The sex gap in cardiometabolic diseases: What we (don't) know and why it matters?

Assoc. Prof Taulant Muka, PD, MD, PhD

Institute of Social and Preventive Medicine (ISPM), University of Bern

taulant.muka@ispm.unibe.ch
Life expectancy

Fig. 1.3
Global life expectancy and HALE, 2000–2016

Top 10 causes of death, Switzerland

Sex differences in risk of cardiovascular disease

In Switzerland, CVD is responsible for 37% of deaths among men and 41% among women.
Top 10 causes of DALY, Switzerland

Total number of adults with diabetes (20-79 years), Globally

In 2017

425 million adults had diabetes
Sex differences in diabetes risk

- The prevalence of prediabetes and diabetes is lower in women than in men aged ≤60 years.

- Women in their 60s and 70s have similar prevalence of diabetes or higher than men of the same age.

Yang W et al. 2010
Diabetic women to men relative risk for CHD and Stroke

Takayama26
DECODE25
Hisayama (2010)13
APCSC (Australia and New Zealand)14
Hisayama (2000)9
NHANES III13
Iso et al11
Rancho Bernado74
SHHEC12
JPHC7
APCSC (Asia)14
Framingham Offspring51
EPIC-Norfolk22
Kuopio and North Karelia8
Dubbo18
ARIC13
Renfrew/Paisley20
Sievers et al13
Total (I² = 0.0-0%, p=0.752)

Relative risk (95% CI) Weight
0.53 (0.19-1.50) 1.90%
0.79 (0.41-1.51) 4.80%
0.80 (0.33-1.90) 2.66%
0.87 (0.53-1.44) 8.09%
1.06 (0.58-1.92) 5.63%
1.13 (0.41-3.14) 1.95%
1.22 (0.53-2.82) 2.89%
1.22 (0.47-3.16) 2.24%
1.30 (0.68-2.49) 4.76%
1.34 (0.84-2.14) 9.19%
1.35 (0.98-1.87) 19.12%
1.40 (0.92-6.04) 0.95%
1.46 (0.65-3.31) 3.04%
1.47 (0.86-2.51) 7.06%
1.53 (0.66-3.53) 2.90%
1.58 (1.15-2.18) 19.64%
1.86 (0.74-4.71) 2.35%
2.88 (0.57-14.46) 0.78%
1.27 (1.10-1.46) 100.00%

Higher relative risk in men
Higher relative risk in women

Peters S.A.E et al. 2014
Lifetime risk for diagnosis of diabetes

Narayan et al. 2003
Age-adjusted all-cause mortality

U.S. population age 35 to 74 years with and without diabetes, by cohort and sex

Greg EW et al. 2007
Effect of sex on treatment outcomes in T2D

6 RCTs of insulin glargine or NPH insulin

Greg EW et al. 2007
Sex differences in cardiometabolic diseases

Women’s life cycle

- Childhood
- Puberty
- Reproductive period
- Menopausal transition
- Menopause
- Old age
Age at menarche
Age at menarche and CVD risk

• The association between the age at menarche and CVD is U-shaped

• Age at menarche could be a potential screening tool for women at risk of adverse CVD events.

• Strong inter-relationship between age at menarche and BMI limits the ability to consider their distinct influences on disease risks in traditional observational studies.

Women’s Ischemia Syndrome Evaluation to assess major adverse CVD outcomes (the first occurrence of all-cause death, nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization)
Contraception and risk of CVD

Venous thromboembolism

Stroke
Gestational diabetes (GDM)

- Hyperglycaemia that develops during pregnancy (late second trimester, 13-26 weeks of gestation) or early in the third trimester (27-40 weeks) and resolves following delivery.
- The most common medical complication of pregnancy (1% to >30%).
- Prevalence of undiagnosed hyperglycaemia and even overt diabetes in young women is increasing.
- Maternal overweight and obesity, later age at childbearing, previous history of GDM, family history of type 2 diabetes mellitus and ethnicity are major GDM risk factors.
Male fetal sex was associated with term pre-eclampsia (pooled OR 1.07 [95%CI 1.06 to 1.09]) and gestational diabetes (pooled OR 1.04 [1.02 to 1.07]). All other pregnancy complications (i.e., gestational hypertension, total pre-eclampsia, eclampsia, placental abruption, and post-partum hemorrhage) tended to be associated with male fetal sex, except for preterm pre-eclampsia, which was more associated with female fetal sex.
Menopause

