Women and Heart Disease: Focus on Diabetes, Metabolic Syndrome, and Obesity

Susan T. Laing, MD, MSc, CPE, FAHA, FACC, FASE
Professor of Medicine
John Edward Tyson Distinguished Professorship in Cardiology
Associate Chief, Division of Cardiology

DISCLOSURES: NONE
Cannot ignore half of the population

If the World Were a Village of 100 People...

51 Women

49 Men

Population by Sex and Age

Total Population: 308,745,538

Men

Female

85+ Years
80
70
60
50
40
30
20
10
0
12,000,000
6,000,000
3,000,000
1,000,000

Women make up nearly half of today’s labor force

47% Women

53% Men

Women’s Health = Family Health

75% of all caregivers are women
2.3 M grandparents raising grandchildren = 63% are women
Ten Leading Causes of Death in Women

- CVD still causes ~1 death per minute among women
- In their lifetime, 1 in 2-3 women will die of heart disease

Global Health Observatory Data Repository, WHO
Cardiovascular Disease Mortality Trends in the US

Mozaffarian et al. Circulation. 2015;131:e29-e322
Trends in Age-Adjusted Mortality Rates from Coronary Heart Disease

Death rate for heart disease in men has declined steadily by 21.5% in men while in women it has declined by only 9.9%

TIME TO TREATMENT

Women wait longer than men to go to the ED when having an ACS
Awareness Gap

Only 53% of women said the first thing they would do if they thought they were having a heart attack was to call 9-1-1. However, 79% said they would call 9-1-1 if someone else was having a heart attack.
Trends in awareness that heart disease is the leading cause of death in women

Time to Treatment

- Physicians are slower in recognizing ACS in women than in men
- 66% of ED and critical care clinicians
  - Primarily assessed for CP in persons with suspected AMI
Chest pain symptoms are less accurate and less precise predictors of obstructive CAD in women.
Different communication patterns

Women are more likely to give full account of symptoms whereas men tend to focus on what is problematic

Fatigue, dyspnea, weakness, upset stomach, hip pain, chest ache, etc.
Definitions are Faulty

Normative standards for symptoms of ACS were set in men

- Current description of "typical" cardiac symptoms is based primarily on the experience of white, middle-aged men, with deviations called "atypical"
Implications

More women have unrecognized AMI

More women are misdiagnosed and discharged from ER
Mortality after Unrecognized MI

Cardiovascular Disease in Women

Metabolic derangements have a disproportionate effect in women.
Coronary Artery Disease Mortality and Diabetes in Women

Most powerful predictor of coronary risk in women

Female diabetics had a RR for CAD of 3.3 compared with female nondiabetics. Relative RR in male diabetics vs. male nondiabetics was 1.8.

## Lowest Survival Rates for Diabetic Women

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Death/MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-vessel ischemia</td>
<td>1-vessel ischemia</td>
</tr>
<tr>
<td>Diabetic men</td>
<td>93.8</td>
<td>93.0</td>
</tr>
<tr>
<td>Nondiabetic men</td>
<td>99.0</td>
<td>96.5</td>
</tr>
<tr>
<td>Diabetic women</td>
<td>99.0</td>
<td>80.0*</td>
</tr>
<tr>
<td>Nondiabetic women</td>
<td>98.8</td>
<td>97.5</td>
</tr>
</tbody>
</table>

*P < .05. Extent of ischemia was determined by the number of vascular territories (0, 1, or 2 vessels) involved in the reversible perfusion defect.

