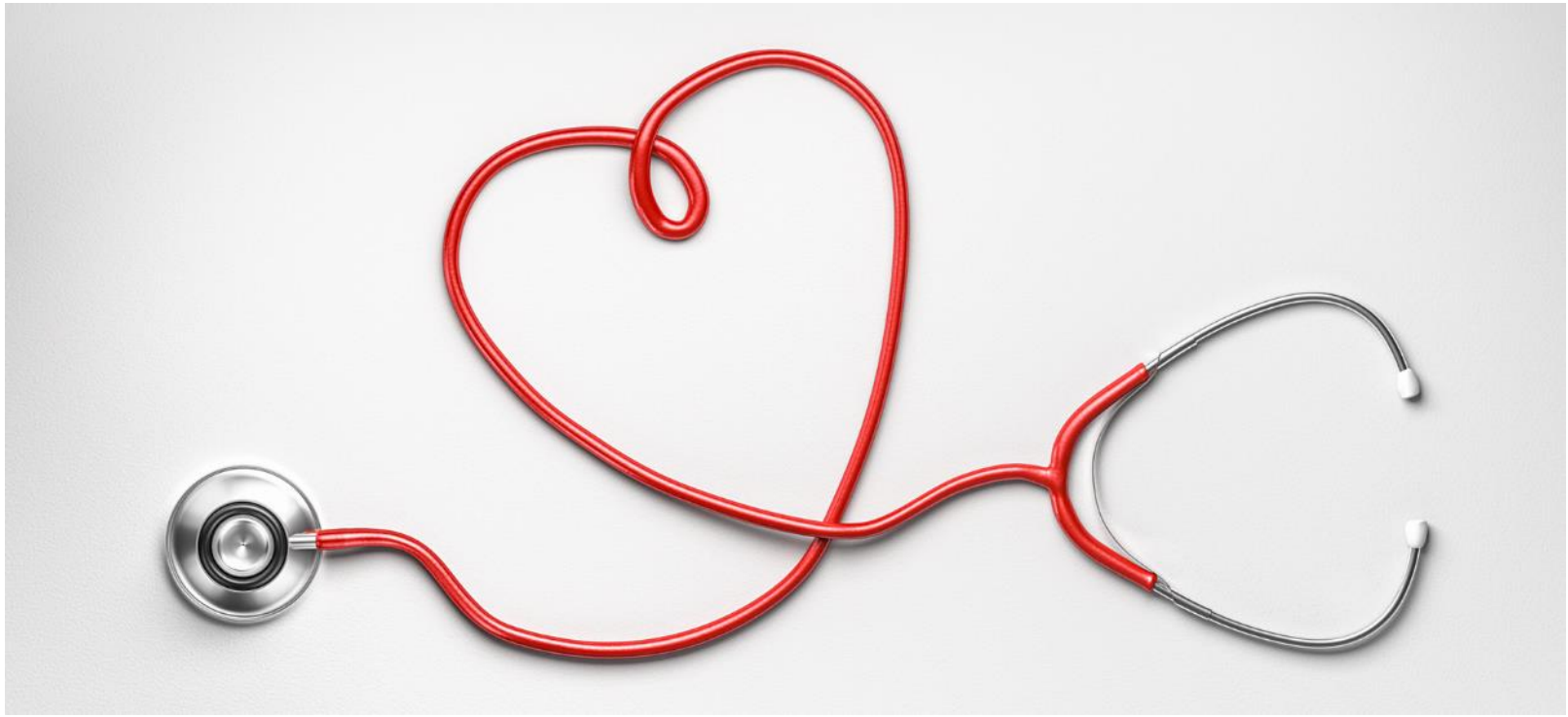

Differential Effects of Cigarette Smoking on Cardiovascular Disease in Females

Diann Gaalema, PhD

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DISCLOSURES

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- No conflicts to disclose

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OUTLINE

- Cardiovascular disease (CVD) and smoking
- Sex differences in smoking and CVD
- Potential mechanism behind increased risk
- Rates of smoking in those with CVD by sex
- Challenges in smoking cessation in those with CVD
- Implications for secondary prevention

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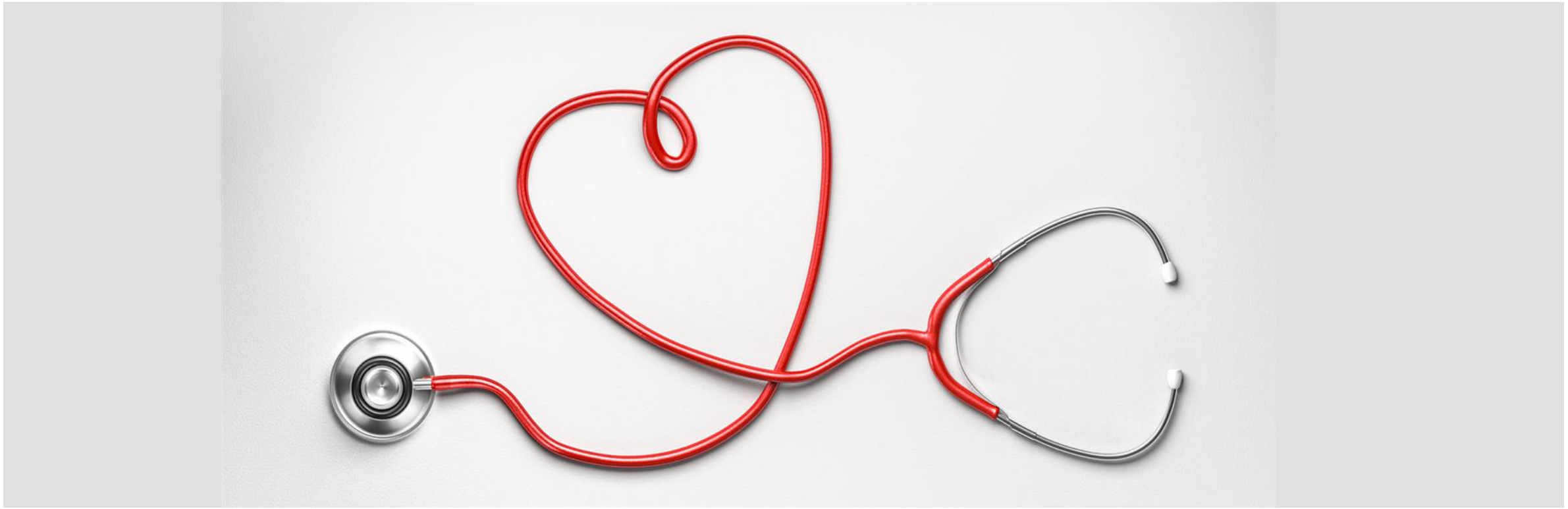
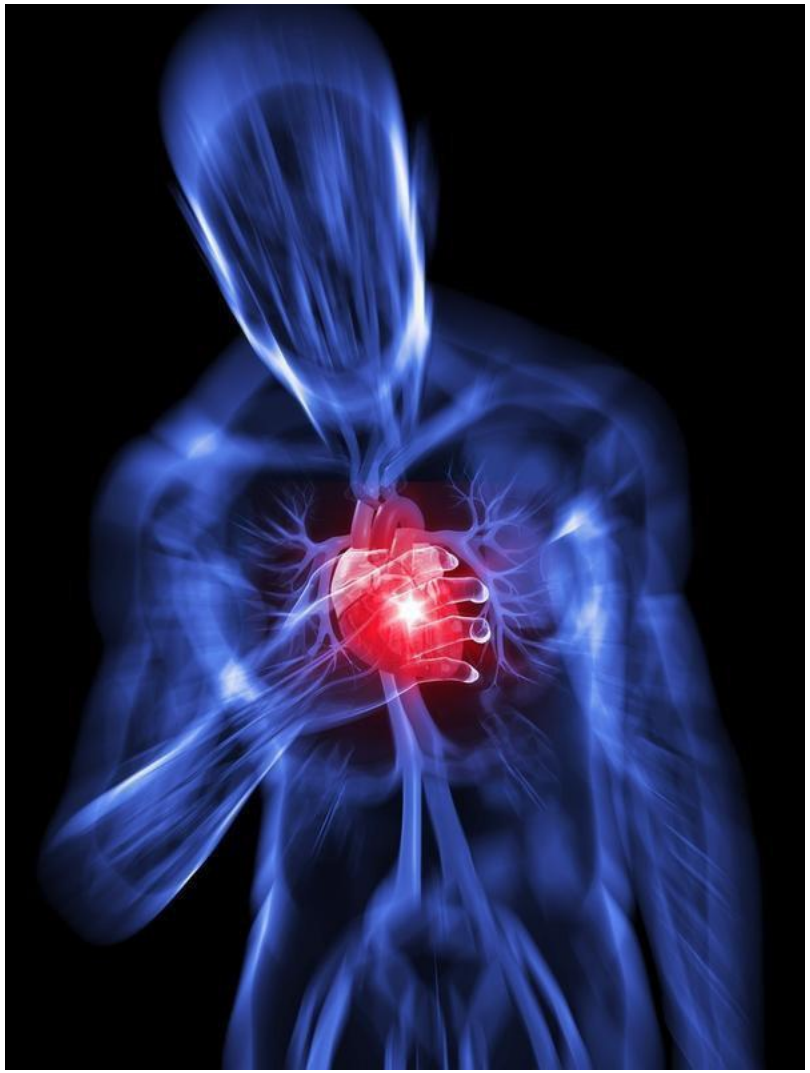


