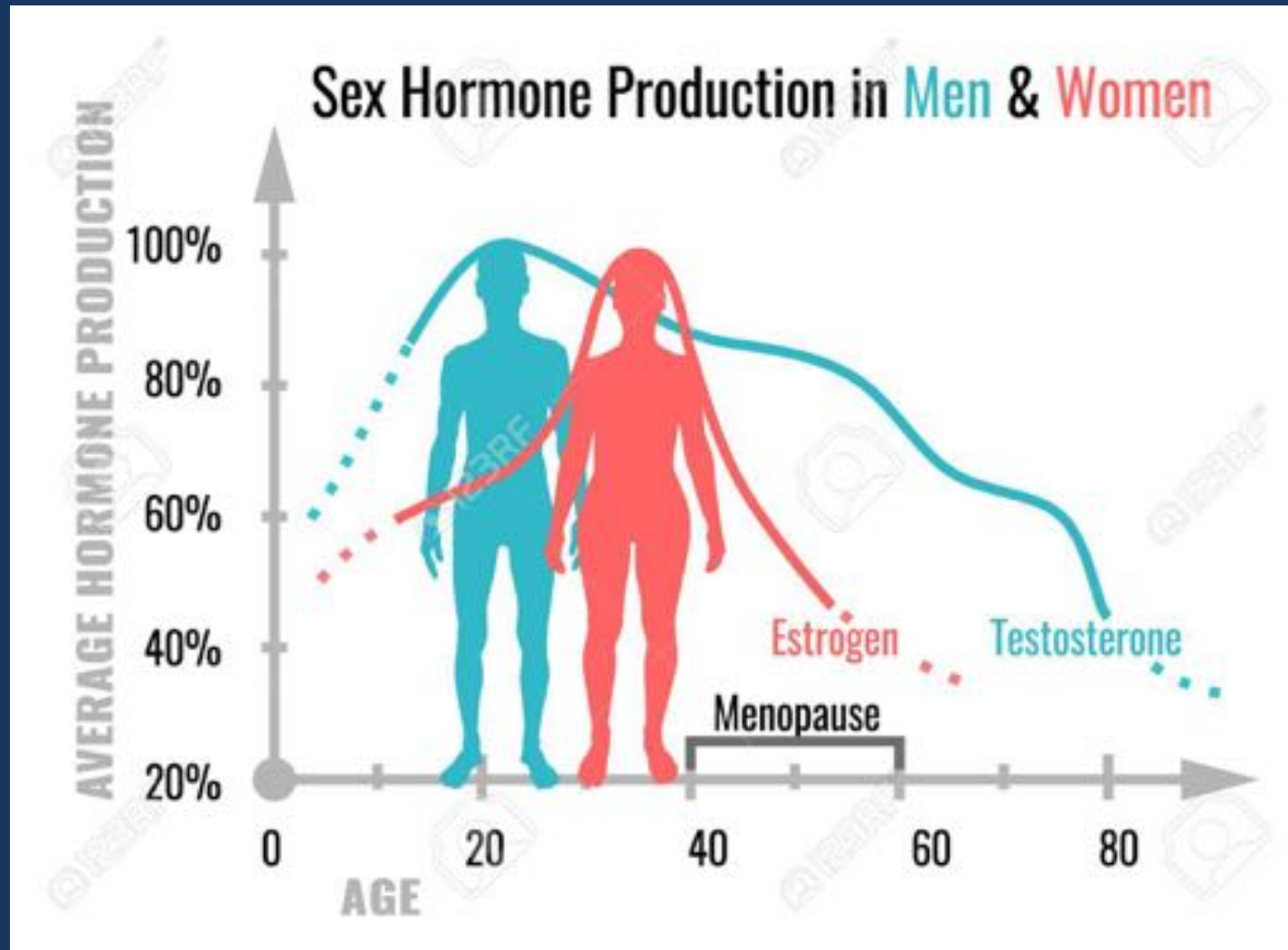
Conversion of Testosterone to Estrogen, Tissue Levels or Circulating Levels?



