

CARDIOVASCULAR DISEASE IN TRANSGENDER ADULTS:

Exploring Sex, Gender Identity and Risk

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DISCLOSURES

- Research Funding:
 - University of Colorado Center for Women's Health Research
 - NIH/Colorado Nutrition Obesity Research Center
 - University of Colorado Clinical and Translational Research Center
 - World Professional Association for Transgender Health
 - VA Geriatric Research, Education and Clinical Center
- Medications discussed are being used off-label
- Abbreviations
 - CVD = Cardiovascular disease
 - Trans = Transgender
 - GAHT = Gender-affirming hormone therapy

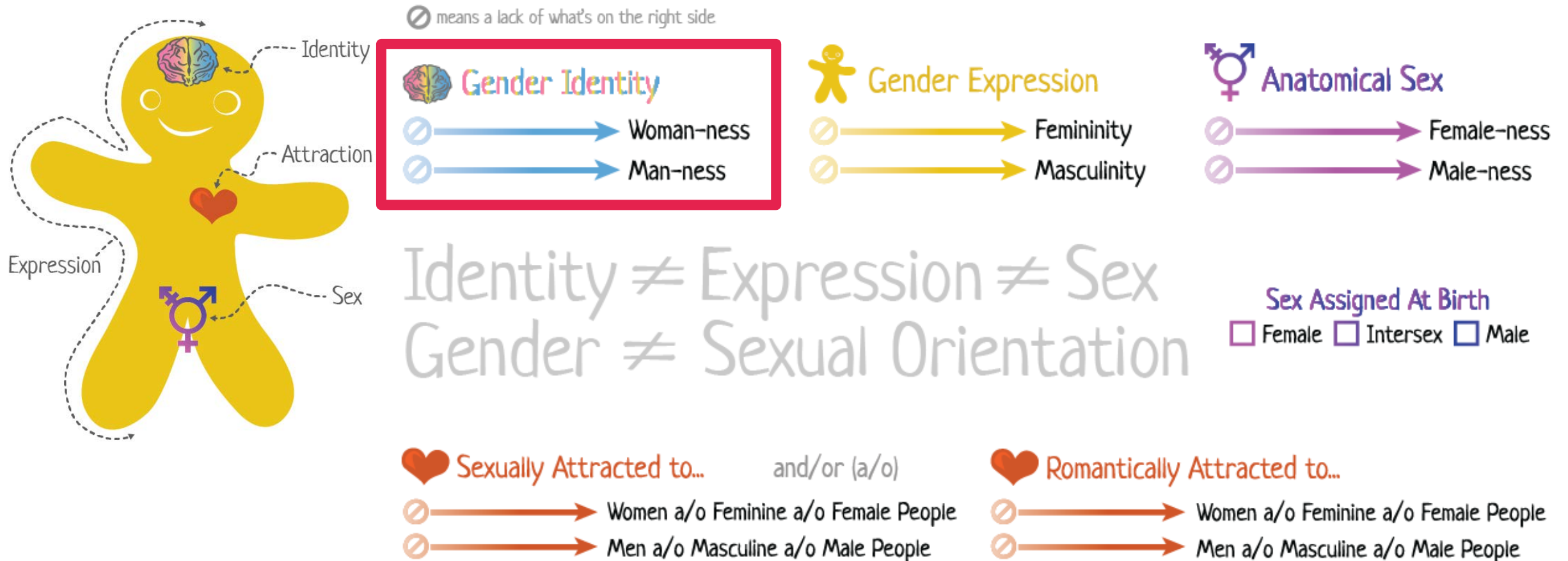


LEARNING OBJECTIVES

- Improve confidence in using trans-related terminology
- Summarize how estradiol and testosterone impact CVD risk in trans adults
- Assess CVD risk in trans adults

TERMINOLOGY

The Genderbread Person_{v4}



TERMINOLOGY

| Term | Definition | Notes |
|----------------------------|--|--|
| Cisgender (Cis) | Gender identity/expression align with the sex assigned at birth | DO NOT say “regular” or “real” |
| Transgender (Trans) | Gender identity/expression differ from the sex assigned at birth | DOES NOT require GAHT or surgery DO NOT use “transgendered” or “transgenders” Inclusive of gender non-binary |
| Gender non-binary | Outside the male/female binary, both or alternating male/female, neither male/female | May include gender-fluid, gender queer, pangender, polygender, agender |

Measuring the Health of an Invisible Population: Lessons from the Colorado Transgender Health Survey

Robin Christian, MD^{1,2}, Amy Anderson Mellies, MPH³, Alison Grace Bui, MPH³, Rita Lee, MD¹, Leo Kattari, MSW⁴, and Courtney Gray⁵

¹University of Colorado School of Medicine, Aurora, USA; ²Department of Obstetrics, Gynecology, and Women's Health Rutgers , New Jersey Medical School, Newark, NJ, USA; ³Colorado Department of Public Health and Environment, Denver, USA; ⁴One Colorado Education Fund, Denver, USA; ⁵GLBT Center of Colorado, Denver, USA.

- Having a **“transgender inclusive” provider** led to significantly **lower %** of:
 - Not having routine checkup in past year
 - Delayed care (fear of discrimination)
 - Currently depression
 - Suicide ideation
 - Suicide attempts
 - Feeling general health is fair/poor
 - # days physical health not good in past month
 - # days mental health not good in past month

