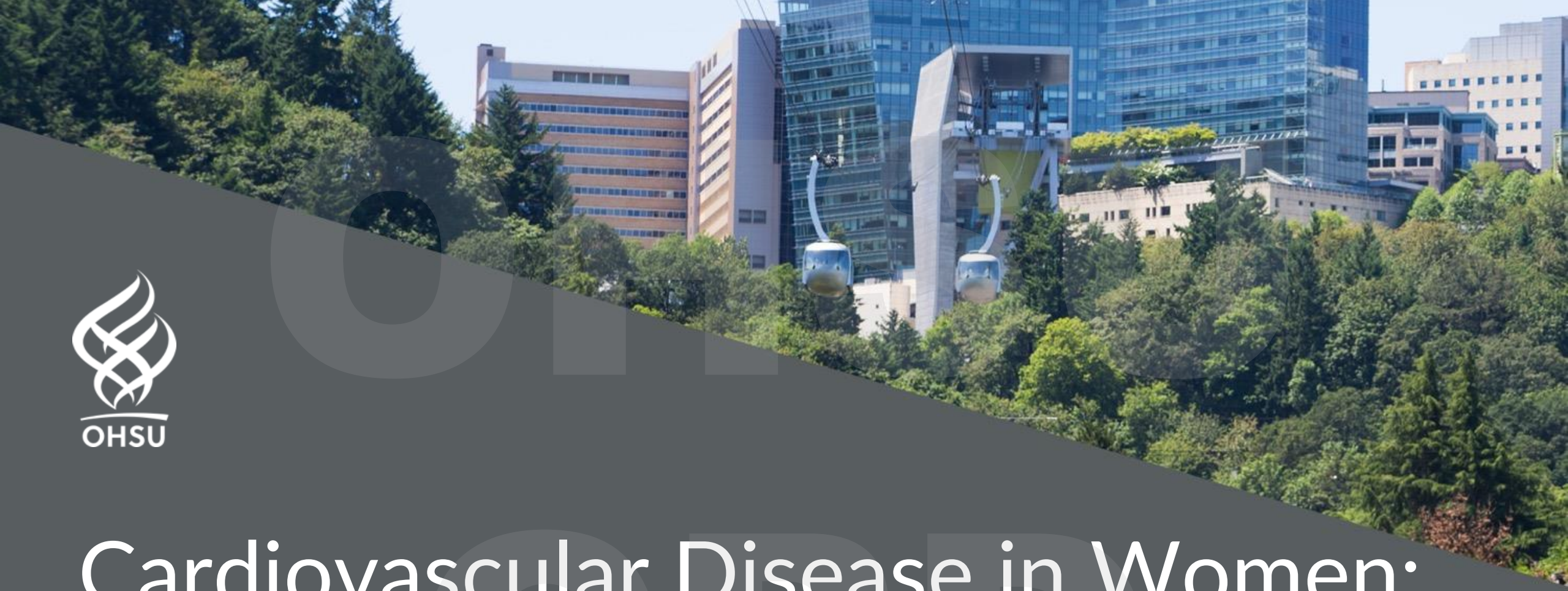

Cardiovascular Disease in Women: Unique Considerations

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4/26/2024

Objectives

01

Review the prevalence of cardiovascular disease in women

02

Discuss gender differences and risk factors specific to women

03

Discuss CVD manifestations that are more common in women

04

Review opportunities for prevention

Prevalence, morbidity, and mortality of CVD in women

Prevalence of CVD in women in the US

- ~60 million (45%) of women over the age of 20 have some form of CVD
- ~56 million (44%) women have HTN (BP ≥130/80 mmHg) or are taking antihypertensives
  - ~1 in 5 women of reproductive age
  - Black women are nearly 60% more likely to have high BP than White women

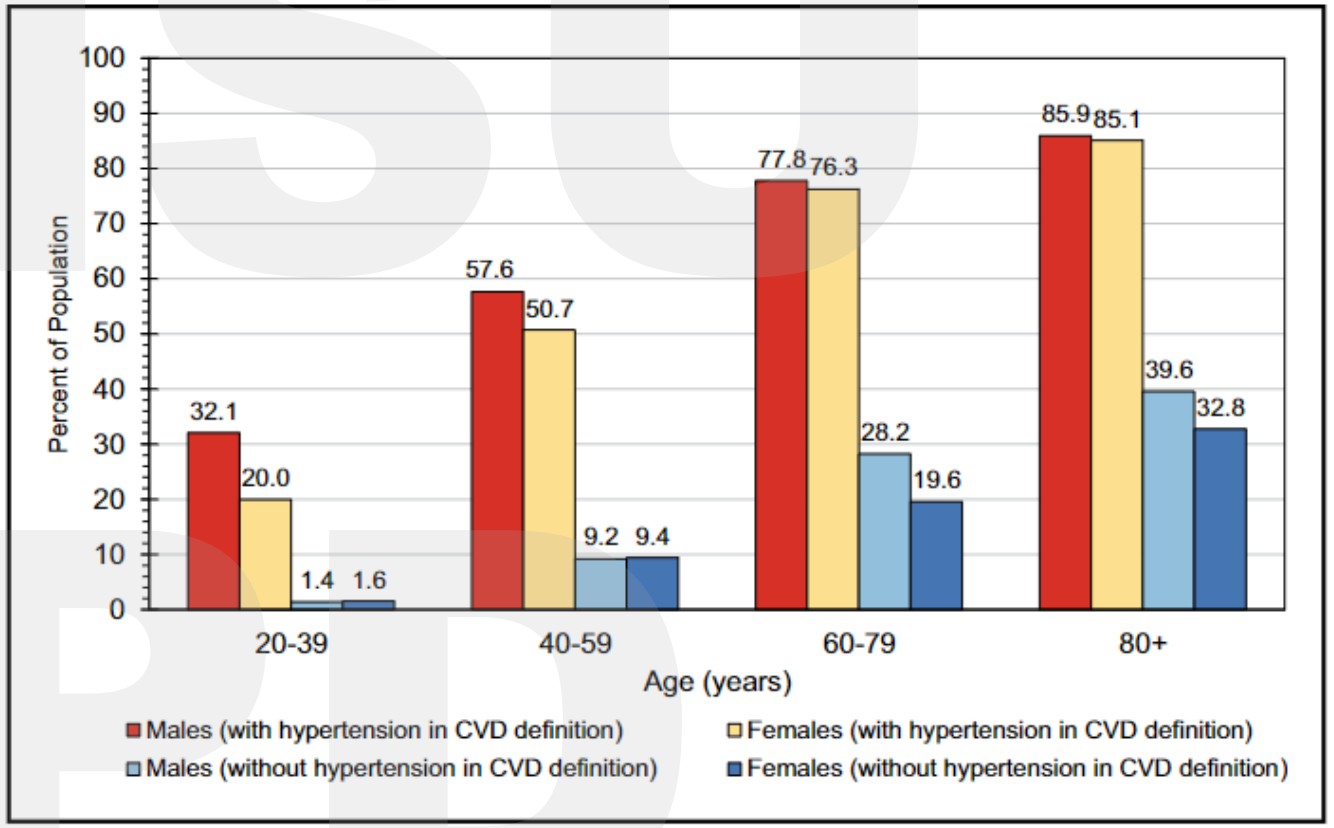
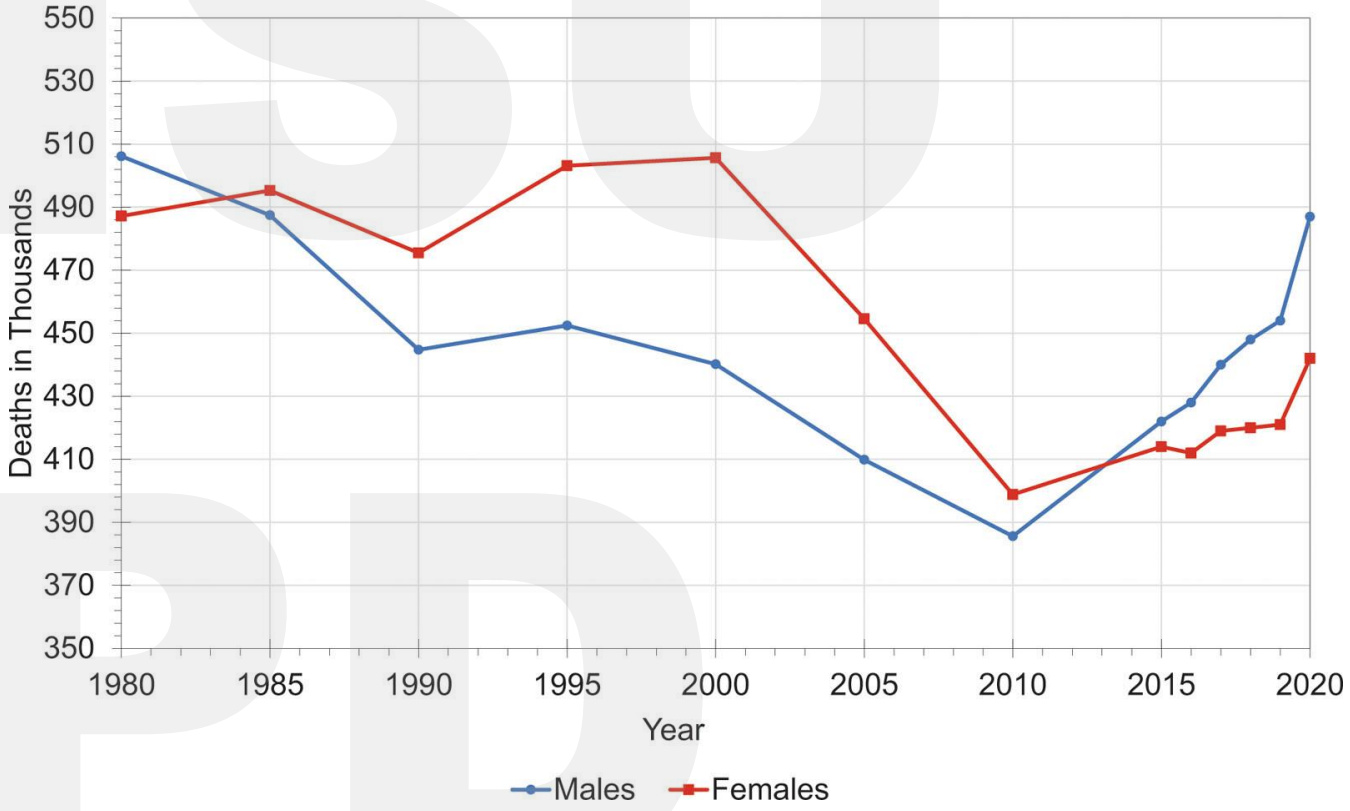


Chart 14-1. Prevalence of CVD in US adults ≥20 years of age by age and sex (NHANES, 2017–2020).
These data include CHD, HF, stroke, and with and without hypertension.

Tsao et al. Circulation. 2023;147:e93–e621.

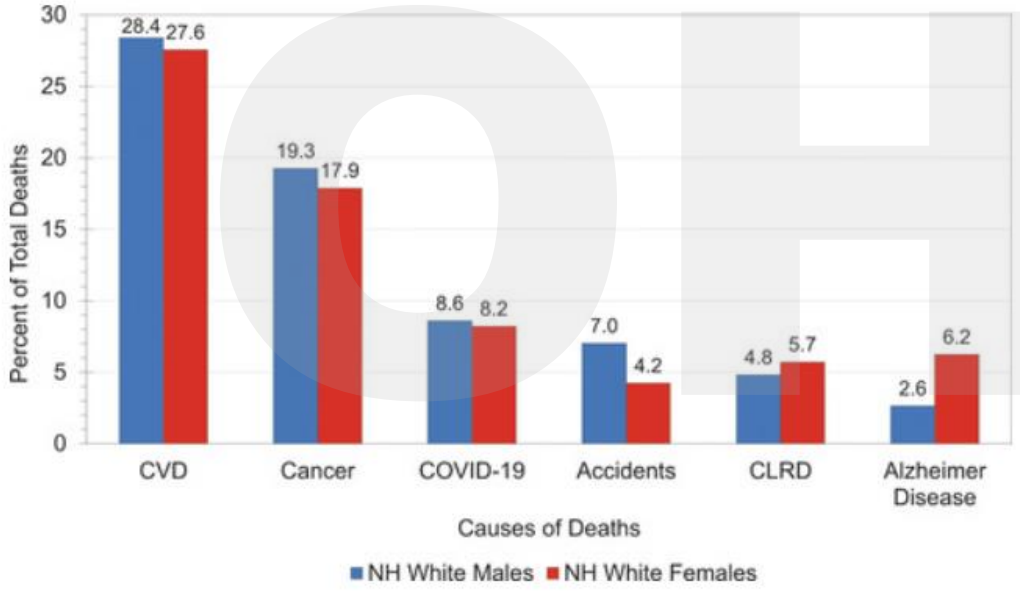
CVD mortality

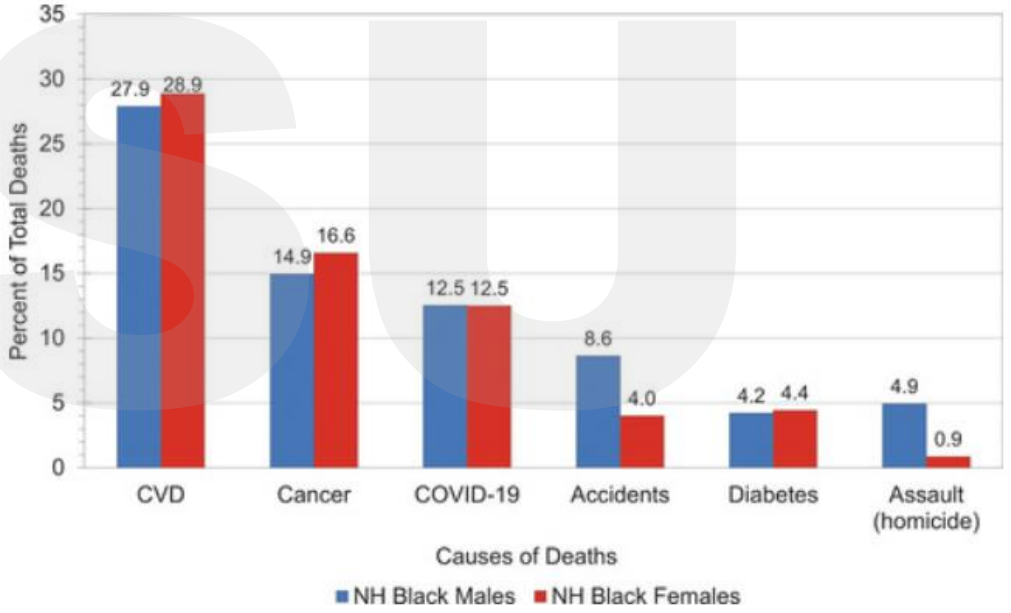
- CVD remains the leading cause of mortality and morbidity in women
  - Higher than all forms of cancer combined
  - In 2020, it was responsible for the deaths of 441,532 women—or about 1 in every 3 female deaths
- Only about half (56%) of US women recognize that heart disease is their number 1 killer

