Sex and Gender Differences in Cardiovascular Risk Factors: What Really Makes the Difference?

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Disclosures

I do not have an affiliation (financial or otherwise) with a for-profit or non-profit organization
Learning Objectives

1. Summarize sex differences in the prevalence of cardiovascular disease risk factors

2. Outline sex differences in the magnitude of effects of cardiovascular disease risk factors
Percent distribution of the ten leading causes of death, by sex

Mauvais-Jarvis et al., 2020, Lancet
Cardiovascular Disease Death Trends for Males and Females in the United States
1979-2011

Mozaffarian D et al. Circulation. 2015;131:e29-e322
Age and Trends in CHD Mortality

CHD mortality in males and females
age <55 years, 1979-2011

CHD mortality in males and females
age 55-64 years, 1979-2011

CHD mortality in males and females
age 65+ years, 1979-2011

Wilmot et al. Circulation, 2015;132:998-1002
Rate of AMI Increased in the Young, Especially in Females

Izadnegahdar et al., 2014, J Women’s Health
• 15.8% of Canadians (4.9 Million) smoke cigarettes (2018)

• Sex Specific prevalence
  ▪ Females: 13%
  ▪ Males: 18.4%
Sex Differences in Impact of Smoking on CVD
Sex Differences in Impact of Smoking on CVD

- 25% increased risk of CVD in female smokers compared to male smokers
- Risk of CVD Development higher in younger (<60 y/o) females compared to males

Huxley 2011
Oliveira 2007
Reitsma 2017
Biological Mechanisms for Severity of Smoking in Females

- Higher degree of carcinogen and toxin (carbon monoxide (CO), serum thiocyanate and serum cotinine) absorption in women
- Higher reduction in HDL compared to men
- Antiestrogenic effect of cigarette smoking
- Synergistic effect of smoking and oral contraceptive use on risk of cardiovascular disease
Sex Difference in Diabetes Prevalence

- 7.3% (2.3 Million) of Canadians are diagnosed with DM (2017)

- Sex Specific prevalence
  - Females: 6.3%
  - Males: 8.4%

Sex Differences in Impact of DM on CVD Outcome

Age-adjusted risk ratio

<table>
<thead>
<tr>
<th>Event</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD Event</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>4.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Coronary Mortality</td>
<td>3.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Relative risk (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD Event</td>
<td>3.69 (2.64 to 5.15)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2.16 (1.77 to 2.64)</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>3.12 (2.34 to 4.17)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.99 (1.69 to 2.35)</td>
</tr>
</tbody>
</table>

P value for heterogeneity

- Heart Failure: 0.007
- Coronary Heart Disease: 0.008
Potential Explanations

- Period from normoglycemia to Type 2 diabetes, females have greater and prolonged exposure to other CV risk factors:
  - Central Obesity
  - Insulin Resistance

  Endothelia dysfunction
  Inflammation
  Hypocoagulability
  Dyslipidemia
  Hypertension

Gestation Diabetes increase the risk of future diagnosis of DM
Sex Differences in Hypertension Prevalence

- Global age-standardized prevalence (2010)
  - Females: 15.8%
  - Males: 18.4%

- 2-3X more common in females who
  - Take OCP
  - Are obese (BMI >30)

- Sharper incline in HTN in females after 3rd decade of life

Hypertension and CVD risk

- Significantly higher AMI attributable risk in females
  - 36% in females
  - 19% in males

- Gestational hypertension in the first pregnancy increases the risk of CVD by 45%

- Pre-eclampsia increase the risk of
  - Hypertension by 4-folds
  - CHD by 2-folds

Ji et al 2020
Wen Lo et al 2020
Yusuf et al 2004
Association between risk factors and incident myocardial infarction (Males vs Females)

Consistently elevated risk of MI in Females compared to Males in the presence of

- Hypertension
- Smoking Status
- Diabetes Mellitus (Type 1 and Type)
Sex Differences in Dyslipidemia Prevalence

- Lower LDL-C (2.66 mmol/L) TC:HDL-C ratio (3.3) in females compared to males (LDL-C: 2.93 mmol/L, TC:HDL-C ratio: 4.1)

- More favorable lipid profile in females after AMI

- Not a major factor contributing to differences in CVD outcomes observed between females and males
63.1% of Canadians (17.2 million adults) are considered overweight or obese (2018)

- Sex Specific prevalence
  - Females: 56.7%
  - Males: 69.4%
Obesity and CVD in Females

- Females predisposed to obesity and metabolic diseases
- Higher rate of insulin resistance in females
- Prevalence of visceral obesity 2X-10X higher in females
- Females with obesity at elevated risk of ischemic heart disease:
  - 64% risk in females
  - 46% risk in males

Wilson et al 2002
Regensteiner et al, 2015
Tonstand 2007
• Only 15% of Canadian adults meet the recommended daily activity

• Females have higher prevalence of inactivity compared to males (31.4% vs. 21.7%)
Significant Improvement in Active Females

- Reduction of Ischemic heart disease and stroke independent of other risk factors in females
  - Increased Protective effect in females than males ($\text{OR}=0.5$ vs $\text{OR}=0.8$)

- Higher risk of CVD in sedentary females ($\leq 1.7$ MET-h/week) than males

Association between physical activity dose-response and cardiovascular disease in 3 prospective studies of females

Carnethon et al, 2009
Why Sex Differences in CVD Outcome?