GOALS OF GAHT

Binary approach

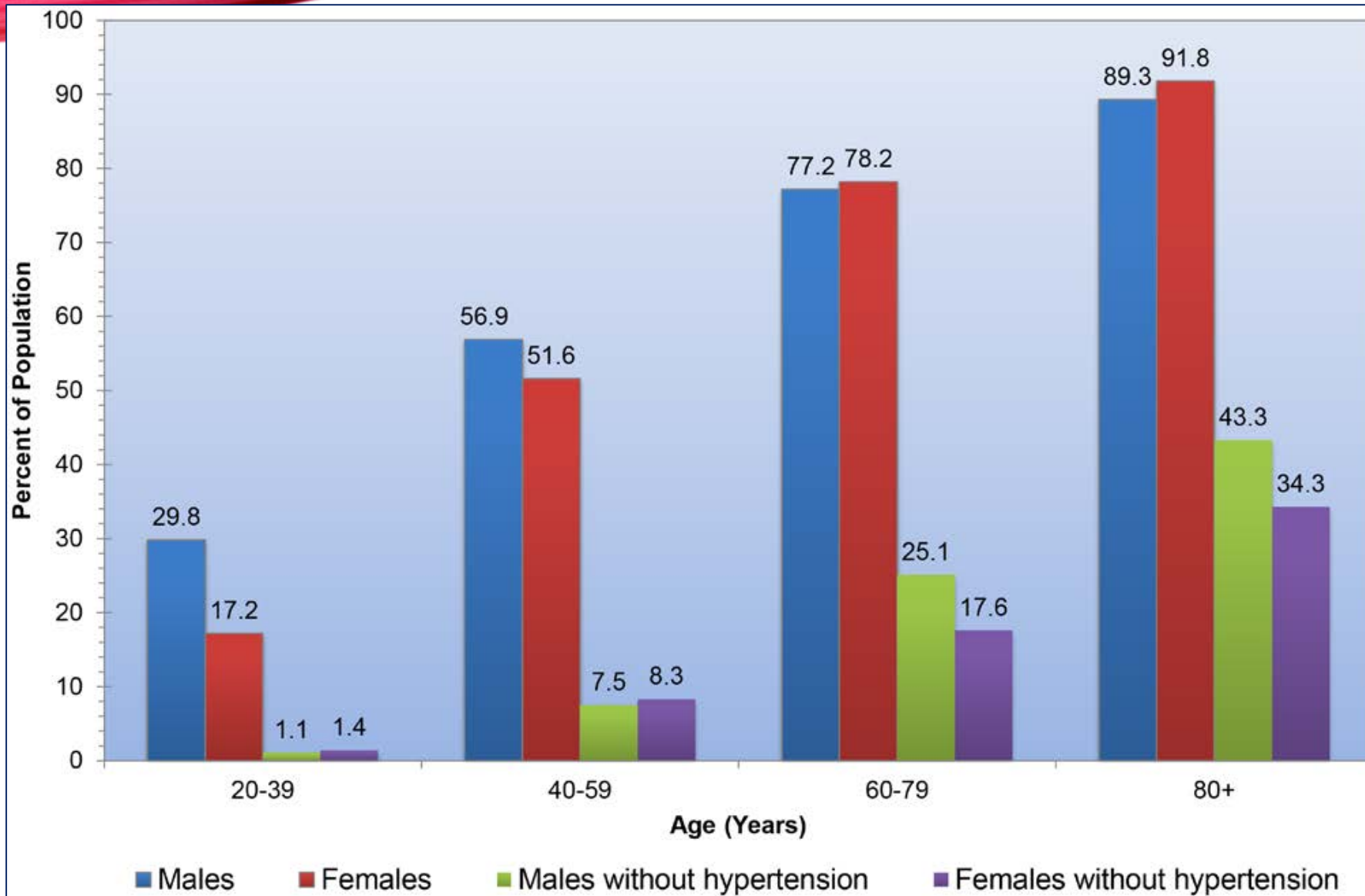
- **Trans women** (assigned male at birth, female gender identity)
 - Use **estrogen** (oral, parenteral, transdermal) plus **anti-androgen**
 - Achieve **female** secondary sex characteristics
 - Achieve **female** physiologic range serum estradiol and testosterone
- **Trans men** (assigned female at birth, male gender identity)
 - Use **testosterone** (parenteral, transdermal)
 - Achieve **male** secondary sex characteristics
 - Achieve **male** physiologic range serum estradiol and testosterone

Non-binary approach

- What are the goals?