Is There An Optimal Ratio Of Androgens To Estrogens And Sex Chromosomes To Protect Against Disease Risk???



Testosterone and Estrogen Production in Men and Women Across the Lifespan



Elevated T/E₂ Ratio Is Associated with an Increased Risk of Cerebrovascular Disease in Elderly Men

Yanping Gong^{1*}, Haiying Xiao^{1*}, Chunlin Li^{1*}, Jie Bai², Xiaoling Cheng¹, Mengmeng Jin¹, Boruo Sun¹, Yanhui Lu¹, Yinghong Shao¹, Hui Tian¹

Biomed Mater Eng. 2012;22(1-3):179-85. doi: 10.3233/BME-2012-0705.

Imbalance of testosterone/estradiol promotes male CHD development.

Zheng HY¹, Li Y, Dai W, Wei CD, Sun KS, Tong YQ.

Free Testosterone

Free Estradiol

T/E₂

T to E Calculator

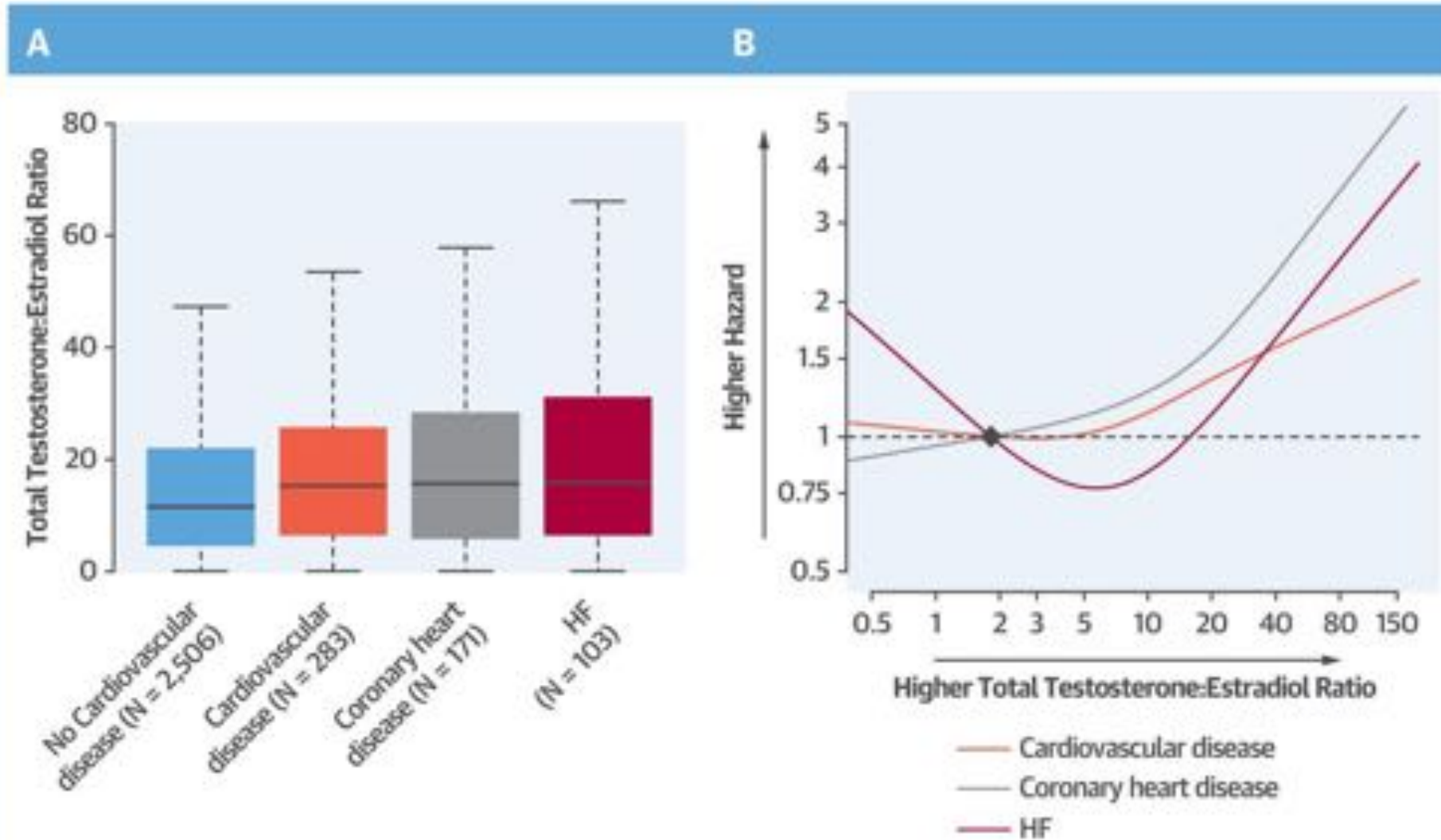
Testosterone to Estradiol Ratio Calculator