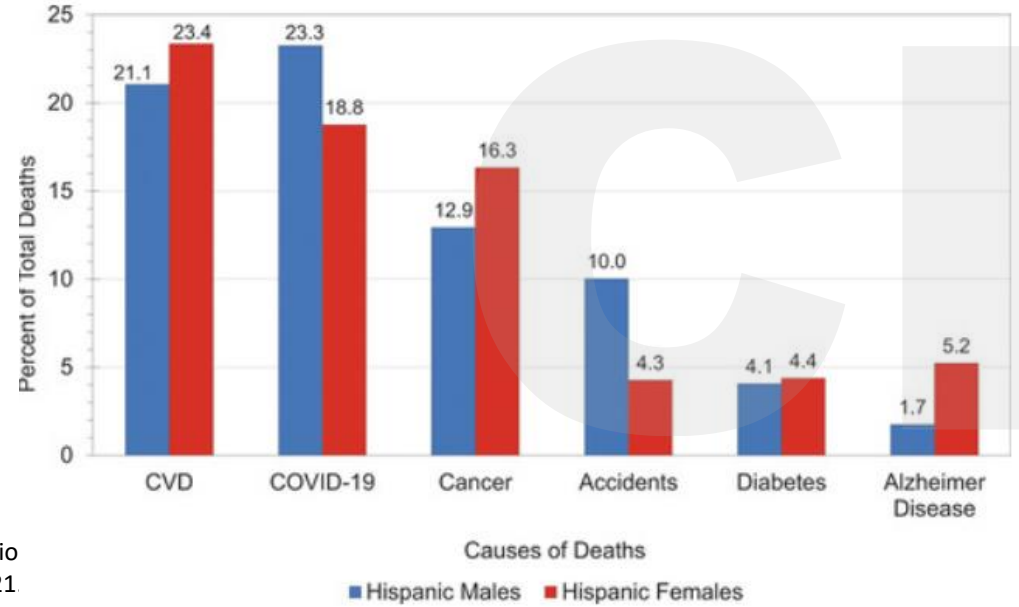


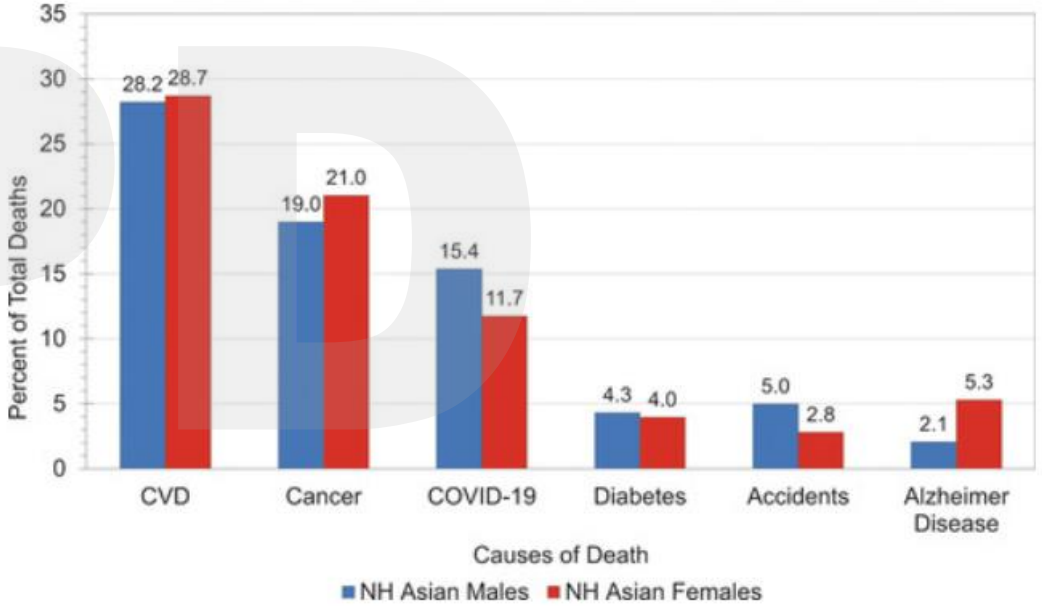
Tsao et al. Circulation. 2023;147:e93–e621.

CVD and other causes of death in the US in 2020



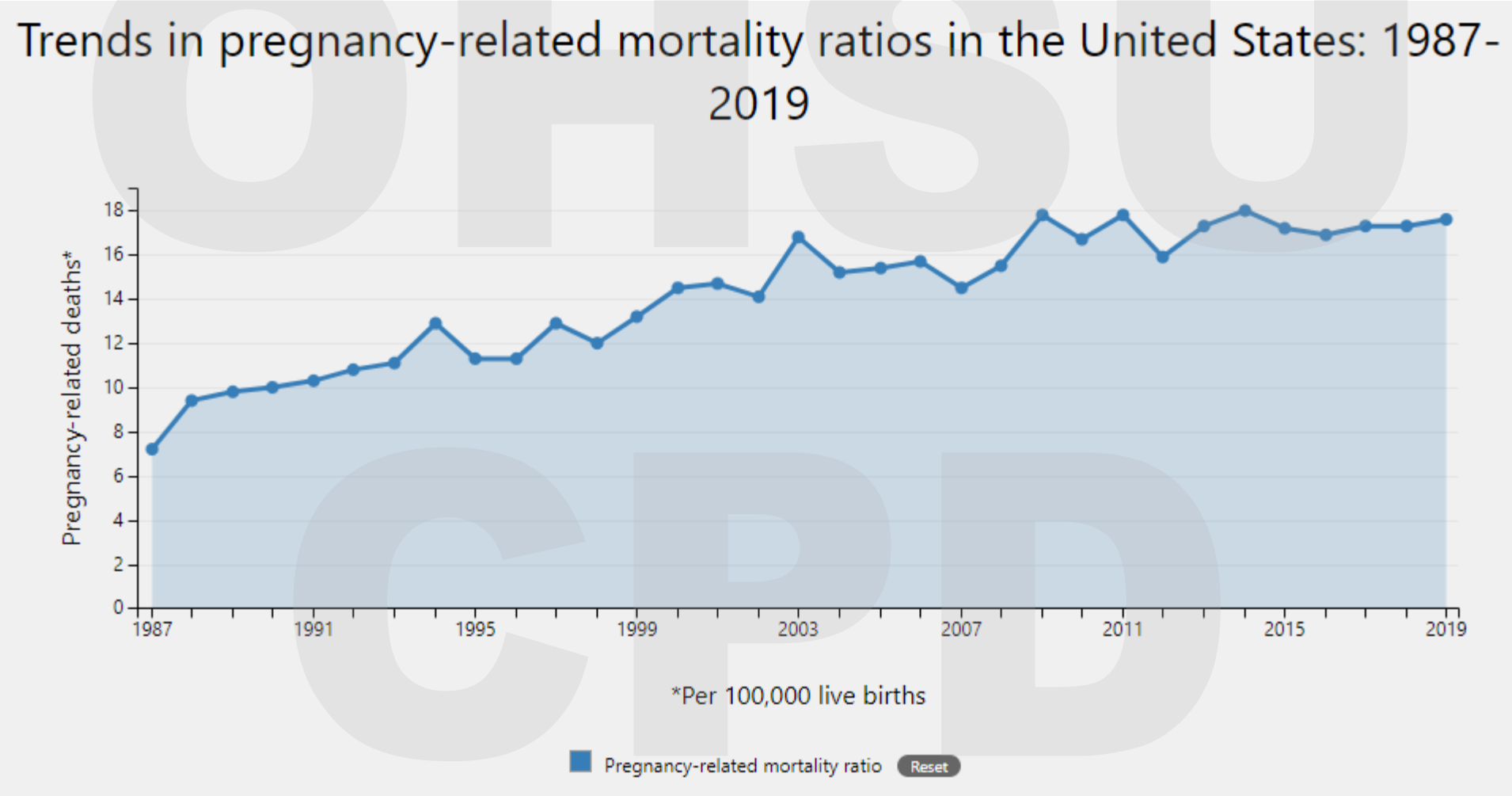






Tsao et al. Circulatio
2023;147:e93–e621

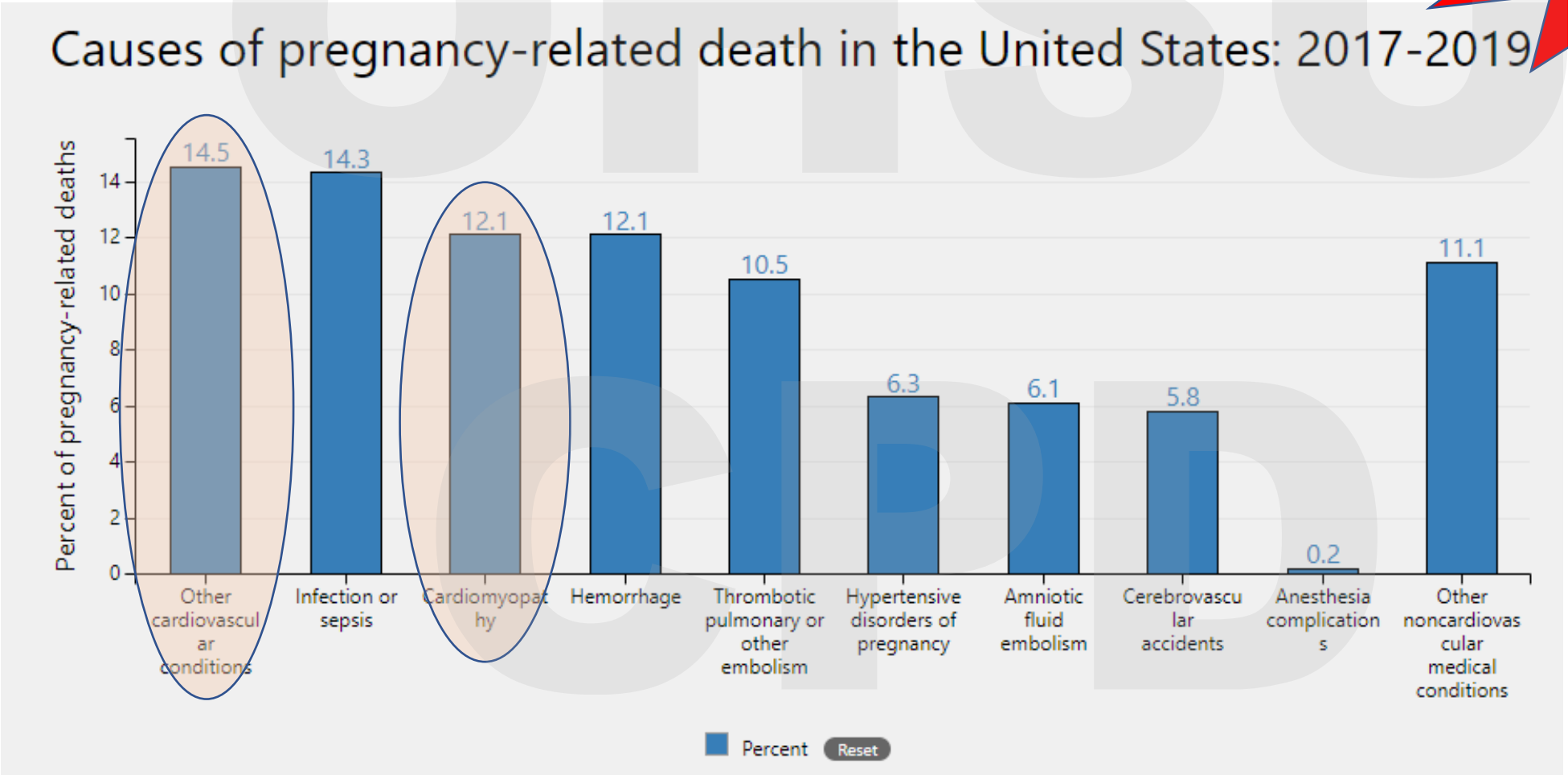
Pregnancy related mortality in the US is increasing



https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm

Causes of mortality

#1 cause: Cardiovascular conditions



https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm

Why?

Higher burden of risk factors

Pre-existing heart disease, obesity, high blood pressure, advanced maternal age

Poor access to healthcare/access to suboptimal care

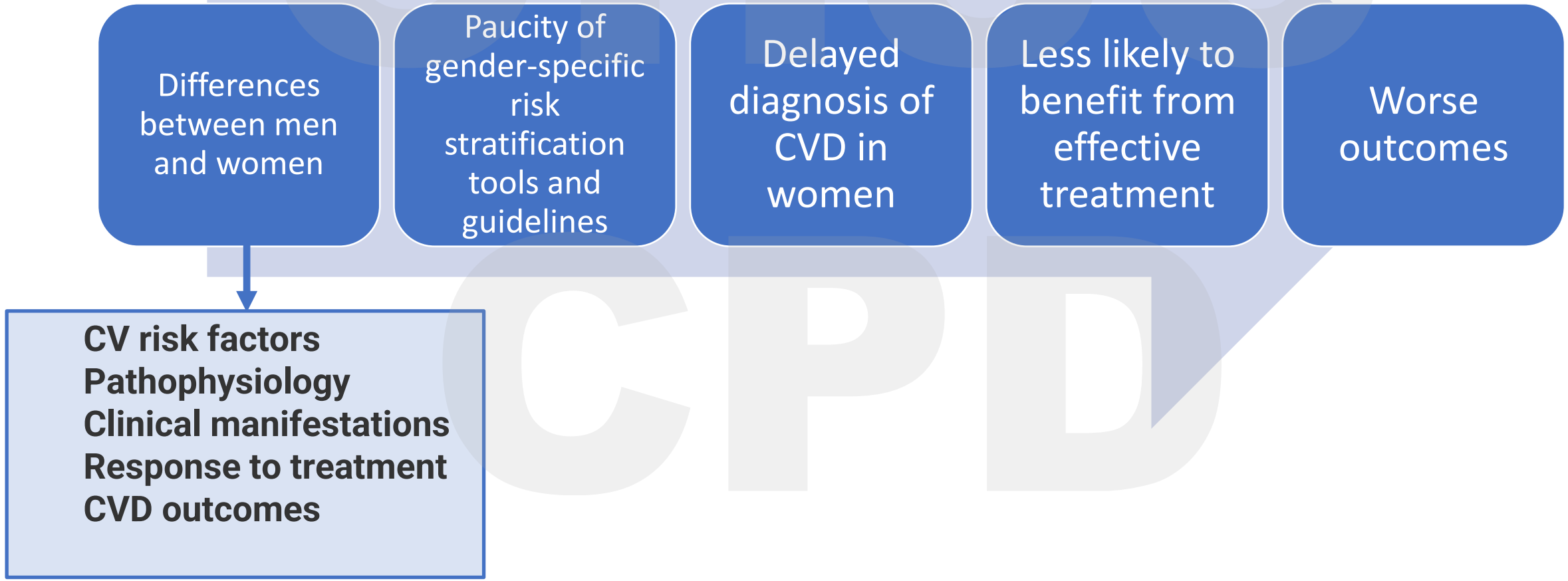
Insufficient follow-up postpartum

Social determinants of health

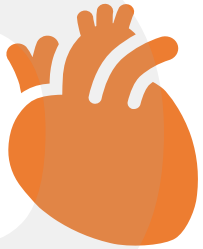
Lack of a societal safety net

Gender differences and risk factors

Gender differences in CVD



Gender differences in CVD



Ischemic heart disease

Prevalence of nonobstructive coronary artery disease is 2-fold higher in women

Baseline hs-troponin levels in women are lower (both healthy and in disease states)

In acute MI, women are less likely to receive guideline-intended medical treatment and less likely to undergo early angiography → higher mortality