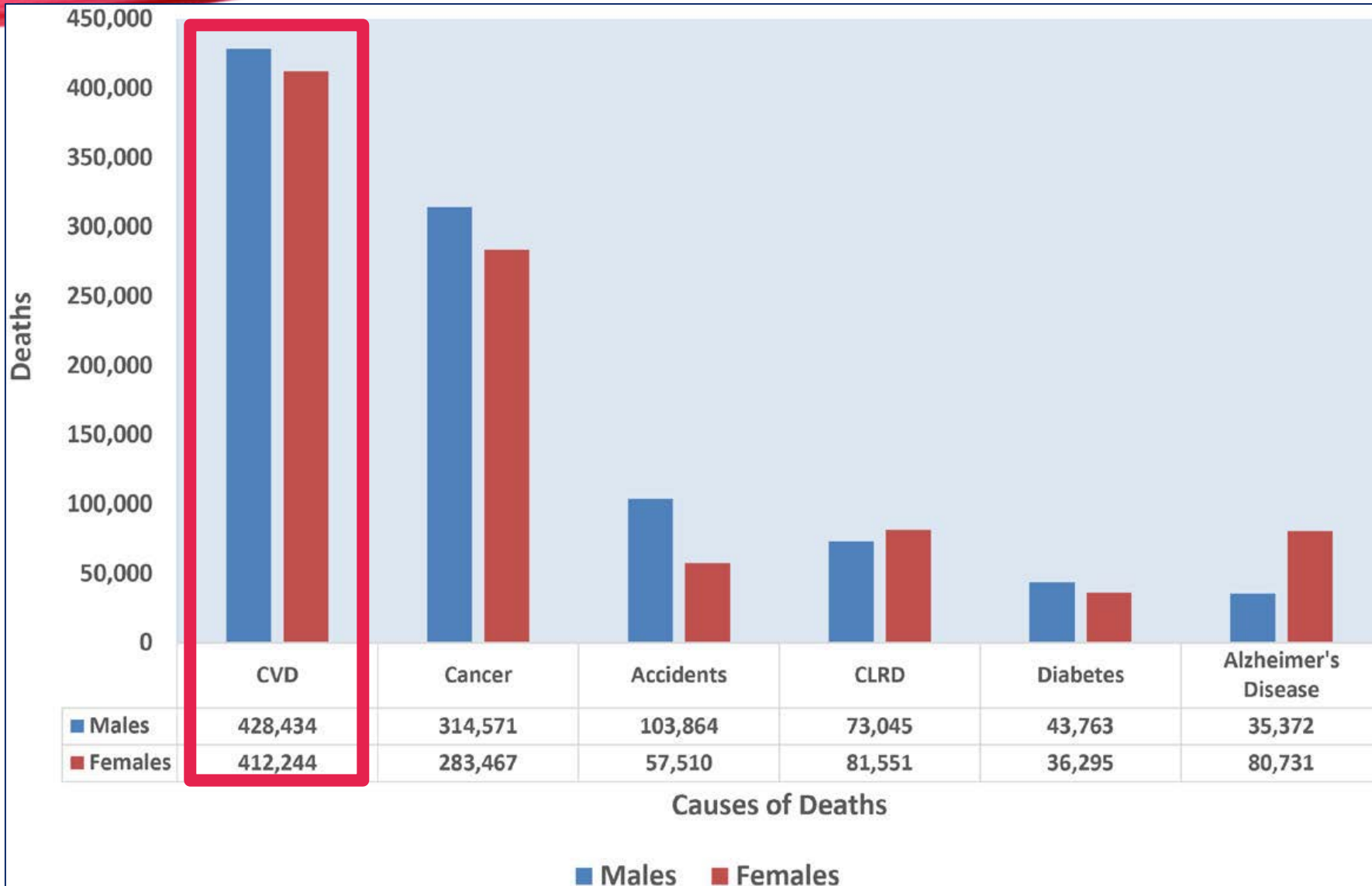
PREVALENCE OF CVD

**NHANES
2013-2016**

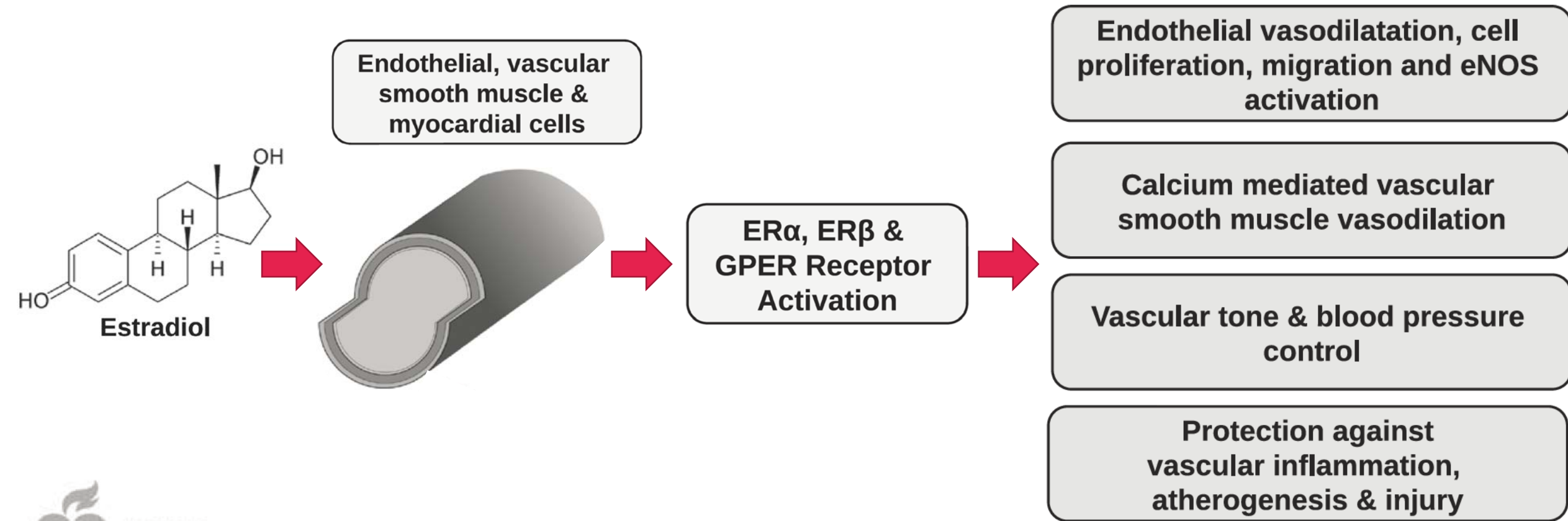


CAUSES OF DEATH

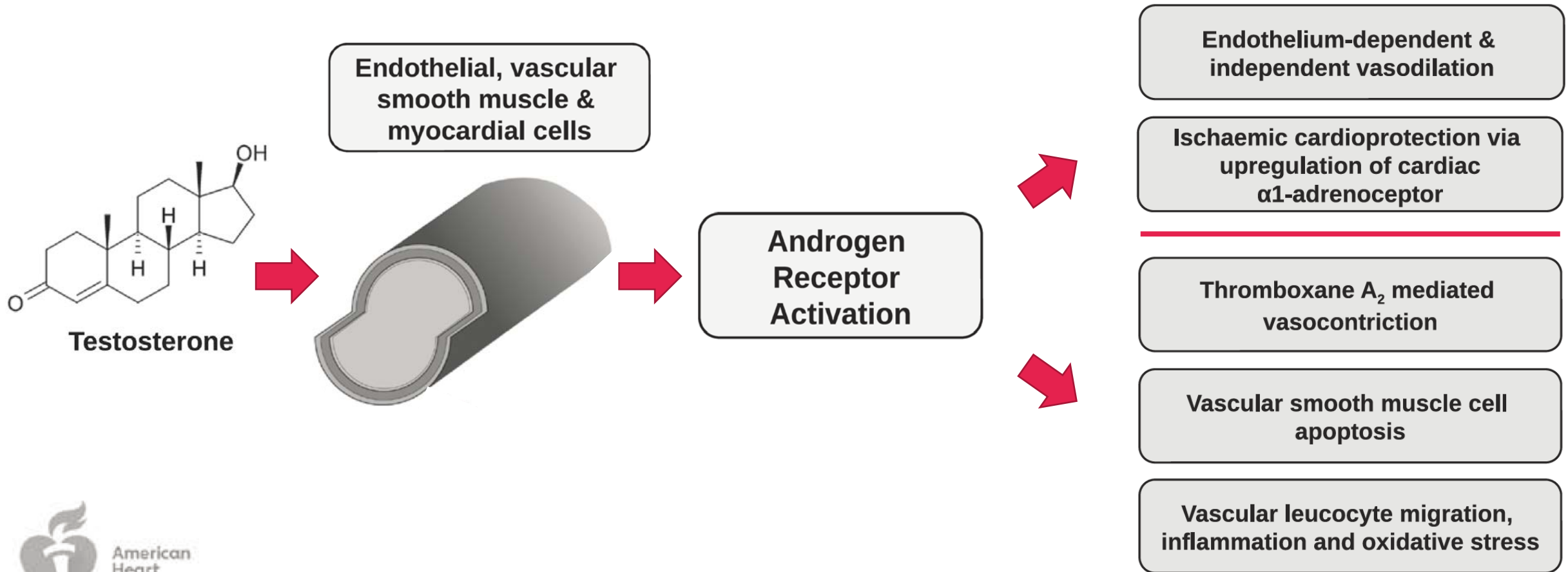
**U.S.
2016**



SEX STEROIDS AND THE CARDIOVASCULAR SYSTEM



SEX STEROIDS AND THE CARDIOVASCULAR SYSTEM



CLINICAL STUDY

A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones

Henk Asscheman¹, Erik J Giltay³, Jos A J Megens², W (Pim) de Ronde¹, Michael A A van Trotsenburg² and Louis J G Gooren¹

- 966 trans women: mean age 31±11 years, **86% gonadectomy**
- 365 trans men: mean age 26±8 years, **94% gonadectomy**
- **Smoking**: ~40% current; ~40% former/unknown
- BMI and rates of HTN, HLD, DM2 – Not reported
- Mean follow up 18.5 years
- Standardized mortality rates (SMR): observed cases vs. expected # of deaths in the general population based on sex assigned at birth