CARDIOVASCULAR DISEASE AND SMOKING

CARDIOVASCULAR DISEASE AND SMOKING

- Dangers of combusted tobacco use[1]
  - Endothelial dysfunction
  - Blood vessel constriction
  - Platelet activation
  - Dyslipidemia
  - Chronic inflammatory state
- Outcomes
  - Accelerate atherosclerosis
  - Destabilize coronary artery plaques
  - Precipitate acute coronary events
- 50 years of smoking has led to 7,787,000 premature deaths due to cardiovascular and metabolic diseases[2]



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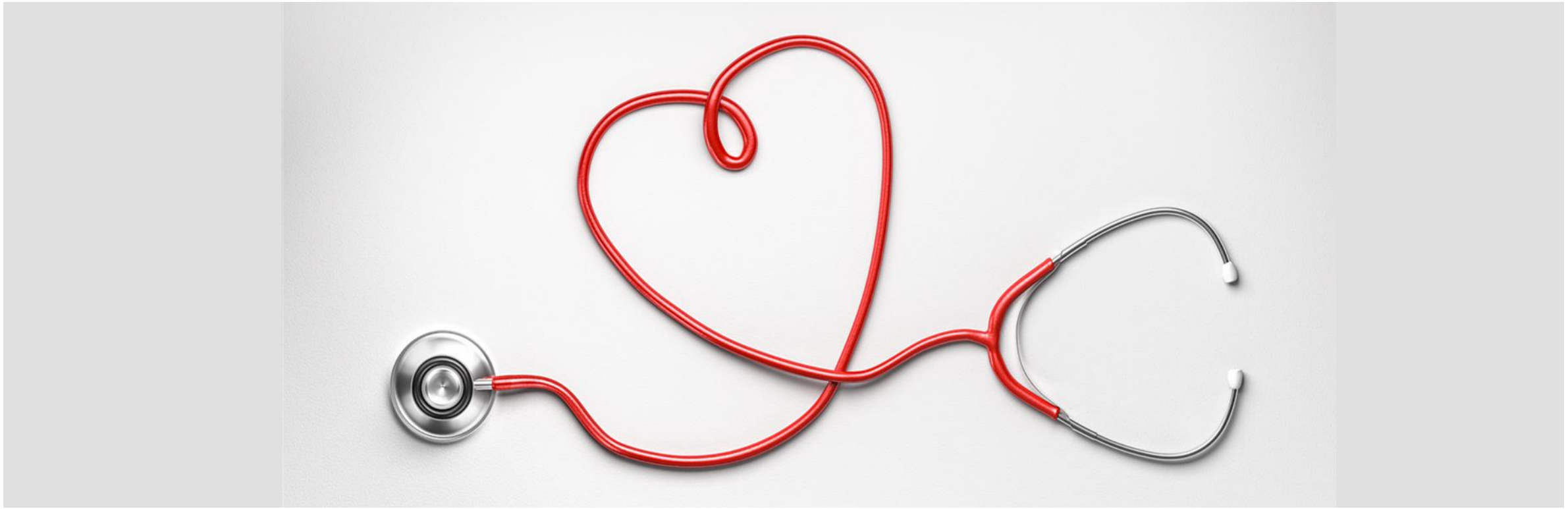
1. Barura et al., 2018. 2. USDHHS, 2014



SEX DIFFERENCES IN CARDIOVASCULAR DISEASE AND SMOKING

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SMOKING AND CVD – SEX DIFFERENCES

- Generally, an age gap in the development of CVD by sex
  - Age of first myocardial infarction[1]
    - 72 for females
    - 65.6 for males
- Smoking appears to eliminate the age gap
  - Study of 11,762 men and 13,206 women
    - Looking at increased risk of MI in females smoking ≥20 cigarettes per day
      - Aged 25-54, HR = 3.8
      - Aged 55-69, HR = 2.2
      - Aged ≥70, HR = 1.6
    - Do not see this same pattern in males
  - Similarly, we see males and females, who smoke, entering cardiac rehabilitation at a similar age[3]
    - Elevated CO – 63, did not differ by sex
    - Low CO – 67, likely differed by sex