Diabetes – the Great Equalizer

The coronary prognosis is substantially worse for diabetic women than diabetic men

- Diabetic women with MI have doubled the risk of reinfarction and 4-fold likelihood of developing heart failure

Far more powerful coronary risk factor for women than men, negating much of the protective effects of the female sex
Metabolic Syndrome

- Hypertension: >130/85 mm Hg
- Impaired fasting glucose: ≥110 mg/dL
- Triglycerides: ≥150 mg/dL
- HDL-cholesterol: <40 mg/dL (males), <50 mg/dL (females)
- Abdominal obesity: Waist ≥40” (males), Waist ≥35” (females)

Asia – Total 31%; 20.9% in Men, 15.5% in women
Africa – 26.6% Men, 32.2% in Women
Australia – 48.2% in men, 29.9% in Women
Antarctica – 20%
Europe – 30-80% in Adults, 20% in Children
South America – 34%
North America – 35%
Metabolic Syndrome

The Metabolic Syndrome is a Predictor of New CVD Events in Women with CAD

Triglyceride and HDL

Hypertriglyceridemia may be a more potent independent risk factor in women

↑ in TGC of 1mmol/L was associated with an increased risk for CV events of 32% in men but 76% in women

Framingham Heart Study

Castelli, Am J Cardiol 1992.
Gender-specific Risk Factors

Pregnancy is a “metabolic stress test” that predicts development of future cardiovascular risk factors

Pregnancy history and birth outcomes are associated with increased future risk of CVD

- History of preeclampsia, gestational DM, or pregnancy-induced hypertension
- Low birth weight, pre-term delivery, delivery of a small for gestational age infant, recurrent miscarriage are also associated with future CVD
- Women who deliver early (< 37 weeks) or have a growth restricted infant have 2x the risk of developing CVD later in life compared to women who have normal weight infants born at term

Unique opportunity to estimate a woman’s lifetime risk for CVD
Diagnoses in Obstetrics and Gynecology: Impact on CVD Risk

- Up to 70% of women with gestational diabetes develop Type 2 diabetes within 5 years of the pregnancy
- Women with hypertension during pregnancy are ~3x as likely to develop hypertension later in life and 2x as likely to develop heart disease

Preeclampsia and CVD share many risk factors

Women with preeclampsia are 3.8 times more likely to develop diabetes, and 11.6 times more likely to develop hypertension requiring drug treatment.

Figure 1   Linking preeclampsia to cardiovascular disease later in life: clinical manifestations and underlying pathophysiological processes.
### Preeclampsia History and CVD Risk

#### Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No of cases/women who had pre-eclampsia</th>
<th>Total No of cases/women who did not have pre-eclampsia</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam 1961</td>
<td>40/13</td>
<td>21/185</td>
<td>14.25</td>
<td>5.91</td>
<td>3.89 to 8.98</td>
</tr>
<tr>
<td>西班牙1994</td>
<td>37/0</td>
<td>7/114</td>
<td>13.52</td>
<td>6.26</td>
<td>1.66 to 8.17</td>
</tr>
<tr>
<td>Bartlett 1990</td>
<td>60/66</td>
<td>23/400</td>
<td>12.7</td>
<td>3.91</td>
<td>2.08 to 6.81</td>
</tr>
<tr>
<td>Kestenhouse 1992</td>
<td>5/1</td>
<td>2/12</td>
<td>2.7</td>
<td>3.90</td>
<td>1.08 to 10.10</td>
</tr>
<tr>
<td>Niswonger 1993</td>
<td>20/0</td>
<td>1/50</td>
<td>2.12</td>
<td>8.80</td>
<td>1.16 to 6.46</td>
</tr>
<tr>
<td>North 1996</td>
<td>3/21</td>
<td>0/22</td>
<td>2.23</td>
<td>20.00</td>
<td>19.35 to 19.35</td>
</tr>
<tr>
<td>Schountz 1997</td>
<td>2/22</td>
<td>0/22</td>
<td>1.03</td>
<td>5.00</td>
<td>0.15 to 95.24</td>
</tr>
<tr>
<td>Hambrecht 2002</td>
<td>377/271</td>
<td>892/1481</td>
<td>18.59</td>
<td>23.5</td>
<td>2.08 to 5.15</td>
</tr>
<tr>
<td>Marín 2007</td>
<td>30/44</td>
<td>12/86</td>
<td>8.88</td>
<td>3.70</td>
<td>1.72 to 7.90</td>
</tr>
<tr>
<td>Shamas 2000</td>
<td>23/7</td>
<td>3/46</td>
<td>5.45</td>
<td>7.50</td>
<td>0.25 to 31.20</td>
</tr>
<tr>
<td>Sibat 2000</td>
<td>10/10</td>
<td>3/30</td>
<td>3.81</td>
<td>5.00</td>
<td>0.19 to 31.96</td>
</tr>
<tr>
<td>Sibat 2003</td>
<td>7/0</td>
<td>2/40</td>
<td>3.49</td>
<td>3.00</td>
<td>0.77 to 11.12</td>
</tr>
<tr>
<td>Wilson 2007</td>
<td>216/43</td>
<td>12/109</td>
<td>14.74</td>
<td>2.62</td>
<td>0.77 to 0.87</td>
</tr>
</tbody>
</table>