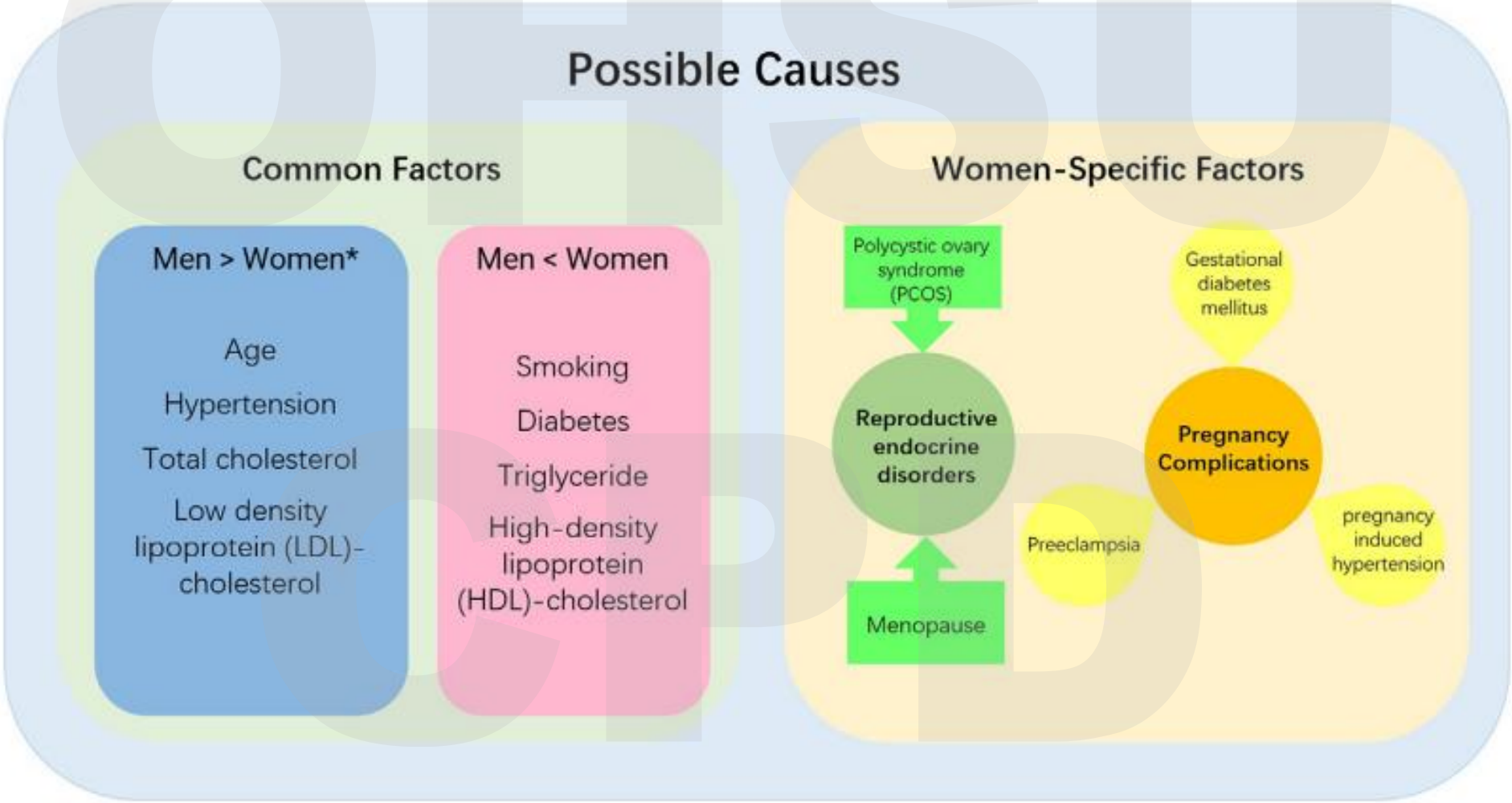
Valvular heart disease

Gender-specific differences in ventricular response to pressure and volume overload→different manifestations of valvular heart disease

Men develop more calcified aortic valve disease, women have more fibrosis and more LVH at low-flow, low-gradient AS

Women are less likely to be considered for surgical valve replacement, and those who do are often older with higher frailty and comorbidities → higher postprocedure mortality

Causes of gender differences in CVD



Gao et al. Medicine in Novel Technology and Devices 4 (2019) 100025

Traditional risk factors for CVD

- **HTN**
  - Underdiagnosed in women
  - Less than 25% of women have optimal BP control
- **DM**
  - 30% greater risk of all-cause mortality
  - Females with diabetes have a 58% greater risk of CHD
- **HLD**
  - Women are less likely to receive statin therapy compared with men
  - Women are more likely to decline initial treatment and less likely to continue prescribed statin therapy
- **Tobacco use**
- **Dietary Na intake**
  - CVD risk is up to 6% higher for every 1-g increase in dietary sodium intake
- **Dietary patterns**
  - Greater adherence to healthy eating patterns → lower CVD risk
  - Mediterranean diet, plant-based whole foods diet

Non-traditional/emerging risk factors for CVD

HIV

Autoimmune disease and inflammatory conditions

SLE (9:1 F:M)

RA (2.5:1 F:M)

Eating disorders (bulimia nervosa)

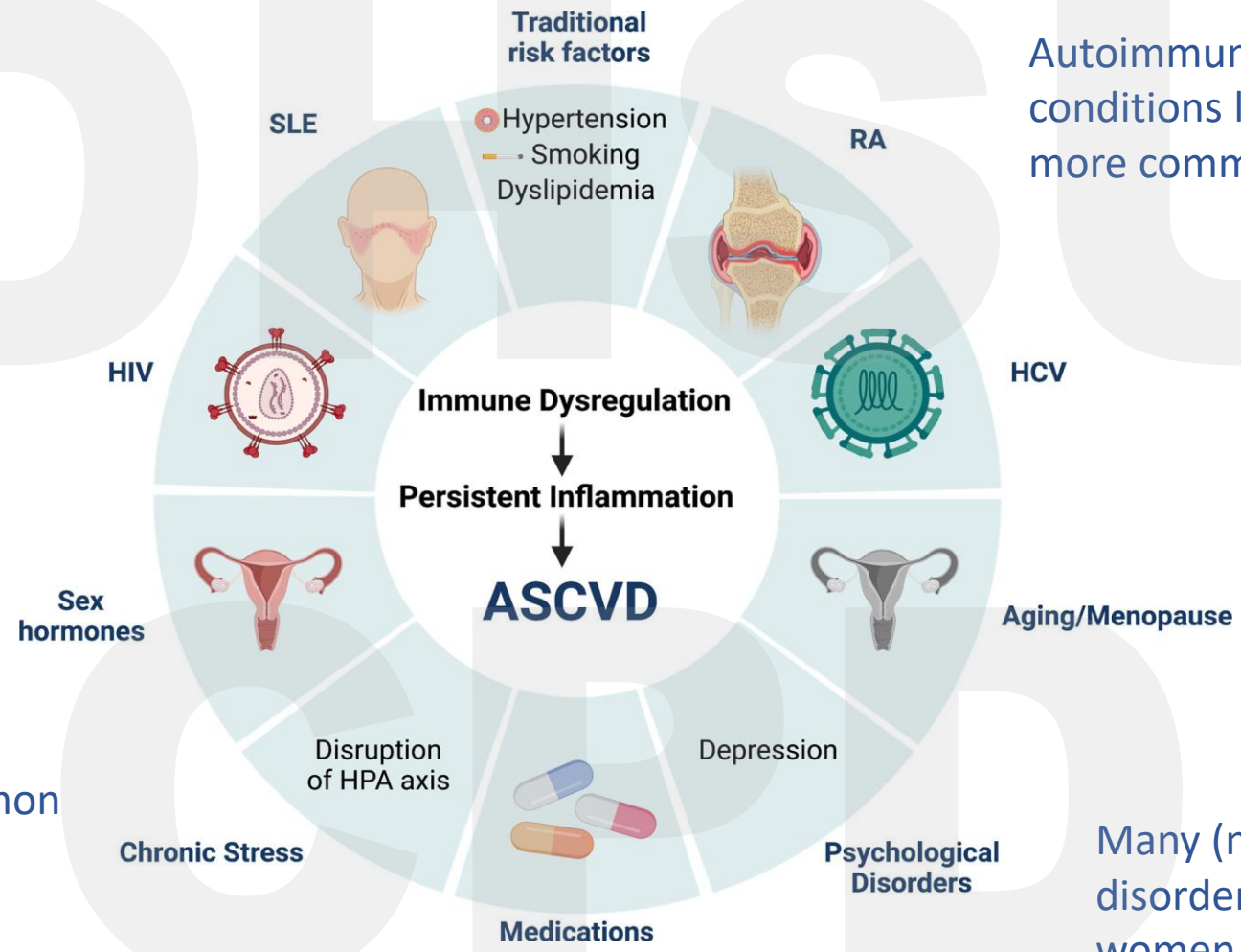
Migraine with aura

Depression

Air pollution

Asthma

Inflammation: A risk factor for heart disease



Autoimmune inflammatory conditions like RA, SLE are more common in women

Chronic stress more common in women

Many (not all) psychological disorders are more common in women

Caitlin A. Moran. Circulation Research. Cardiovascular Implications of Immune Disorders in Women, Volume: 130, Issue: 4, Pages: 593-610, DOI: (10.1161/CIRCRESAHA.121.319877)

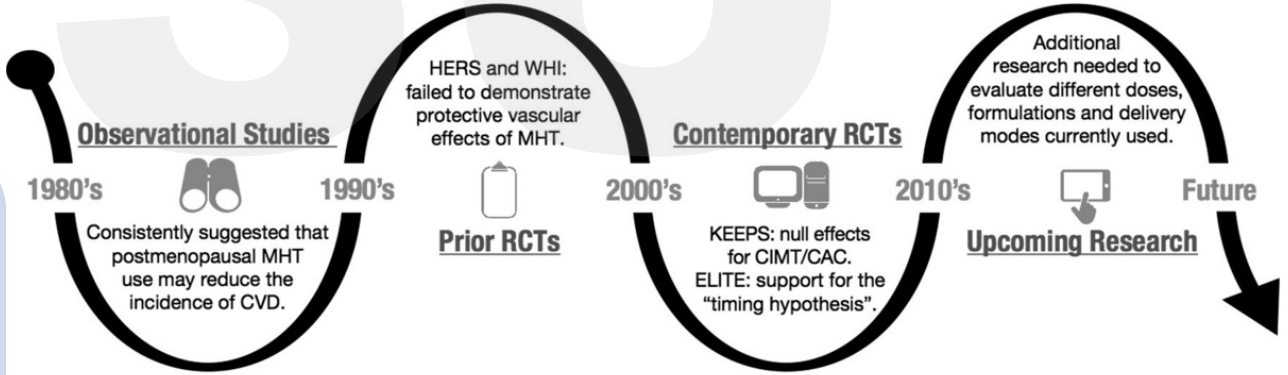
Women-specific CVD risk factors

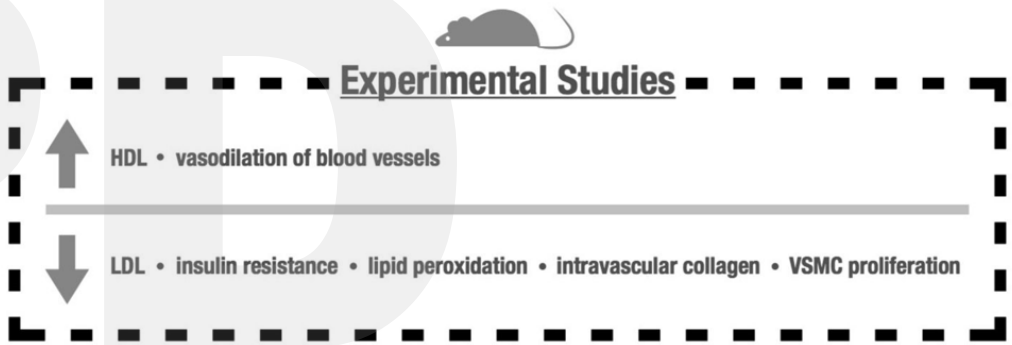
PCOS

Premature menopause

Radiation and chemotherapy for breast cancer

- Estrogen withdrawal → changes in body fat distribution, ↓ glucose tolerance, abnormal lipids, ↑ BP, ↑sympathetic tone, endothelial dysfunction, vascular inflammation
- Mixed data re MHT for CVD prevention
  - Long-term use of MHT for CVD prevention is not recommended
  - "Timing hypothesis": women who start MHT closer to menopausal onset have ↓ risk of developing CVD





Garcia et al. Circulation Research. 2016;118:1273–1293

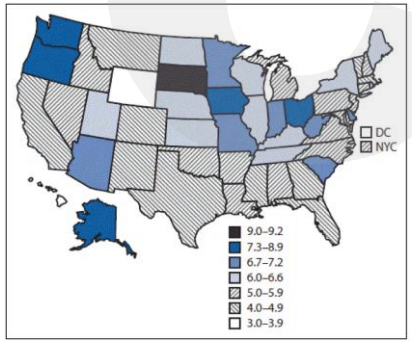
Adverse pregnancy outcomes increase future risk of CVD

Hypertensive disorders of pregnancy

- ↑risk of HTN after delivery and overall CVD
- **Pre-eclampsia:** 3.7x risk of HTN, 2.2x risk of ischemic heart disease, 1.8x risk of stroke, and 1.5x risk of overall mortality
- Pre-eclampsia is a "risk-enhancer" in the guidelines on primary prevention of CVD

Gestational DM

- ↑ risk of future CVD, including a 1.4- to 20x increased risk of type 2 DM, 2x risk of HTN, 2x risk of stroke, and 2.8x risk of ischemic heart disease



Preterm birth (delivery before 37 weeks gestation)

- 2x↑ risk of CVD and deaths caused by CAD even when adjusted for pre-pregnancy lifestyle and CVD risk factors

Pregnancy loss (miscarriage and stillbirth)

- 2x ↑ risk of MI, CVA, and HTN

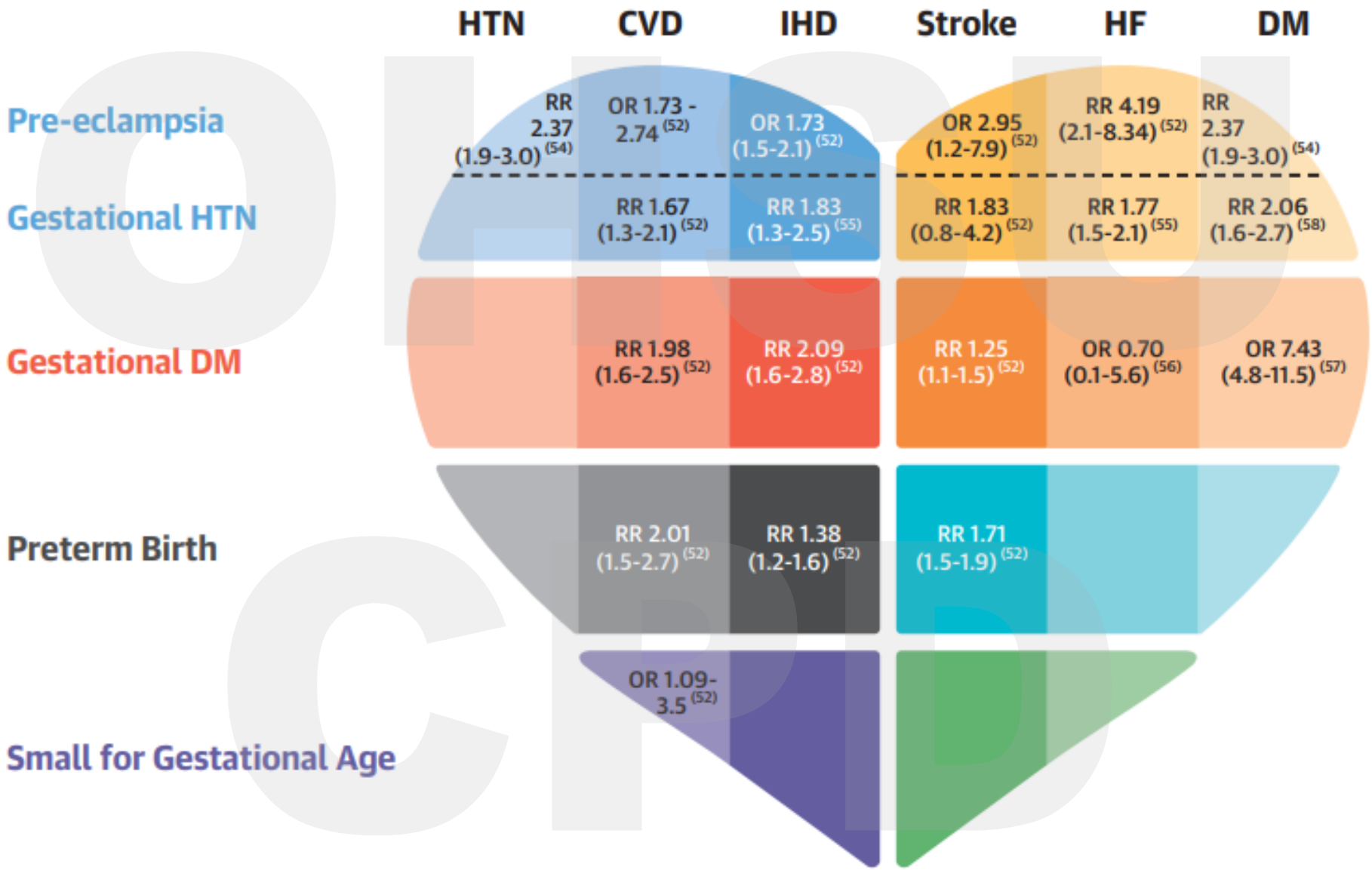
IUGR (fetal weight <10th percentile for GA)

- ↑ risk of HLD, ↑ TG, and insulin resistance
- More diastolic dysfunction, less cardiac reserve

Persistent weight gain after pregnancy

- ↑ risk of adverse cardiometabolic profile

FIGURE 7 APOs and Future Cardiovascular Risk



Davis et al. JACC 2021.