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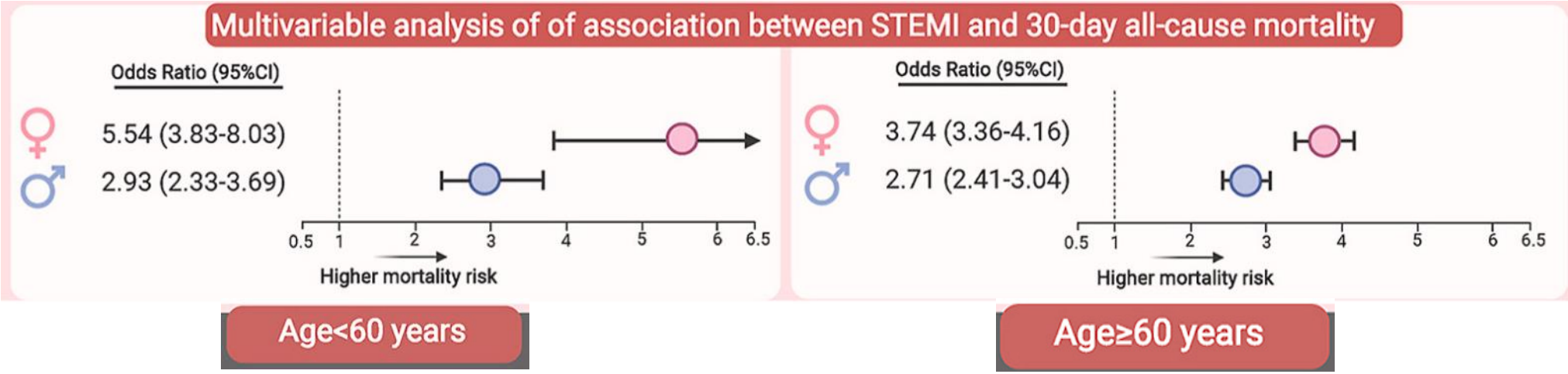
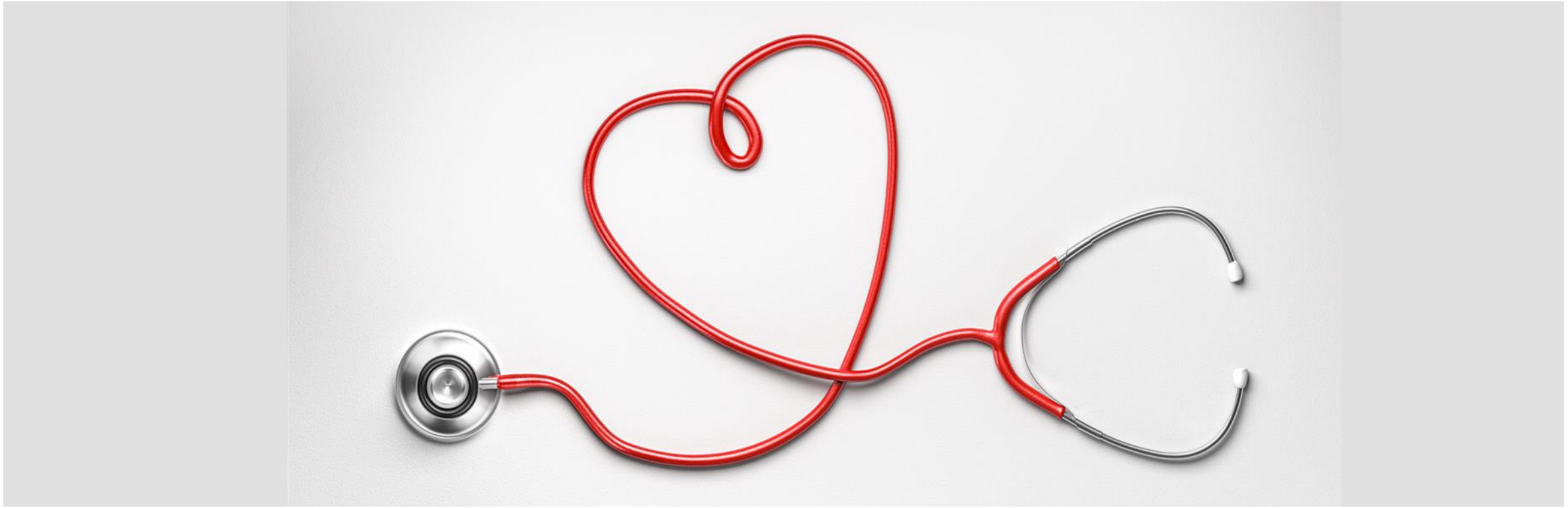
1. Tsao et al., 2022. 2. Everson et al., 2013. 3. Khadanga et al., 2022.

SMOKING AND CVD – MORE THAN JUST AGE AT FIRST EVENT

- Disparities in development of disease and outcomes
  - Within those who smoke, females have a 25% increased risk of developing CHD than males[1]
  - Multivariate-adjusted RR for CHD mortality: males 2.50 (95% CI, 2.34–2.66), females, 2.86 (95% CI, 2.65–3.08)[2]
- These discrepancies are even higher for certain types of CHD
- STEMI
  - Smoking is associated with a significantly greater increase in STEMI for females than males (IRR: 6.62 vs. 4.40)[3]
  - Outcomes disparate here too, higher association between STEMI and 30-day mortality in females compared to males (OR 3.86 vs. 2.75)[4]



1. Huxley et al., 2011. 2. USDHHS 2014. 3. Palmer et al., 2019. 4. Vasiljevic et al., 2021



POTENTIAL MECHANISM OF INCREASED RISK

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USE OF NICOTINE/COMBUSTION REDUCES ESTROGEN LEVELS

- The relationship between tobacco use, estrogen levels, and the risk of cardiovascular disease (CVD) in females is complex and multi-faceted
  - **Hypothalamic-pituitary-Ovarian Dysfunction**: Nicotine has been shown to adversely impact ovarian function by inhibiting the secretion of gonadotropin-releasing hormone (GnRH), essential for estrogen synthesis[1]
  - **Hepatic Enzyme Induction**: Compounds in tobacco smoke induce the activity of cytochrome P450 liver enzymes, which accelerate the metabolism (e.g. 2'-hydroxylation) and clearance of estrogen from the body[2]
  - **Inhibition of Aromatase Enzyme**: The aromatase enzyme (CYP19A1) converts androgens to estrogens. Nicotine and polycyclic aromatic hydrocarbons (PAH) appear to inhibit aromatase activity, reducing the endogenous production of estrogen[3,4]

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1. Mohaddghasemi 2012. 2. Michnovicz et al., 1986. 3. Biegon et al. 2012. 4. Tiwari et al. 2021

MECHANISMS OF INCREASED CVD RISK

- **Endothelial Dysfunction**: Estrogen plays a pivotal role in maintaining vascular health by enhancing nitric oxide (NO) production, an endothelial-derived vasodilator. Reduced estrogen levels diminish NO availability, promoting vasoconstriction and thereby increasing the risk of cardiovascular events[1]
- **Pro-inflammatory State:** Reduced estrogen levels tip the balance towards a pro-inflammatory state characterized by elevated levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, further contributing to the pathogenesis of CVD[2]
- **Altered Lipid Metabolism**: Estrogen has a favorable effect on lipid profiles, increasing high-density lipoprotein (HDL) and reducing low-density lipoprotein (LDL) levels. Lowered estrogen due to tobacco use exacerbates dyslipidemia, a known risk factor for CVD[3]
- **Increased Platelet Aggregation**: Lower levels of estrogen have been linked to increased platelet aggregation and elevated plasma fibrinogen levels, enhancing the pro-thrombotic milieu conducive to MI and CVA[4]
- **Synergistic Negative Effects**: Combusted tobacco itself directly contributes to endothelial dysfunction, inflammation, and platelet aggregation. When combined with reduced estrogen levels, this results in a synergistic deleterious impact on cardiovascular health[5]

