Associations of Postmenopausal Estrogen Use With Cardiovascular Disease and Its Risk Factors in Older Women

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**Background.** Postmenopausal estrogen replacement therapy has been associated with favorable levels of cardiovascular disease risk factors, but these associations and the relations between estrogen use and subclinical disease have not been examined in large samples of older women.

**Methods and Results.** Present and past estrogen use was ascertained in 2955 women ≥65 years old in the Cardiovascular Health Study, a study of risk factors for coronary heart disease and stroke in the elderly. Present estrogen use was reported by 12% of these women and past use by an additional 26.5%. Estrogen use (past or present) was strongly associated with lower low-density lipoprotein cholesterol, fibrinogen, glucose, insulin, obesity, and age and higher high-density lipoprotein cholesterol and socioeconomic status (all P<.0001). Estrogen users also had lower levels of subclinical disease as measured by carotid intimal-medial thickness, carotid stenosis grade, ECG left ventricular mass, and Doppler mitral peak flow velocities (each P<.02). Relations were similar in younger and older women (65 to 74 versus ≥75 years) and smokers and nonsmokers and were unchanged after women with poor medication compliance were excluded. After adjustment for other factors, estrogen use was associated with decreased carotid wall thickness, although this association was of borderline significance after further adjustment for lipids.

**Conclusions.** Postmenopausal estrogen use in this sample of older women was associated with favorable cardiovascular disease risk factor profiles and with lower measures of subclinical disease. These findings suggest that postmenopausal estrogen use may be associated with lower risk of cardiovascular disease in women well into the eighth decade of life. (Circulation. 1993;88[part 1]:2163-2171.)

**Key Words** • cardiovascular diseases • aging • epidemiology • risk factors • hormones

Despite the relatively low rates of cardiovascular disease among premenopausal women, cardiovascular disease is the leading cause of morbidity and mortality in postmenopausal women, with associated medical care costs exceeding $11 billion per year.1 The increase in heart disease risk after menopause has been suggested to result from unfavorable changes in lipid profiles associated with relative lack of estrogen.2 Postmenopausal estrogen replacement has been suggested as a useful preventive therapy, but a clear assessment of its therapeutic effect awaits clinical trial evidence.3 Several observational studies have demonstrated favorable associations between postmenopausal estrogen use and cardiovascular mortality, morbidity, and risk factors. Estrogen use has been associated with decreased total mortality,3-6 decreased cardiovascular mortality,6,7 and improved risk factor profiles.5,8 Duration of use appears to be related to magnitude of protective effect.5,8 Evidence of a benefit has not been found in all studies, however, with one study showing higher mortality among estrogen users.9,10 although this finding has been contested.11 Three angiographic studies have demonstrated significantly less coronary artery stenosis in postmenopausal women using estrogens compared with nonusers.12-14 Cross-sectional data have shown strong associations between estrogen use and risk factor levels,8 but these studies have not included sufficient numbers of women ≥65 years old to determine whether these associations persist at older ages. In addition, risk factor levels in past and present users have not been compared, nor have correlations been reported between estrogen use and subclinical disease (ie, abnormalities detected noninvasively but not yet having produced signs or symptoms), as measured by carotid stenosis and wall thickness, left ventricular mass, or Doppler mitral flow velocities.
The Cardiovascular Health Study (CHS) is a prospective, observational, epidemiological study of risk factors for coronary heart disease and stroke in 5201 men and women ≥65 years old. It includes a large, multicenter sample of older women undergoing systematic determination of subclinical disease, with concurrent measurements of coagulation factors and indicators of medication compliance. Data from the baseline examination were analyzed (1) to describe the frequency and duration of estrogen use in a multicenter sample of older women; (2) to examine associations of past and present estrogen use with demographic factors, cardiovascular disease risk factors, subclinical disease, and prevalent disease; and (3) to determine the independence of associations between estrogen use and subclinical disease as measured by ECG left ventricular (LV) mass, carotid arterial wall thicknesses, and carotid stenosis.

