The Women’s Health Initiative Hormone Trials
The Estrogen Only (women with a hysterectomy at baseline) and the Estrogen + Progestin (women with a uterus) Cohorts

Marcia L. Stefanick, Ph.D.
Professor of Medicine
and, Professor of Obstetrics and Gynecology
Stanford Prevention Research Center
Stanford University
WHI Principal Investigator, Stanford
Chair, WHI Steering Committee
WHI Hormone Program Design

Hysterectomy

YES
N= 10,739

CEE (Conjugated equine estrogens) 0.625 mg/d
Placebo

CEE 0.625 mg/d + medroxyprogesterone acetate (MPA) 2.5 mg/d
Placebo

NO
N= 16,608

* Initially: CEE only (N=331), CEE+MPA, or Placebo
(CEE only were subsequently converted to CEE+MPA)

Current HT required 3-month wash-out before baseline testing.
WHI Hormone Sample Size, Outcomes, Follow-up

Women, aged 50-79  Total HT trials = 27,347

Hormone Trials
Primary Outcome:
Coronary Heart Disease
Secondary Outcomes:
Breast, Colon, Endometrial Cancers
Hip Fracture; Other Fractures
Stroke, Pulmonary Emboli
WHI Memory Study (WHIMS)
- for women aged ≥ 65: Dementia

E-Alone
CEE 10,739
Average Follow-up 6.8 years*

E+P
CEE+MPA 16,608
Average Follow-up 5.6 years*

*design = 8.5 years
WHI HT: Baseline Age Distribution

Mean ± SD:
- HystX-E only = 63.6 ± 7.3
- Uterus-E+P = 63.3 ± 7.1

Goal:
- 50-54 = 10%; 55-59 = 20%; 60-69 = 45%; 70-79 = 25% (E=31%; E+P=33%)
- 60-69 = 45%; E+P=45%
- 70-79 = E=24%; E+P=22%

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI HT: Minority Distribution (% of Cohort)

E-Only: 2511/10,739 (23.3%)  
E+P: N = 2531/16,608 (14.6%)

- **Blacks (N)**  
  E: 1617  
  E+P: 1124

- **Hispanic (N)**  
  E: 655  
  E+P: 888

- **Asian/Pl (N)**  
  E: 164  
  E+P: 363

- **Native Amer.**  
  E: 75  
  E+P: 56

- **Other**  
  1.4  
  1.4

**Legend:**
- **Red**: Hysterectomy - E only (75.3% White)  
- **Yellow**: Uterus - E+P (84.0% White)

*Stefanick, Cochrane, Hsia, Barad, Liu, Johnson* Ann Epidemiol 2003; 13: S78-S86
### WHI Hormone Trials: Minority Distribution by Age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>E</td>
<td>32.7%</td>
</tr>
<tr>
<td></td>
<td>E+P</td>
<td>21.5%</td>
</tr>
<tr>
<td>60-69</td>
<td>E</td>
<td>22.0%</td>
</tr>
<tr>
<td></td>
<td>E+P</td>
<td>12.5%</td>
</tr>
<tr>
<td>70-79</td>
<td>E</td>
<td>13.9%</td>
</tr>
<tr>
<td></td>
<td>E+P</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

*Stefanick, Cochrane, Hsia, Barad, Liu, Johnson*  
*Ann Epidemiol 2003; 13: S78-S86*
WHI HT: Baseline Body Mass Index (kg/m²)

Mean BMI:
- E only = 30.1 ± 6.2
- E+P = 28.5 ± 5.9

% Overweight+Obese:
- 79.3 %
- 69.4%

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI Hormone Trials: BMI (kg/m²) by Age

50-59: E (31.2) E+P (28.9)  
60-69: E (30.2) E+P (28.6)  
70-79: E (28.6) E+P (27.5)

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI Hormone Trial Cohorts: Family Income

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI Hormone Trial Cohorts: Number of Live Births

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI Hormone Trial Cohorts: Age at 1st Birth

- Never had term pregnancy:
  - Hysterectomy: 2.7%
  - Uterus: 2.9%

- < 20 yrs:
  - Hysterectomy: 16.4%
  - Uterus: 27.3%

- 20-29 yrs:
  - Hysterectomy: 64.8%
  - Uterus: 70.8%

- 30+ yrs:
  - Hysterectomy: 5.3%
  - Uterus: 9.8%

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
## WHI E-alone (CEE) Trial: Reproductive History