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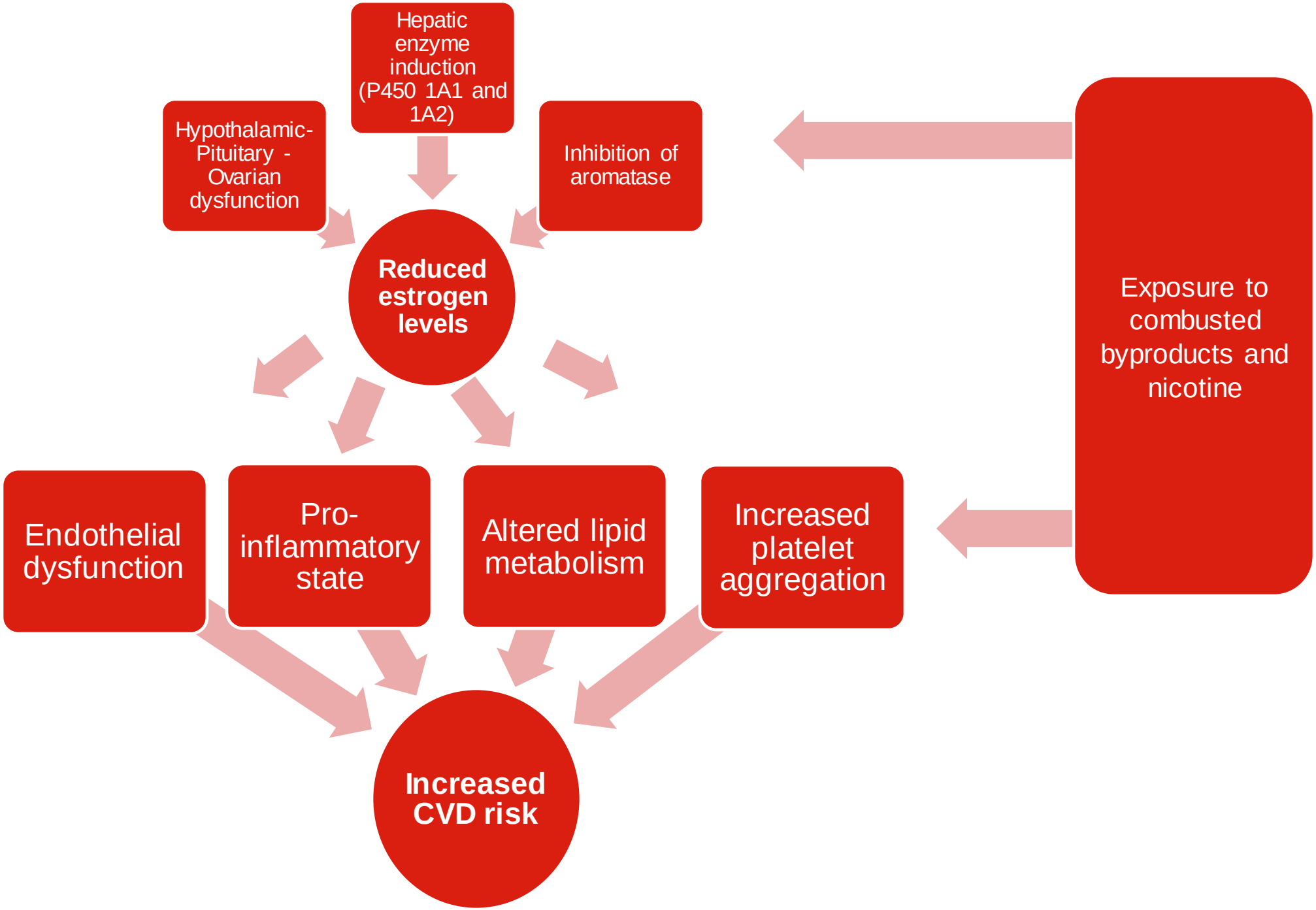
1. Mendelsohn & Karas, 1999. 2. Ridker et al., 2002. 3. Walsh et al., 1991. 4. Scarabin et al., 1997. 5. Ambrose & Barua, 2004


Hepatic enzyme induction (P450 1A1 and 1A2)
Hypothalamic-Pituitary - Ovarian dysfunction
Inhibition of aromatase
Reduced estrogen levels
Exposure to combusted byproducts and nicotine
Endothelial dysfunction
Pro-inflammatory state
Altered lipid metabolism
Increased platelet aggregation
Increased CVD risk

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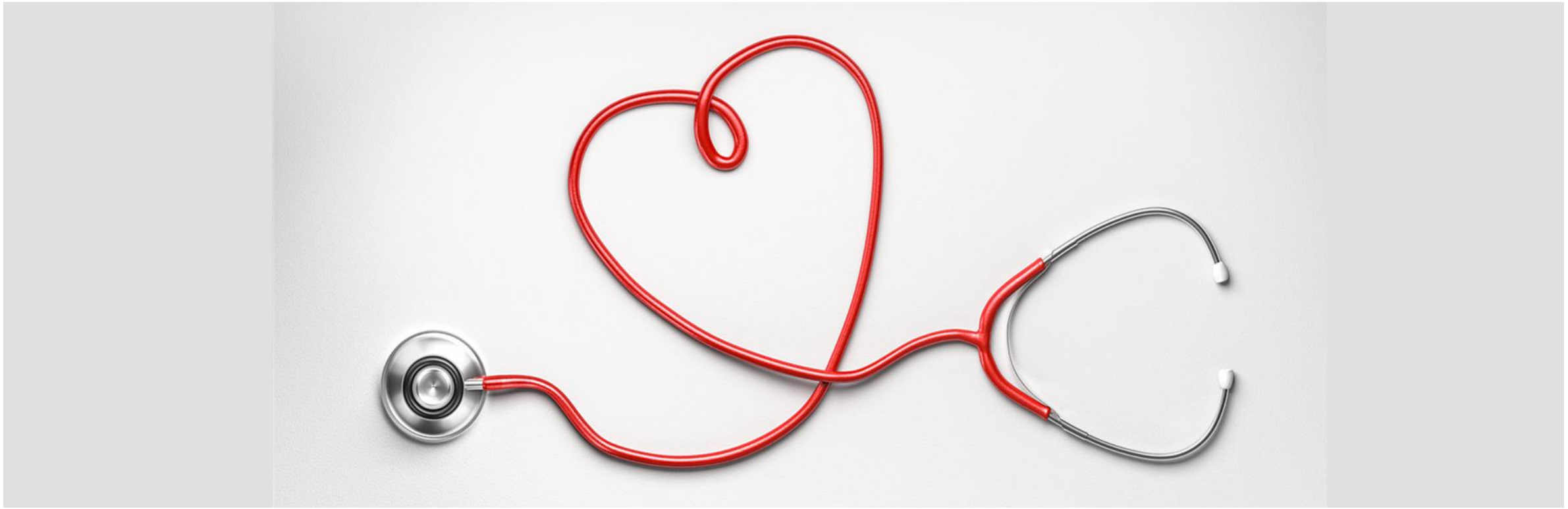