**Test for heterogeneity:** $\chi^2=32.05$, df=12, $P<0.001$, $I^2=62.5$

**Test for overall effect:** $z=8.20$, $P<0.001$

#### Ischaemic heart disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No of cases/women who had pre-eclampsia</th>
<th>Total No of cases/women who did not have pre-eclampsia</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Total No of cases/women who had pre-eclampsia</td>
<td>Total No of cases/women who did not have pre-eclampsia</td>
<td>Relative risk (random) (95% CI)</td>
<td>Weight (%)</td>
<td>Relative risk (random) (95% CI)</td>
</tr>
<tr>
<td>Hammersley 1997</td>
<td>25/2371</td>
<td>93/1463</td>
<td>1.39</td>
<td>0.89</td>
<td>1.21 to 2.17</td>
</tr>
<tr>
<td>Rogers 2001</td>
<td>11/24</td>
<td>292/620</td>
<td>2.17</td>
<td>0.43</td>
<td>0.23 to 10.92</td>
</tr>
<tr>
<td>Wilson 2003</td>
<td>50/1043</td>
<td>18/796</td>
<td>2.41</td>
<td>1.39</td>
<td>0.23 to 10.92</td>
</tr>
<tr>
<td>Ray 2005</td>
<td>64/36</td>
<td>351/950</td>
<td>1.90</td>
<td>1.42</td>
<td>1.06 to 2.54</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 153/54 355

**Test for heterogeneity:** $\chi^2=2.33$, df=3, $P=0.61$, $I^2=0$

**Test for overall effect:** $z=5.21$, $P<0.001$

#### Venaes thromboembolism

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No of cases/women who had pre-eclampsia</th>
<th>Total No of cases/women who did not have pre-eclampsia</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammersley 1997</td>
<td>32/2371</td>
<td>116/1463</td>
<td>1.62</td>
<td>2.09</td>
<td>1.09 to 3.41</td>
</tr>
<tr>
<td>Kestenhouse 2003</td>
<td>43/20</td>
<td>113/920</td>
<td>1.73</td>
<td>1.07</td>
<td>1.27 to 2.79</td>
</tr>
<tr>
<td>Van Waarden 2001</td>
<td>15/12</td>
<td>149/284</td>
<td>2.20</td>
<td>1.30</td>
<td>1.07 to 3.17</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 97/35 772