<table>
<thead>
<tr>
<th>Event</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilateral Oophorectomy</strong></td>
<td>40.7%</td>
</tr>
<tr>
<td>by Decade:</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>36.0%</td>
</tr>
<tr>
<td>60-69</td>
<td>42.5%</td>
</tr>
<tr>
<td>70-79</td>
<td>43.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at Hysterectomy (by Decade)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>39.8%</td>
</tr>
<tr>
<td>(55.5%, 36.6%, 25.5%)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>42.7%</td>
</tr>
<tr>
<td>(38.3%, 46.2%, 41.8%)</td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>17.5%</td>
</tr>
<tr>
<td>(6.2%, 17.2%, 32.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Stefanick, Cochrane, Hsia, Barad, Liu, Johnson* *Ann Epidemiol* 2003; 13: S78-S86
WHI Hormone Trials: Smoking Status by Age

50-59 (baseline)
- Never: 47%
- Past: 38%
- Current: 15%

60-69 (baseline)
- Never: 50%
- Past: 39%
- Current: 15%

70-79 (baseline)
- Never: 58%
- Past: 37%
- Current: 5%

### Stewardship

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86

- Hysterectomy- E only (75.3% White)
- Uterus - E+P (84.0% White)
WHI Hormone Trial Cohorts: Alcohol Intake

<table>
<thead>
<tr>
<th>Category</th>
<th>Hysterectomy -E only</th>
<th>Uterus-E+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Drinker</td>
<td>13.7</td>
<td>11.6</td>
</tr>
<tr>
<td>Past Drinker</td>
<td>23.9</td>
<td>17</td>
</tr>
<tr>
<td>Current Drinker</td>
<td>62.4</td>
<td>71.4</td>
</tr>
</tbody>
</table>

WHI Hormone Trials: Physical Activity by Age

50-59 (baseline)
- None: 25%
- 2-<4/wk: 20%
- 4+/>wk: 16%

60-69 (baseline)
- None: 22%
- 2-<4/wk: 18%
- 4+/>wk: 16%

70-79 (baseline)
- None: 17%
- 2-<4/wk: 16%
- 4+/>wk: 15%

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI Hormone Trials: Blood Pressure by Age

50-59 (baseline) 60-69 (baseline) 70-79 (baseline)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>SBP ² 120</th>
<th>&gt;120-140</th>
<th>SBP ³ 140</th>
<th>SBP ² 120</th>
<th>&gt;120-140</th>
<th>SBP ³ 140</th>
<th>SBP ² 120</th>
<th>&gt;120-140</th>
<th>SBP ³ 140</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>43</td>
<td>51</td>
<td>42</td>
<td>37</td>
<td>16</td>
<td>12</td>
<td>45</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
WHI Hormone Trials: Diastolic Blood Pressure by Age

Stefanick, Cochrane, Hsia, Barad, Liu, Johnson Ann Epidemiol 2003; 13: S78-S86
## WHI Coronary Heart Disease by Age: Annualized Rates, HRs

### CEE only Trial

<table>
<thead>
<tr>
<th>Baseline Age (decade)</th>
<th>Total: HR 0.91 (95% CI = 0.75-1.12)</th>
<th>HR (decade): 0.56</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>14</td>
<td>0.56</td>
</tr>
<tr>
<td>60-69</td>
<td>24</td>
<td>0.92</td>
</tr>
<tr>
<td>70-79</td>
<td>54</td>
<td>1.04</td>
</tr>
</tbody>
</table>

### CEE+MPA Trial

<table>
<thead>
<tr>
<th>Baseline Age (decade)</th>
<th>HR 1.24 (95% CI = 1.00-1.54)</th>
<th>HR (decade): 1.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>22</td>
<td>1.27</td>
</tr>
<tr>
<td>60-69</td>
<td>17</td>
<td>1.05</td>
</tr>
<tr>
<td>70-79</td>
<td>3534</td>
<td>1.44</td>
</tr>
</tbody>
</table>

The number of events per 10,000 per year is shown in the diagram.
**WHI Stroke by Age: Annualized Rates, HRs**

<table>
<thead>
<tr>
<th></th>
<th>CEE only Trial</th>
<th>CEE+MPA Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>HR 1.39 (95% CI = 1.10-1.77)</td>
<td>HR 1.31 (95% CI = 1.02-1.68)</td>
</tr>
<tr>
<td><strong>HR (decade):</strong></td>
<td>1.08 1.65 1.25</td>
<td>1.46 1.35 1.26</td>
</tr>
</tbody>
</table>

**Baseline Age (decade):**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CEE</th>
<th>Placebo</th>
<th>CEE+MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>1616</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>60-69</td>
<td>30</td>
<td>71</td>
<td>10</td>
</tr>
<tr>
<td>70-79</td>
<td>57</td>
<td>57</td>
<td>23</td>
</tr>
</tbody>
</table>