RATES OF SMOKING IN THOSE WITH CARDIOVASCULAR DISEASE BY SEX

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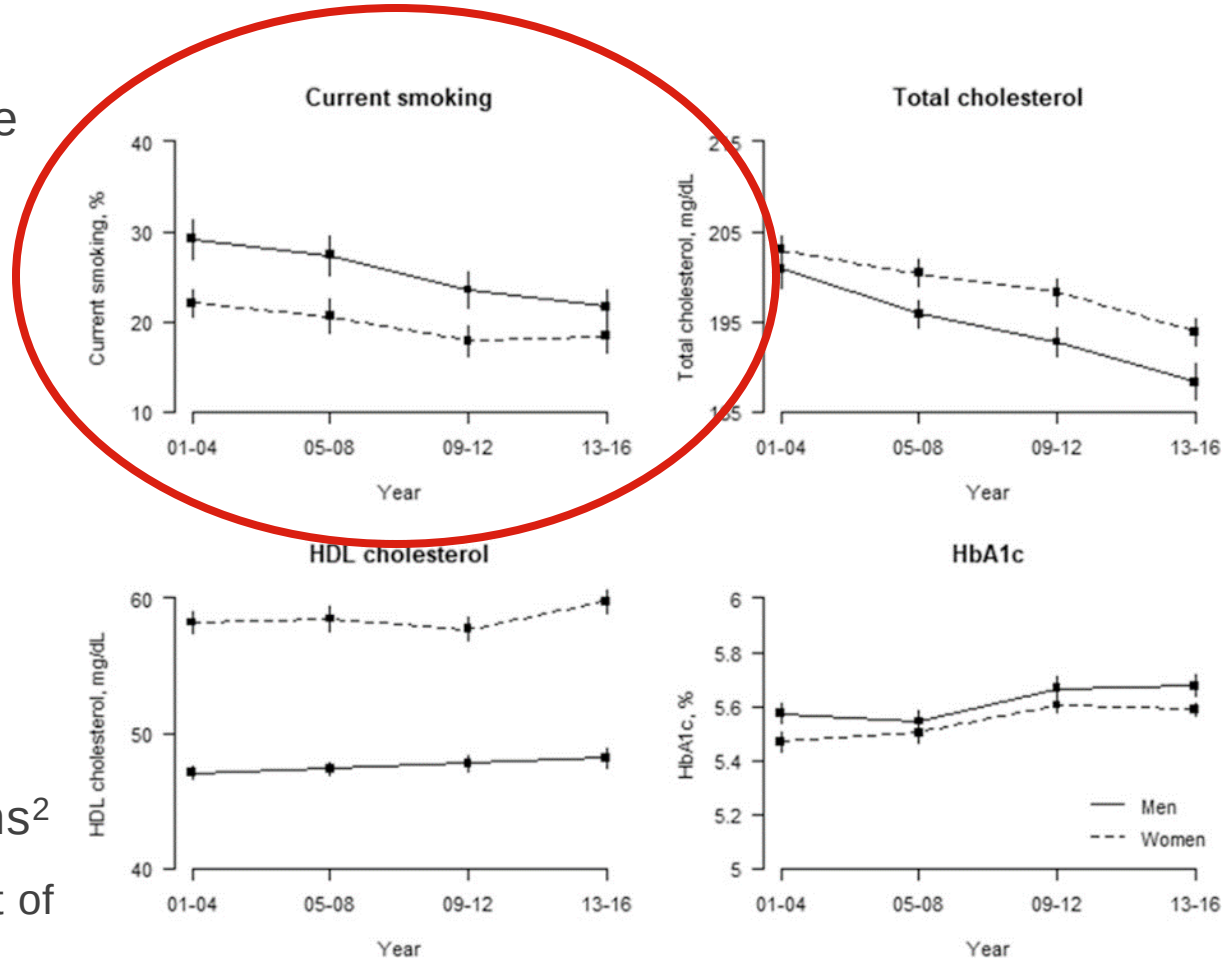
SMOKING RATES BY SEX IN THOSE WITH CVD

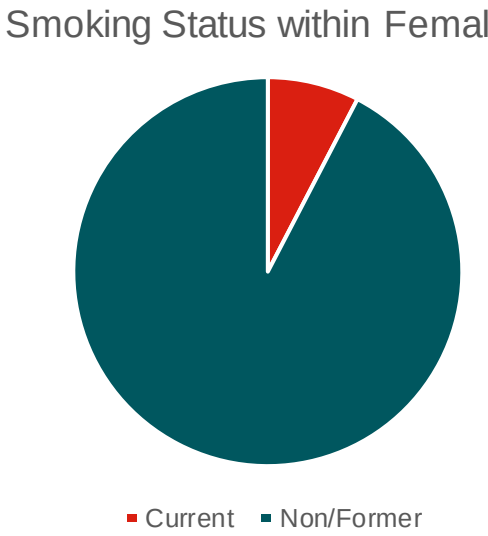
- Historically, males have been more likely to smoke which may have led to less focus on the issue of smoking in females
- Over the last several decades, the prevalence of smoking in the United States has dramatically decreased
  - Decreasing faster in certain populations
- Looking at the NHANES, risk factors by sex over time in those 20-79 years of age[1]
  - Current smoking decreasing faster in males
- A pattern replicated in other vulnerable populations[2]
  - Female smoking rates may actually overtake that of males

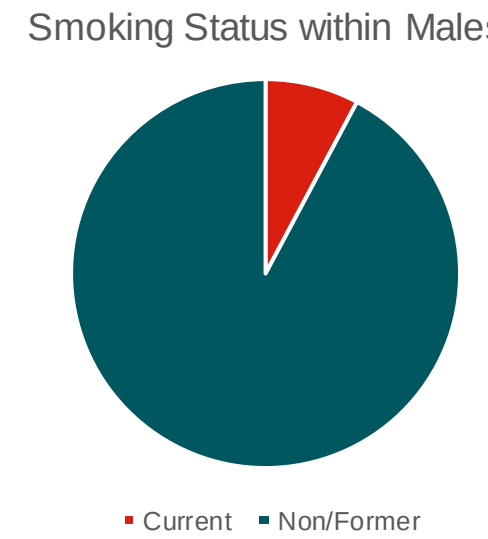


1. Peters et al., 2019. 2. Cepeda-Benito et al., 2018

SMOKING RATES BY SEX IN CARDIAC REHABILITATION

- AACVPR Registry Database
  - Data from certified programs nation-wide
  - Over 400,000 patients from 2012-2021
    - ~30% female
- Current smoking rates at entry are equal
  - Females: 7.6%
  - Males: 7.8%





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CHALLENGES OF SMOKING CESSATION IN THOSE WITH CARDIOVASCULAR DISEASE

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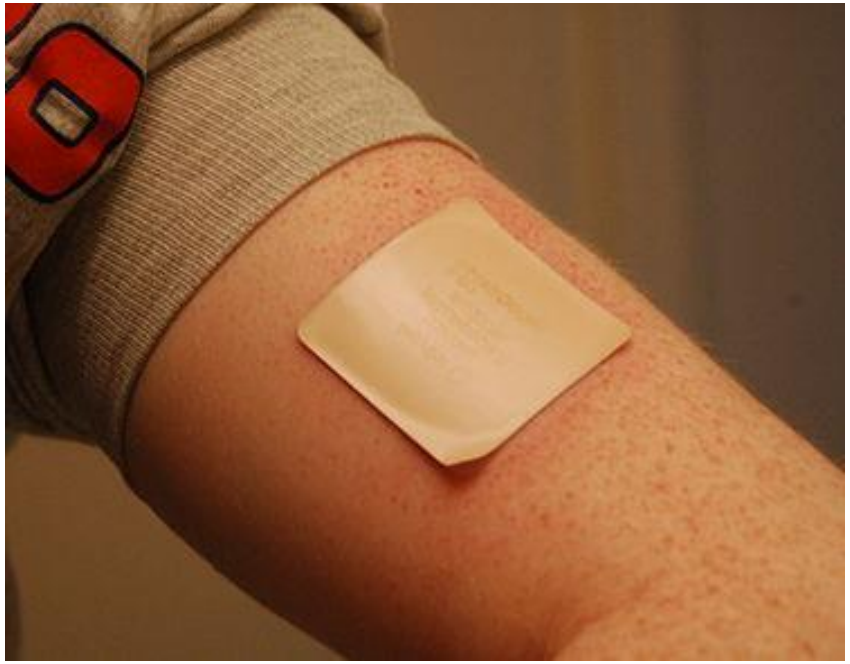
SMOKING CESSATION IS CHALLENGING

- Efficacious medications available
  - NRT
  - Bupropion
  - Varenicline
  - Combination therapies likely best
- Efficacy and safety demonstrated, including in those with CVD[1-5]
  - Still strong hesitancy for use in populations with CVD
- In a study of 282 hospitals and over 30,000 patients hospitalized with CHD who were currently smoking[6]
  - Only 22.7% of patients received any sort of medication for smoking cessation
  - 90% of those were for nicotine patch alone



1. Anthenelli et al., 2016; 2. Pack, Priya, et al., 2018; 3. Benowitz et al., 2018; 4. Woolf et al., 2012, 5. Mills et al., 2014. 6. Pack et al., 2017.