Methods

CHS participants were recruited from a random sample of the Health Care Financing Administration Medicare eligibility lists in four US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), Pennsylvania. Potential participants were excluded if they were institutionalized, wheelchair-bound in the home, expecting to move from the Field Center area in the next 3 years, or undergoing radiation or chemotherapy for cancer. The sample included 2955 women 65 to 100 years old, with a mean age of 72.4 years. Details of design and methods have been published.15

Eligible subjects who gave informed consent answered standard questionnaires on personal habits, reproductive history, and medical history (including hospitalizations, diagnoses, and cardiac procedures). Cognitive function was measured by the Mini–Mental state examination16 and physical activity with a modified Minnesota leisure time questionnaire.17 Prescription medication use in the preceding 2 weeks was collected directly from prescription bottles,18 including the number of doses prescribed in the past 2 weeks. The number of doses taken in the preceding 2 weeks was reported by the participant. Use of nonprescription drugs such as aspirin, calcium supplements, and fish-oil preparations was ascertained by questionnaire. In addition to current medications, women were asked whether they had ever used estrogens or other hormones for menopausal symptoms and the duration of use. Reported duration was available in 61% of past users and 80% of present users.

Blood pressure was measured in the right arm of seated subjects after a 5-minute rest using a random-zero sphygmomanometer. The average of two measurements was used for analysis. Duplicate measurements of supine blood pressure in both arms and both ankles were taken with a standard mercury sphygmomanometer and an 8-MHz Doppler probe. A low ratio of these measurements (the ankle-arm index) was used as a measure of arterial occlusive disease in the lower extremities.

Anthropometric measurements included weight, height, and waist and hip circumferences. Bioelectric impedance was used as an estimate of body fat; the bioresistance estimate from this measurement was used as an estimate of lean body mass. Twelve-lead, resting ECGs were obtained on all participants, and abnormalities were defined by the Minnesota code.19

Venipuncture was performed early in the clinic visit after a 12-hour fast. Multiple aliquots of plasma were prepared, frozen at −70°C, and shipped weekly on dry ice to a central laboratory. Fasting serum chemistry analyses included measurement of potassium, creatinine, uric acid, albumin, and glucose. Serum insulin was measured by radioimmunoassay according to the method of Herbert et al.20 All participants except diabetics treated with insulin or oral hypoglycemic agents drank a 75-g oral glucose load, and repeat venipuncture was performed 2 hours later for measurement of postchallenge serum glucose and insulin levels.21

Fasting plasma lipid analyses included measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, standardized according to the Centers for Disease Control. Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald equation.22 Plasma fibrinogen levels were measured by the Dade method,23 and assays for factors VII and VIII were standardized against World Health Organization reference materials.

Spirometric lung volumes (including forced vital capacity and 1-second forced expiratory volume [FEV1]) were measured with a water-sealed spirometer. Carotid stenosis was defined by duplex ultrasonography and classified for this analysis as 0%, 1% through 49%, and ≥50%. Near and far wall maximal intimal-medial thicknesses of the carotid arteries were measured and averaged as an indicator of atherosclerosis; separate measurements were made for common and internal carotid arteries. CHS ultrasound methods and initial quality control results have been published.24 Abnormalities of LV ejection were detected by inspection of two-dimensional echocardiographic images and classified on a qualitative basis as normal, borderline, or abnormal. The borderline and abnormal classifications were combined into a single abnormal category for analysis. Mitral early and late peak diastolic flow velocities were measured by Doppler. CHS echocardiographic methods and initial quality control results have been published.25

Definitions

Present estrogen users were defined as women with prescriptions for oral estrogen recorded by medication inventory, regardless of self-reported past use. Past estrogen users were women responding positively to ever having taken Premarin or other estrogens for hot flashes or other symptoms of menopause and not having a current prescription. Four women reporting use of topical estrogen preparations only (ie, transdermal patches or vaginal cream) were considered to be nonusers. In addition, 97 women with missing data were considered to be nonusers.

Definite myocardial infarction, angina, congestive heart failure, stroke, transient ischemic attack, and peripheral vascular disease were defined as positive answers to the question, "Has a doctor ever told you that you had...?" confirmed by review of hospital or physicians' records.26 Subjects with major Q/QS waves on resting ECG or ankle-arm index <0.8 were also considered to have prevalent myocardial infarction or peripheral vascular disease, respectively, regardless of
reported history. Definite coronary heart disease (CHD) included any of the following: reported and confirmed (or silent) myocardial infarction, reported and confirmed angina, or prior coronary revascularization procedures. Carotid stenosis of ≥1% was defined as focal carotid thickening of any discernible degree, whether encroachment on the lumen was detected or not. Carotid stenosis of ≥50% was defined as Doppler flow velocity >1.5 m/s at a site of focal thickening.