- Body Composition
- Iron Levels
- Estrogen
- Hormone Therapy
- Vasomotor Symptoms
- Age at Menopause
Adverse metabolic changes related to menopause

ACCUMULATION OF ADIPOSE TISSUE

- Inflammation (Interleukin, C-reactive protein)
- Adipokine (Adiponectin, Leptin)
- Hepatic Dysfunction (Gamma-glutamyltransferase)
- Hormonal Changes (Estradiol)
- Menopausal symptoms

ALTERATION OF THE METABOLIC PROFILE

- Oxidative Stress (Reactive oxygen species)
- Dyslipidemia (Triglycerides, HDL-cholesterol)
- Hyperglycemia (Glycated hemoglobin)
- Autonomic activation

MODIFIERS

- Lifestyle factors (diet)

DECREASED PANTIC FUNCTION

- Glucose intolerance
- Insulin Resistance

INCREASED BLOOD PRESSURE

- Endothelial dysfunction

DIABETES & CARDIOVASCULAR DISEASE
Is chronological ageing or stage of reproductive aging the dominant factor contributing to cardiometabolic changes in women?

Classification of Women (N=2558)  
5-year follow-up  
(Phase I 2003-2006 and Phase II 2009-2012)

- 1,214 PRE menopausal
- 1,344 POST menopausal

Cardiometabolic outcomes
- Blood pressure, serum lipids, glucose level, inflammatory markers, and body mass index

Independent variable
- Reproductive age (Pre, Trans, Early, Late) (PRIMARY)
- Chronologic age (SECONDARY)

Confounding factors
- Medications and Hormone replacement therapy
- Baseline comorbid CV disease
- Smoking, alcohol, physical activity, education
- Body mass index*
Is chronological ageing or stage of reproductive aging the dominant factor contributing to cardiometabolic changes in women?

Cross-sectional analysis of risk factors

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>TRANS</th>
<th>Early POST</th>
<th>Late LPOST</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Ref 0.513 [-0.0814, 0.997]</td>
<td>1.500 [-0.722, 2.213]*</td>
<td>2.049 [1.142, 2.645]*</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>Ref -0.616 [-2.489, 1.257]</td>
<td>-1.663 [-4.259, 0.933]</td>
<td>-0.417 [-3.387, 2.554]</td>
<td>0.691</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>Ref 1.959 [0.791, 3.209]*</td>
<td>3.367 [1.635, 5.099]*</td>
<td>3.196 [1.214, 5.178]*</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>Ref 0.087 [-0.0275, 0.203]</td>
<td>0.440 [0.260, 0.600]*</td>
<td>0.380 [0.198, 0.563]*</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/L)</td>
<td>Ref 0.050 [0.0012, 0.099]*</td>
<td>0.072 [0.0043, 0.139]*</td>
<td>0.066 [-0.0109, 0.144]</td>
<td>0.104</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>Ref 0.015 [-0.037, 0.066]*</td>
<td>0.008 [-0.063, 0.0796]</td>
<td>0.057 [-0.0244, 0.139]</td>
<td>0.206</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>Ref 0.090 [0.0022, 0.177]*</td>
<td>0.143 [0.022, 0.264]*</td>
<td>0.214 [0.075, 0.352]*</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Insulin (microU/mL)</td>
<td>Ref -0.031 [-0.0999, 0.038]</td>
<td>-0.026 [-0.120, 0.068]</td>
<td>0.067 [-0.0397, 0.175]</td>
<td>0.222</td>
<td></td>
</tr>
<tr>
<td>High sensitivity c-reactive protein (mg/L)</td>
<td>Ref -0.057 [-0.182, 0.068]</td>
<td>-0.126 [-0.298, 0.0472]</td>
<td>0.031 [-0.167, 0.229]</td>
<td>0.866</td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>Ref -0.019 [-0.098, 0.059]</td>
<td>0.064 [-0.043, 0.171]</td>
<td>0.086 [-0.0371, 0.209]</td>
<td>0.136</td>
<td></td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>Ref -0.004 [-0.085, 0.076]</td>
<td>0.138 [0.0285, 0.247]*</td>
<td>0.173 [0.0479, 0.299]*</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Tumor necrosis factor-alpha (pg/mL)</td>
<td>Ref -0.007 [-0.125, 0.109]</td>
<td>0.042 [-0.118, 0.203]</td>
<td>0.050 [-0.135, 0.236]</td>
<td>0.536</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6 (pg/mL)</td>
<td>Ref 0.164 [-0.0258, 0.353]</td>
<td>0.343 [0.0847, 0.601]*</td>
<td>0.436 [0.138, 0.734]*</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Interleukin 1b (pg/mL)</td>
<td>Ref -0.170 [-0.402, 0.063]</td>
<td>-0.096 [-0.419, 0.223]</td>
<td>-0.088 [-0.459, 0.284]</td>
<td>0.703</td>
<td></td>
</tr>
</tbody>
</table>