Trans Women

Trans Men

| Cause of death | Observed cases | SMR (95% CI) | Observed cases | SMR (95% CI) |
|--|----------------|-------------------|----------------|-------------------|
| Malignant neoplasm | 28 | 0.98 (0.88–1.08) | 5 | 0.99 (0.65–1.44) |
| Lung | 13 | 1.35 (1.14–1.58) | 1 | 1.06 (0.26–3.19) |
| Digestive tract | 3 | 0.42 (0.28–0.60) | 2 | 2.41 (0.90–5.18) |
| Hematological | 6 | 2.58 (1.97–3.30) | 1 | 2.86 (0.69–8.57) |
| Brain | 2 | 1.59 (0.95–2.46) | 0 | – |
| Other: kidney, melanoma, bone, and prostate in MtF. In FtM: leiomyosarcoma | 4 | 0.79 (0.57–1.07) | 1 | 0.77 (0.25–1.77) |
| Ischemic heart disease | 18 | 1.64 (1.43–1.87) | 1 | 1.19 (0.39–2.74) |
| Cerebrovascular accidents | 5 | 1.26 (0.93–1.64) | 0 | – |
| AIDS | 16 | 30.20 (26.0–34.7) | 0 | – |
| Endocrine/diabetes | 2 | 0.85 (0.41–1.32) | 0 | – |
| Respiratory system diseases | 4 | 0.85 (0.61–1.14) | 0 | – |
| Digestive system diseases | 3 | 1.01 (0.68–1.45) | 1 | 2.56 (0.62–7.69) |
| Genitourinary system disease (ESRD) | 1 | 1.21 (0.58–2.17) | 0 | – |
| Nervous system disease (MS) | 0 | | 1 | 3.57 (0.86–10.7) |
| External causes | 24 | 7.67 (6.84–8.56) | 2 | 2.22 (1.07–5.44) |
| Illicit drugs use | 5 | 13.20 (9.70–17.6) | 1 | 25.00 (6.00–32.5) |
| Suicide | 17 | 5.70 (4.93–6.54) | 1 | 2.22 (0.53–6.18) |
| Unknown/ill-defined symptoms | 21 | 4.00 (3.52–4.51) | 2 | 2.08 (0.69–4.79) |
| Total | 122 | 1.51 (1.47–1.55) | 12 | 1.12 (0.89–1.59) |

CVD RISK IN TRANS WOMEN

- **Systematic review and meta analysis¹**
 - 23 **mostly-European** “low-quality” studies
 - 3,231 trans women; mean age range **19-44** years; >80% gonadectomy
- Take home points:
 - E2 associated with ↑ triglycerides 32mg/dL (95% CI 4-60) at ≥24 mos (more w/ oral)
 - VTE 0-5%
 - Mortality 0-13% (of those reporting death, 17% CVD, 19% suicide)
 - Absolute rates were low
 - Long-term risks in older individuals are unknown
- **Blood pressure²**
 - Mean SBP ↑ 6-18 mmHg, DBP ↑ 3-6 mmHg
- **Bodyweight and composition³**
 - ↑ bodyweight 1-3 kg/yr
 - ↑ fat mass (2-4 kg) and ↓ lean mass (2-4 kg) in the first year



¹ Maraka S et al. *J Clin Endocrinol Metab.* 2017

² Irwig MS. *Rev Endocr Metab Disord.* 2018

³ Tangpricha V, den Heijer M. *Lancet Diabetes Endocrinol.* 2017

CVD RISK IN TRANS MEN

- **Systematic review and meta analysis¹**
 - 20 **mostly-European** “low-quality” studies
 - 1,500 trans men; mean age range **22-38** years; >80% gonadectomy
- Take home points:
 - T was associated with ↑ triglycerides 21mg/dL (95% CI 0.1-43) at ≥24 mos
 - Also ↑ LDL, ↓ HDL to a lesser extent
 - Insufficient data: MI, stroke, VTE, mortality
 - Long-term risks in older individuals are unknown
- **Blood pressure²**
 - Mean SBP ↑ 1-13 mmHg, DBP ↑ 1.5-4 mmHg
- **Bodyweight and composition³**
 - ↑ bodyweight 2.2-3.5 kg/yr
 - ↓ fat mass (2.3-4 kg) and ↑ lean mass (1.7-6.0 kg) in the first 1-2 years



¹ Maraka S et al. *J Clin Endocrinol Metab.* 2017

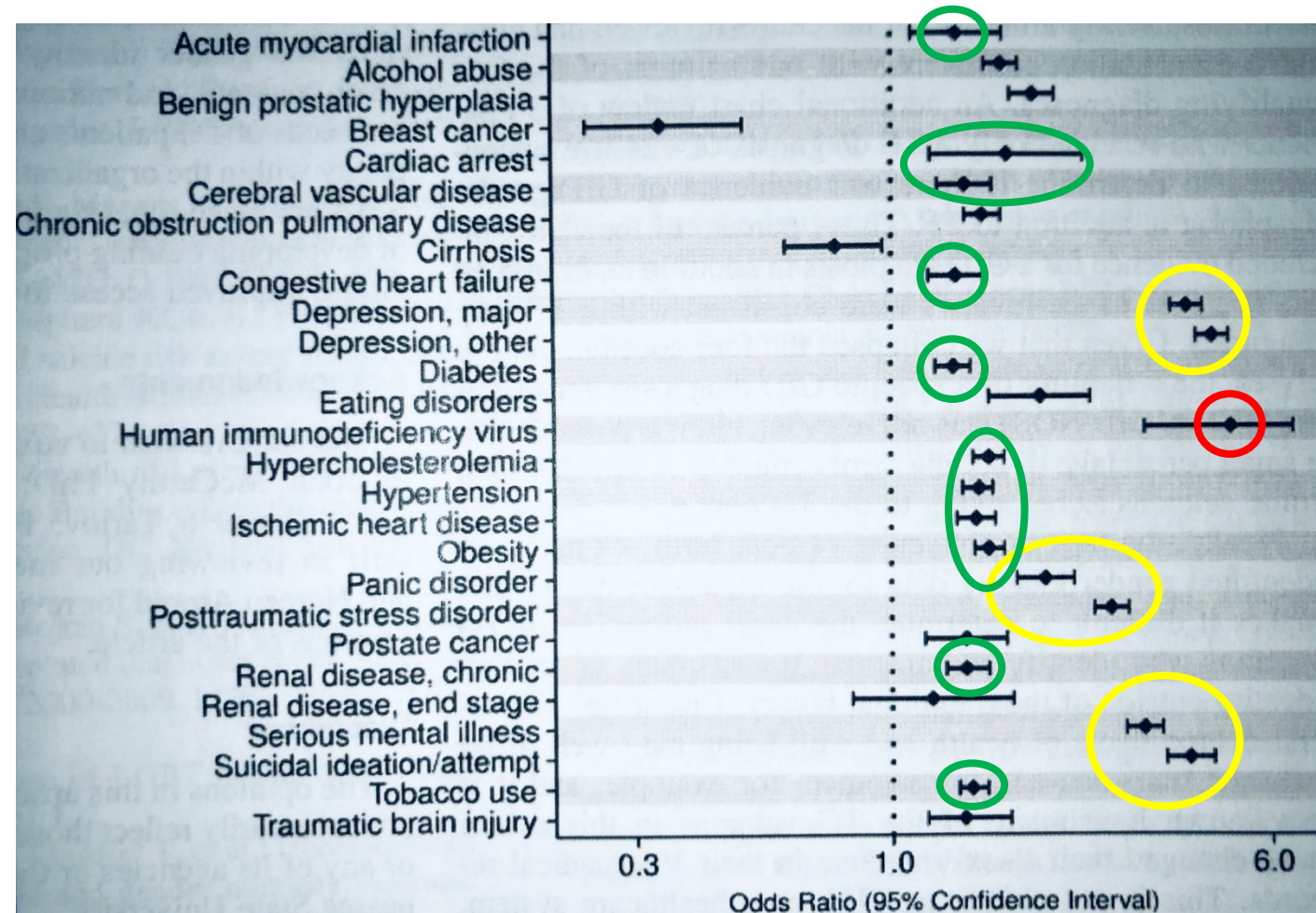
² Irwig MS. *Rev Endocr Metab Disord.* 2018