✓ Biological Variations Between males and females

✓ Limited evidence available for females in clinical trials

✓ Non-Biological Considerations; Social Determinants of Health
Biological Mechanism for Worst CVD Outcome in Females

• Hypothesized that compared to males, females have more:
  - Abnormal Coronary reactivity
  - Microvascular Dysfunction
  - ↑ Plaque erosion
  - ↑ Distal microembolization
  - Impaired endothelium-dependent vasodilation
  - Hypercoagulable state

Garcia et al., 2017
Possible Non-biological Factors for Worst CVD Outcome in Females

• Less aggressive treatment regimen → less likely to be prescribed optimal dose
  - Lower statin prescription in women with DM and hyperlipidemia compared to men
  - Blood pressure typically not optimized by medication in women

• Women are less likely to be referred to and participate in cardiac rehabilitation

• Current CVD risk score threshold determined in male-based populations

Garcia et al., 2017
Lower Enrolment of Females in Cardiovascular Clinical Trials

Of 740 RCTs 862 652 adults, only 38.2% were female

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Trials, N (%)</th>
<th>Female, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>740</td>
<td>329 633 (38.2)</td>
</tr>
<tr>
<td>Disease</td>
<td>740</td>
<td>329 633 (38.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>87 (11.8)</td>
<td>114 561 (52.3)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>106 (14.3)</td>
<td>86 036 (40.5)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>141 (19.1)</td>
<td>25 783 (27.3)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>61 (8.2)</td>
<td>37 012 (26.9)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>36 (4.9)</td>
<td>4853 (76.3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>102 (13.8)</td>
<td>12 948 (28.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (18.4)</td>
<td>22 875 (42.4)</td>
</tr>
<tr>
<td>Multioutcome</td>
<td>71 (9.6)</td>
<td>25 565 (27.3)</td>
</tr>
</tbody>
</table>
Sex ≠ Gender

Sex
✓ Male or female
✓ Biologically defined

Gender
✓ Self-representation or societal characterization of femininity and masculinity
✓ Shaped by environment and experience
Sex and Gender Differences

SEX as biological variable across the lifespan

EXPOSURE

OUTCOMES

Gender as a cultural variable across the lifespan

GENDER RELATIONS
(e.g. emotional support, civil status)

GENDER ROLE
(e.g. work situation, household primary earner, childcare responsibility, responsibility for housework)

INSTITUTIONALIZED GENDER
(e.g. personal income, level of education, job value and quality, social standing)

GENDER IDENTITY
(e.g. personality traits, stress level)
# Four Aspects Representing Gender

Table 1. Four aspects representing gender according to the Women Health Research Network of the Canadian Institutes of Health Research

<table>
<thead>
<tr>
<th>Gender Aspects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Roles</td>
<td>Represent the behavioral norms applied to men and women in society, which influence individuals’ everyday actions, expectations, and experiences. Gender roles often categorize and control individuals within institutions such as the family, the labor force, or the educational system.</td>
</tr>
<tr>
<td>Gender Identity</td>
<td>Describes how we see ourselves as female or male (or as a third gender), and affects our feelings and behaviors.</td>
</tr>
<tr>
<td>Gender Relations</td>
<td>Refer to how we interact with or are treated by people in the world around us, based on our ascribed gender.</td>
</tr>
<tr>
<td>Institutionalized Gender</td>
<td>Reflects the distribution of power between men and women in the political, educational, and social institutions in society. The institutionalized aspect of gender also shapes social norms that define, reproduce, and often justify different expectations and opportunities for men and women.</td>
</tr>
</tbody>
</table>

GENESIS PRAXY Study

Study Design

- Case-only Study (in-built prospective follow-up of ACS cases)
- Target sample size: 1,576
- Multicenter: 24 sites in Canada, 1 site in US, 1 site in Switzerland

Inclusion Criteria

- ACS case definition (enzymes or symptoms or EKG)
- Age 18-55 years
- Fluent in English and/or French
- Able to provide informed consent
Gender Score Distribution in Men and Women With Premature Acute Coronary Syndrome