Diabetes was defined as self-report of physician-diagnosed diabetes, current use of insulin or oral hypoglycemic medication, fasting glucose ≥140 mg/dL, or 2-hour postload glucose ≥200 mg/dL. Number of medications included all current prescriptions for medications other than oral estrogen or progesterone. Compliance with medication use was assessed in the subset of women taking diuretics or antihypertensive medications once daily (n=1291) as the number of doses taken divided by the number prescribed in the preceding 2 weeks. Coexisting illnesses included self-reported lung disease, nervous disorders, kidney disorders, hypertension, cancer, CHD, congestive failure, stroke, claudication, diabetes, and arthritis.

Statistical Analysis

Significance of differences among estrogen use categories, adjusted for age, was assessed by ANCOVA for continuous variables and χ² (two df) on age-adjusted proportions for dichotomous variables. Significance of differences among frequencies of never, past, and present smoking and among clinics was adjusted for age using the Cochran-Mantel-Haenszel test stratified by 5-year age groups. Continuous variables with skewed distributions such as insulin, glucose, triglycerides, cognitive function, factor VII, physical activity, number of births, ankle-arm index, and number of medications were log-transformed to improve normality. Means of continuous variables adjusted for age were calculated by ANCOVA.

Independent associations of estrogen use were assessed by multiple linear regression for continuous measures and multiple logistic regression for dichotomous measures such as carotid stenosis. Education, income, and cognitive function were dichotomized in multivariate analyses (<12 years versus ≥12 years, <$12,000/y versus ≥$12,000/y; ≤25 versus >25). All factors except lipids associated in age-adjusted analyses with each dependent variable were included with the three hormonal use categories in initial models of all women. Factors remaining after backward elimination, as well as age and hysterectomy status (if these were not significant after elimination), were used to adjust all models of a given dependent variable. Additional models with these variables plus lipids were also estimated. Since there were at least five logical combinations of estrogen categories, only two of which are independent, the ever versus never comparison was identified a priori as the main contrast of interest because it has been most widely examined in the past. Other comparisons are presented for interest but should not be overinterpreted. Because of the large number of comparisons performed, associations were considered to be significant at P<.01. All analyses were performed by use of the Statistical Analysis System (SAS).27

Results

Of 2955 women interviewed, 356 (12%) were currently using oral estrogen or combined estrogen/progesterone. Two hundred eighty-one (79%) of these women were taking unopposed estrogen. An additional 784 women (26.5%) reported past use of hormones but did not have current prescriptions, making a total of 39% of women who were ever users of postmenopausal estrogens. Estrogen use was more common in younger women and in those with prior hysterectomy for both present and past use (Fig 1). Median duration of use was 18 years in present users compared with 3 years in past users (P<.0001, Fig 2).

Estrogen Use Versus Nonuse

Estrogen users (past or present) were younger and more highly educated and had higher incomes than nonusers (Table 1). They were also more likely to be white, to be living in Sacramento, to have had recent influenza and pneumonia vaccinations, to have had prior hysterectomy and oophorectomy, and to be past smokers. Estrogen users (past or present) had higher levels of HDL cholesterol, factor VII, bioresistance, alcohol intake, and FEV₁ than did never users. They had lower levels of LDL cholesterol, fibrinogen, albumin, fasting insulin and glucose, obesity, carotid wall thicknesses, ECG LV mass, and ratio of late to early Doppler mitral peak flow velocities (ie, A/E ratio) than did nonusers. Users were less likely than nonusers to
TABLE 1. Comparison of Selected Risk Factors and Subclinical and Clinical Diseases in Present, Past, and Never Users of Estrogen

