

REPRINTS AND REFLECTIONS

Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence^{1,2}

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Considerable epidemiological evidence has accumulated regarding the effect of post-menopausal estrogens on coronary heart disease risk. Five hospital-based case-control studies yielded inconsistent but generally null results; however, these are difficult to interpret due to the problems in selecting appropriate controls. Six population-based case-control studies found decreased relative risks among estrogen users, though only 1 was statistically significant. Three cross-sectional studies of women with or without stenosis on coronary angiography each showed markedly less atherosclerosis among estrogen users. Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. A reanalysis of the data showed a nonsignificant protective effect among younger women and a nonsignificant increase in risk among older women. Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors. This benefit is consistent with the effect of estrogens on lipoprotein subfractions (decreasing low-density lipoprotein levels and elevating high-density lipoprotein levels). A quantitative overview of all studies taken together yielded a relative risk of 0.56 (95% confidence interval 0.50–0.61), and taking only the internally controlled

perspective and angiographic studies, the relative risk was 0.50 (95% confidence interval 0.43–0.56).

Introduction

The risk in mortality from coronary heart disease (CHD) around the age of menopause¹ has lead to speculation that endogenous estrogen in premenopausal women has a protective effect. Although risk of CHD does not abruptly increase at the moment of natural menopause,^{2,3} rates of heart disease rise sharply during the period of the climacteric. The increased risk of atherosclerosis and CHD among women with bilateral oophorectomy³ further suggests that estrogen replacement therapy might decrease the risk of heart disease. We review the epidemiological evidence regarding postmenopausal estrogen use and CHD, and provide a quantitative overview.

Methods for quantitative overview

Through computer searches and review of references, we sought to collect all articles with quantitative data on the effect of postmenopausal estrogens on risk of CHD. We calculated a weighted average of the estimated relative risks by giving each study a weight proportional to its precision (i.e., the inverse of the variance). Thus, larger studies (with more precise estimates and narrower confidence limits) were given greater weight than small ones.⁴ An estimate of the variance was derived, when necessary, by calculating the standard error from the confidence interval of each study.

Separate analyses were performed within each category of study design, and an additional analysis was conducted including the internally controlled cohort and cross-sectional angiography studies (which are less prone to bias). When they were given, we used estimates adjusted for confounding factors. Where several disease endpoints were studied, we chose the one closest to major CHD (nonfatal myocardial infarction (MI) and death due to CHD, or, for the angiography studies, the highest category of occlusion). For comparability, we used estimates associated with ever use of estrogens whenever possible. These analyses make the assumption that each of the

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studies was estimating the same underlying parameter. We recognize that the requirements for this assumption are not strictly met, because the studies were conducted using different designs among different populations. Despite these and other limitations in the metaanalysis of observational data,⁴ this approach can provide a meaningful guide to the strength of the evidence.

Hospital-based case-control studies

Table 1 summarizes the findings from six hospital-based case-control studies.^{5–10} This design faces some noteworthy limitations, including the possibility of recall bias and the more difficult problem of proper selection of controls. It is essential to select controls diagnosed with diseases unrelated to estrogen use. This can be difficult because many diseases are related in some way to estrogen use. For example, in one study,⁷ many controls were fracture patients. The study was designed before it was widely appreciated that estrogens reduce osteoporosis and fracture. These controls are less likely to be estrogen users than comparably aged women in the population; this would tend to reduce the magnitude of the inverse association between estrogens and risk of CHD. Even exclusion of all diseases that are biologically related to estrogen use from the control pool may not completely solve this problem. For some patients, physicians may be reluctant to prescribe estrogens to avoid possible interactions with other medications or simply to avoid overburdening the patient with many different medications. Hence, the results could be biased even with a nonbiological link between disease status among the controls and likelihood of estrogen usage. Generally, the bias would be such that estrogen usage in the controls would be reduced. Therefore, one would expect that hospital-based case-control studies might underestimate the reduction in risk of CHD due to estrogen.

Both hospital-based case-control studies with null findings were conducted by Rosenberg *et al.* In the first,⁵ the investigators initially observed a relative risk of 0.7 for estrogen use. After adjusting for an array of variables the relative risk was changed to 1.0. Of the 336 cases in that study, only 8 were current users of estrogens. The second study⁷ was conducted among women under age 50, limiting generalizability. Moreover, a substantial proportion of controls were fracture patients.