Prevalence of HDP is increasing

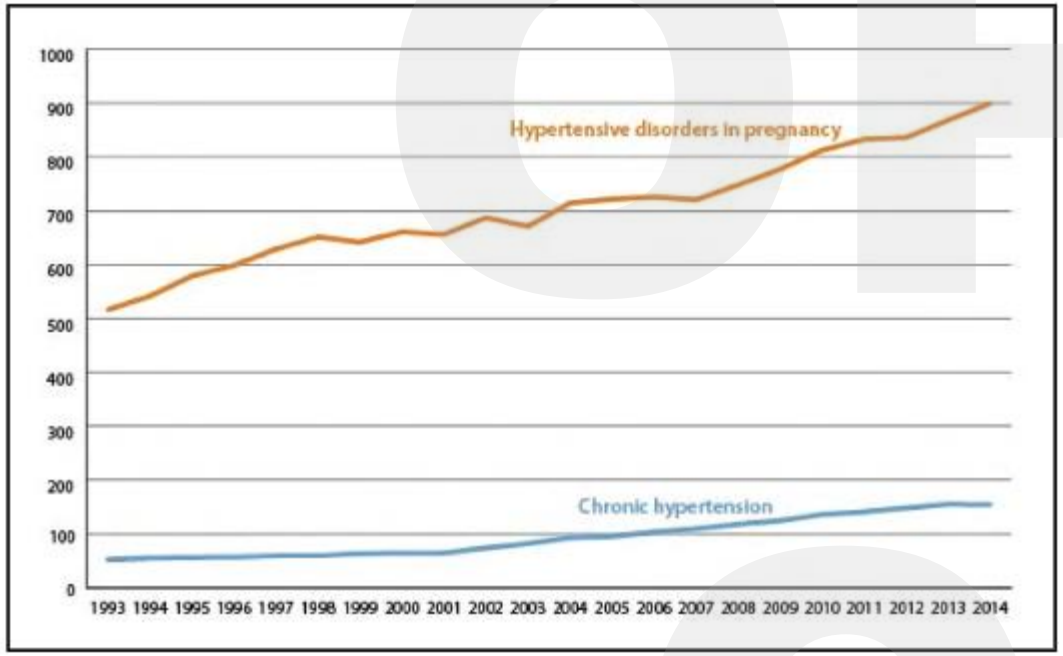
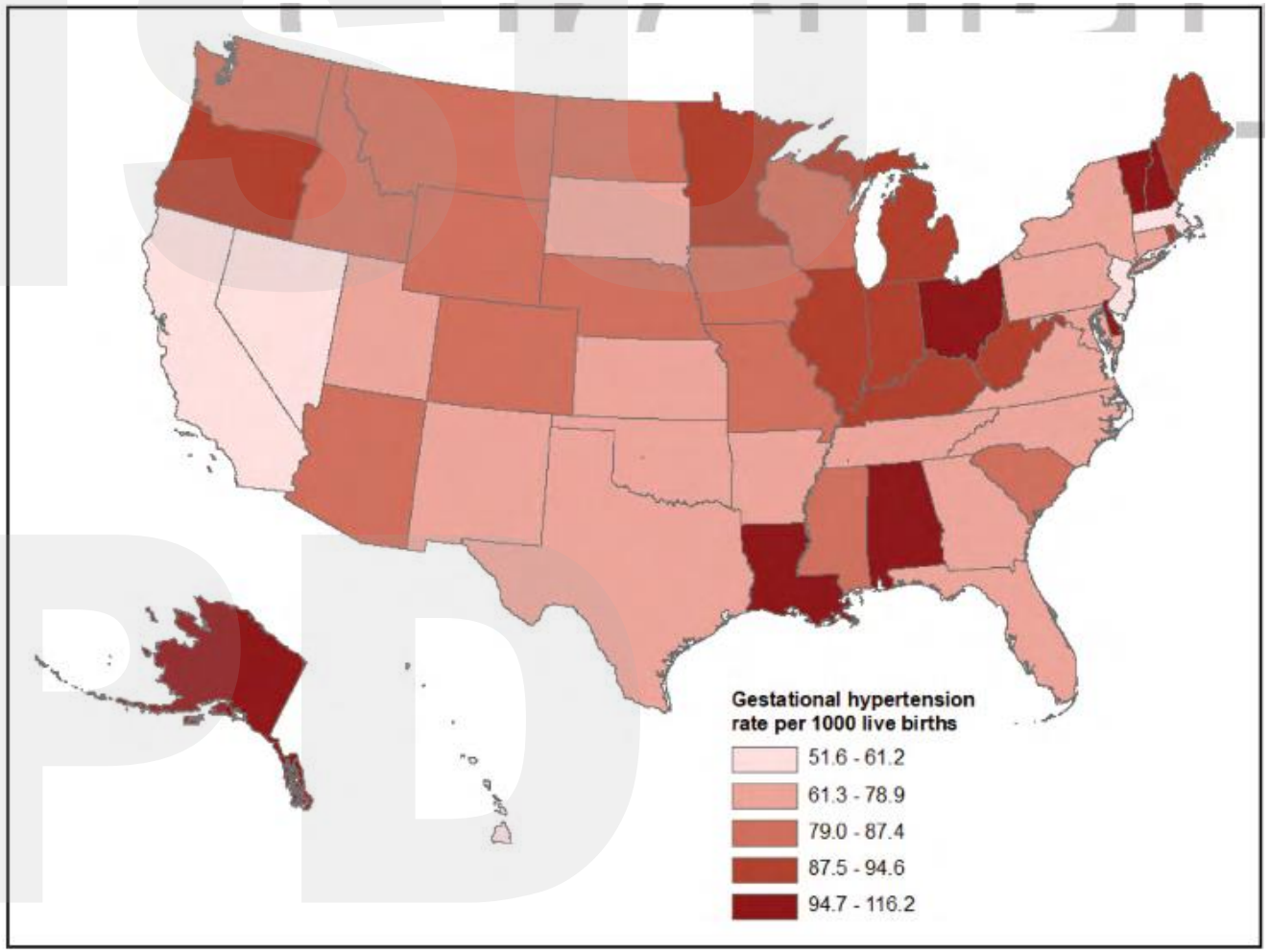


Chart 11-2. Trends in the rates of hypertensive disorders per 10 000 delivery hospitalizations, United States, 1993 to 2014.

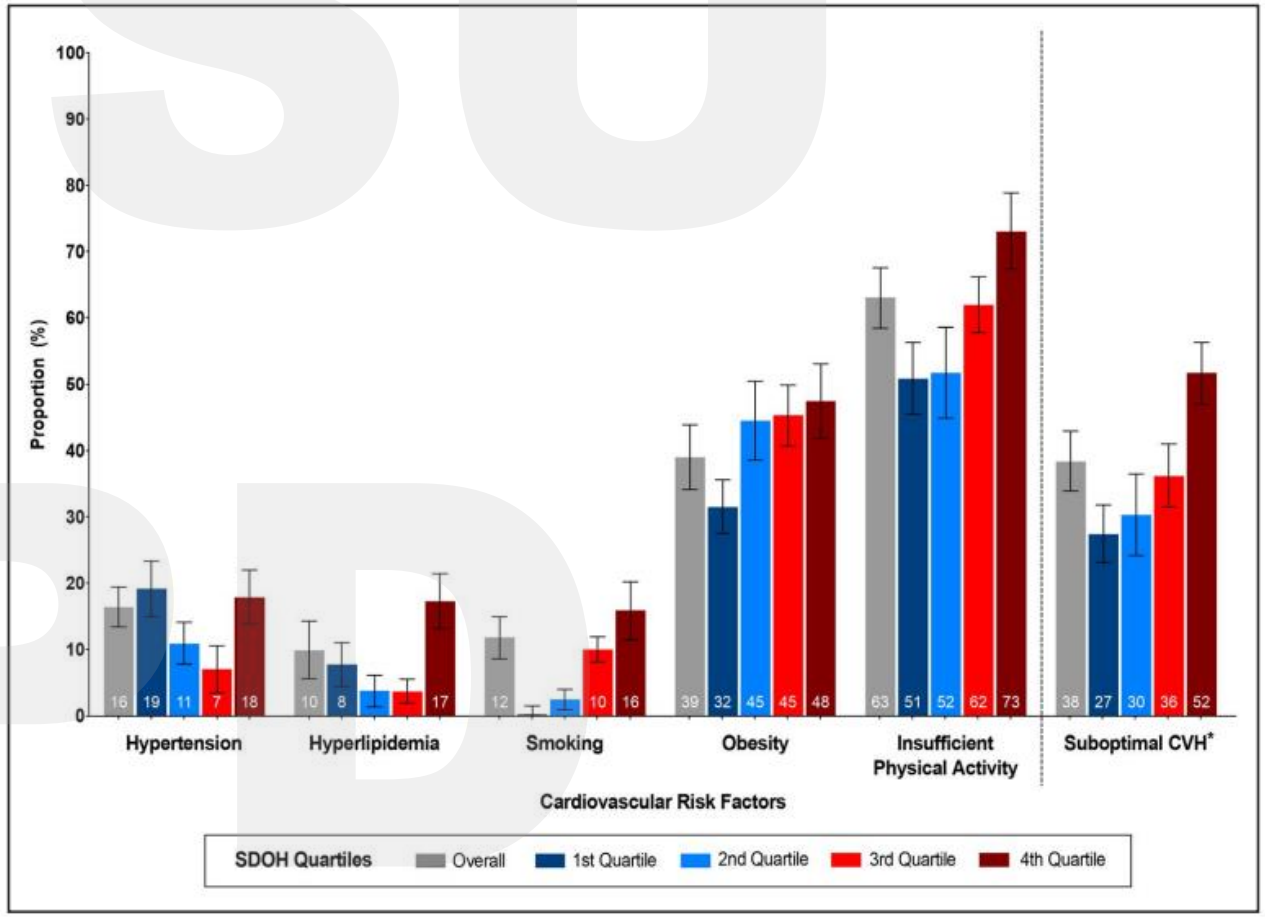


Prevalence of HDP: ~10-15%
Highest in Black women (20.9%)
Among deaths occurring during delivery hospitalization, 31.6% had a diagnosis code for HDP documented

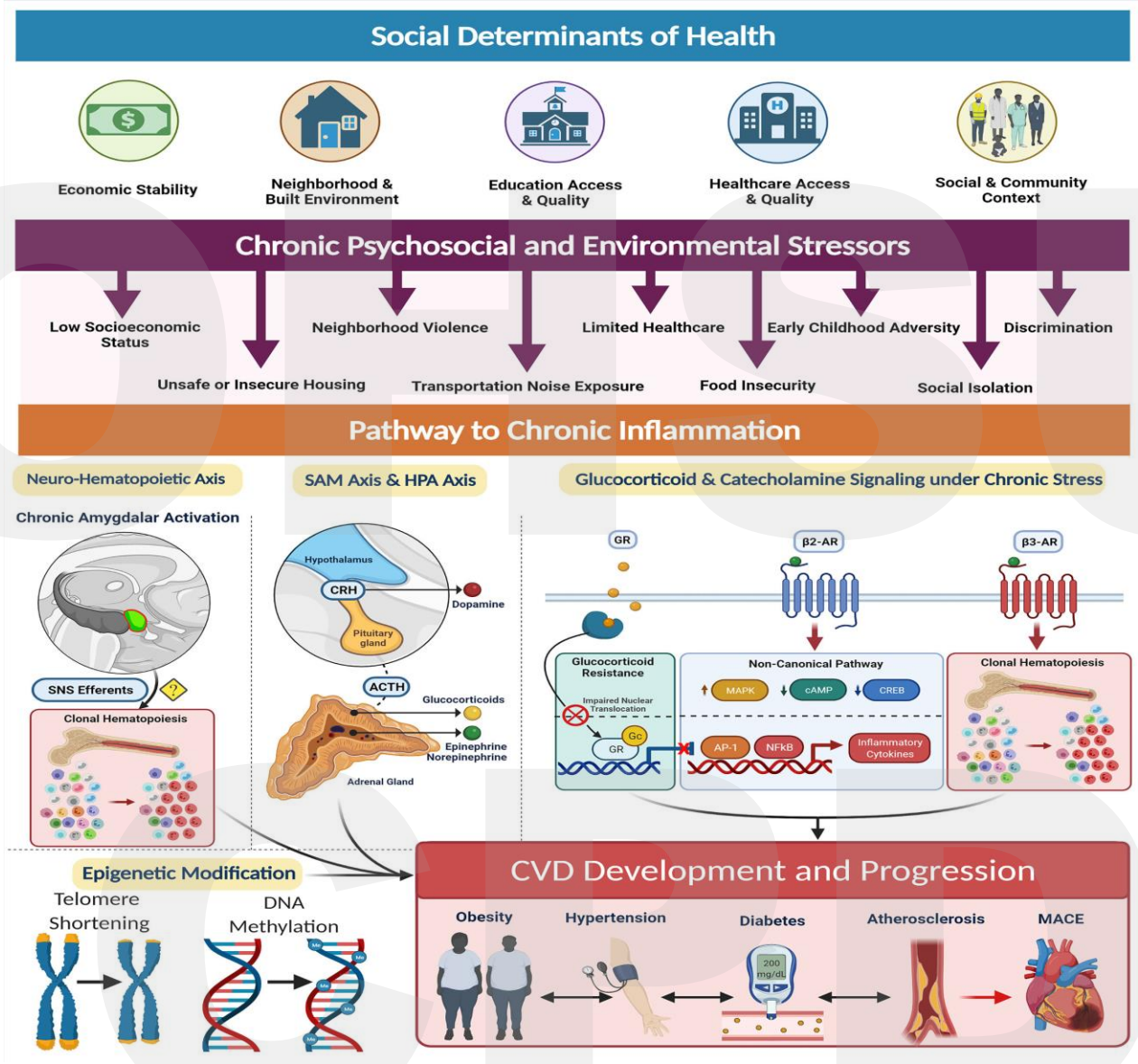
Tsao et al. Circulation. 2023;147:e93–e621

Social determinants of health as a risk factor for CVD

- **Highest tertile of neighborhood socioeconomic deprivation → higher risk of CVD mortality** (aHR for M: 1.47; aHR for F: 1.78) after accounting for individual socioeconomic factors and CVD risk factors
- Weighted social determinants of health score: highest quartile → higher CVD risk
  - Foreign-born status
  - Underrepresented race or ethnicity status
  - Social isolation
  - Financial strain
  - Health literacy
  - Education
  - Stress
  - Delayed care
  - Census-based income



Sharma et al. J Am Heart Assoc. 2022;11:e022837. DOI: 10.1161/JAHA.121.022837

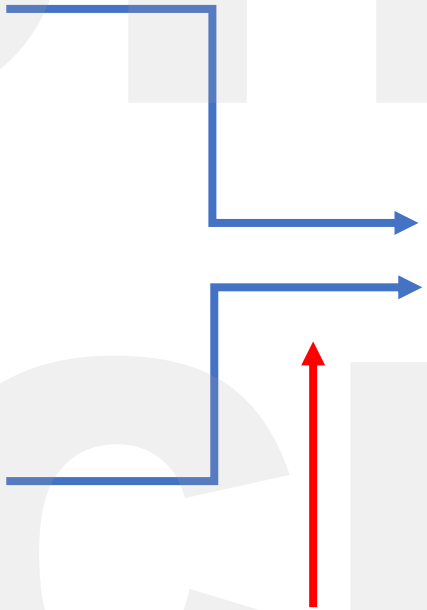


Tiffany M. Powell-Wiley. Circulation Research. Social Determinants of Cardiovascular Disease, Volume: 130, Issue: 5, Pages: 782-799, DOI: (10.1161/CIRCRESAHA.121.319811)

Mental health and cardiovascular disease

20-30% experience post-traumatic stress disorder after an ICU stay

Anxiety, depression common after cardiac events



Higher risk of future cardiac events

Opportunity to intervene?