Testosterone 43 [ng/dL](#) ▼

Estradiol 101 [pg/mL](#) ▼

Ratio 4.02

CENTRAL ILLUSTRATION: Testosterone/Estradiol Ratio and the Risk of Incident CVD, CHD, and HF in Post-Menopausal Women: MESA

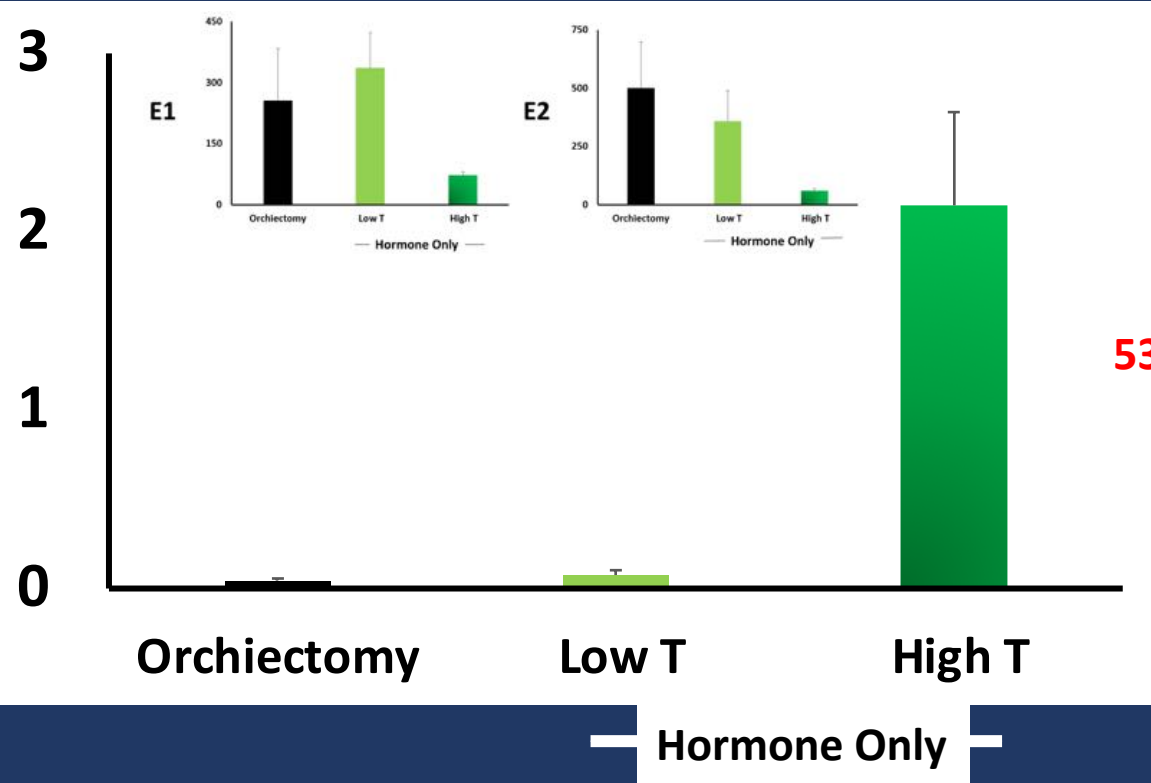


Zhao, D. et al. J Am Coll Cardiol. 2018;71(22):2555-66.