### TABLE 4. Patient Demographic and Clinical Characteristics According to Tertiles of the Gender Score

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Tertile 1 Masculine Characteristics</th>
<th>Tertile 2 Masculine and Feminine Characteristics</th>
<th>Tertile 3 Feminine Characteristics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>48 (8)</td>
<td>48 (7)</td>
<td>48 (7)</td>
<td>.70</td>
</tr>
<tr>
<td>Married or common law</td>
<td>258 (86)</td>
<td>116 (58)</td>
<td>186 (60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Women</td>
<td>6 (2)</td>
<td>60 (20)</td>
<td>207 (66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men</td>
<td>294 (98)</td>
<td>240 (80)</td>
<td>102 (34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race, white</td>
<td>267 (89)</td>
<td>266 (85)</td>
<td>272 (88)</td>
<td>.43</td>
</tr>
<tr>
<td>Clinical profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>132 (44)</td>
<td>133 (43)</td>
<td>173 (56)</td>
<td>.004</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>175 (59)</td>
<td>165 (55)</td>
<td>162 (52)</td>
<td>.32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37 (12)</td>
<td>38 (13)</td>
<td>71 (23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>120 (40)</td>
<td>113 (38)</td>
<td>124 (40)</td>
<td>.77</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>62 (21)</td>
<td>58 (19)</td>
<td>84 (27)</td>
<td>.046</td>
</tr>
<tr>
<td>Smoking</td>
<td>111 (37)</td>
<td>121 (40)</td>
<td>133 (43)</td>
<td>.95</td>
</tr>
<tr>
<td>Significant depression (score ≥8 on the HADS)</td>
<td>58 (19)</td>
<td>66 (22)</td>
<td>90 (29)</td>
<td>.013</td>
</tr>
<tr>
<td>Significant anxiety (score ≥8 on the HADS)</td>
<td>92 (31)</td>
<td>122 (41)</td>
<td>167 (54)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

IQR = interquartile range; CVD = cardiovascular disease; HADS = Hospital Anxiety and Depression Scale.

Data are presented as n (%) unless otherwise indicated.
## Impact of Gender on Traditional Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Hypertension, OR (95% CI)</th>
<th>Diabetes, OR (95% CI)</th>
<th>Family Hx, OR (95% CI)</th>
<th>Depressive Sx, β (95% CI)</th>
<th>Anxious Sx, β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender score</td>
<td>2.11 (1.36–3.26)**</td>
<td>3.04 (1.74–5.29)*****</td>
<td>1.94 (1.17–3.19)****</td>
<td>3.09 (2.11–4.54)*****</td>
<td>4.47 (3.04–6.60)*****</td>
</tr>
<tr>
<td><strong>Univariable models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1.45 (1.12–1.88)*</td>
<td>1.88 (1.35–2.61)****</td>
<td>1.33 (0.97–1.81)</td>
<td>1.81 (1.44–2.29)*****</td>
<td>2.21 (1.75–2.80)*****</td>
</tr>
<tr>
<td><strong>Multivariable models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender score</td>
<td>1.85 (1.04–3.29)*</td>
<td>2.07 (1.00–2.39)*</td>
<td>1.93 (1.00–3.78)*</td>
<td>2.68 (1.61–4.44)*****</td>
<td>3.62 (2.17–6.01)*****</td>
</tr>
<tr>
<td>Sex</td>
<td>1.14 (0.78–1.67)</td>
<td>1.46 (0.89–2.39)</td>
<td>1.00 (0.64–1.56)</td>
<td>1.16 (0.83–1.61)</td>
<td>1.24 (0.89–1.73)</td>
</tr>
</tbody>
</table>

Pelletier et al., *Psychosomatic Medicine*, V 77 • 517-526
CV HEALTH BALANCE

TRADITIONAL RISK FACTORS
- Hypertension
- Smoking
- Obesity
- Diabetes
- Dyslipidemia

CV HEALTH BALANCE

BIOLOGICAL SEX

SOCIO CULTURAL GENDER

NON-TRADITIONAL RISK FACTORS
- Physical Activity
- Depression
- Gender Roles, Relations, Identity, and Institutionalized Gender

CV HEALTH BALANCE

CV DISEASE

WHAT IS NEEDED
- Sex-disaggregated data
- Understanding the intersectionality between sex and gender
Conclusions

• Magnitude of effect for many traditional cardiovascular risk factor is higher in women compared to men

• Biological (sex) and non-biological (gender) factors may explain these differences

• Primary prevention approach for improvement of cardiovascular health must take into account social determinants
Emerging Risk Factors

- SLE: 3-fold higher risk of IHD events [18]
- Rheumatoid arthritis: elevates IHD risk as much as DM [18]
- Gestational diabetes
  - 4-fold higher risk of DM
  - 59% higher risk of MI [17]
- Hypertension in pregnancy:
  - Gestational HTN and preclampsia: 3-fold higher risk of IHD [18]
- Early menopause confers 4.5 times higher risk of IHD [99]
- Depression is more prevalent in women
  - Doubles the risk of IHD [16]

Traditional Risk Factors

- Menopause results in ↑TG, ↑LDL, ↓HDL
  - Women are less likely to achieve lipid goals (OR 0.50) [97]
- 80% of women ≥75 have HTN
  - Only 29% have adequate BP control [22,98]
- Diabetes confers a 45% higher risk of IHD [16]
- Smoking confers a 25% higher risk of IHD [96]
- Obesity confers a higher risk of IHD in women
  - (64% vs 46%) [94]
- Women have a higher prevalence of inactivity
  - 25% of US women get no regular physical activity [95]
- Family History of premature atherosclerosis confers a 2 fold higher risk of IHD in men and women [100]

Aggarwal et al., 2018, Circulation: Cardiovascular Quality and Outcomes