Depression, isolation, and psychological issues as risk factors

Higher CVD risk with:

- Being divorced/separated, widowed or living alone
- Social isolation
- Marital stress
- Work stress
- Childhood abuse or trauma

Psychosocial stress tends to be a more important risk factor for cardiometabolic diseases in women than in men

Depression, early-life adversities, socioeconomic deprivation, and PTSD are more prevalent in women and have more robust associations with cardiometabolic risk in women than in men

- Depression in women is associated with a doubling of risk of CVD even over a period of decades
- Women with >5 PTSD symptoms have a 3-fold higher risk of ischemic heart disease compared with those without PTSD symptoms

Responses to mental stress

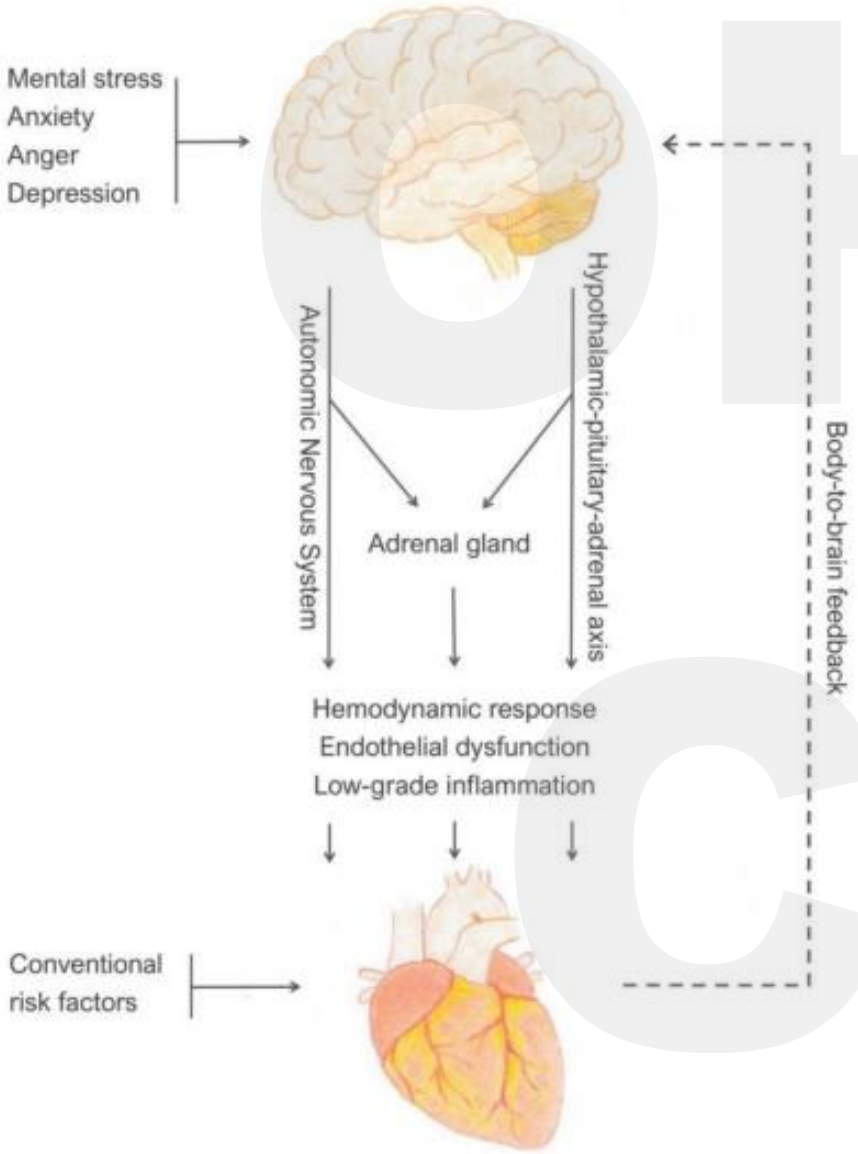


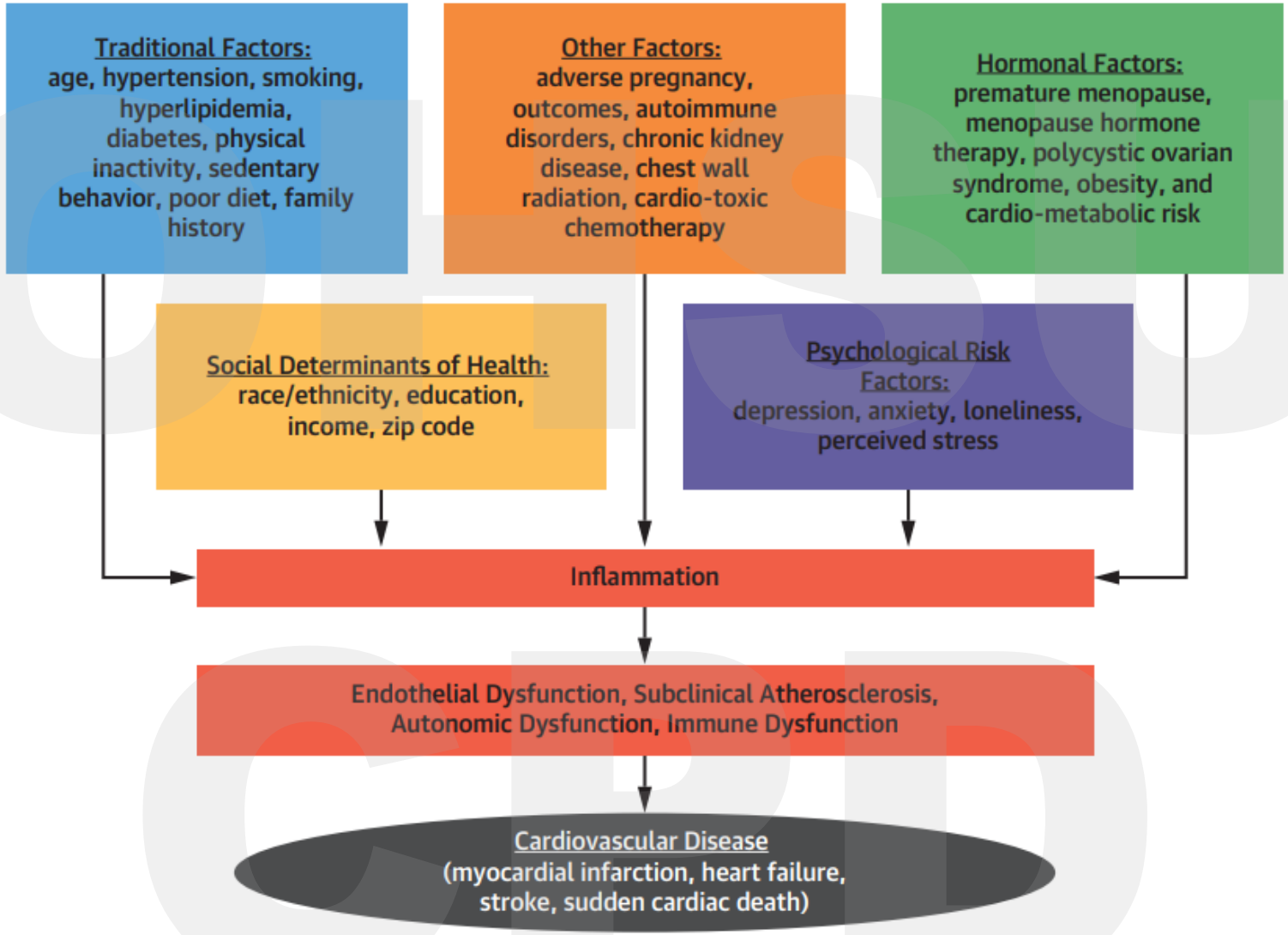
Table 1. Hemodynamic responses to physical exercise and mental stress.

	Physical Exercise	Mental Stress
Cardiac output	↑↑	↑
Rate-pressure product	↑↑	↑
Myocardial oxygen demand	↑↑	↑
Systemic vascular resistance	↓	↑
LV afterload	↓	↑

Physical exercise is associated with greater increase in cardiac output and rate-pressure product, resulting in greater increase in myocardial oxygen demand. Systemic vascular resistance and left ventricular (LV) afterload fall during exercise while increase in response to mental stress.

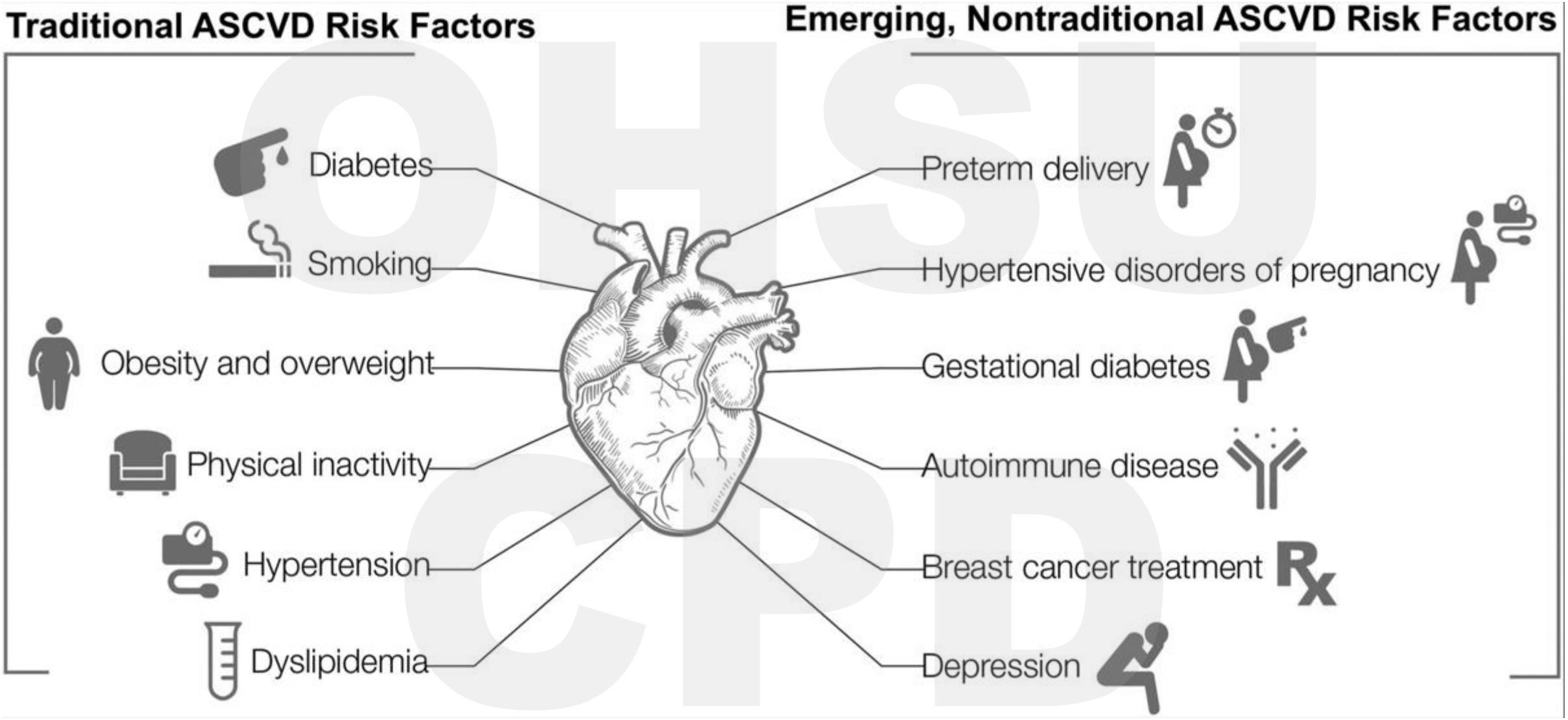
Vancheri et al. J. Clin. Med. 2022, 11, 3353

CENTRAL ILLUSTRATION Cardiovascular Disease Risk Factors in Women



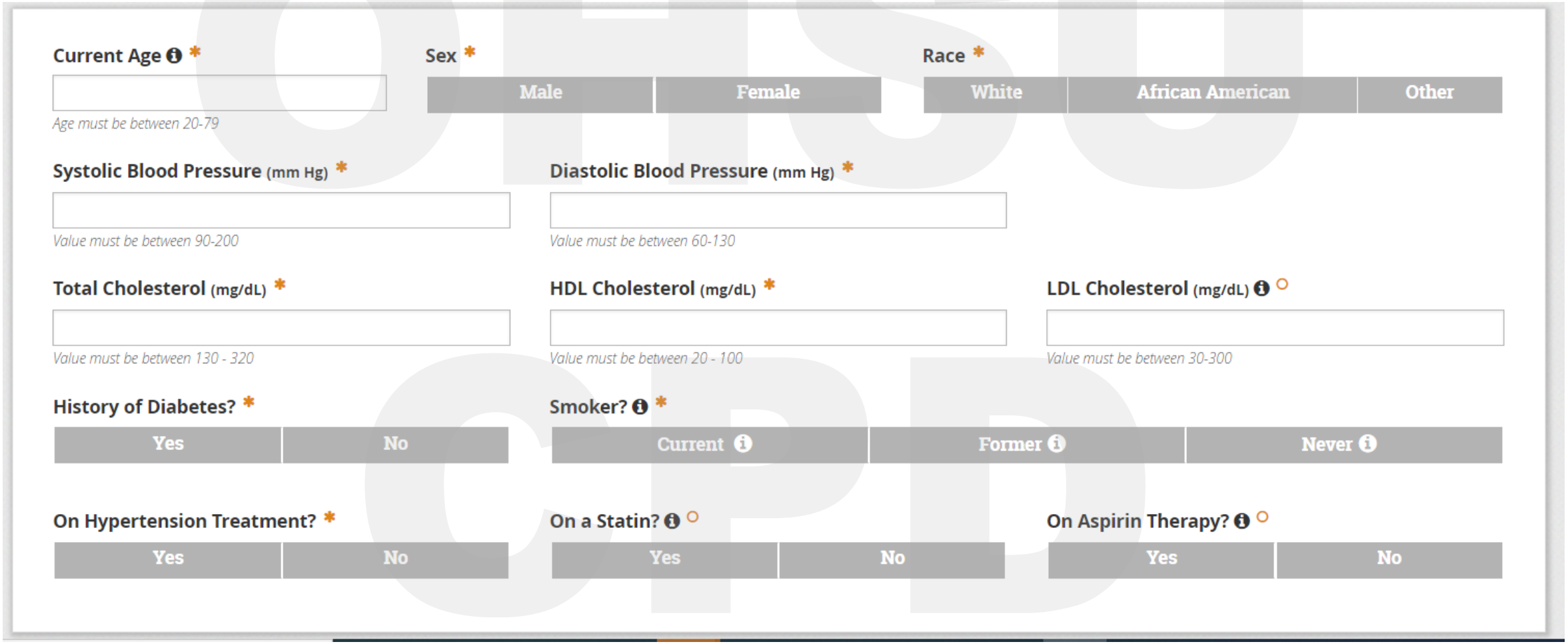
Cho, L. et al. J Am Coll Cardiol. 2020;75(20):2602-18.

The factors shown in **orange** are incorporated in the atherosclerotic cardiovascular disease risk calculator. However, there are unique sex-specific factors as well as psychosocial factors that contribute to CVD risk and adverse outcomes.