³ Irwig MS. *Lancet Diabetes Endocrinol.* 2017

U.S. COHORT: VETERANS

Lifetime mental health and medical illnesses

- Veterans Health Administration 1996-2013
- 5,135 trans veterans (ICD-9 codes)
- **69% were identified as “male-to-female”**
- **>25% were 65+ y/o**
- Matched to 15,405 non-trans controls



Health and Cardiometabolic Disease in Transgender Adults in the United States: Behavioral Risk Factor Surveillance System 2015

Natalie J. Nokoff,^{1,2} Sharon Scarbro,^{3,4,5} Elizabeth Juarez-Colunga,^{4,6}
Kerrie L. Moreau,^{7,8,9} and Allison Kempe^{1,2,4}

2a

FTM

OR LCI UCI P_value

| | | | | | |
|-----------------------|--|--|--|------|-----------------|
| Overweight/obese | | | | | |
| FTM vs Cis F | | | | 1.82 | 0.88 3.79 0.107 |
| FTM vs Cis M | | | | 0.96 | 0.46 2.00 0.92 |
| Hypertension | | | | | |
| FTM vs Cis F | | | | 1.23 | 0.59 2.56 0.58 |
| FTM vs Cis M | | | | 0.84 | 0.40 1.75 0.64 |
| Myocardial Infarction | | | | | |
| FTM vs Cis F | | | | 1.28 | 0.41 3.98 0.68 |
| FTM vs Cis M | | | | 0.48 | 0.16 1.51 0.21 |
| Angina/CHD | | | | | |
| FTM vs Cis F | | | | 2.27 | 0.93 5.54 0.070 |
| FTM vs Cis M | | | | 1.02 | 0.42 2.47 0.97 |
| Stroke | | | | | |
| FTM vs Cis F | | | | 1.23 | 0.48 3.11 0.67 |
| FTM vs Cis M | | | | 0.97 | 0.38 2.45 0.95 |
| Diabetes | | | | | |
| FTM vs Cis F | | | | 0.59 | 0.30 1.17 0.134 |
| FTM vs Cis M | | | | 0.43 | 0.22 0.86 0.017 |

0.1 1 10
Odds Ratio and 95% CL

2b

MTF

OR LCI UCI P_value

| | | | | | |
|-----------------------|--|--|--|------|-----------------|
| Overweight/obese | | | | | |
| MTF vs Cis M | | | | 0.93 | 0.58 1.48 0.76 |
| MTF vs Cis F | | | | 1.77 | 1.11 2.82 0.017 |
| Hypertension | | | | | |
| MTF vs Cis M | | | | 0.81 | 0.56 1.18 0.28 |
| MTF vs Cis F | | | | 1.19 | 0.82 1.73 0.37 |
| Myocardial Infarction | | | | | |
| MTF vs Cis M | | | | 1.09 | 0.59 2.03 0.78 |
| MTF vs Cis F | | | | 2.87 | 1.55 5.34 <.001 |
| Angina/CHD | | | | | |
| MTF vs Cis M | | | | 0.87 | 0.37 2.05 0.75 |
| MTF vs Cis F | | | | 1.95 | 0.83 4.59 0.128 |
| Stroke | | | | | |
| MTF vs Cis M | | | | 0.84 | 0.36 1.94 0.68 |
| MTF vs Cis F | | | | 1.06 | 0.46 2.46 0.89 |
| Diabetes | | | | | |
| MTF vs Cis M | | | | 1.21 | 0.68 2.18 0.52 |
| MTF vs Cis F | | | | 1.66 | 0.93 2.97 0.089 |