Is the Ratio Between T and E2 More Important Than Their Absolute Quantities?



T/E2

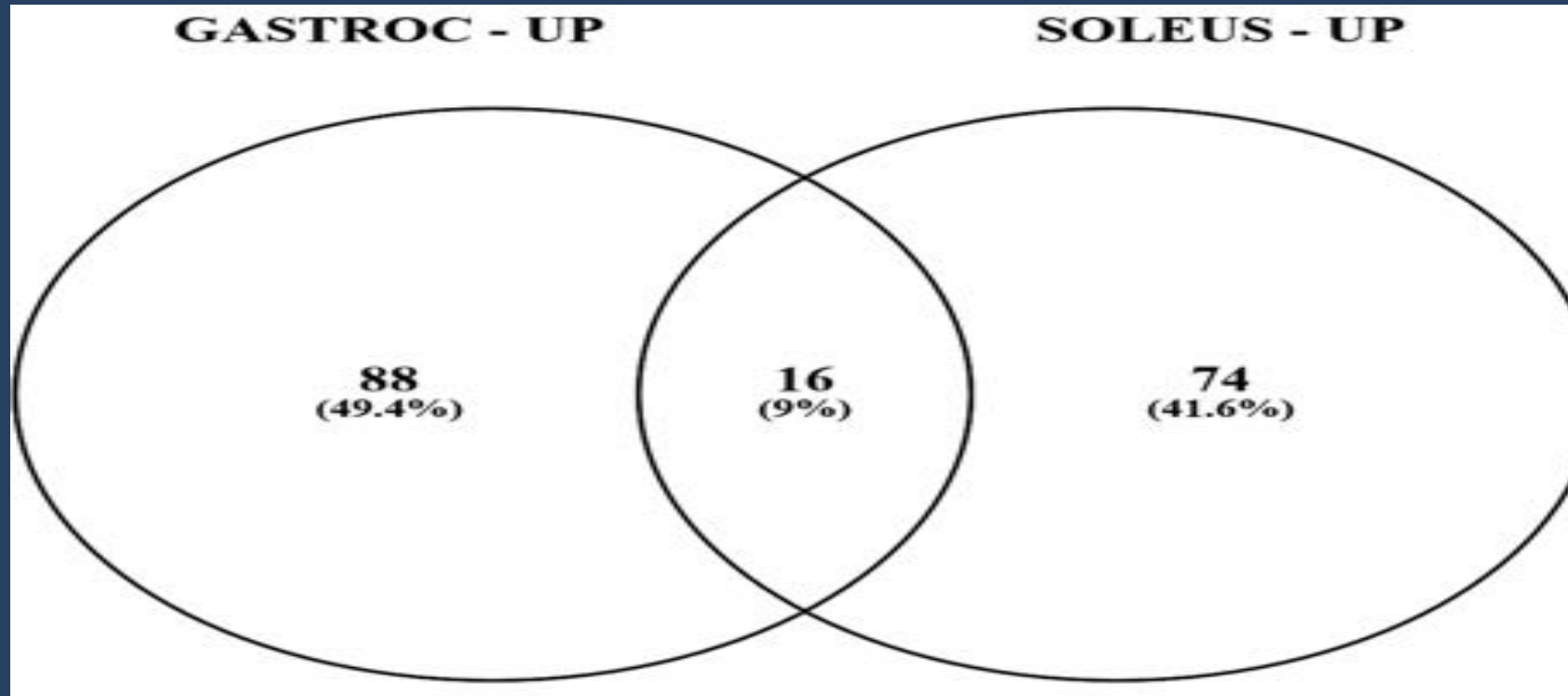


ORIGINAL ARTICLE

Sex differences in skeletal muscle revealed through fiber type, capillarity, and transcriptomics profiling in mice

Juliana O'Reilly¹ | Kikumi D. Ono-Moore² | Sree V. Chintapalli^{2,3} |
Jennifer M. Rutkowski^{4,5} | Todd Tolentino^{5,6} | K. C. Kent Lloyd^{5,6,7} |
I. Mark Olfert¹ | Sean H. Adams⁷

TRANSCRIPTS EXPRESSED IN FEMALES AT LEVELS 200% OF THE LEVEL IN MALES, IN BOTH MUSCLES



Xist
Akr1cl
Mrgprg
Slc39a12
Adrb3
Dhrs9

Ces2g
Car12
H2-Q10
AW551984
Fasn
Scg3

Greb1
Elovl6
Ngfr
Otoa

A 6-Minute Difference

Ever wonder how much faster (or slower) you'd run if you were the opposite sex?