Garcia et al. Circulation Research. 2016;118:1273–1293

Most common risk calculator does not assess female-specific risk factors



https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

Comprehensive cardiac risk assessment in women

Current practice

Known cardiac conditions

Traditional cardiac risk factors

- Diabetes
- Hypertension
- High cholesterol
- Smoking

Future practice

Pregnancy complications

Non-traditional risk factors

- Autoimmune

Social determinants of health

- Poverty
- Poor nutrition
- Domestic violence
- Chronic stress

Mental health

Unique manifestations of CVD in women

Acute myocardial infarction in women

Young women are 50% more likely than similar aged men to present without chest pain in STEMI

- 1 in 5 women perceive their symptoms as being related to anxiety or stress
- Most women do experience chest pain with AMI

Young women with AMI have more comorbidities compared with similarly aged men

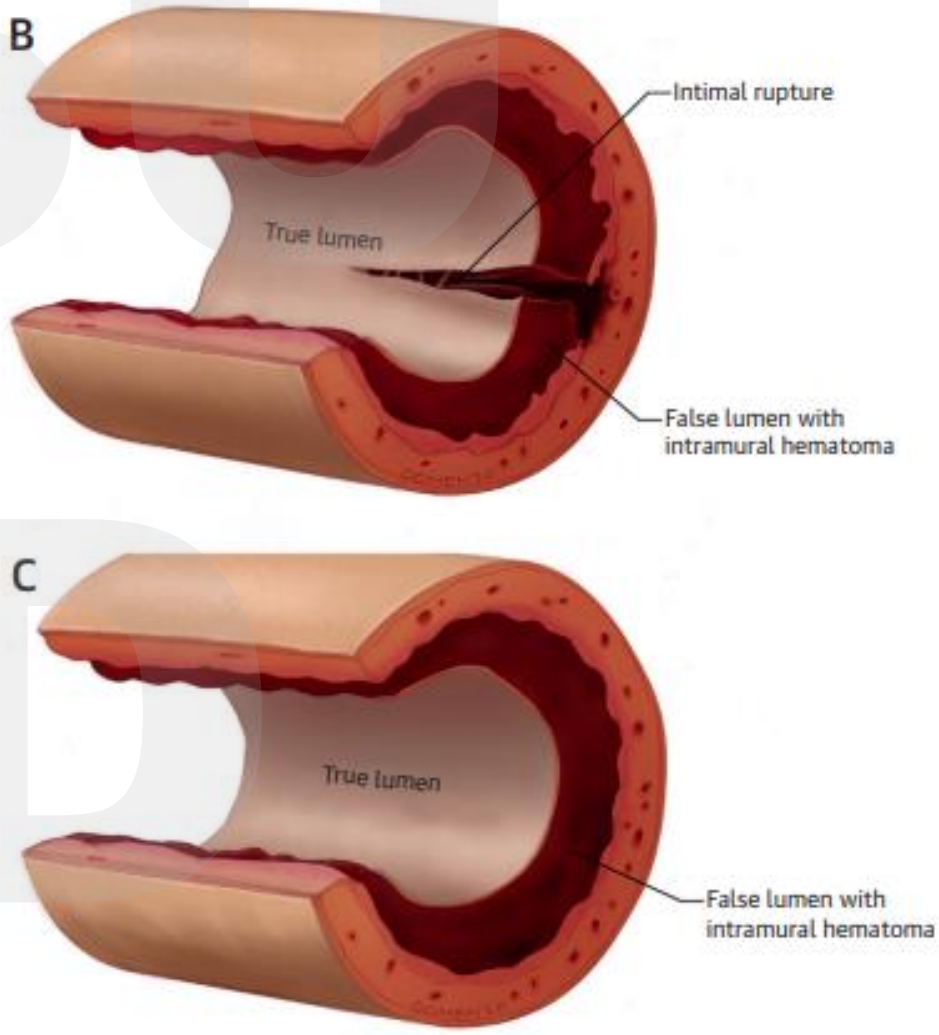
- Higher prevalence of DM, HTN, CKD
- Greater prevalence of depression and stress, poorer physical and mental health status, and lower quality of life

Medical and invasive treatment of ACS are underutilized in women

- Less likely to be diagnosed with and treated for AMI even when troponin is abnormal
- Less likely to receive guideline-recommended therapies
- Less likely to achieve a door-to-balloon time of <90 minutes
- Greater in-hospital mortality rates during hospitalization for AMI

Spontaneous coronary artery dissection (SCAD)

- **Non-traumatic, non-iatrogenic separation of the coronary arterial wall**
- **Absence of atherosclerosis** on intracoronary imaging
- Rare cause of acute MI (1.7-4% of cases based on contemporary series)
  - more common in **younger patients** (mean age 44 to 55 years) and in **women** (>90% women)
  - **~22-43% of ACS (#1 cause of MI) in women ≤50 years old**
  - **Most frequent cause of pregnancy-related MI (43%), predominately in third trimester or postpartum**
  - Also common in older, post-menopausal women



SCAD causes/associations

- Most cases are sporadic
- Predisposing arterial disease/predisposing factors in most cases:
  - **Fibromuscular dysplasia (FMD; ~70%)**
  - Postpartum status
  - Multiparity (≥4 births)
  - Connective tissue disorders (Marfan, EDS): 5-8% prevalence in those with SCAD
  - Systemic inflammatory conditions
  - Hormonal therapy
- Idiopathic in 20%
- ~50% have **precipitating stressors** that increase cardiocirculatory stress (intense exercise, emotional stress, intense Valsalva, L&D, drug use)

TABLE 1 Potential Predisposing and Precipitating Factors for SCAD

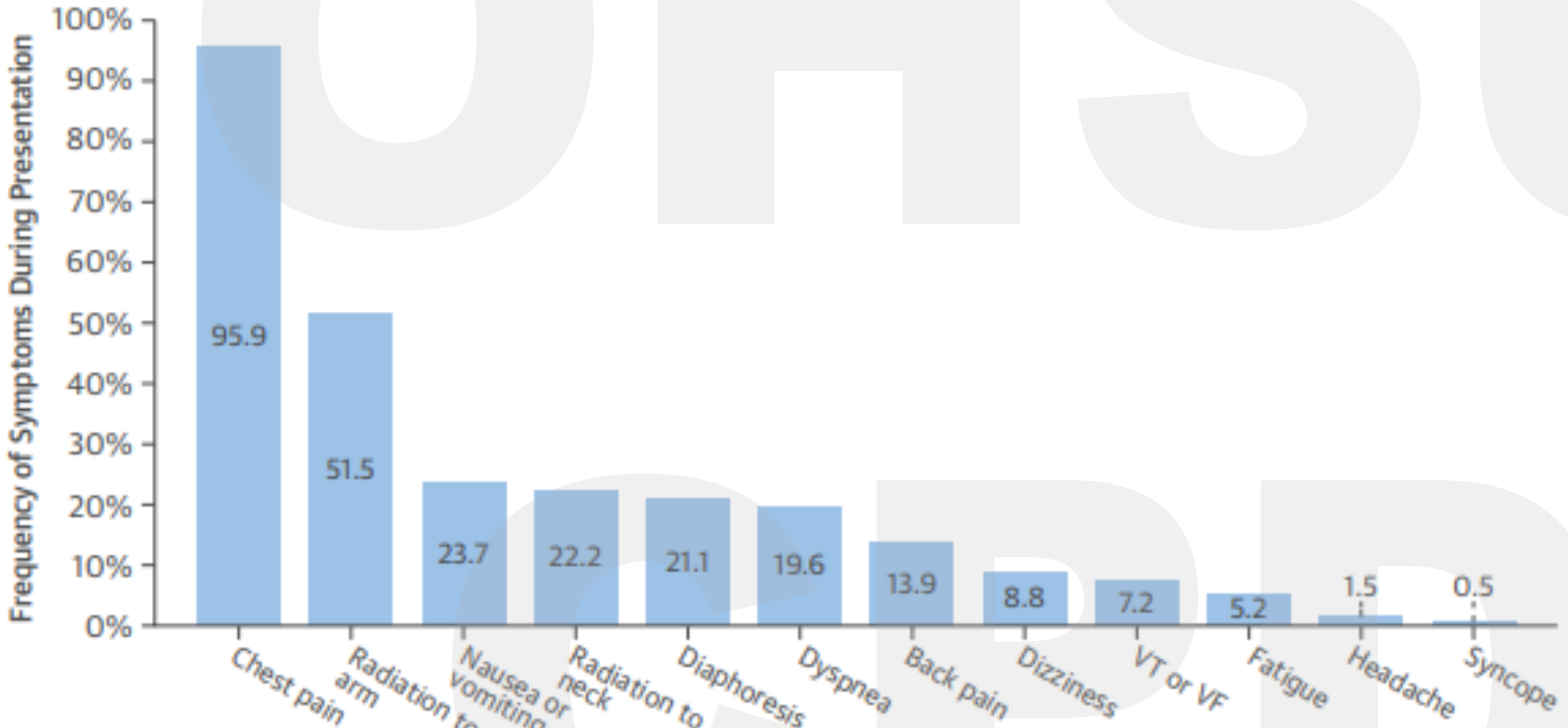
Predisposing causes
Fibromuscular dysplasia
Pregnancy-related: antepartum, early post-partum, late post-partum, very late post-partum
Recurrent pregnancies: multiparity or multigravida
Connective tissue disorder: Marfan syndrome, Loeys-Dietz syndrome, Ehler-Danlos syndrome type 4, cystic medial necrosis, alpha-1 antitrypsin deficiency, polycystic kidney disease
Systemic inflammatory disease: systemic lupus erythematosus, Crohn's disease, ulcerative colitis, polyarteritis nodosa, sarcoidosis, Churg-Strauss syndrome, Wegener's granulomatosis, rheumatoid arthritis, Kawasaki, giant cell arteritis, celiac disease
Hormonal therapy: oral contraceptive, estrogen, progesterone, beta-HCG, testosterone, corticosteroids
Coronary artery spasm
Idiopathic
Precipitating stressors
Intense exercises (isometric or aerobic activities)
Intense emotional stress
Labor and delivery
Intense Valsava-type activities (e.g., retching, vomiting, bowel movement, coughing)
Recreational drugs (e.g., cocaine, amphetamines, metamphetamines)
Intense hormonal therapy (e.g., beta-HCG injections, corticosteroids injections)

HCG = human chorionic gonadotropin; SCAD = spontaneous coronary artery dissection.

Saw et al. Contemporary Review on Spontaneous Coronary Artery Dissection. *JACC* 2016.

SCAD symptoms

FIGURE 2 Frequency of Symptom Presentation of SCAD



Chest pain is the most commonly reported symptom with SCAD presentation (51). SCAD = spontaneous coronary artery dissection; VF = ventricular fibrillation; VT = ventricular tachycardia.

- STEMI in 25-50%, NSTEMI in 50-75%
- VT in 4-14%
- >90% present as MI with chest pain
- 2% cardiogenic shock

Saw et al. Contemporary Review on Spontaneous Coronary Artery Dissection. *JACC* 2016.

Pregnancy-associated SCAD

Can occur **antepartum, early post-partum** (within 6 weeks of delivery), **late post-partum** (6 weeks to 12 months), and **very late post-partum** (12-24 months)

Hemodynamic stresses (↑CO and circulatory volume→ ↑ shear stress) and **hormonal effects** (↑ progesterone weakening the coronary arterial wall, ↑estrogen creating a hypercoagulable state)

P-SCAD patients may have a **worse prognosis** than other SCAD cohorts

- Larger infarcts, lower mean LV EF, and more proximal artery dissections

Continued use of hormonal therapy should be avoided; IUD best for contraception

Future pregnancy in women with prior SCAD should "likely be avoided" (~14% risk of recurrent SCAD)

SCAD management

Conservative (medical) management preferred in most cases

- **Long term ASA, 1-12 months of clopidogrel**
- **Long term BB** (may have an additional benefit in preventing SCAD recurrence)
- **Statin** only in those with dyslipidemia or another indication
- **ACE-I/ARB** and **GDMT** in those with reduced systolic function
- Nitrates, calcium-channel blockers, and ranolazine for ongoing angina

Revascularization with PCI or CABG, mechanical circulatory support, or cardiac transplantation in those with high risk features

- Persistent chest pain with evidence of ongoing or worsening ischemia or ventricular arrhythmias
- Hemodynamic instability/shock
- Multivessel severe proximal dissections or of the LM or the LAD

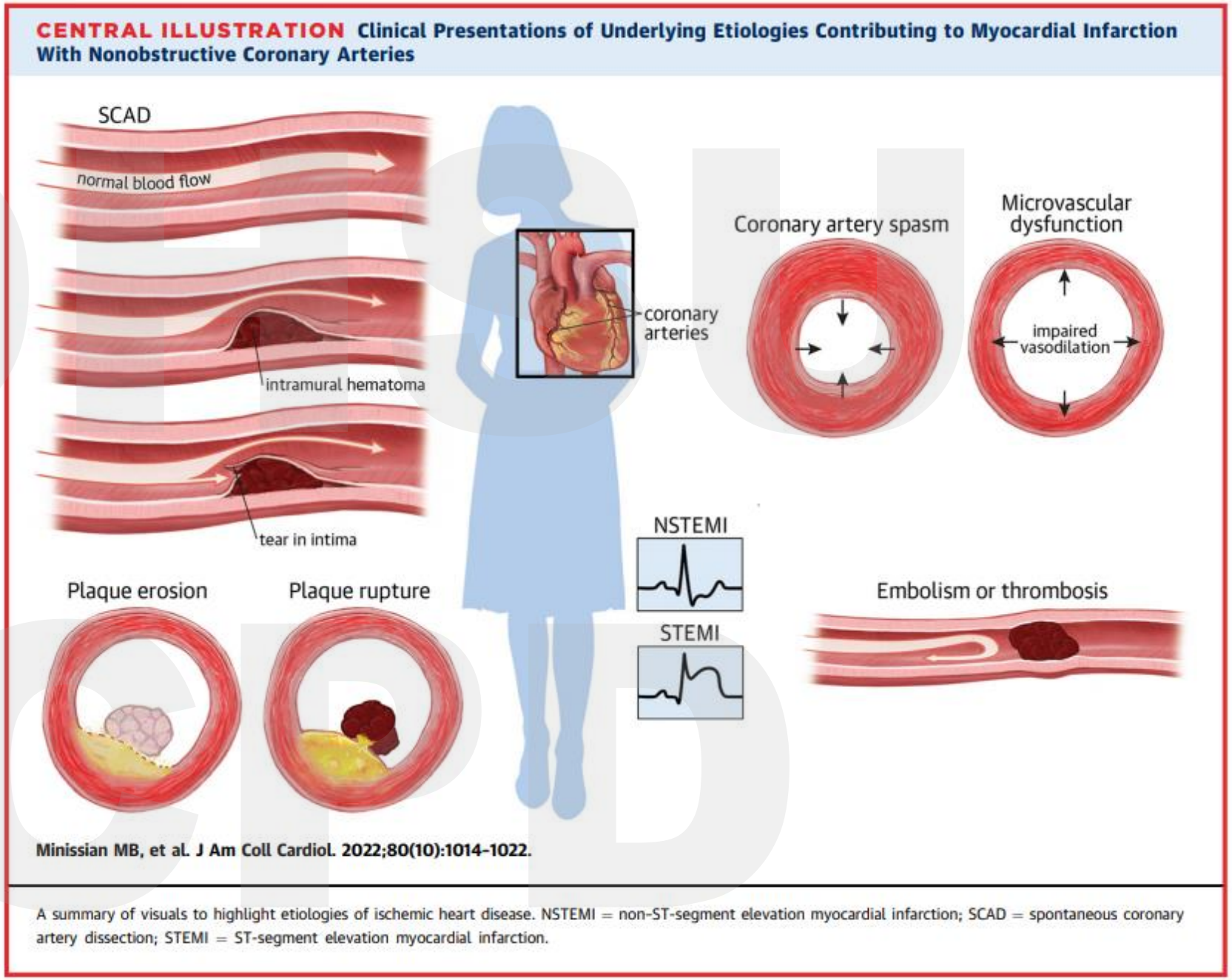
Cardiac rehab

- Avoid isometric exercise, high-intensity endurance training, exercising to the point of exhaustion, and activities that involve a prolonged Valsalva maneuver

Screening for predisposing arteriopathy

- Cross sectional imaging and consideration of genetic testing

MINOCA


CENTRAL ILLUSTRATION Clinical Presentations of Underlying Etiologies Contributing to Myocardial Infarction With Nonobstructive Coronary Arteries
SCAD
normal blood flow
intramural hematoma
tear in intima
coronary arteries
Coronary artery spasm
Microvascular dysfunction
impaired vasodilation
NSTEMI
STEMI
Plaque erosion
Plaque rupture
Embolism or thrombosis
Minissian MB, et al. J Am Coll Cardiol. 2022;80(10):1014-1022.
A summary of visuals to highlight etiologies of ischemic heart disease. NSTEMI = non-ST-segment elevation myocardial infarction; SCAD = spontaneous coronary artery dissection; STEMI = ST-segment elevation myocardial infarction.