The only case-control study which showed an increased risk for CHD was conducted by Jick *et al.*⁶ who observed a relative risk of 7.5 among women less than age 46. Among postmenopausal women, the relative risk was 4.2 (95% confidence interval 1.0–18.8). Of the 14 cases, at least 13 were current smokers. In the larger study of which that analysis was part, of 954 initially eligible patients, only 95 enrolled, which may have introduced a bias. The small sample size and the restriction to women under age 46 render the findings difficult to interpret. In a parallel paper, Jick *et al.*⁹ studied estrogen users under age 46 with a high CHD risk profile, and observed a relative risk of 0.5 (0.1–3.4).

La Vecchia *et al.*¹⁰ reported an Italian study of women under age 55. Because the majority were premenopausal and no analysis was presented for postmenopausal women, these results are not included in the quantitative overview.

Population-based case-control studies

The population-based case-control studies,^{11–17} summarized in Table 2, share some of the methodological limitations of retrospective studies, including selection and enrollment of controls, but avoids hospital controls. Hence, one would not expect a systematic underestimate of the effect of estrogens. All six studies of MI observed an apparent protective effect of

Table 1 Hospital-based case-control studies of estrogen use among patients hospitalized for MI

Study	Age of patients (years)	Number of cases	Percentage estrogen users in cases	Endpoint	Exposure to estrogen	Relative risk (95% CI)	
						Age-adjusted	Risk factor-adjusted
Rosenberg <i>et al.</i> (5)	40–75; median age of exposed cases = 54	336	2.4	Nonfatal MI	Current use	0.71 (0.34–1.46) ^a	0.97 (0.48–1.95)
Jick <i>et al.</i> (6)	39–45	14	50	First nonfatal MI	Current use	4.25 (0.96–18.84) ^a	
Jick <i>et al.</i> (9)	35–45	12	17	First nonfatal MI	Current use	0.50 (0.07–3.44) ^a	
Rosenberg <i>et al.</i> (7)	30–49; median = 45	99 postmenopausal	18 24	First MI	Current use Past use	1.39 (0.71–2.74) ^a 1.88 (1.09–3.24) ^a	
Szklo <i>et al.</i> (8)	35–64	39	28	First MI	Ever use	0.8	0.6 (0.2–1.9)
La Vecchia <i>et al.</i> (10) ^b	Under 55 median = 48 60% premenopausal	168	5 3	First MI First MI	Current use Past	1.85 (0.68–5.01) 1.01 (0.31–3.27)	2.95 (0.80–10.80) 0.77 (0.16–3.60)

^a These figures were derived from data given in this chapter.

^b Not included in metaanalysis because of the predominance of postmenopausal women.

Table 2 Community/population-based case-control studies of estrogen use on heart disease risk

Study	Age of patients (years)	Number of patients	Endpoint	Exposure to estrogen	Percentage estrogen users	Relative risk (95% CI)	
						Age-adjusted	Risk factor-adjusted
Talbott <i>et al.</i> (11)	39–64 mean = 56.6	64(unknown number post-menopausal)	Sudden death	Current use	5	0.34 (0.09–1.30) ^a	
Pfeffer <i>et al.</i> (12)	50–98 mean = 75	171	First MI	Ever use Current use	30 8.7		0.86 (0.54–1.37) 0.68 (0.32–1.42)
Ross <i>et al.</i> (13)	Under 80 mean = 73	133	Fatal CHD	Ever use	Not given	Living control 0.43 (0.24–0.75) Dead controls 0.57 (0.33–0.99)	No change No change
Bain <i>et al.</i> (14)	30–55	120	First MI	Ever use Current use	53 27	0.9 (0.6–1.2) 0.7 (0.5–1.1)	0.8 (0.6–1.3) 0.7 (0.4–1.1)
Adam <i>et al.</i> (15)	50–59	76	Fatal MI	Ever use Current use	12 3	0.65 (0.29–1.45) ^a 0.97 (0.41–2.28)	
Beard <i>et al.</i> (16)	40–59	86	MI or sudden death	Ever use	27		0.55 (0.24–1.30)
Thompson <i>et al.</i> (17)	45–69	603	MI and stroke	Ever use 94% past use	Estrogen alone Estrogen and progesterone	1.12 (0.79–1.57) 0.86 (0.43–1.74)	1.09 (0.65–1.82) 1.16 (0.43–3.12)

^a These figures represent the crude relative risk.

estrogens, which was statistically significant in only one.¹³ A seventh¹⁷ reported on a combined endpoint of stroke and MI, with essentially null results.