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Present Use (n=356)</th>
<th>Past Use (n=784)</th>
<th>Never Use (n=1815)</th>
<th>P, Ever vs Never*</th>
<th>P, Present/Past/Never†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.5</td>
<td>71.6</td>
<td>73.0</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>&lt;High school, n (%)</td>
<td>64 (19)</td>
<td>161 (21)</td>
<td>575 (31)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Income &lt;$12,000, n (%)</td>
<td>43 (15)</td>
<td>162 (23)</td>
<td>601 (34)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nonwhite, n (%)</td>
<td>10 (2.8)</td>
<td>31 (3.9)</td>
<td>125 (6.9)</td>
<td>0.0002</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cognitive ≤25, n (%)</td>
<td>23 (7.1)</td>
<td>61 (7.7)</td>
<td>220 (10)</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Clinic</td>
<td>Forsyth, n (%)</td>
<td>100 (28)</td>
<td>170 (21)</td>
<td>483 (27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sacramento, n (%)</td>
<td>159 (46)</td>
<td>269 (35)</td>
<td>318 (17)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hagerstown, n (%)</td>
<td>33 (9.3)</td>
<td>139 (18)</td>
<td>576 (32)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pittsburgh, n (%)</td>
<td>64 (18)</td>
<td>206 (26)</td>
<td>438 (24)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Medical care/health behavior</td>
<td>Calcium use, n (%)</td>
<td>158 (45)</td>
<td>268 (35)</td>
<td>412 (23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Influenza vaccine, n (%)</td>
<td>192 (56)</td>
<td>386 (50)</td>
<td>698 (38)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pneumonia vaccine, n (%)</td>
<td>129 (38)</td>
<td>260 (35)</td>
<td>389 (22)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;3 Medications, n (%)</td>
<td>103 (30)</td>
<td>187 (22)</td>
<td>423 (23)</td>
<td>0.3</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt;3 Diseases, n (%)</td>
<td>29 (8.7)</td>
<td>143 (19)</td>
<td>330 (17)</td>
<td>0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Always eats skin of chicken/fat meat, n (%)</td>
<td>36 (10)</td>
<td>73 (9.5)</td>
<td>258 (14)</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>High fat in cooking, n (%)</td>
<td>91 (26)</td>
<td>163 (21)</td>
<td>492 (27)</td>
<td>0.005</td>
<td>0.004</td>
</tr>
<tr>
<td>Reproductive history</td>
<td>Hysterectomy, n (%)</td>
<td>263 (74)</td>
<td>349 (45)</td>
<td>485 (27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oophorectomy, n (%)</td>
<td>153 (46)</td>
<td>245 (33)</td>
<td>336 (20)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Live births, n</td>
<td>2.5</td>
<td>2.4</td>
<td>2.8</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Risk factors</td>
<td>HDL cholesterol, mg/dL</td>
<td>71</td>
<td>59</td>
<td>56</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>118</td>
<td>139</td>
<td>141</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>218</td>
<td>226</td>
<td>225</td>
<td>0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>301</td>
<td>317</td>
<td>327</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Factor VII, % activity</td>
<td>153</td>
<td>132</td>
<td>132</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.88</td>
<td>3.99</td>
<td>4.01</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>13.8</td>
<td>15.3</td>
<td>17.9</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>98</td>
<td>106</td>
<td>110</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>140</td>
<td>145</td>
<td>149</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9</td>
<td>26.1</td>
<td>26.9</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bioresistance</td>
<td>613</td>
<td>601</td>
<td>588</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.876</td>
<td>0.893</td>
<td>0.894</td>
<td>0.06</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>87</td>
<td>90</td>
<td>92</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>99</td>
<td>101</td>
<td>103</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; and CHD, coronary heart disease.

Means of continuous variables adjusted for age; counts of frequencies are unadjusted, but proportions are adjusted for age.

*Ever vs never* indicates two-way comparison using ANCOVA adjusted for age for continuous variables, χ² (one df) for dichotomous variables, comparing ever (past+present) vs never users.

†*Present/past/never* indicates three-way comparison adjusted for age using ANCOVA for continuous variables and χ² (two df) on age-adjusted proportions for dichotomous variables. Denominators for some variables may vary because of missing data.

*Not adjusted for age.