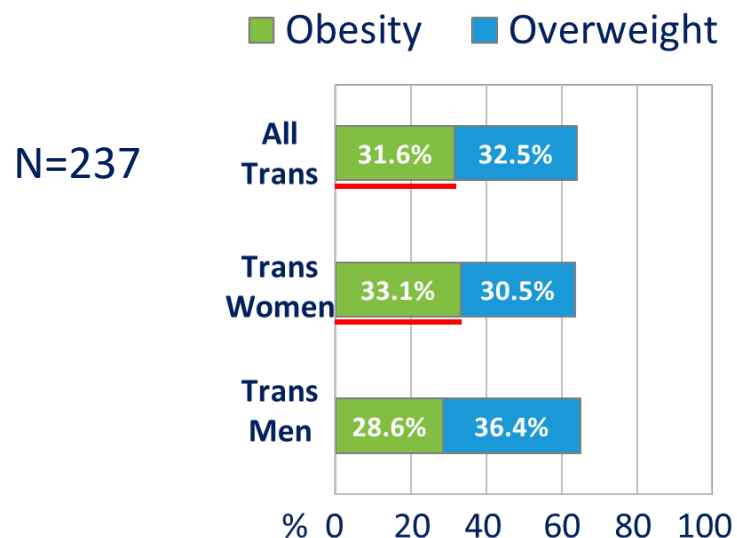
0.1 1 10
Odds Ratio and 95% CL



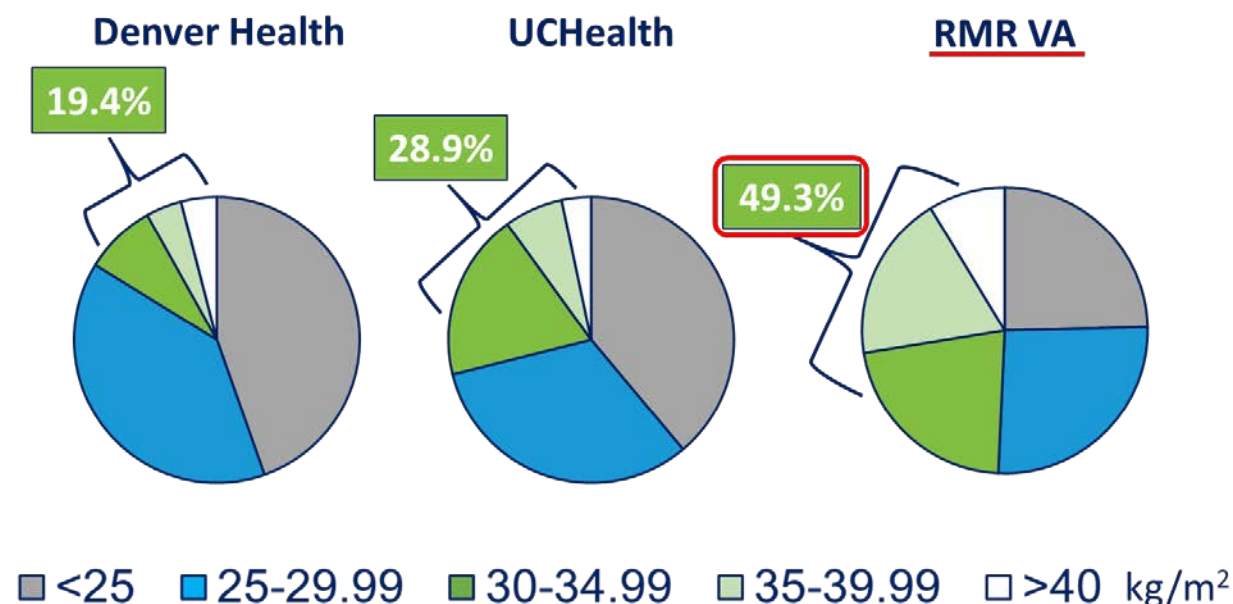
CO Dept of Public Health and Environment. 2014

TRANS OBESITY: LOCAL DATA

Overweight/Obesity: Transgender, All Hospitals



Overweight/Obesity: All Patients, Individual Hospitals



Presented at: Endocrine Society Annual Meeting. 2018

U.S. COHORT: **STRONG**

Annals of Internal Medicine

ORIGINAL RESEARCH

Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons

A Cohort Study

Darios Getahun, MD, PhD, MPH; Rebecca Nash, MPH; W. Dana Flanders, MD, MPH, DSc; Tisha C. Baird, MD; Tracy A. Becerra-Culqui, PhD; Lee Cromwell, MS; Enid Hunkeler, MA; Timothy L. Lash, PhD; Andrea Millman, MA; Virginia P. Quinn, PhD; Brandi Robinson, MPH; Douglas Roblin, PhD; Michael J. Silverberg, PhD; Joshua Safer, MD; Jennifer Slovis, MD; Vin Tangpricha, MD, PhD; and Michael Goodman, MD, MPH

Study of
TRansition,
Outcomes
and **G**ender

- Kaiser Northern & Southern CA, Georgia: 2006-2016

U.S. COHORT: STRONG

- **“Transfeminine” cohort: 2,842**

- Non-Hispanic whites: 54%
- >45 yrs old: 36%
- Non-current smokers: 85%
- Overweight/Obesity: 52%
- Orchiectomy: 1.5%

- **“Transmasculine” cohort: 2,118**

- Non-Hispanic whites: 60%
- >45 yrs old: 15.7%
- Non-current smokers: 82%
- Overweight/Obesity: 57%
- Oophorectomy: 11%