**Test for heterogeneity:** $\chi^2=1.37$, df=2, $P=0.66$, $I^2=0$

**Test for overall effect:** $z=4.31$, $P<0.001$

#### Group of studies

<table>
<thead>
<tr>
<th>Relative risk of future ischemic heart disease (random) (95% CI)</th>
<th>Relative risk of future ischemic heart disease (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Primiparous: 6 studies /4502 cases</td>
<td>1.89 (1.40 to 2.55)</td>
</tr>
<tr>
<td>Any pregnancy: 2 studies /595 cases</td>
<td>1.23 (1.71 to 4.69)</td>
</tr>
<tr>
<td>Outcome severity</td>
<td></td>
</tr>
<tr>
<td>Fatal ischaemic heart disease: 4 studies /741 cases</td>
<td>2.60 (1.94 to 3.69)</td>
</tr>
<tr>
<td>Combined (fatal and non-fatal) ischaemic heart disease: 4 studies /4356 cases</td>
<td>2.17 (1.92 to 2.45)</td>
</tr>
<tr>
<td>Onset of disease</td>
<td></td>
</tr>
<tr>
<td>Early pre-eclampsia: 2 studies /50 cases*</td>
<td>7.71 (4.40 to 13.52)</td>
</tr>
<tr>
<td>Severity of pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>Severe pre-eclampsia: 2 studies /2434 cases</td>
<td>2.06 (2.05 to 3.45)</td>
</tr>
<tr>
<td>Mild pre-eclampsia: 2 studies /347</td>
<td>1.92 (1.45 to 2.56)</td>
</tr>
<tr>
<td>Overall relative risk</td>
<td></td>
</tr>
<tr>
<td>Decreased risk</td>
<td>Increased risk</td>
</tr>
<tr>
<td>0.5 1 2 5 10</td>
<td>2.16 (1.86 to 2.52)</td>
</tr>
</tbody>
</table>
Graded Relationship between Severity of Preeclampsia and CVD Risk

Mongraw-Chaffin M L et al. Hypertension 2010;56:166-171
Preeclampsia History and CVD Risk

Whether preeclampsia is the initial point of expression of an inherent adverse phenotype associated with CVD or whether preeclampsia itself causes subclinical vascular damage that leads to atherosclerosis is not clear.

Women should be monitored closely and treated aggressively for modifiable risk factors.
CVD Risk Stratification: At Risk

Cigarette smoking
Hypertension: SBP ≥ 120 mm Hg, DBP ≥ 80 mm Hg or treated hypertension
Total cholesterol ≥200 mg/dL, HDL-C <50 mg/dL, or treated for dyslipidemia
Obesity, particularly central obesity
Family history of premature CVD in a 1st degree relative
  (CVD at < 55 years in a male relative, or < 65 years in a female relative)
Metabolic syndrome
Poor diet
Physical inactivity
Evidence of advanced subclinical atherosclerosis (eg, CAC, carotid plaque, or thickened IMT)
Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after exercise
A history of pregnancy-induced hypertension, gestational diabetes, preeclampsia
Systemic autoimmune collagen-vascular disease (e.g. lupus, rheumatoid arthritis)
Global Burden of Obesity

Estimated Overweight & Obesity (BMI ≥ 25 kg/m²) Prevalence, Males, Aged 15+, 2010

Estimated Overweight & Obesity (BMI ≥ 25 kg/m²) Prevalence, Females, Aged 15+, 2010


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Obesity Trends Among U.S. Adults

Source: CDC
The State of Risk

• 2 out of 3 Americans are overweight or obese
• Obese Americans (34%) now outnumber overweight Americans (33%)
• 30.1% of children and adolescents (2-19 yrs) are overweight or obese
• If trends continue, by year 2030, 51.1% will be obese
# Cameron County Hispanic Cohort

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.1 ± 11.7</td>
<td>55.0 ± 14.7</td>
<td>52.3 ± 10.6</td>
</tr>
<tr>
<td>Smoker*</td>
<td>24.1%</td>
<td>40.5%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>19.9%</td>
<td>16.2%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>27.7%</td>
<td>24.3%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)*</td>
<td>188.6 ± 37.2</td>
<td>177.0 ± 34.3</td>
<td>192.2 ± 37.5</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>53.2%</td>
<td>56.8%</td>
<td>51.9%</td>
</tr>
<tr>
<td>BMI (kg/m2)*</td>
<td>31.7 ± 5.9</td>
<td>29.9 ± 4.5</td>
<td>32.3 ± 6.3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>104.3 ± 13.1</td>
<td>104.1 ± 10.4</td>
<td>104.3 ± 13.9</td>
</tr>
<tr>
<td>Obese (BMI ≥30 kg/m2)</td>
<td>58.9%</td>
<td>45.9%</td>
<td>63.4%</td>
</tr>
</tbody>
</table>

Women have higher prevalence of overweight and obesity

Age-adjusted prevalence of obesity in adults 20 to 74 years of age by sex and survey year

Go A S et al. Circulation 2013;127:e6-e245
Body Weight and CHD Mortality Among Women