#Adjusted for age and standing height.

| Adjusted for age and mitral early peak flow velocity. |
TABLE 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>Ever Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present Use</td>
</tr>
<tr>
<td></td>
<td>(n=370)</td>
</tr>
<tr>
<td>Alcohol intake, mL/wk</td>
<td>2.71</td>
</tr>
<tr>
<td>Never smokers, n (%)</td>
<td>179 (54)</td>
</tr>
<tr>
<td>Past smokers, n (%)</td>
<td>134 (37)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>39 (9.2)</td>
</tr>
<tr>
<td><strong>Subclinical disease</strong></td>
<td></td>
</tr>
<tr>
<td>FEV1, L$^1$</td>
<td>1.87</td>
</tr>
<tr>
<td>Common carotid thickness, mm</td>
<td>0.94</td>
</tr>
<tr>
<td>Internal carotid thickness, mm</td>
<td>1.25</td>
</tr>
<tr>
<td>Carotid stenosis ≥1%, n (%)</td>
<td>188 (56)</td>
</tr>
<tr>
<td>Carotid stenosis ≥50%, n (%)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>ECG-LV mass, g</td>
<td>164</td>
</tr>
<tr>
<td>Doppler A/E ratio</td>
<td>1.11</td>
</tr>
<tr>
<td>Doppler mitral late peak flow velocity, m/s</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Prevalent disease</strong></td>
<td></td>
</tr>
<tr>
<td>Definite CHD, n (%)</td>
<td>29 (8.5)</td>
</tr>
<tr>
<td>Reported emphysema/bronchitis, n (%)</td>
<td>31 (8.9)</td>
</tr>
</tbody>
</table>

Report markers of high fat intake and to have low

cognitive function scores, and carotid stenosis.

Increased duration of use showed a weak positive association

with HDL cholesterol and a weak negative association

with LDL cholesterol and fibrinogen in ever

users after adjustment for age ($P<.05$, data not shown).

**Present, Past, and Never Use**

In many ways, past users had characteristics interme-

ciate between those of present and nonusers. This

observation was true of factors such as age, income,

calcium use, prior hysterectomy or oophorectomy, levels

of fibrinogen, fasting insulin and glucose, weight, body

mass index, bioresistance, waist and hip circumferences,

alcohol use, and ECG LV mass. In other ways, past

users were much more like nonusers, particularly in

regard to number of medications or illnesses, levels of

lipoproteins, factor VII, albumin, waist/hip ratio, FEV1,

internal carotid thickness, carotid stenosis, and definite

CHD. Past users were more like present users in regard
to education, cognitive function, vaccination history,

and number of live births.

No differences were noted among past, present, and

never users (or between ever and never users) in the use

of lipid-lowering drugs, aspirin, fish oil, or diuretics or in

prevalence or levels of special diet, age at menopause,

triglycerides, systolic or diastolic blood pressure, bio-

reactance, physical activity, ankle-arm index, cardiac in-

jury score, minor Q/QS waves or ST-T changes, pro-

longed QT interval, orthostatic hypotension, ST

depression ≥1 minute duration, major Q/QS waves,

definite congestive heart failure, definite stroke, or
definite diabetes. Increased duration of use was weakly

associated with decreased factor VII and fibrinogen

levels in present users only, after adjustment for age

($P<.04$, data not shown).

**Associations With Estrogen Use Stratified by Age, Smoking, and Compliance**

Analyses stratified by age of participants (65 to 74

years and ≥75 years) and smoking status (ever versus

never) showed similar associations of estrogen use with

risk factors and disease measures in younger and older

women and in smokers and nonsmokers (data not shown).

Excluding 137 women with poor medication

compliance (taking <80% of prescribed dose) did not

change the results observed for the 1291 women taking

diuretics or antihypertensives once daily.

**Associations With Subclinical Disease**

To determine whether estrogen use was associated

with less subclinical disease independent of other card-

iovascular disease risk factors or indicators of health

consciousness, multiple linear regression was used to

model subclinical disease measures on estrogen use

while adjusting for other covariates (Table 2). Contrasts

were estimated to compare ever users with never users,
present with past users, and past with never users.

Comparisons of the present with never users were the

sum of the present/past and past/never comparisons.

Ever use of estrogen was associated with 0.035 mm

thinner common carotid walls after adjustment for age,
hysterectomy, race, income, cognitive function, smok-
ing, lipid-lowering medications, fasting glucose, and

factor VII level ($P<.0001$). Present use was associated

with a similar decrement in wall thickness compared

with past users, and past use with about half this
decrement compared with never use. Further adjust-
ment for HDL and LDL cholesterol reduced the mag-
TABLE 2. Multiple Linear Regression Models of Subclinical Disease Measures in All Women and in Subset Without Prevalent CHD

A. Maximum common carotid wall thickness, adjusting for age, hysterectomy, race, income, cognitive function, past smoking, present smoking, lipid-lowering medications, fasting glucose level, factor VII