Corrected for use of hypoglycemic drugs, statins and antihypertensive drugs, AGE, smoking history, alcohol-use, baseline physical activity, baseline cardiovascular disease, use of hormone replacement therapy, and body mass index

Unpublished data
Is chronological ageing or stage of reproductive aging the dominant factor contributing to cardiometabolic changes in women?

## Longitudinal analysis of risk factors

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
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<th>Early POST</th>
<th>Late POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Ref 2.927 (-2.762, 8.617)</td>
<td>1.492 (-5.606, 8.591)</td>
<td>0.338 (-4.781, 5.452)</td>
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</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>Ref -1.348 (-19.40, 16.70)</td>
<td>-11.98 (-34.47, 10.52)</td>
<td>7.346 (-8.911, 23.60)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>Ref 2.161 (-9.808, 14.13)</td>
<td>-2.720 (-17.64, 12.20)</td>
<td>4.806 (-5.977, 15.59)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>Ref 0.530 (-0.585, 1.645)</td>
<td>1.112 (-0.279, 2.504)</td>
<td>0.984 (-0.0188, 1.987)</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/L)</td>
<td>Ref -0.189 (-0.691, 0.314)</td>
<td>-0.347 (-0.974, 0.280)</td>
<td>0.0465 (-0.405, 0.498)</td>
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</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>Ref 0.440 (-0.0590, 0.940)</td>
<td>0.199 (-0.424, 0.822)</td>
<td>0.0334 (-0.416, 0.482)</td>
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<tr>
<td>Fasting glucose (mmol/L)</td>
<td>Ref 0.274 (-0.461, 1.010)</td>
<td>0.0152 (-0.902, 0.932)</td>
<td>0.137 (-0.524, 0.798)</td>
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</tr>
<tr>
<td>Insulin (microlU/mL)</td>
<td>Ref -0.337 (-0.928, 0.253)</td>
<td>-0.207 (-0.936, 0.523)</td>
<td>-0.0757 (-0.592, 0.440)</td>
<td></td>
</tr>
<tr>
<td>High sensitivity c-reactive protein (mg/L)</td>
<td>Ref 0.0574 (-1.122, 1.237)</td>
<td>-0.778 (-2.239, 0.684)</td>
<td>-0.0779 (-1.135, 0.979)</td>
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</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>Ref 0.175 (-0.833, 1.183)</td>
<td>0.715 (-0.494, 1.924)</td>
<td>0.251 (-0.638, 1.139)</td>
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<tr>
<td>Adiponectin (ng/mL)</td>
<td>Ref -0.102 (-0.857, 0.653)</td>
<td>-0.00553 (-0.928, 0.917)</td>
<td>0.330 (-0.332, 0.992)</td>
<td></td>
</tr>
<tr>
<td>Tumor necrosis factor alpha (pg/mL)²</td>
<td>Ref 0.107 (-1.007, 1.220)</td>
<td>0.158 (-1.190, 1.507)</td>
<td>0.222 (-0.766, 1.211)</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6 (pg/mL)</td>
<td>Ref 0.0159 (-1.825, 1.857)</td>
<td>-0.170 (-2.399, 2.059)</td>
<td>-0.586 (-2.224, 1.053)</td>
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</tr>
<tr>
<td>Interleukin 1b (pg/mL)²</td>
<td>Ref 0.133 (-1.742, 2.009)</td>
<td>-1.041 (-3.356, 1.275)</td>
<td>-0.215 (-1.901, 1.471)</td>
<td></td>
</tr>
</tbody>
</table>

*Unpublished data*
Is chronological ageing or stage of reproductive aging the dominant factor contributing to cardiometabolic changes in women?