In the largest community-based case-control study on MI, with 171 cases from a retirement community, Pfeffer *et al.*¹² observed a relative risk of 0.7 (0.3–1.4) among current users of estrogens, based on pharmacy records. In a later analysis,¹³ these records were found to be inadequate. This misclassification of estrogen use would tend to bias the results toward the null. The mean duration of use was less than 3 months, which also would bias the findings toward an underestimate because such a short duration is unlikely to be sufficient for a plausible biological effect.

In another case-control study in the same retirement community, Ross *et al.* used medical records to assess use of estrogens.¹³ They observed a relative risk of 0.4 (0.2–0.8) compared with living controls and 0.6 (0.3–1.0) compared with deceased controls. In the overview, we used the higher (less protective) estimate based on dead controls, since all the cases were dead, and ignored the small correlation between results induced by overlap of patients with the previous study.

Thompson *et al.*¹⁷ used a combined endpoint of MI and stroke in a practice-based case-control study of women ages 45–69 years. Cases were matched to controls by age and practitioner, which would tend to drive the results toward the null if the physicians differed in their usual practice for prescribing hormone therapy. For estrogens alone, they observed a relative risk of 1.1 (0.7–1.8), and for estrogen plus progesterone, the relative risk was 1.2 (0.4–3.1). In this study from the UK, conjugated estrogen use was less predominant than in the United States. In the overview, we use these risk estimates, but their weight was decreased by 244/603 (the fraction of strokes among the cases). Results from this study were not presented separately for MI and stroke.

Cross-sectional studies

Table 3 summarizes findings from three cross-sectional studies^{18–20} in which degree of coronary disease and use of postmenopausal estrogens were ascertained among women undergoing coronary arteriography. This design avoids recall bias and the problems of control selection and response bias that can appear in case-control studies. Also, there is no loss to follow-up or misclassification of exposure status during follow-up that can occur in prospective studies. However, perhaps estrogen users, who have greater contact with the health care system, may be more likely to have angiography than nonusers with the same equivocal symptoms. Gruchow *et al.*¹⁹ specifically addressed this issue and found that estrogen users had a pattern of symptoms identical to that of non-users, suggesting the absence of any bias.

Sullivan *et al.*¹⁸ found that current estrogen use among 1444 postmenopausal women with greater than 70% occlusion was 2.7% compared with 7.7% among the 744 with no stenosis on angiography ($P < 0.01$). After multivariate analysis adjustment for risk factors, the relative risk for CHD was 0.6 (0.4–1.0).

Gruchow *et al.*¹⁹ examined the records of 933 postmenopausal women with coronary angiography; 17% were current users of estrogens. The degree of occlusion among estrogen users was significantly lower than that among nonusers ($P < 0.01$). After controlling for a variety of coronary risk factors, the relative risk for severe coronary occlusion for current estrogen users was 0.4 (0.3–0.5). For moderate occlusion it was 0.6 (0.5–0.7). Controlling for cholesterol and triglycerides in the regression model had no material effect on the inverse association between estrogen use and coronary occlusion. However, when high-density lipoprotein cholesterol (HDL-C) was added to the model, it substantially reduced that association such that it was no longer statistically significant. This suggests that elevations in

Table 3 Results of cross-sectional surveys of coronary artery occlusion among women with and without postmenopausal estrogen who had coronary angiography

Study	Age of patients (years)	Number of patients	Percentage estrogen users/type of use	Relative risk (95% CI)	
				Age-adjusted	Risk factor-adjusted
Sullivan <i>et al.</i> (18)	Mean, 62.8	2,188	4.4% current	0.44 (0.29–0.67) for occlusion 70+ % vs no stenosis	0.58 (0.35–0.97)
Gruchow <i>et al.</i> (19)	Range, 50–75	933	15.5% current	0.59 (0.48–0.73) moderate vs low occlusion score 0.37 (0.29–0.46) severe vs low occlusion score	
McFarland <i>et al.</i> (20)	Range, 35–59	283	41% ever	0.5 (0.3–0.8) for occlusion 70+ vs no stenosis	0.50 (no CI given)

HDL-C and a decrease in low-density lipoprotein cholesterol (LDL-C) are the most likely mechanisms for the benefit of estrogen. In most analyses, it is inappropriate to adjust for HDL since it is in the causal pathway.