MINOCA

The presence of universal AMI criteria in the setting of nonobstructive CAD with no overt cause such as pulmonary embolism

- 5% to 15% of AMI patients
- More prevalent in women (40%-60%) than MI-CAD, (~25%) and occurs at younger ages
- ~50% of MINOCA patients are aged <60 years, and ~25% present at <50 years

Etiologies:

mild-to-moderate atherosclerosis with positive remodeling of the coronary artery, coronary artery spasm, plaque microrupture and/or erosion, coronary embolism, and microthrombosis

Recurrent MI in ~7% over 4 years

Post-MI angina in ~25% at 12 months

~40% increase in all-cause mortality vs patients with stable angina who have nonobstructive CAD

MINOCA patients are less likely to receive secondary prevention medications at hospital discharge vs MI-CAD patients

- Likely to benefit from statins and ACE-I/ARB, but not DAPT
- Not revascularization candidates

Coronary artery spasm

Presentation

- Angina at night or early morning hours
- Spasm→myocardial ischemia→life-threatening arrhythmias in 5-10% of patients

Mechanism

- Vascular smooth muscle cell hyperreactivity and endothelial dysfunction with superimposed vasoconstrictor stimuli due to sympathetic activity, allergic reactions, hyperventilation-induced alkalosis, or platelet activation

Risk factors

- Smoking, cocaine, methamphetamine, chemo (5-fluorouracil, paclitaxel)

Treatment

- Vasodilator therapy (calcium-channel blockers, nitrates)
- Avoidance of vasoconstrictor stimuli

Coronary microvascular dysfunction (CMD)

Impaired coronary flow reserve (CFR) and/or high index of microvascular resistance

CMD and/or endothelial dysfunction are seen in ~50% of women with symptoms of ischemia with no obstructive CAD

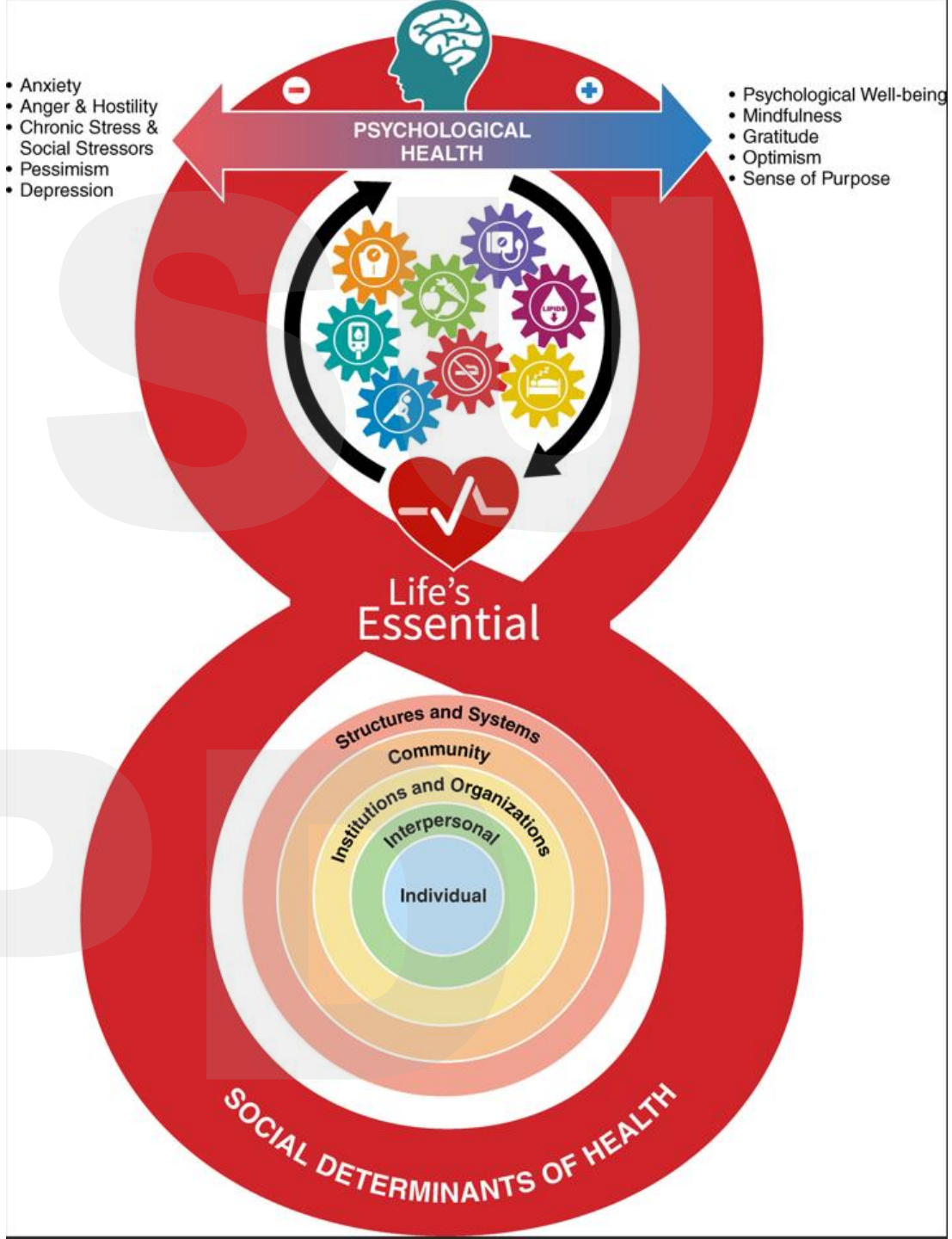
Treatment: risk factor modification, angina relief with BB and ?ACE-I, aspirin and statin for concomitant nonobstructive CAD

Opportunities for prevention and improvement

Core health behaviors and factors contributing to CV health

Figure. AHA's My Life Check–Life's Essential 8.
Source: Reprinted from Lloyd-Jones et al.[1] Copyright © 2022, American Heart Association, Inc.

Impact of modifying risks is greater in women than in men



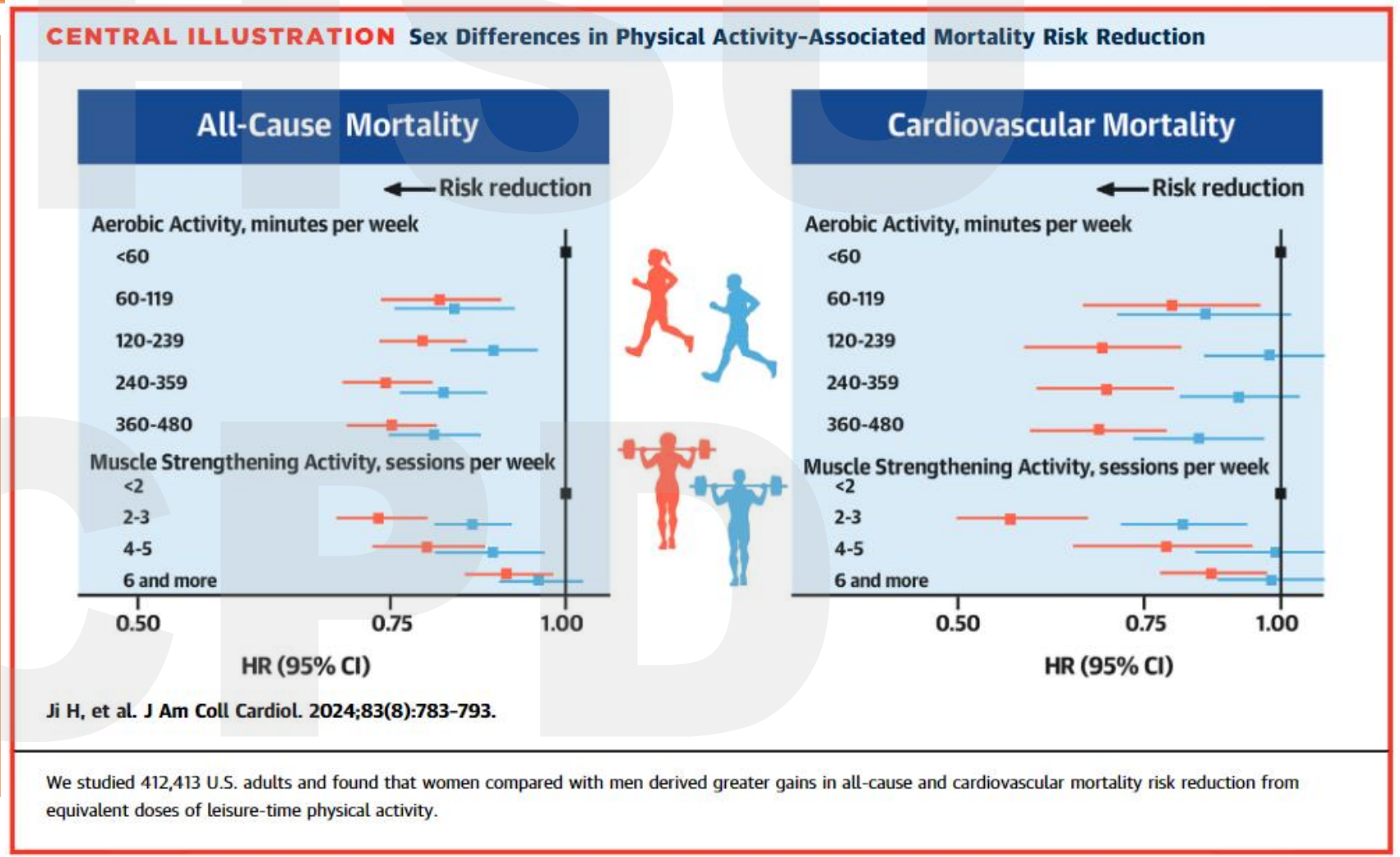
Lloyd-Jones et al. Circulation. 2022;146:e18–e43

Benefits of exercise are more significant in women

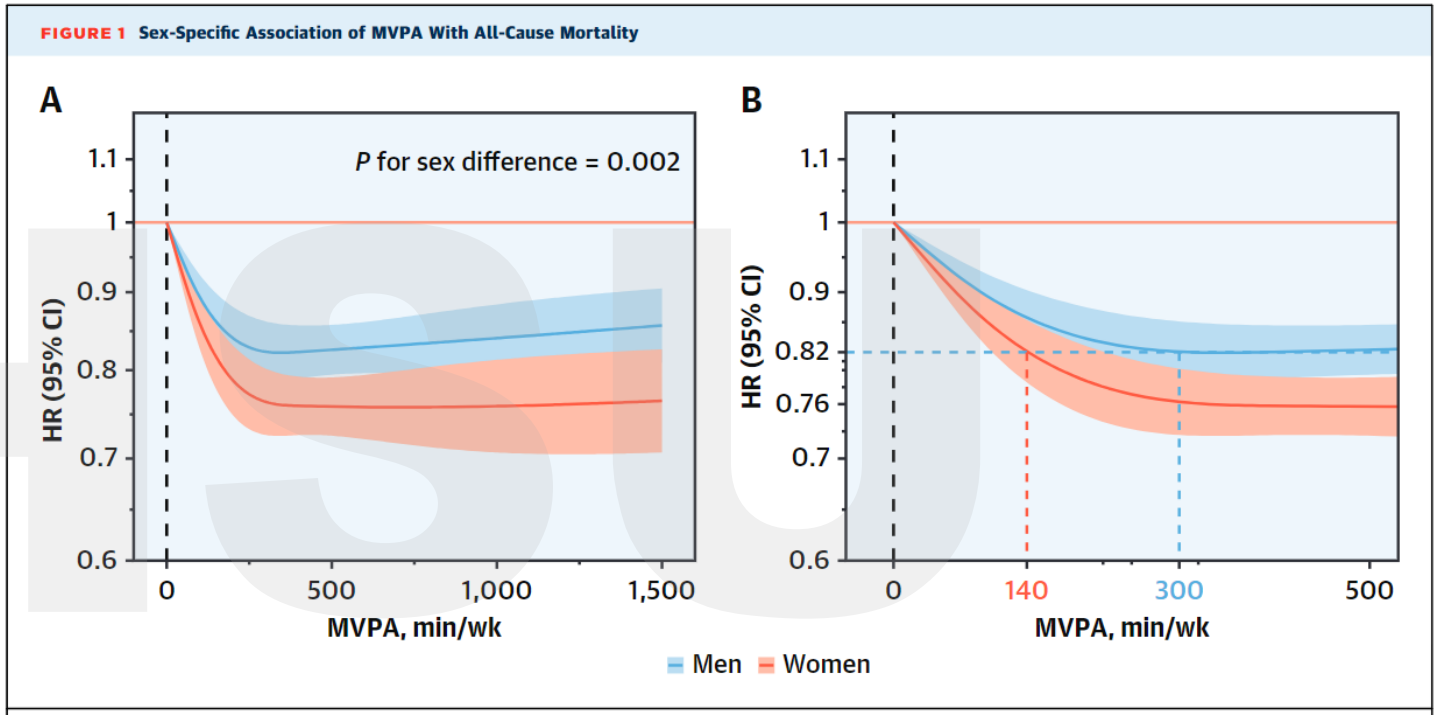
Women derive greater gains in all-cause and CV mortality risk reduction from equivalent doses of leisure-time physical activity than men (24% VS 15%)

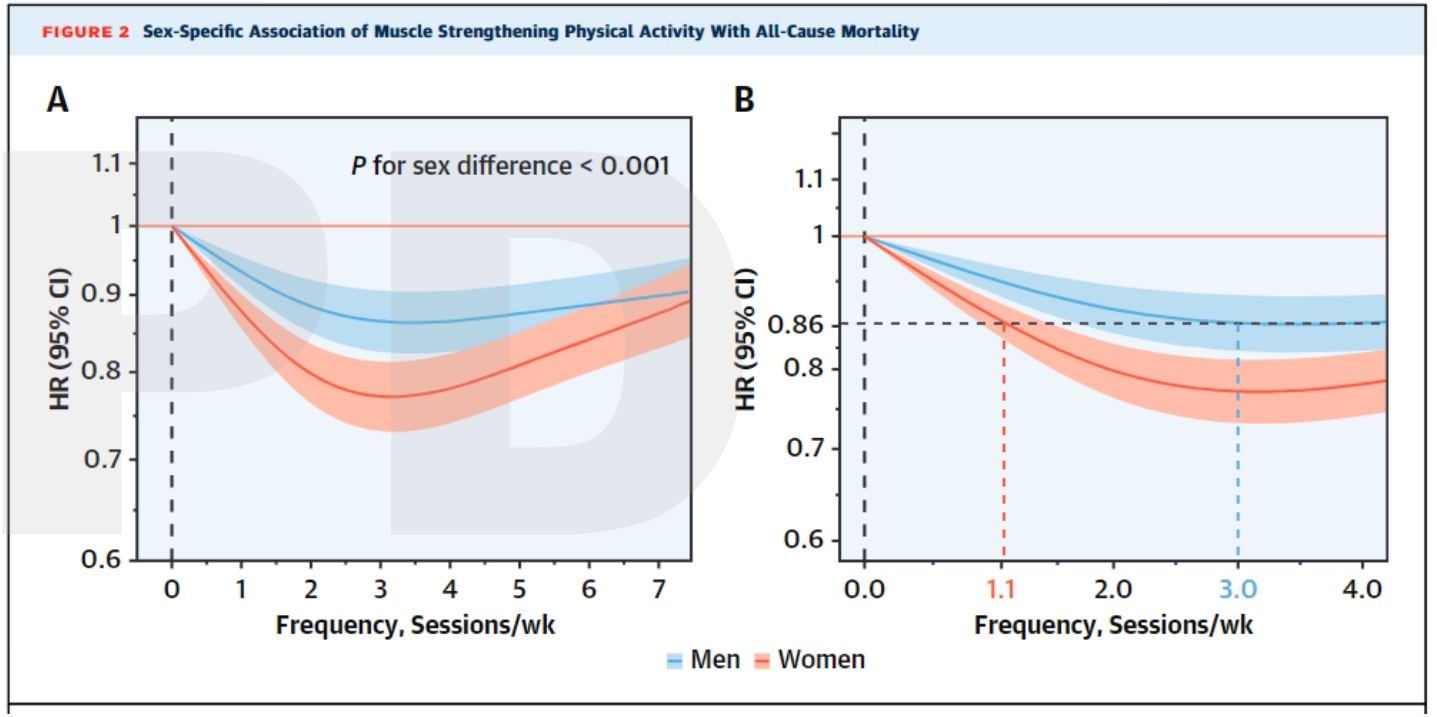
Men reached their maximal survival benefit (HR 0.81) from 300 min/wk of moderate-to-vigorous physical activity