Longitudinal analysis of risk factors (using AGE)

<table>
<thead>
<tr>
<th>Beta</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.014</td>
<td>(-0.041, 0.014)</td>
<td>0.330</td>
</tr>
<tr>
<td>0.736</td>
<td>(0.649, 0.824)</td>
<td>&lt;0.000</td>
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<tr>
<td>0.018</td>
<td>(-0.040, 0.076)</td>
<td>0.541</td>
</tr>
<tr>
<td>0.023</td>
<td>(0.022, 0.032)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>0.006</td>
<td>(0.004, 0.009)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>0.006</td>
<td>(0.004, 0.008)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>0.0038</td>
<td>(0.002, 0.007)</td>
<td>0.038</td>
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<tr>
<td>0.0007</td>
<td>(-0.002, 0.003)</td>
<td>0.614</td>
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<tr>
<td>0.002</td>
<td>(-0.003, 0.008)</td>
<td>0.455</td>
</tr>
<tr>
<td>-0.002</td>
<td>(-0.006, 0.003)</td>
<td>0.422</td>
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<tr>
<td>0.009</td>
<td>(0.005, 0.012)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>0.006</td>
<td>(0.001, 0.011)</td>
<td>0.022</td>
</tr>
<tr>
<td>-0.013</td>
<td>(-0.021, -0.004)</td>
<td>0.004</td>
</tr>
<tr>
<td>-0.007</td>
<td>(-0.014, -0.0002)</td>
<td>0.042</td>
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</tbody>
</table>

Our findings suggest that the accumulation of deleterious exposures and damage with aging might contribute to menopause-related changes in CVD, and future studies will need to disentangle the relative contribution of effect of age and menopause in CVD risk.
Menopause and Diabetes: independent of age

- Older age and postmenopausal status alone significantly associated with an elevated OR for dysglycemia
- The postmenopausal condition and older age additively influence an elevated risk
- Early onset of menopause is associated with increased risk of T2D

Heianza Y et al. 2013; Muka et al. 2017
Age at menopause

**Global**

<table>
<thead>
<tr>
<th>Age at menopause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
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<tr>
<td>40-44</td>
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<tr>
<td>45-49</td>
<td>10%</td>
</tr>
<tr>
<td>50-54</td>
<td>40%</td>
</tr>
<tr>
<td>≥55</td>
<td>10%</td>
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</table>

**Rotterdam Study**

<table>
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<tr>
<td>≥55</td>
<td>10%</td>
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Early menopause and cardiometabolic risk

Muka et al. 2017 Jama Cardiology; Muka et al. 2018 Diabetologia
Early menopause and cardiometabolic risk

### CHD

<table>
<thead>
<tr>
<th>Dataset</th>
<th>HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>FHS</td>
<td>1.29</td>
<td>[1.08; 1.54]</td>
</tr>
<tr>
<td>Aric</td>
<td>1.14</td>
<td>[0.89; 1.45]</td>
</tr>
<tr>
<td>RS-1</td>
<td>1.04</td>
<td>[0.91; 1.18]</td>
</tr>
<tr>
<td>RS-2</td>
<td>1.13</td>
<td>[0.55; 2.33]</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1.12</td>
<td>[1.02; 1.24]</td>
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</table>

### Composite CVD

<table>
<thead>
<tr>
<th>Dataset</th>
<th>HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>FHS</td>
<td>1.22</td>
<td>[1.08; 1.37]</td>
</tr>
<tr>
<td>Aric</td>
<td>1.06</td>
<td>[0.93; 1.22]</td>
</tr>
<tr>
<td>RS-1</td>
<td>1.06</td>
<td>[0.99; 1.14]</td>
</tr>
<tr>
<td>RS-2</td>
<td>1.27</td>
<td>[0.95; 1.04]</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1.10</td>
<td>[1.04; 1.16]</td>
</tr>
</tbody>
</table>
Early menopause and life expectancy