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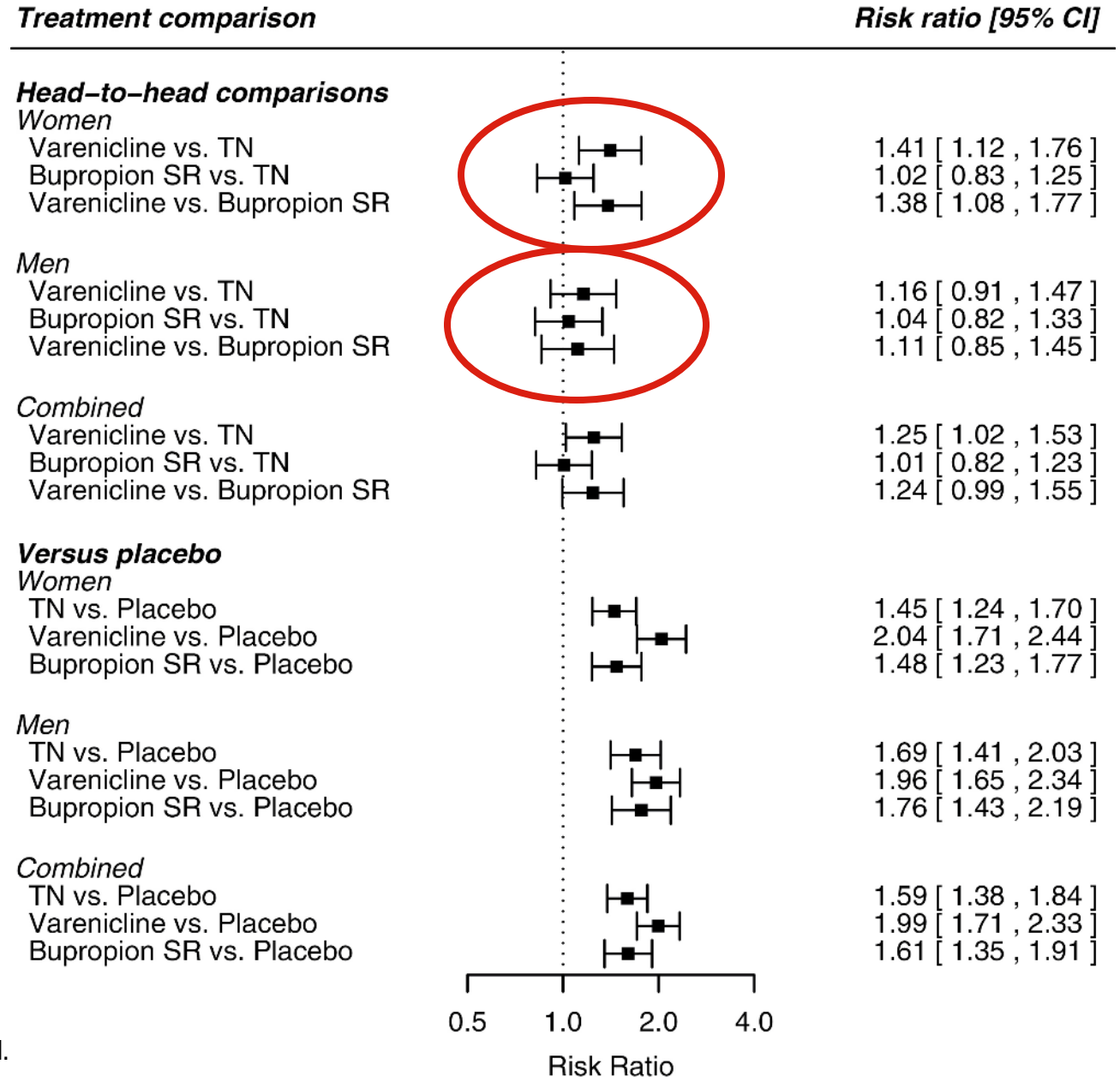
RELYING ON NRT MAY BE PROBLEMATIC FOR FEMALES

- NRT may not be as effective for females as males[1,2]
  - Females may be less sensitive to the pharmacological effects of nicotine[3]
  - Females metabolize nicotine faster than males
    - Under dosed on nicotine replacement therapy?