<table>
<thead>
<tr>
<th></th>
<th>All Women Adjusted only for factors listed in (A)</th>
<th>All Women Additional adjustment for HDL-C and LDL-C</th>
<th>Prevalent CHD Excluded Adjusted only for factors listed in (A)</th>
<th>Prevalent CHD Excluded Additional adjustment for HDL-C and LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( P )</td>
<td>( \beta )</td>
<td>( P )</td>
</tr>
<tr>
<td>Ever vs never use</td>
<td>(-0.035)</td>
<td>0.0001</td>
<td>(-0.025)</td>
<td>0.01</td>
</tr>
<tr>
<td>Present vs past use</td>
<td>(-0.038)</td>
<td>0.01</td>
<td>(-0.021)</td>
<td>0.2</td>
</tr>
<tr>
<td>Past vs never use</td>
<td>(-0.015)</td>
<td>0.08</td>
<td>(-0.015)</td>
<td>0.09</td>
</tr>
<tr>
<td>Present vs never use</td>
<td>(-0.054)</td>
<td>0.0001</td>
<td>(-0.036)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

B. Maximum Internal carotid wall thickness, adjusting for age, hysterectomy, past smoking, present smoking, alcohol intake, lipid-lowering medications, diabetes, waist circumference, fibrinogen and albumin levels

<table>
<thead>
<tr>
<th></th>
<th>All Women Adjusted only for factors listed in (B)</th>
<th>All Women Additional adjustment for HDL-C and LDL-C</th>
<th>Prevalent CHD Excluded Adjusted only for factors listed in (B)</th>
<th>Prevalent CHD Excluded Additional adjustment for HDL-C and LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( P )</td>
<td>( \beta )</td>
<td>( P )</td>
</tr>
<tr>
<td>Ever vs never use</td>
<td>(-0.077)</td>
<td>0.006</td>
<td>(-0.042)</td>
<td>0.15</td>
</tr>
<tr>
<td>Present vs past use</td>
<td>(-0.123)</td>
<td>0.004</td>
<td>(-0.065)</td>
<td>0.13</td>
</tr>
<tr>
<td>Past vs never use</td>
<td>(-0.016)</td>
<td>0.6</td>
<td>(-0.009)</td>
<td>0.8</td>
</tr>
<tr>
<td>Present vs never use</td>
<td>(-0.139)</td>
<td>0.001</td>
<td>(-0.074)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

C. ECG LV mass, adjusting for age, hysterectomy, education, past smoking, definite CHD (in model including prevalent CHD only), fasting insulin and glucose levels

<table>
<thead>
<tr>
<th></th>
<th>All Women Adjusted only for factors listed in (C)</th>
<th>All Women Additional adjustment for HDL-C and LDL-C</th>
<th>Prevalent CHD Excluded Adjusted only for factors listed in (C)</th>
<th>Prevalent CHD Excluded Additional adjustment for HDL-C and LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( P )</td>
<td>( \beta )</td>
<td>( P )</td>
</tr>
<tr>
<td>Ever vs never use</td>
<td>(-3.61)</td>
<td>0.02</td>
<td>(-3.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>Present vs past use</td>
<td>(-1.13)</td>
<td>0.7</td>
<td>(-1.88)</td>
<td>0.5</td>
</tr>
<tr>
<td>Past vs never use</td>
<td>(-3.05)</td>
<td>0.05</td>
<td>(-2.98)</td>
<td>0.05</td>
</tr>
<tr>
<td>Present vs never use</td>
<td>(-4.18)</td>
<td>0.05</td>
<td>(-4.85)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and LV, left ventricular.

The magnitude and significance of these associations such that only ever versus never and present versus never use retained borderline associations with wall thickness \(P < .01\). Exclusion of women with prevalent CHD did not substantially alter these associations.

A similar model of maximum internal carotid thickness showed significant associations for ever versus never, present versus past, and present versus never use after adjustment for age, hysterectomy, smoking, alcohol intake, lipid-lowering medications, diabetes, waist circumference, fibrinogen and albumin levels. 
circumference, and fibrinogen and albumin levels. The magnitude of these associations was greater than that for common carotid thickness, with ever users having approximately 0.08 mm thinner internal carotid walls than never users. Addition of lipids to this model effectively removed these associations. Duration of use was not associated with internal or common carotid thickness in these multivariate models.