Asllanaj et al. 2019 Diabetologia
Menopausal symptoms

- **Vasomotor symptoms**
  - Hot flashes and night sweats
- **Other menopausal symptoms**
  - Anxiety
  - Depression
  - Irritability
  - Fatigue
  - Decreased libido
  - Insomnia

Gold EB et al. 2006
Vasomotor symptoms

Muka et al. 2017 Plos One; Kristen et al. 2018 Menopause
Treatment of menopausal symptoms

G Sarri et al. 2017
Hormone therapy and cardiovascular disease

**Coronary Heart Disease**
- For every 10,000 women in their 50s on HT for 1 year, **5 extra cases**
- For every 10,000 women in their 70s on HT for 1 year, **19 extra cases**

**Stroke**
- For every 10,000 women, **9 extra cases**

**Blood clots**
- For every 10,000 women on HT for 1 year, **3 extra cases**
Hormone therapy and cardiovascular disease

Table 5. Cardiovascular and Global Index Events by Years Since Menopause at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Combined Trials</th>
<th>CEE Trial</th>
<th>CEE + MPA Trial</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cases per</td>
<td>Cases per</td>
<td>Cases per</td>
</tr>
<tr>
<td></td>
<td>100 Person-Years</td>
<td>100 Person-Years</td>
<td>100 Person-Years</td>
</tr>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hormone Therapy (n = 3608)</td>
<td>39</td>
<td>113</td>
<td>194</td>
</tr>
<tr>
<td>Placebo (n = 3529)</td>
<td>51</td>
<td>103</td>
<td>158</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.76 (0.50-1.16)</td>
<td>1.10 (0.84-1.45)</td>
<td>1.28 (1.03-1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone Therapy (n = 4483)</td>
<td>41</td>
<td>100</td>
<td>142</td>
</tr>
<tr>
<td>Placebo (n = 4494)</td>
<td>23</td>
<td>79</td>
<td>113</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1.77 (1.05-2.98)</td>
<td>1.23 (0.92-1.66)</td>
<td>1.26 (0.98-1.62)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Total mortality</td>
<td>53</td>
<td>142</td>
<td>267</td>
</tr>
<tr>
<td>Placebo (n = 4081)</td>
<td>67</td>
<td>149</td>
<td>240</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.76 (0.53-1.09)</td>
<td>0.98 (0.78-1.24)</td>
<td>1.14 (0.96-1.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Global index§</td>
<td>222</td>
<td>482</td>
<td>675</td>
</tr>
<tr>
<td>Placebo (n = 4122)</td>
<td>203</td>
<td>440</td>
<td>632</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1.05 (0.86-1.27)</td>
<td>1.12 (0.98-1.27)</td>
<td>1.09 (0.98-1.22)</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

P Value for Trend†

- .02
- .36
- .51
- .82

Rossouw et al. 2007
Hormone therapy and cardiovascular disease

- **Route of administration**
  - The most commonly prescribed is oral HT
- **Formula**
  - Conjugated equine estrogen (CEE), the most common
  - Synthetic conjugated estrogens
  - Micronized 17b-estradiol and ethinyl estradiol
  - Progestins: medroxyprogesterone, acetate (MPA), norethindrone acetate and native progesterone
Hormone therapy and cardiovascular disease
Hormone therapy and cardiovascular risk

- Assess the baseline CVD risk before advising for or against hormone therapy and before selecting the formulation, dose and route of administration of hormone therapy.

- In women with increased baseline thrombotic risk, transdermal estradiol alone or with micronized progesterone shall be suggested as first-line treatment.

- Low dose HT formulations (0.625mg/3 of estrogen in oral formulations and ≤50 μg/1 in transdermal formulations) are safer with regard of CVD risk.

- In women who have not undergone hysterectomy, and use of progesterone is necessary, micronized progesterone might be a safer alternative as compared to the other types of progestins.

- The age-related pre-existing conditions (coronary/cerebral atherosclerosis— even subclinical) at the time of HT initiation should be considered when prescribing HT, as they may have a profound impact on the effect of HT on CVD outcomes.