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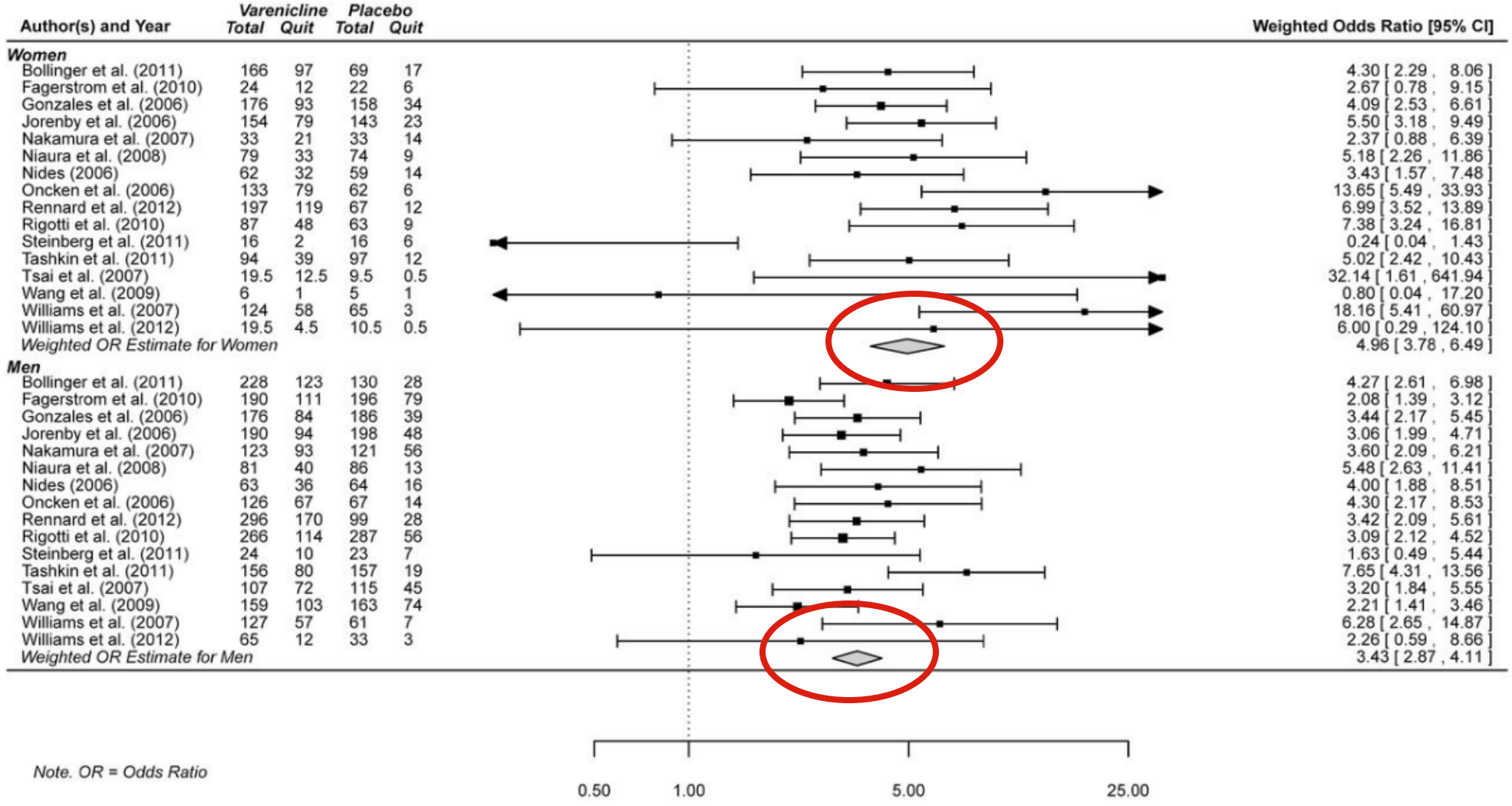
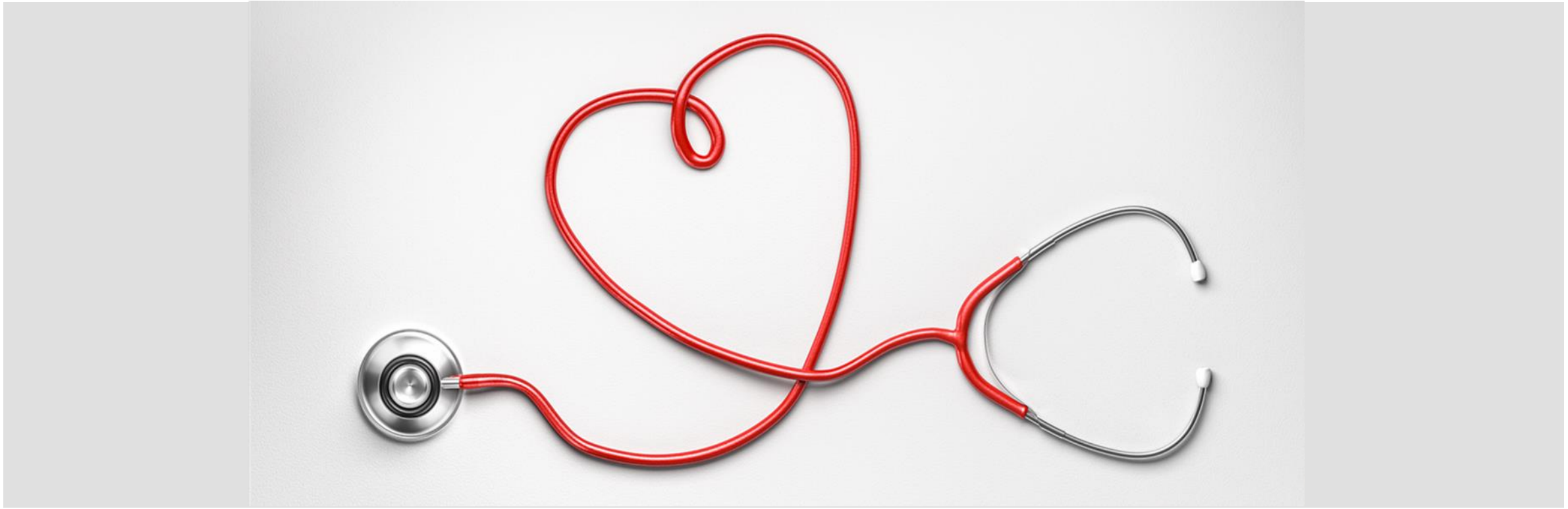
1. Smith et al., 2017. 2. Piper et al., 2010.3. Perkins et al.

RELYING ON NRT MAY BE PROBLEMATIC FOR FEMALES

- Other medications may work better for females[1]
- Relying on NRT for treating smoking in those with CVD may continue to widen sex disparities



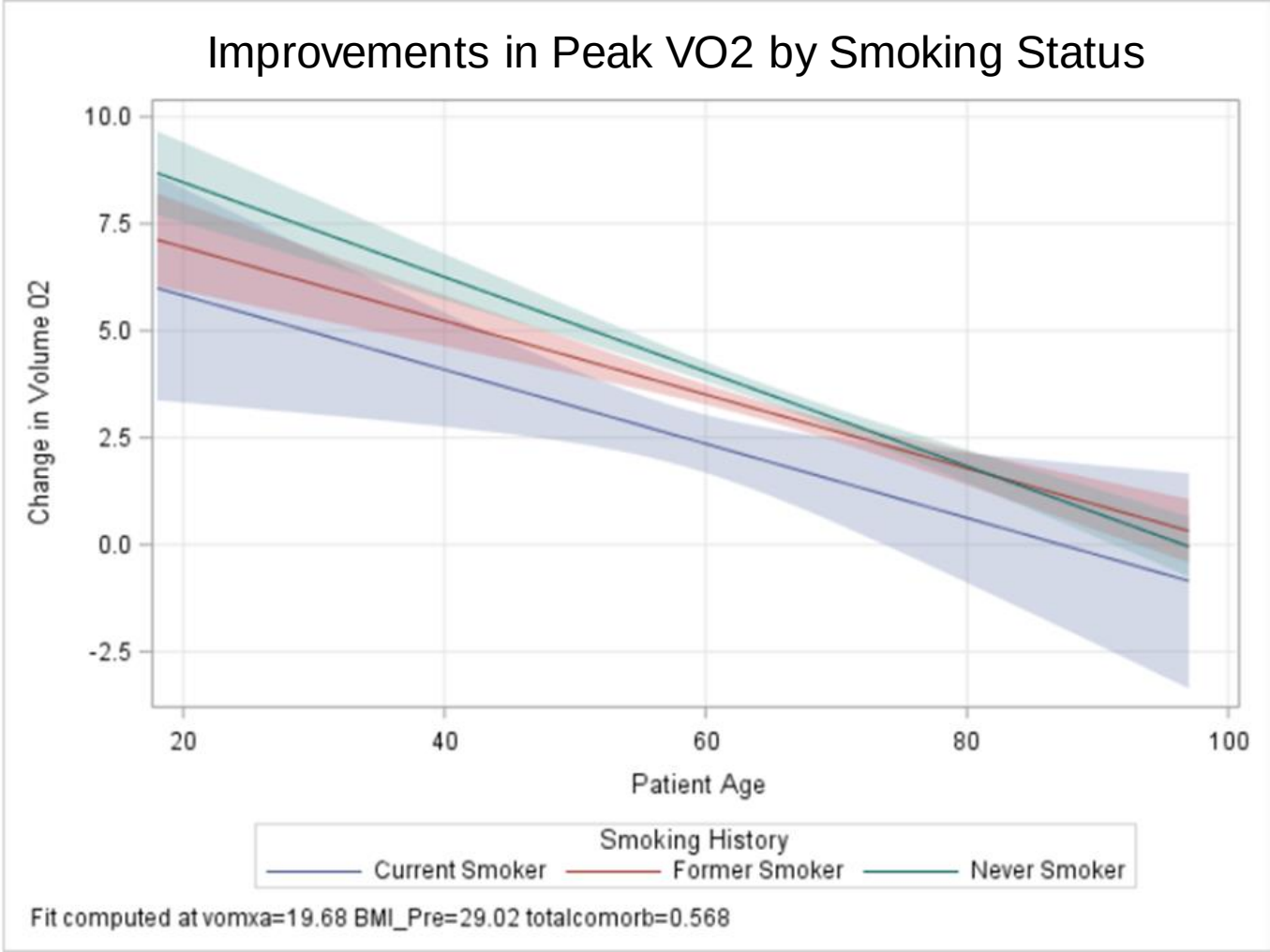
1. McKee et al., 2016



IMPLICATIONS FOR SECONDARY PREVENTION/CARDIAC REHABILITATION

IMPLICATIONS FOR CARDIAC REHABILITATION/SECONDARY PREVENTION

- Smoking can interfere with gains during CR
- UVMMC Clinical CR database
  - 2208 patients who completed CR
    - 553 female
- Improvement in fitness (Peak VO2)
  - Effect of current smoking (self-report)
  - No sex effect