Estrogen use was associated with 3.6 g lower ECG LV mass in comparing ever with never users after adjustment for age, hysterectomy, education, past smoking, definite CHD (in models including women with prevalent CHD), and insulin and glucose levels. Addition of lipids to this model tended to increase the magnitude of these associations, and exclusion of women with prevalent CHD tended to reduce them. Duration of use was not associated with LV mass in these multivariate models. Multiple logistic regression of carotid stenosis did not demonstrate independent associations with estrogen use.

Discussion
Past or present estrogen use was strongly associated with favorable risk factor profiles, including lower levels of LDL cholesterol, fibrinogen, glucose, insulin, obesity, and age; higher levels of HDL cholesterol and socioeconomic status (as measured by age and education); and increased medical care utilization as measured by vaccination. Past or present estrogen users (ever users) also had lower levels of subclinical disease as measured by carotid intimal-medial thickness or stenosis, ECG LV mass, and Doppler A/E ratio, as well as lower prevalence of chronic obstructive pulmonary disease. Although present estrogen use was associated with thinner carotid intimal-medial thickness after adjustment for covariates other than lipid levels, after inclusion of lipids the associations with common carotid thickness and ECG LV mass were of borderline significance in ever versus never users and generally were not significant for other comparisons.

Prevalence Compared With Other Studies
Present estrogen use was reported by 12% of women in CHS, considerably lower than the 22% to 35% prevalences previously reported. Part of this difference may be a result of the older age of the CHS sample, since prevalence of present estrogen use was 17.3% in a cohort of women of similar age. Differences between the present study and earlier studies may also be caused by secular trends, since estrogen use declined in the late 1970s after reports of increased risk of endometrial cancer. Geographic patterns may also be a factor, since the Sacramento subsample in CHS showed usage patterns more like those reported by other California studies. The high prevalence of unopposed estrogen use may reflect carryover of prescribing practices in women placed on estrogens many years before but was identical to that reported by Barrett-Connor et al.

Associations With Risk Factors
Risk factor associations detected in CHS are similar to those reported previously and represent, particularly in regard to risk factors measured directly, the first demonstration of these relations in a large cohort of older women. Although the Leisure World Study of southern California had a larger sample of women (n = 8881), its risk factor information was based entirely on questionnaires without laboratory or noninvasive measurements.

Differences in levels of glucose, obesity, HDL cholesterol, LDL cholesterol, and social class between estrogen users (past or present) and nonusers in the present study were similar to those reported by Criqui et al and Barrett-Connor et al in samples of younger women. The 12- to 15-mg/dL average difference in HDL cholesterol in present CHS estrogen users contrasts strongly, however, with the 3.3-mg/dL difference reported in Framingham and may have been a result of inclusion of past users in the Framingham estrogen use group. Triglyceride levels did not differ by estrogen use in the present study, similar to findings in Framingham but in contrast to data from other cohorts. Estrogen therapy has been shown to increase triglyceride levels in a dose-dependent fashion within individuals, but this relation may be confounded by obesity and other factors in cross-sectional data. Like Framingham and the Lipid Research Clinics Follow-Up Study and unlike the California studies, there were no differences in blood pressure among users and nonusers in the present study. Cigarette smoking, particularly past smoking, was more common among estrogen users in this and other studies.

Estrogen use has not been strongly related to hemostatic factors, although the lack of information in this area has been cited previously. Lower fibrinogen levels and higher levels of factor VII have been reported after oral estrogen therapy in 18 postmenopausal women, although the differences observed were not significant. Available data are conflicting, however, since other investigators have reported declines in factor VII activity after estrogen therapy without a change in fibrinogen. The large sample size in CHS may provide more stability to estimates of these cross-sectional associations, but interventional studies are needed to assess the true effects of estrogen on hemostatic factors.

Past users formed an interesting "intermediate" group of women, often having risk factor levels between those of present and never users. Study of past users may shed some light on social class and medical care utilization as confounders of estrogen-risk factor relation, since past users are likely to have socioeconomic status and access to care similar to those of present users. That laboratory values among past users were so much more like nonusers than present users suggests that present use, rather than sociodemographics, may be the more important factor in these associations.