Janet Furman Bowman may be the only runner in America who knows

Runners World

May 4, 2005

Janet's Story

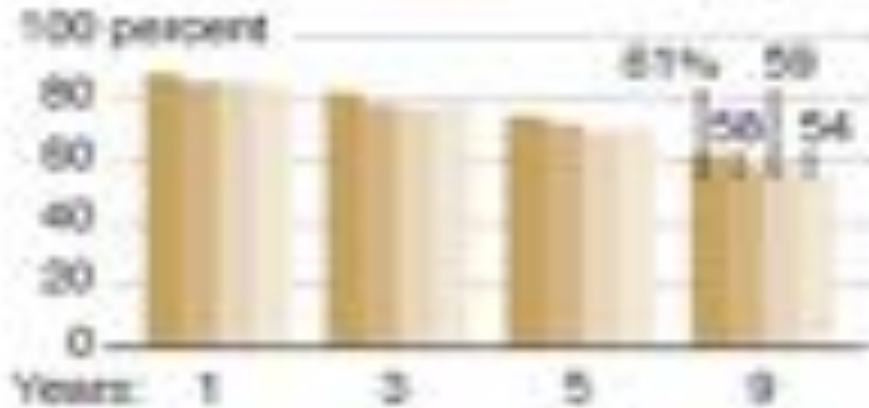
- Jim Furman, a 5'11", 148-pound middle-aged man in excellent physical shape, extremely fast runner.
- As Janet Furman, a 5'11", 148-pound middle-aged woman in excellent physical shape. When Janet sprints across the finish line- and checks her watch for her time, 23:27, she knows instantly how it compares to her PR for the 5-K: six minutes, 25 seconds slower, or more than two minutes per mile.

Sex And Trans.....Transplant

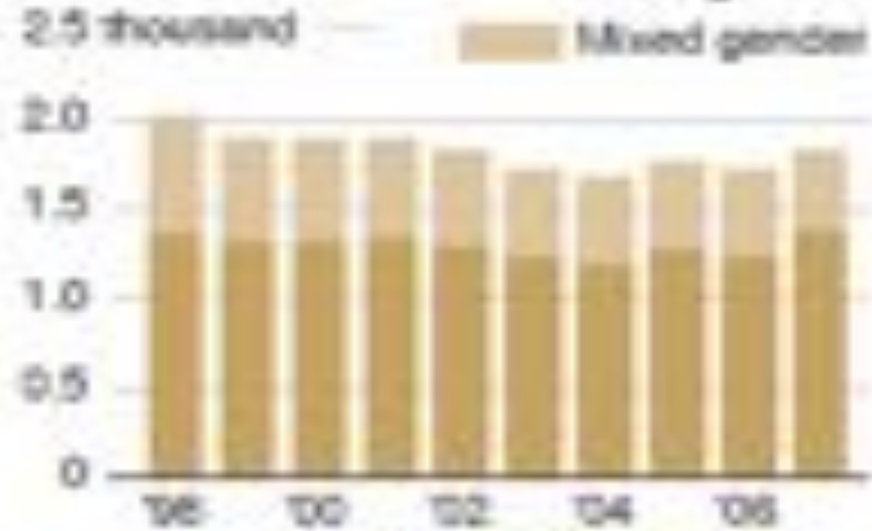
Matching donors improve survival odds

Survival rates increase if heart transplants are from donors of the same sex. Last year, 71 percent of recipients were of the same gender.