Relative Risk of CHD Mortality Compared to BMI < 19

P for trend < 0.001

DOES ANYONE ELSE FIND IT WEIRD THAT CHOCOLATE MAKES YOUR CLOTHES SHRINK?
NHANES
Primarily to greater average carbohydrate intake, in particular, of starches, refined grains, and sugars
Also related to larger portion sizes, greater food quantity and calories per meal, increased consumption of sugar-sweetened beverages, snacks, commercially prepared (fast food) meals

Go A S et al. Circulation 2013;127:e6-e245
Per capita calories consumed from different beverages by US adults

Mozaffarian et al. Circulation. 2015;131:e29-e322
Low Risk Diet is Associated with Lower Risk of Myocardial Infarction in Women

Relative Risk of MI*

*Adjusted for other cardiovascular risk factors

Akesson et al Arch Int Med 2007; 167: 2122-2127
Sedentary Lifestyles
Prevalence of insufficient physical activity* among adults, ages 18+ (age standardized estimates)
Females, 2010

Prevalence (%)
- <20.0
- 20.0–29.9
- 30.0–39.9
- 40.0–49.9
- ≥50.0
- Data not available
- Not applicable

* Less than 150 minutes of moderate-intensity physical activity per week, or less than 75 minutes of vigorous-intensity physical activity per week, or equivalent

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Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

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Prevalence of meeting 2008 Federal physical activity guidelines

32% of adults reported engaging in no aerobic leisure-time physical activity

Writing Group Members et al. Circulation 2012;125:e2-e220
Physical Inactivity

Ranks second as the most important contributor to population ill-health

Ranks first as leading contributor to preventable illness and morbidity in women and second in men

- Women are more likely to lead sedentary lifestyles than men
Risk Reduction for CHD Associated with Exercise in Women

Quintile Group for Activity (MET - hr/wk)

Women and CAD Risk Factors

Risk factors tend to occur in clusters

Higher prevalence of avoidable risk factors

↑ physical inactivity

↑ overweight and obesity

Diabetes is a more powerful risk factor for CAD

3- to 7-fold in women vs 2- to 3-fold in men

↑ TG and ↓ HDL cholesterol levels more predictive of CAD

Women counseled less about nutrition, exercise, and weight control

AHA 2020 Impact Goal

By 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%
AHA 2020 Impact Goal

By 2020, to improve the **cardiovascular health** of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%.
Ideal Cardiovascular Health

<table>
<thead>
<tr>
<th>Ideal cardiovascular health (all of these)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence from smoking</td>
</tr>
<tr>
<td>BMI &lt;25 kg/m2</td>
</tr>
<tr>
<td>Physical activity at goal for adults &gt;20 y/o: ≥150 min/wk moderate intensity, ≥ 75 min/wk vigorous intensity, or combination</td>
</tr>
<tr>
<td>Healthy (DASH-like) diet</td>
</tr>
<tr>
<td>Total cholesterol &lt;200mg/dL (untreated)</td>
</tr>
<tr>
<td>BP &lt;120/&lt;80 mmHg (untreated)</td>
</tr>
<tr>
<td>Fasting blood glucose &lt;100 mg/dL (untreated)</td>
</tr>
</tbody>
</table>

Mosca L et al. Circulation 2011;123:1243-1262
Incidence of CVD according to Number of Ideal Health Factors

Writing Group Members et al. Circulation 2012;125:e2-e220
Prevalence of Low CHD Risk Factors

Mozaffarian et al. Circulation. 2015;131:e29-e322
Heart Disease is Preventable

Education and Empowerment
Preeclampsia survivors
Affect the health of the family

Educate MDs
Opportunity for preventive screening in OB-Gyne offices, midwifes, family practice, internal medicine offices for women of reproductive age

Legislation – involve women in decision making

Research

Physicians Recognizing that more Women Die of Heart Disease than Men Each Year

- Primary Care Physicians: 8%
- Obstetrician-Gynecologists: 13%
- Cardiologists: 17%
Prevention and treatment that takes into account individual variations in genes, lifestyle, and environment.
The New Face of Heart Disease