Stratification by age showed similar relations between estrogen use and many cardiovascular disease risk factors, suggesting that associations between estrogen use and favorable risk factor profiles are sustained well into the eighth decade of life. The lack of associations with duration of use probably reflected the unreliability of the duration data, which depended on recall of sometimes distant events and which were missing in a large proportion of estrogen users.

Stratification by smoking status showed very few differences in risk factor or subclinical disease associations with estrogen use in ever and never smokers. Criqui et al reported a puzzling interaction between...
estrogen use and smoking status such that estrogen use was protective against cardiovascular mortality in present and never smokers but associated with increased risk in past smokers. These authors concluded that they "...find no evidence to support the alternative hypothesis that postmenopausal estrogen use is somehow selectively dangerous in past smokers." In the present study, present and past smokers were analyzed together because the great majority were past smokers and because a selective effect on past smokers appears to be biologically implausible. Examination of possible interactions between past smoking, estrogen use, and mortality must await longitudinal analysis of this group of women.

Analyses stratified by medication compliance were performed to examine the hypothesis that estrogen users represent a highly compliant group with decreased cardiovascular risk regardless of estrogen use. To the extent that increased compliance is associated with increased health awareness and in turn with improved cardiovascular disease risk profiles, high levels of compliance in estrogen users and nonusers might be expected to diminish an association between estrogen and risk factors if this association is primarily a result of healthy behavior alone. Although the poor compliance group was small, exclusion of these women demonstrated relations with estrogen use that were almost identical to those in the group as a whole, suggesting that high compliance as measured in this study was not a major confounder of the estrogen–cardiovascular risk relation.

**Associations With Subclinical Disease**

The use of multiple noninvasive measures of subclinical disease in CHS provided a unique opportunity to examine associations of estrogen use and early cardiovascular disease independent of any diagnosis or detection biases related to estrogen use. The lower levels of internal and common carotid wall thicknesses and ECG LV mass in estrogen users were largely but not entirely explained by risk factor differences, as confirmed by multivariate models. Excluding lipid levels from these models demonstrated strong relations between present estrogen use and carotid wall thicknesses independent of other nonlipid factors. If 25% to 50% of the beneficial effects of estrogen on CHD risk is related to changes in lipid levels, as has been estimated, adjustment for lipids might substantially underestimate even cross-sectional relations with subclinical disease measures. This may be particularly true for carotid wall thickness, which is known to be related to lipid levels.

Adjusted differences in common and internal carotid wall thicknesses were greater in present users than past users compared with never users. This is not surprising, given the considerable difference in duration of use between present and past users, although duration was not significantly associated with wall thickness in multivariate models. It is also of interest that associations with present use were substantially diminished after adjustment for lipids, whereas associations with past use were minimally affected. Differences in wall thicknesses were, with one exception, also greater between present and past users than between past and never users. Had past users been closer to present users in regard to wall thicknesses, one might have inferred that factors other than duration or recentness of use, such as demographics, were somehow underlying this relation. The fact that past users differed little from never users suggests that present use or the factors associated with it are more strongly related to wall thickness than are past use and factors that accompany it.

The finding that associations with LV mass were, if anything, slightly strengthened by adjustment for lipids is intriguing and suggests that lipids are somehow negatively confounding this association. We are unaware of any evidence of a relation between adverse lipid profiles and lower LV mass and would have expected to find just the opposite, given the strong associations of both with obesity. Alternatively, lipids may be related to some unknown factor associated with both estrogen use and lower LV mass, but at present, the weak enhancement of this association defies explanation. The small differences between present and past users in LV mass compared with those between ever users or past users and never users suggests that factors related to ever use, such as demographics, may be more important in the relation of estrogen use to LV mass than currentness of use may be.

**Summary**

Postmenopausal estrogen use in this sample of older women was associated with favorable risk factor profiles that are similar to those reported in younger women who use estrogen. Estrogen use was also associated with lower levels of subclinical disease, although much of this relation is accounted for by risk factor differences. These findings suggest that postmenopausal estrogen use may be associated with lower risk of cardiovascular disease in women well into the eighth decade of life.

**Acknowledgments**

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**Appendix**

**Participating Institutions and Principal Staff**

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Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. The CHS Collaborative Research Group.
T A Manolio, C D Furberg, L Shemanski, B M Psaty, D H O'Leary, R P Tracy and T L Bush

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