Heart transplant survival estimates



Annual transplants



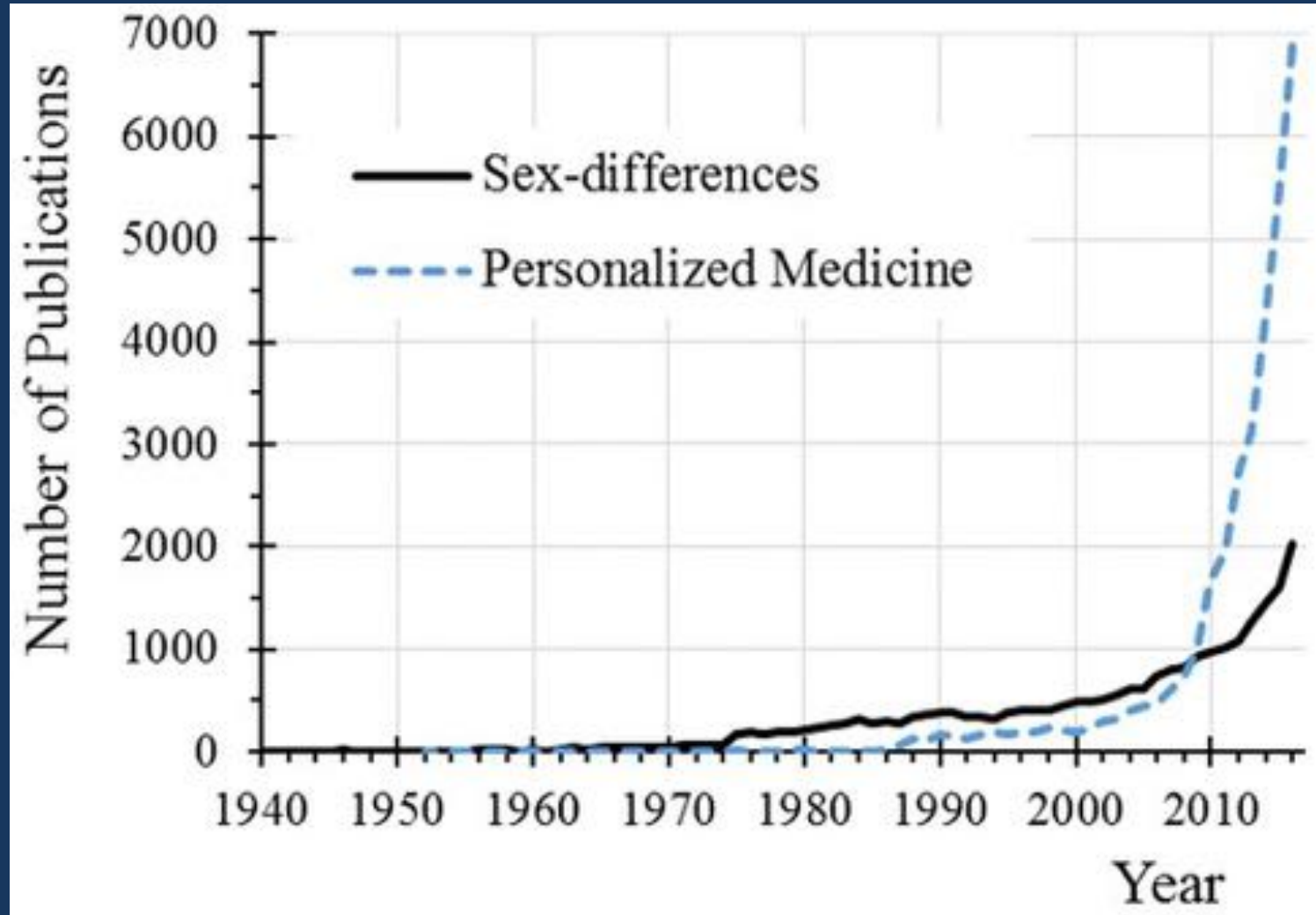
Summary of Our Findings

- Our preliminary data suggest transgender women who elected for bi-lateral orchiectomy had improved metabolic health when compared to those transgender women who retained their testes.
- Transgender women who retained their testes were stratified according to circulating T levels, those with the highest T also had the greatest level of hepatic steatosis and insulin resistance.