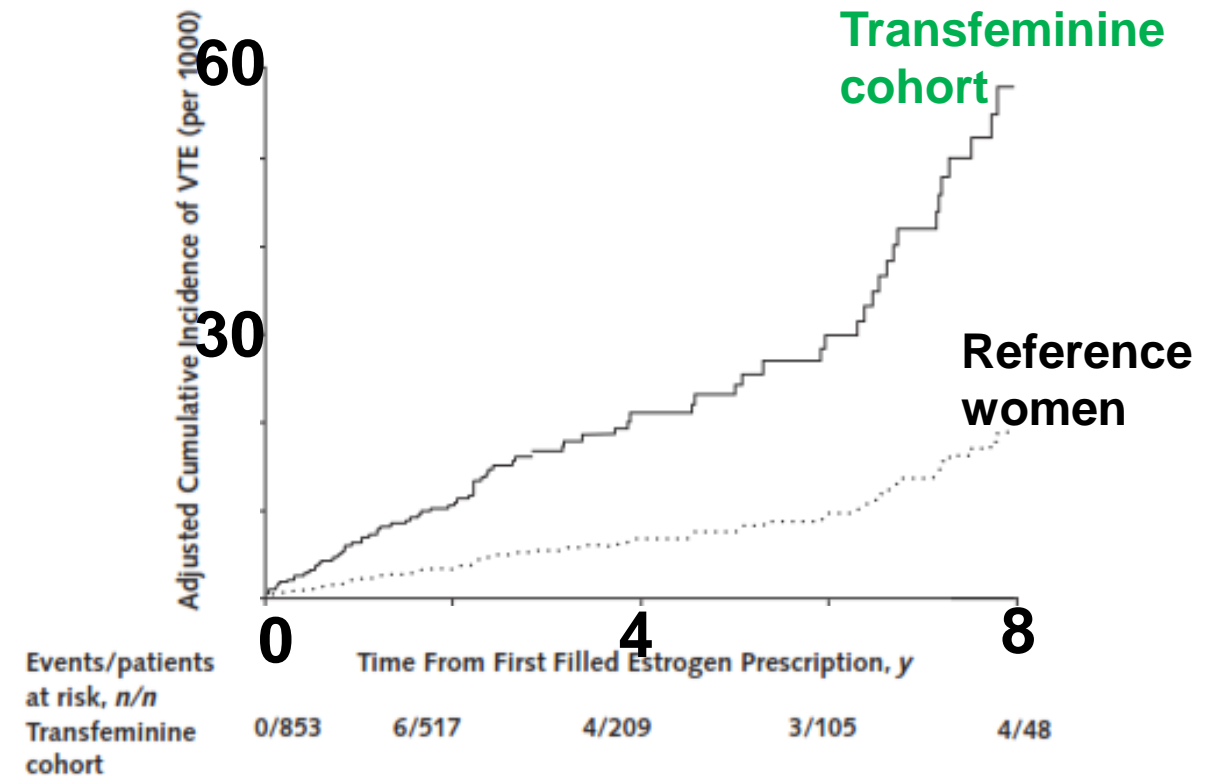
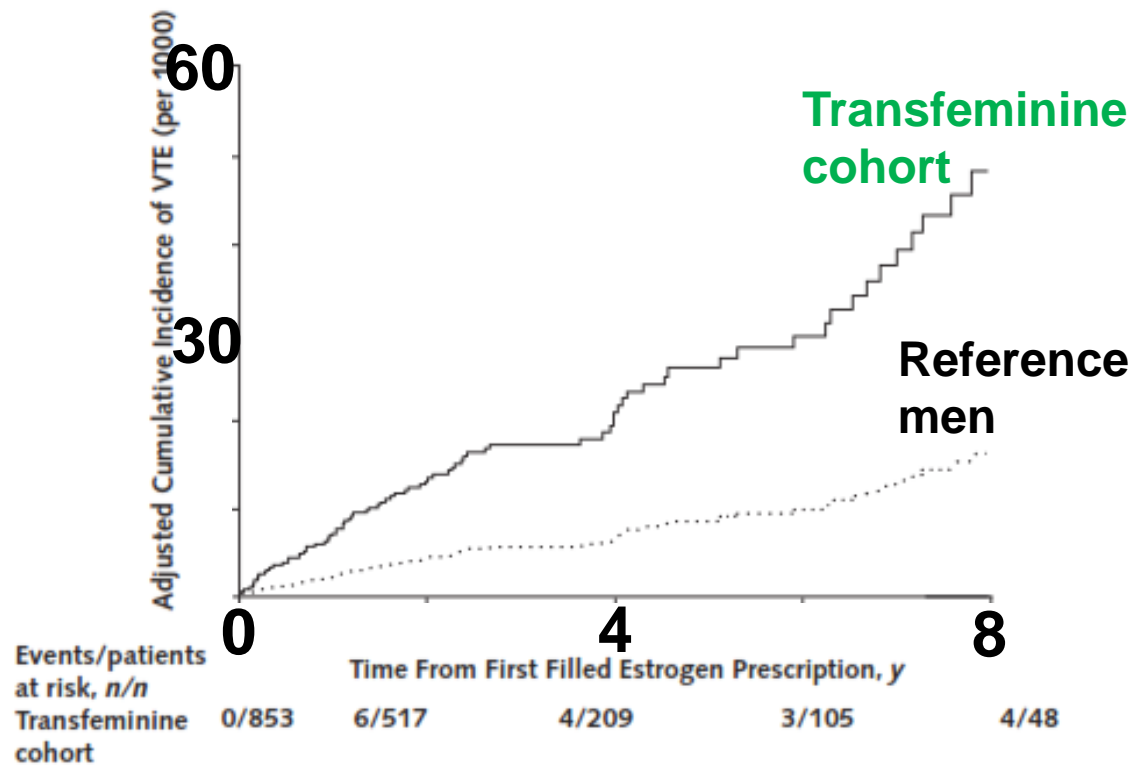
- *Reference men: 27,906*
- *Reference women: 27,968*

- *Reference men: 20,780*
- *Reference women: 20,807*

Transfeminine cohort who initiated estrogen therapy during the study period

X-axis: Years from first filled estrogen prescription

Y-axis: Adjusted cumulative incidence of **VTE** (ischemic stroke similar)



U.S. COHORT: STRONG

Table 3. Incidence Rates and Adjusted HRs for ACVEs Among Transmasculine Cohort Members Compared With Matched Reference Cohorts From KPNC, KPSC, and KPGA, 2006-2016

| Cohort and Event of Interest | Adjusted HR (95% CI)* | |
|--|-----------------------|------------------------|
| | Versus Reference Men | Versus Reference Women |
| Transmasculine overall cohort (n = 2118) | | |
| VTE | 1.6 (0.9-2.9) | 1.1 (0.6-2.1) |
| Ischemic stroke | 1.1 (0.6-2.0) | 1.3 (0.7-2.5) |
| Myocardial infarction | 0.7 (0.3-1.8) | 1.3 (0.5-3.9) |

CVD RISK SUMMARY

| Condition | Effect of GHT | | Strength of Evidence* |
|-------------------------|---------------------|-------------------|-----------------------|
| | Transgender Females | Transgender Males | |
| Ischemic heart disease | ↑↔ | ↔ | B-NR |
| Cerebrovascular disease | ↑ | ↔ | B-NR |
| Blood pressure | ↑↔ | ↑↔ | B-NR |
| Venous thromboembolism | ↑ | ↔ | B-NR |
| Lipids (HDL) | ↔ | ↓ | B-NR |
| Diabetes mellitus | ↔ | ↔ | B-NR |

* B-NR (nonrandomized) =

- 1) Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- 2) Meta-analyses of such studies