*N per 10,000 per year*
**WHI Invasive Breast Cancer: Annualized Rates, HRs**

**CEE only Trial**
- Total: HR 0.77 (95% CI = 0.59-1.01)
- HR (decade): 0.72 0.72 0.94

**CEE+MPA Trial**
- HR 1.24 (95% CI = 1.01-1.54)
- HR (decade): 1.20 1.22 1.34

---

<table>
<thead>
<tr>
<th>Baseline Age (decade)</th>
<th>CEE only Trial</th>
<th>CEE+MPA Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>21 29</td>
<td>31 26</td>
</tr>
<tr>
<td>60-69</td>
<td>26 36</td>
<td>44 36</td>
</tr>
<tr>
<td>70-79</td>
<td>32 34</td>
<td></td>
</tr>
</tbody>
</table>

**N per 10,000 per year**
- 0
- 10
- 20
- 30
- 40
- 50
- 60
WHI Hip Fracture by Age: Annualized Rates, Hazard Ratios

**CEE only Trial**
- Total: HR 0.61 (95% CI = 0.41-0.91)
- HR (decade): 5.04, 0.33, 0.62

**CEE+MPA Trial**
- HR 0.67 (95% CI = 0.47-0.96)
- HR (decade): 0.17, 0.76, 0.69

Baseline Age (decade):
- 50-59
  - CEE: 4
  - Placebo: 1
  - CEE+MPA: 9
- 60-69
  - CEE: 4
  - Placebo: 11
  - CEE+MPA: 3
- 70-79
  - CEE: 32
  - Placebo: 52
  - CEE+MPA: 11
**WHI Colorectal Cancer by Age: Annualized Rates, HRs**

**CEE only Trial**
- Total: HR 1.08 (95% CI = 0.75-1.55)
- HR (decade): 0.59 0.88 2.09

**CEE+MPA Trial**
- HR 0.61 (95% CI = 0.42-0.87)
- HR (decade): 0.79 0.54 0.51

<table>
<thead>
<tr>
<th>Baseline Age (decade)</th>
<th>CEE</th>
<th>Placebo</th>
<th>CEE+MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>32</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>10</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>14</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>
WHI Total Death by Age: Annualized Rates, HRs

**CEE only Trial**
Total: HR 1.04  (95% CI = 0.88-1.22)
HR (decade): 0.73 1.01 1.20

**CEE+MPA Trial**
HR 0.98  (95% CI = 0.82-1.28)
HR (decade): 0.75 1.05 1.02

<table>
<thead>
<tr>
<th>Baseline Age (decade)</th>
<th>CEE</th>
<th>Placebo</th>
<th>CEE+MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>29</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td>7979</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>154</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>60-69</td>
<td>5147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>108</td>
<td>103</td>
<td></td>
</tr>
</tbody>
</table>
WHI Global Index by Age: Annualized Rates, HRs

CEE only Trial
Total: HR 1.01 (95% CI = 0.91-1.12)
HR (decade): 0.80 0.98 1.16 1.16 1.18 1.10

CEE+MPA Trial
HR 1.15 (95% CI =1.03-1.28)
HR (decade): 1.16 1.18 1.10

Baseline Age (decade)
50-59 60-69 70-79 50-59 60-69 70-79
N per 10,000 per year
89 195 328 92 172 303
111 197 288 80 148 276

- CEE
- Placebo
- CEE+MPA
WHI E-Alone Trial: Participant Retention

373,092 Women Initiated Screening

11,941 Provided Consent and reported a hysterectomy

10,739 Randomized

CEE (N = 5310)

- Status on 02/29/04
  - Alive & Outcomes data submitted in last 18 months (n = 4757) 89.6%
  - Withdrew (n = 136) 2.6%
  - Lost to follow-up (n = 126) 2.3%
  - Deceased (n = 291) 5.5%

Placebo (N = 5429)

- Status on 02/29/04
  - Alive & Outcomes data submitted in last 18 months (n = 4839) 89.1%
  - Withdrew (n = 185) 3.4%
  - Lost to follow-up (n = 116) 2.1%
  - Deceased (n = 289) 5.3%

The Women’s Health Initiative Steering Committee: JAMA 2004; 291: 1701-1712
WHI E-Alone (CEE) Trial: Baseline Characteristics
Age, BMI, Prior Hormone Therapy (HT) Use

Mean age = 63.6 years
Mean BMI = 30.1 kg/m²

Age (yrs)

- **50-59**: n=3310 (30.8%)
- **60-69**: n=4852 (45.2%)
- **70-79**: n=2577 (24.0%)