- Transdermal HT with ≤50 μg/1 of estrogen, as compared to oral estrogen preparations, might be a safer treatment option with regards to CVD risk.

- Assess the baseline CVD risk and underlying atherosclerosis in large arteries before prescribing the HT. Consider the alternative non-hormonal medications in case of coronary/cerebral atherosclerosis is present.

- HT shall be advised only when difficult climacteric symptoms are present, and shall be used for the shortest time possible and in the lowest possible dose.
Hormone therapy: benefits and harms

Four in ten women on hormone replacement therapy can't get their medication amid mass shortages

- HRT shortage is forcing some women to go 'cold turkey' on the advice of GPs
- Others are flying to Greece or Spain to get the drugs or rationing the medication
- Survey of 1,500 women found 40 per cent told the medication is not available

HRT shortage in UK expected to continue until next year

Around half of HRT products have been reported as out of stock in UK pharmacies due to supply issues in China, leading to a shortage.

34% HT users in Switzerland
Estrogen hypothesis: the evidence is amenable to alternative explanations
Adverse metabolic changes related to menopause

et al., 2018; Glisic et al., 2019
Sex hormones and risk of type 2 diabetes

384 women developed diabetes over a median follow-up of 11.1 years

Muka et al. 2017. Diabetes
3rd vs. 1st tertiles of steroid sex hormones and type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG</td>
<td>0.56</td>
<td>(0.40–0.79)</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>0.88</td>
<td>(0.67–1.16)</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>1.15</td>
<td>(0.85–1.54)</td>
</tr>
<tr>
<td>Total estradiol</td>
<td>1.42</td>
<td>(1.01–2.00)</td>
</tr>
</tbody>
</table>

Models adjusted for age, cohort, fasting status, insulin, glucose, and BMI, alcohol intake, smoking status, coronary heart disease, serum total cholesterol, statin use, systolic blood pressure, treatment for hypertension, hormone replacement therapy, age of menopause, CRP, and sex hormones for each other.
Sex hormones and risk of type 2 diabetes

<table>
<thead>
<tr>
<th>Hormone</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG</td>
<td>0.44</td>
<td>[0.14; 0.22]</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>1.32</td>
<td>[0.79; 2.21]</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>1.76</td>
<td>[0.92; 3.30]</td>
</tr>
<tr>
<td>Estradiol</td>
<td>1.99</td>
<td>[1.21; 3.27]</td>
</tr>
</tbody>
</table>

Muka et al. 2017. Diabetes
Sex hormones and stroke risk
Time to shift from estrogen to iron hypothesis?
Time to shift from estrogen to iron hypothesis?
Estrogen Signaling

Estrogen receptor β actions in the female cardiovascular system: A systematic review of animal and human studies


Arnold et al. 2005
Alternative treatment

polyphenols that are structurally similar to endogenous estrogen and have weak estrogenic properties

- Soybeans
- Sesame Seed
- Beans
- Flaxseed
- Rice
- Red Clover
- Wheat Germ
- Sunflower Seed
- Walnuts
- Fruits
Alternative treatment

Muka et al. 2017 JAMA; Muka et al. Plos One

Phytoestrogens
Phytoestrogens and risk of T2D in women

- Higher phytoestrogen dietary intake as compared to lower intake was associated with 10% decreased diabetes risk in women.
- Phytoestrogen supplements improved glucose homeostasis in women without type 2 diabetes.
- Overall phytoestrogen supplementation did not affect body composition in postmenopausal women.

Glisic at al. 2018 Adv Nutr
Phytoestrogens, cardiovascular disease and all-cause mortality

Bondonno NP et al. 2019
Major health issues for menopausal women

- Depression
- Dementia
- Sleep Disturbances
- Migraine
- Vasomotor Symptoms
- Cardiovascular Disease
- Metabolic Syndrome
- Diabetes Mellitus
- Chronic Respiratory Disease
- Cancer
  - Lung, Breast, Colon/Rectal, Pancreatic, ovarian, cervical
- Musculoskeletal Diseases
Women’s life cycle

Hormone Levels

Age

Childhood
Puberty
Reproductive period
Menopausal transition
Menopause
Old age

Healthy Lifestyle
Cardiometabolic Research Group

Thank you!