Is Health Influenced by *Sex?*



“Personalized” by Sex??



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Luciana Fatima Ph.D.

Aaron Frank

Mike Nelson Ph.D.
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Funding:

Distinguished Researcher Award

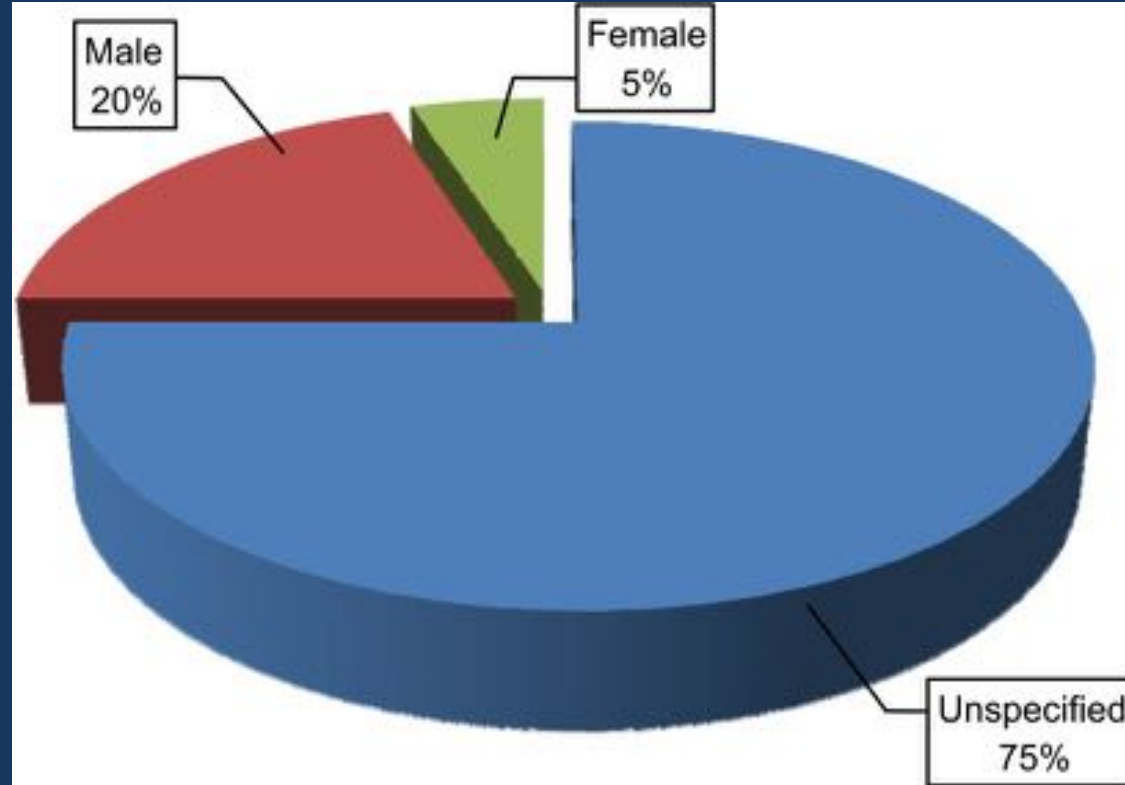
NIH: R01 DK073689

NIH: P01 088761-01

Society for Womens Health Foundation

Klarman Foundation

2001 U.S. Institute of Medicine Declared That Every Cell Has A Sex



Cell Sex Underreported In Medicine And Science

Males And Females Have Partially Different Genomes

- Male and female germ cells differentially imprint the genetic information to be transmitted to their progeny
- In females, the majority of the cells on one of the X chromosomes are silenced
- However, some genes on the inactive X chromosome are not silenced, leading to higher levels of their products in female cells
- The Y chromosome carries genes that are involved in basic cellular functions

X Chromosome Excluded From > 90% of GWAS

- Not 'genome wide association'
- 'Neutrome' wide association – virtually devoid of the X chromosome