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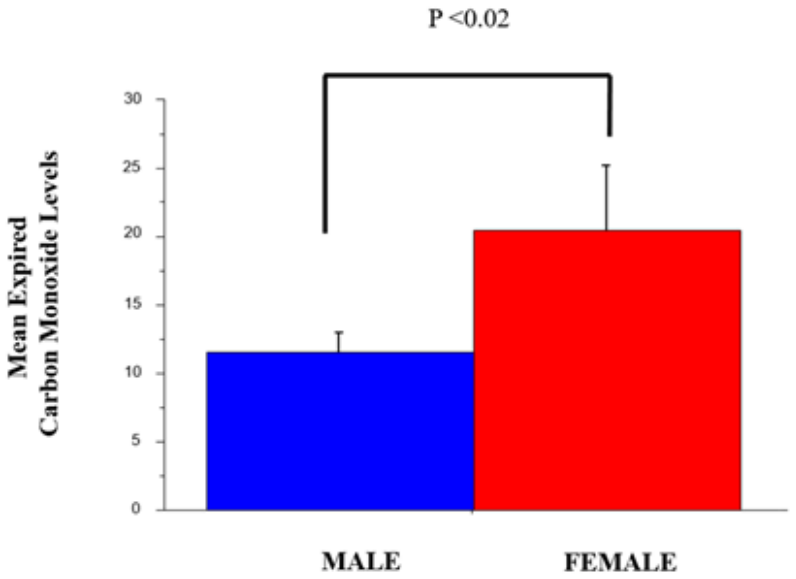
IMPLICATIONS FOR CARDIAC REHABILITATION/SECONDARY PREVENTION

- Do those who smoke differ by sex?
- Carbon monoxide measured on 1122 patients entering CR
  - 322 females
- Focused on those with CO ≥ 4
  - Examined differences by sex



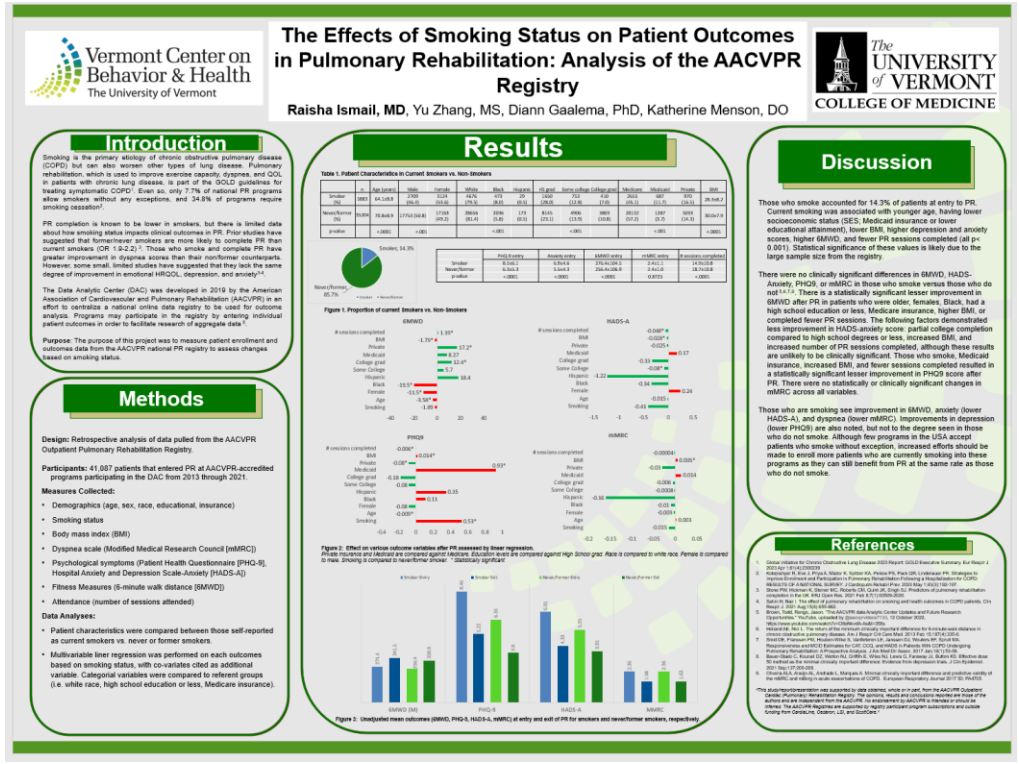
Females with elevated CO had CO levels double that of males

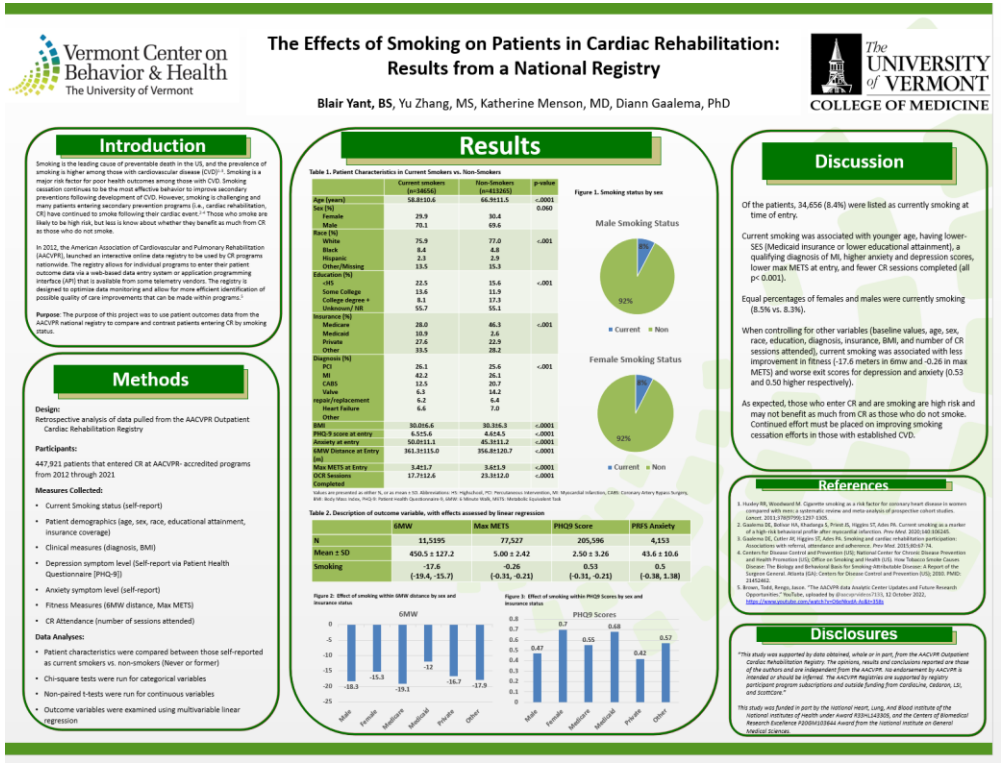
Khadanga et al., 2022

EFFECT OF SMOKING ON OUTCOMES IN CR/PR

Check out the poster session

More in-depth on how smoking affects outcomes





THANK YOU

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