Women achieved similar benefit at 140 min/wk and then continued to reach a maximum survival benefit (HR 0.76) at ~300 min/wk



Sex-specific findings consistent across all measures of aerobic activity and muscle strengthening activity

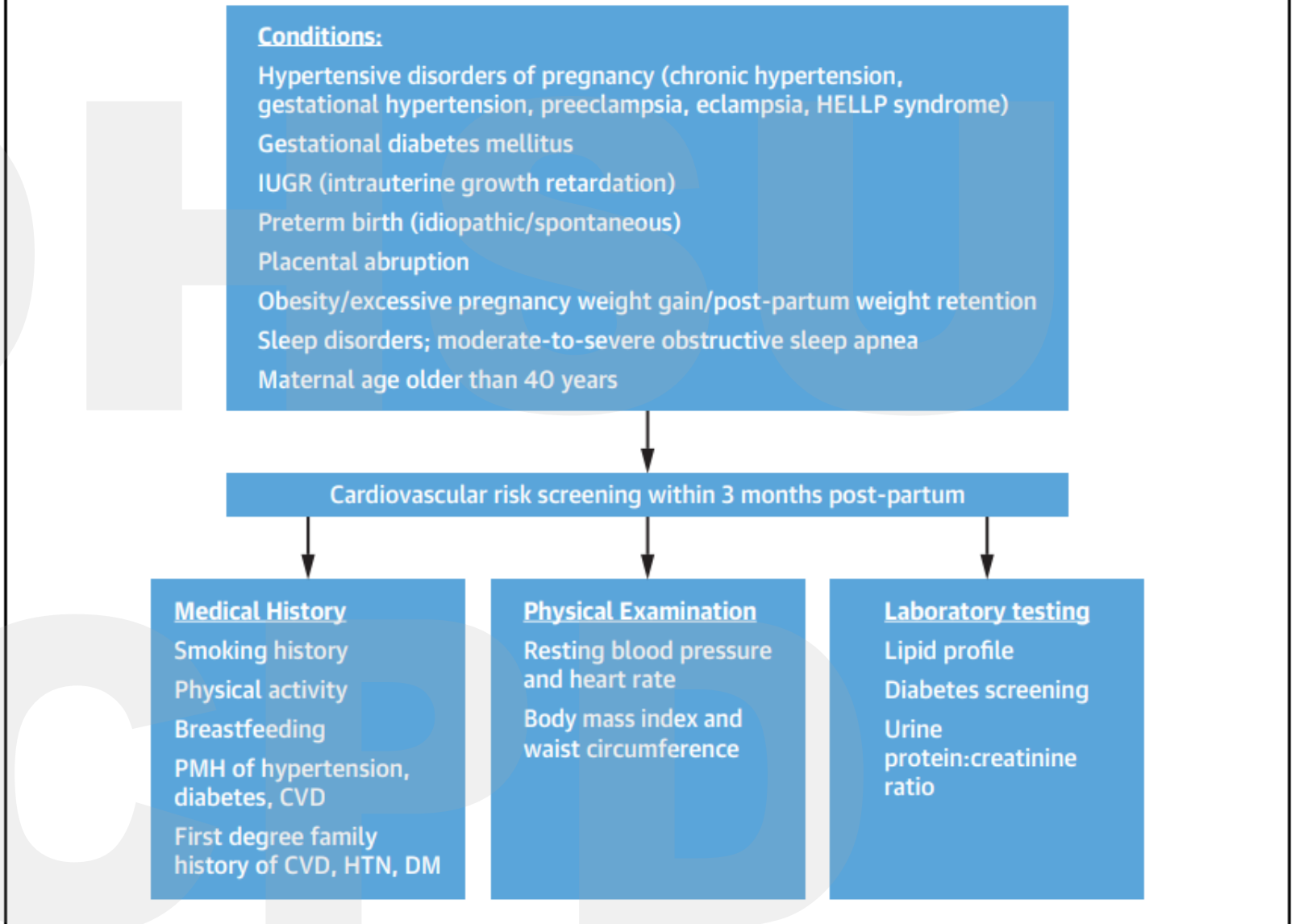




Ji et al. JACC 2024.

CV risk screening after adverse pregnancy outcomes is essential

FIGURE 1 Recommendations for Cardiovascular Risk Screening After Adverse Pregnancy Outcomes



Adverse pregnancy conditions that require further cardiovascular screening within 3 months post-partum based on medical history, physical examination, and laboratory. CVD = cardiovascular disease; DM = diabetes mellitus; HELLP = hemolysis, elevated liver enzyme, low platelet count; HTN = hypertension; IUGR = intrauterine growth restriction; PMH = past medical history.

Cho, L. et al. J Am Coll Cardiol. 2020;75(20):2602–18.

Stepping to Success: Reducing CVD Risk in Women

Step 1

Screen for Sex-specific Risk Factors:

- Prematurity
- Age at menarche
- Polycystic ovarian syndrome
- Hormone-based contraceptive use
- Recurrent spontaneous pregnancy loss
- Gestational diabetes
- Gestational HTN
- Pre-eclampsia
- Pre-term delivery
- Delivery of small for gestational age infant
- Early menopause/ premature ovarian failure

Step 2

If sex-specific risk factors are present:

1. Assess for traditional CVD risk factors early and more frequently
2. Screen for, prevent, & treat intermediate phenotypes

Hypertension
Diabetes
Hyperlipidemia
Metabolic Syndrome

Step 3

Begin aggressive risk factor management

Implement lifestyle modifications with AHA's Life's Simple 7:

1. Manage blood pressure
2. Control cholesterol
3. Reduce blood sugar
4. Stay active
5. Eat Healthy
6. Lose weight
7. Stop Smoking

Step 4

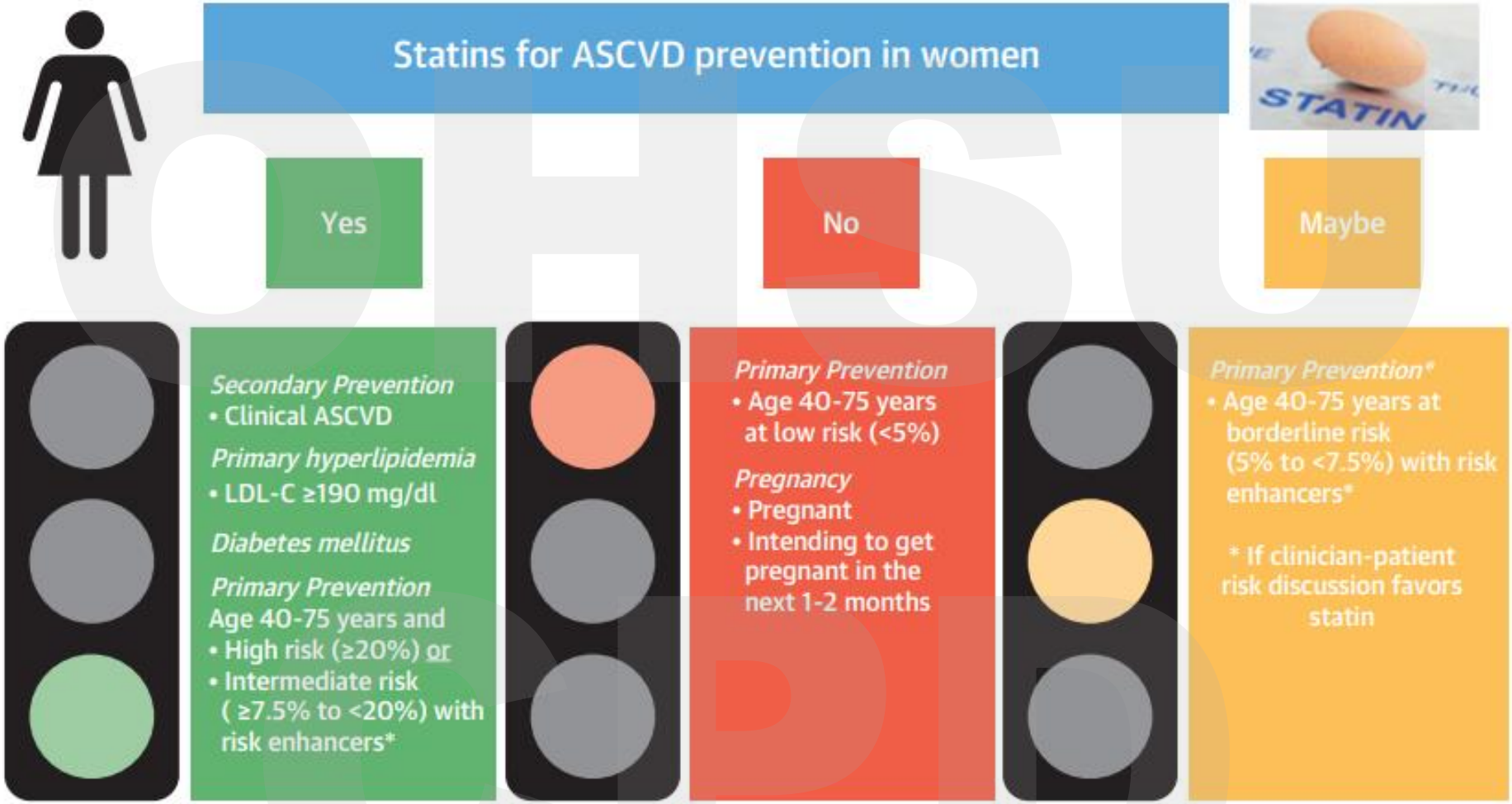
Estimate risk & treat accordingly with consideration of sex-specific risk factors:

1. Assess 10-year ASCVD Risk/ Lifetime risk

2. Treat early if borderline or intermediate risk and if sex-specific risk factors are present

Anandita Agarwala. Circulation. The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk, Volume: 141, Issue: 7, Pages: 592-599, DOI: (10.1161/CIRCULATIONAHA.119.043429)

FIGURE 3 Recommendations for Statin for ASCVD Prevention in Women

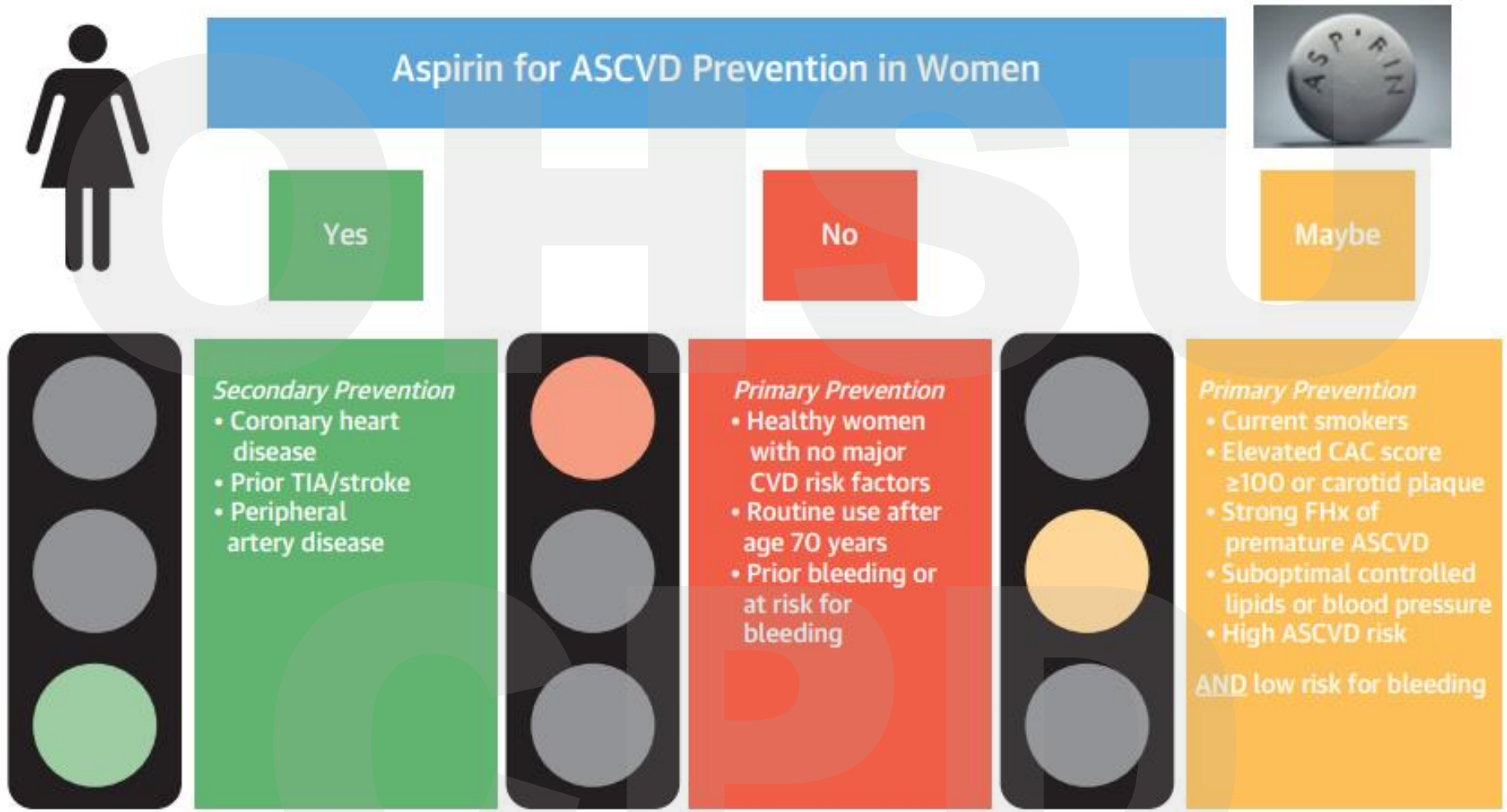


* Consider sex-specific risk enhancers: premature menopause and pregnancy-associated conditions that increase ASCVD risk

Statin therapy recommendations based on studies and guidelines. ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Cho, L. et al. J Am Coll Cardiol. 2020;75(20):2602–18.

FIGURE 4 Recommendation for Aspirin for ASCVD Prevention in Women



Aspirin therapy recommendation based on studies and guidelines. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CVD = cardiovascular disease; FHx = family history; TIA = transient ischemic attack.

Cho, L. et al. J Am Coll Cardiol. 2020;75(20):2602–18.

Opportunities for improvement

- Early screening for CVD
  - After pregnancy, during/after menopause
- Comprehensive CVD risk assessment
  - Consider sex-specific risk enhancers
  - Ask about pregnancy history
- Power clinical trials to identify sex-specific differences to produce reliable and effective guidelines and recommendations
  - Need more women enrolled in clinical trials
- Need increased awareness among clinicians about undertreatment and implicit bias
  - Suboptimal adherence to the prescription of GDMT is a well-recognized issue
  - Delayed diagnosis, under-referral, and a higher threshold to referral for invasive procedures remain major hurdles → outcome disparities

Summary

CVD remains the leading cause of mortality and morbidity in women, though it remains under-recognized and under-treated

CVD may present differently in women than men (symptoms and disease manifestation)

In addition to traditional CVD risk factors, sex-specific factors further increase CVD risk in women; some emerging risk factors have a higher influence in women

Prevention is key; impact of modifying risks is greater in women than in men

Thank You