BUT...NEWEST NEWS: AMSTERDAM COHORT

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

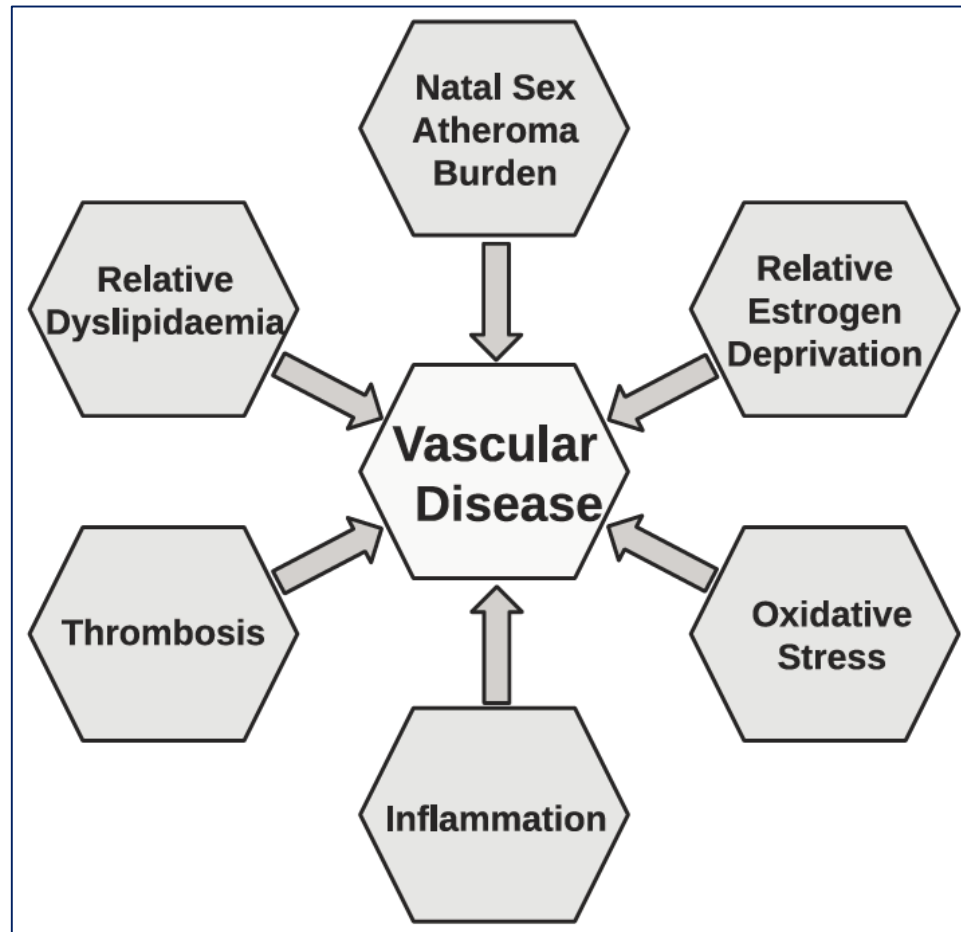
| Acute Cardiovascular Events | OCs (IR)* | Using Women as Reference | | Using Men as Reference | |
|-----------------------------|-----------|--------------------------|-------------------|------------------------|-------------------|
| | | ECs | SIR (95% CI) | ECs | SIR (95% CI) |
| Transwomen | | | | | |
| 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 (320) | 13.22 | 5.52 (4.36–6.90)† | 16.04 | 4.55 (3.59–5.69)† |
| Transmen | | | | | |
| Stroke | 6 (55) | 3.49 | 1.72 (0.70–3.58) | 4.10 | 1.46 (0.59–3.04) |
| 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) | 5.56 | 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.

TRANS WOMEN AND INCREASED CVD RISK



CVD RISK FACTOR SCREENING IN TRANS ADULTS

Dr. Iwamoto—Do we
need special CVD
screening considerations
in trans adults?

At this point, we
don't know. We
need more data!

- Future:
 - What are the underlying mechanisms for increased CVD risk in trans adults?
 - Different screening tests?
 - Screen earlier?
 - More aggressive treatment of CVD risk factors than in healthy young adults?
 - Trans-sensitive behavioral modification strategies?

MANAGEMENT CONSIDERATIONS RE: CVD RISK

- **Trans women**

- Estradiol tabs are cheapest
 - *Avoid ethinyl estradiol (increased VTE risk)*
 - *Avoid conjugated equine estrogens (can't reliably measure estradiol level)*
- Estradiol patch (starting/switching to) – If age >40-50 yrs, smoking, h/o blood clot, migraines, hypertriglyceridemia, hormone-sensitive cancer, significant CVD risk
- Discuss expectations of weight gain and behavioral modification (diet/exercise) early

- **Trans men**

- Injections are cheapest
- IM/SC routes have similar efficacy (but *anecdotally* SC may reduce peak/trough sx's)
- Testosterone patch/gel (starting/switching to) – If significant peak/trough sx's, polycythemia, smoking, older age
 - But may have harder time suppressing breakthrough bleeding



Kerrie Moreau, PhD



Marc-Andre Cornier, MD



Micol Rothman, MD



Margaret Wierman, MD

OUR RESEARCH

- Cross-sectional studies
 - Trans women (COMIRB #18-2558)
 - Trans men (COMIRB #19-2323)
- **Older age (50-75 yrs) vs. younger age (18-40 yrs)**
- GAHT ≥ 1 , pre-gonadectomy
- Primary outcome:
 - Brachial artery flow-mediated dilation
- Secondary outcomes:
 - Vascular endothelial cell oxidative stress/inflammation
 - Carotid artery stiffness and IMT
 - Transcranial Doppler
 - Lipids, BMI, physical activity, appetite
 - D-dimer



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



Colorado Clinical and Translational
Sciences Institute (CCTSI)
UNIVERSITY OF COLORADO DENVER | ANSCHUTZ MEDICAL CAMPUS



U.S. Department of Veterans Affairs

Veterans Health Administration
Geriatric Research, Education, and Clinical Centers



Marnie Janson, PharmD



Margaret Wierman, MD

OUR RESEARCH

- Retrospective chart review (COMIRB #19-2171)
- Effects of estrogen formulations on CVD risk in older vs. younger trans women
- Primary outcomes:
 - Rates of stroke and VTE
- Secondary outcomes:
 - Rates of PE and MI
 - Rates of tobacco smoking
 - Pre-post differences in lipids, BP, DM2, BMI

VA



U.S. Department of Veterans Affairs

Veterans Health Administration

Geriatric Research, Education, and Clinical Centers



Stuart Lind, MD



Micol Rothman, MD



David Saxon, MD

OUR RESEARCH



- Prospective study (COMIRB #20-0104)
- Effects of estrogen plus spironolactone on biomarkers of coagulation and thrombosis in trans women
- Baseline, 6 months
- Co-primary outcomes
 - D-dimer
 - vWF
 - Factor VIII

UCHEALTH INTEGRATED TRANSGENDER PROGRAM



**UCHealth Integrated Transgender
Program - Anschutz Medical
Campus**

Location

Anschutz Outpatient Pavilion
1635 Aurora Court, 6th Floor
Aurora, CO 80045

Phone [720.848.2650](tel:720.848.2650)

[See Transgender Health specialists](#)

**Clinic contact:
Keily Fisher**

keily.fisher@uchealth.org

Referral:
Adult
Endocrinology
F64.9
Gender Dysphoria





LEARNING OBJECTIVES

- Improve confidence in using trans-related terminology
- Summarize how estradiol and testosterone impact CVD risk in trans adults
- Assess CVD risk in trans adults

THANK YOU / QUESTIONS



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 - <https://www.genderbread.org/resource/genderbread-person-v4-0>
 - Colorado Department of Public Health & Environment: <https://drive.google.com/file/d/0B2nM-3jK5N8pbUpLdEg1Sk1JMIk/view>
 - UCHealth Integrated Transgender Program: <https://www.uchealth.org/services/diabetes-endocrinology-care/uchealth-integrated-transgender-program/>