Body Mass Index

- **<25**: n=2206 (20.7%)
- **25-29.9**: n=3707 (34.7%)
- **≥30**: n=4759 (44.6%)

Prior HT Use

- **Past**: n=3819 (35.6%)
- **Current**: n=1377 (12.8%)
- **Never**: n=5539 (51.6%)

The Women's Health Initiative Steering Committee: JAMA 2004; 291: 1701-1712
WHI E-Alone (CEE) Trial: Absolute (annualized) Risk (6.8 Yrs)

The Women’s Health Initiative Steering Committee: JAMA 2004; 291: 1701-1712
WHI E-Alone Trial: Attributable Risk Summary

- **Excess risk per 10,000 women per year on CEE**
  - 12 more women with *strokes*
  - 6 more *Deep Vein Thrombosis (DVT)*
  - *unclear:* more total blood clots in lungs (PE) + legs (DVTs)

- **Risk reduction per 10,000 women per year**
  - 6 fewer *hip fractures*
  - 6 fewer *clinical vertebral fractures*
  - *unclear:* 7 fewer *breast cancer* (Tumor characteristics unknown)

- **Neutral (no differences)**
  - *Coronary Heart Disease*
  - *Colorectal cancer* (Tumor characteristics unknown)
  - *Deaths*

*The Women’s Health Initiative Steering Committee: JAMA 2004; 291: 1701-1712*
WHI E+P Trial: Participant Retention

373,092 Women Initiated Screening

18,845 Provided Consent and reported no hysterectomy

16,608 Randomized

CEE+MPA (N = 8506)

<table>
<thead>
<tr>
<th>Status on 04/30/02</th>
<th>Alive &amp; Outcomes data submitted in last 18 months (n = 7968)</th>
<th>93.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown Vital Status</td>
<td>(n = 307)</td>
<td>3.6%</td>
</tr>
<tr>
<td>Deceased</td>
<td>(n = 231)</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Placebo (N = 8102)

<table>
<thead>
<tr>
<th>Status on 04/30/02</th>
<th>Alive &amp; Outcomes data submitted in last 18 months (n = 7608)</th>
<th>93.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown Vital Status</td>
<td>(n = 276)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Deceased</td>
<td>(n = 218)</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Writing Group for the Women’s Health Initiative Steering Committee: JAMA 2002; 288: 321-333
WHI E+P Trial: Baseline Age, BMI, Prior HT Use

Age (yrs) | Mean = 63.3 yrs | % of Enrolled Population
50-59 | n=5522 (33.3%) | 45.2%
60-69 | n=7510 (45.2%) | 33.3%
70-79 | n=3576 (21.5%) | 21.5%

Body Mass Index | Mean = 28.5 kg/m²
<25 | n=5058 (36.6%) | 36.6%
25-29.9 | n=5826 (35.3%) | 35.3%
³30 | n=5636 (34.1%) | 34.1%

Prior HT Use | % of Enrolled Population
Past | n=3262 (19.6%) | 19.6%
Current | n=1035 (6.2%) | 6.2%
Never | n=12,304 (74.1%) | 74.1%

WHI E+P (CEE) Trial: Absolute (annualized) Risk (5.6 Yrs)

Effects of Estrogen-Plus-Progestin and Placebo on Disease Rates

<table>
<thead>
<tr>
<th>Number of cases per year in 10,000 women</th>
<th>Risks</th>
<th>Benefits</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attacks</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strokes</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood clots</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fractures</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CEE+MPA
- Placebo

[Graph showing the comparison of risks and benefits for different conditions]
WHI E+P (CEE+ MPA) Trial: Key Findings
average of 5.2 years of follow-up (updated to 5.6 years)
In white, findings which were similar in CEE only trial

• does not reduce (increases) heart disease
• increases the risk of stroke
• increases blood clots in the lungs + legs (DVTs)
• decreases the risk of hip fracture
• increases breast cancer risk
• decreases colorectal cancer diagnoses
• does not affect endometrial cancer
• no affect on overall mortality (death)
WHI E+P and E-Alone Trials: Absolute (annualized) Risk

**Effects of Estrogen-Plus-Progesterin and Placebo on Disease Rates**

<table>
<thead>
<tr>
<th>Disease</th>
<th>CEE+MPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attacks</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Strokes</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Blood clots</td>
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<td>5</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Deaths</td>
<td>60</td>
<td>40</td>
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</tbody>
</table>

**Effects of Estrogen-Alone and Placebo on Disease Rates**

<table>
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<tr>
<th>Disease</th>
<th>CEE</th>
<th>Placebo</th>
</tr>
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<td>20</td>
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<tr>
<td>Strokes</td>
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<tr>
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