McFarland *et al.*²⁰ used a design identical to that of Sullivan *et al.*¹⁸ Estrogen exposure was defined as ever use, but since the mean age of the postmenopausal women was 52 years, most of the use was probably current and of fairly short duration. Comparing 70% or more occlusion with no stenosis, they observed a relative risk of 0.5 (0.3–0.8)

Prospective studies

Results from 16 prospective studies^{21–38} have been published. One is a small clinical trial²⁵ and the rest are observational studies. All observed a protective effect, though the results from the Framingham Study are equivocal.^{28,29} Prospective studies have important advantages over case-control studies in avoiding recall bias and the difficulties of control selection and participation. A problem with some prospective studies is that estrogen use was often ascertained only at baseline, and not updated, potentially leading to misclassification and an underestimate of the effect of estrogen, particularly since the benefits of estrogen are most pronounced among current or recent users.

Most prospective studies followed women with and without estrogen exposure, and thus had an internal control group. Such a design is preferable because the exposed and unexposed individuals are generally comparable. These studies are summarized in Table 4. In three studies,^{22,23,26} summarized in Table 5, the entire cohort was taking estrogens, and their morality was compared with national statistics. Usually estrogen users will be healthier than the general population, in part by virtue of their connection with the medical care system. Despite the estrogen exposure misclassification that would attenuate the apparent benefit, the bias due to a comparison with general population statistics is likely to be more important; hence these studies probably overstate the benefit of estrogen. The findings from several prospective studies with internal controls, including the Framingham Study, are reviewed below.

In a landmark study, Bush *et al.*^{30,35} reported on findings from the Lipid Research Clinics follow-up of 2,270 women ages 40–69 at the outset, who were followed for an average of 81/2 years. Estrogen use was ascertained at baseline and was not further updated. The age-adjusted relative risk of cardiovascular death among current estrogen users compared with nonusers was 0.34 (0.12–0.81). Further adjustment for other potential confounding factors including age, blood pressure, smoking, and prior cardiovascular disease had little impact on the apparent protective-effect of estrogen. However, when HDL-C and LDL-C were included in the model, the coefficient for estrogen use was markedly reduced and no longer statistically significant. This supports the view that the effect of estrogen is mediated primarily (though not exclusively) through alterations in HDL-C and LDL-C.

Stampfer *et al.* reported results from the Nurses' Health Study.²⁷ The Nurses' Health Study was established in 1976 when 121 700 nurses ages 30 to 55 completed a mailed questionnaire regarding health status and a variety of lifestyle practices. This information was updated by a follow-up questionnaire sent in 1978. A total of 32 317 postmenopausal women without prior CHD were followed for an average of 31/2 years for a total follow-up of 105 786 person-years. Nonfatal MI was reported by the participants on the 1978 and 1980 questionnaires. Only cases documented by medical records or other confirmatory information are included in the analysis. Deaths from CHD were documented by medical records. Follow-up was nearly complete. Ever users of estrogens had a relative risk of 0.5 (0.3–0.8). Adjustment for a variety of coronary risk factors including hypercholesterolemia, family history of heart disease, hypertension, diabetes, obesity, and smoking did not alter these relative risk estimates.

Results from the Leisure World Study were reported by Henderson *et al.*³³ In this study, 8841 women ages 40 through 101 completed a health survey in 1981. After 51/2 years of follow-up (40 919 person years) 1019 deaths (149 due to MI) had occurred. For all-cause mortality, the relative risk was 0.8 (0.7–0.91) for ever users of estrogen compared with never users, and for fatal MI it was 0.59 (0.42–0.82). Estrogen use was

Table 4 Prospective studies with internal controls

Study	Age at baseline (mean or range)	Number in population	Percentage estrogen users	Follow-up (years) (mean or range)	Endpoint (number of cases)	Relative risk (95% CI)	
						Age-adjusted	Risk factor-adjusted
Potocki (21)	60–70	158	52%	10 ?	MI (4)	0.31 (0.04–2.57) ^a	
Hammond <i>et al.</i> (24)	46.3	619	49%	1.3	CHD (58)	0.33 (0.19–0.56) ^a	
Nachtigall <i>et al.</i> (25)	55	168	50%	10	MI (4)	0.33 (0.04–2.82) ^a	
Lafferty and Helmuth (26)	45–60 (53.7)	124	49%	3–16 (8.6)	MI (7)	0.17 (0.03–1.06) ^a	
Stampfer <i>et al.</i> (27)	30–55	32 317	Past 18% Current 35% Ever 57%	3.3	Nonfatal MI and CHD death (90)	Past 0.7 (0.4–1.2) Current 0.3 (0.2–0.6) Ever 0.5 (0.3–0.8)	0.59 (0.33–1.06) 0.30 (0.14–0.64) 0.52 (0.34–0.80)
Framingham Heart Study ^b							
Wilson <i>et al.</i> (28)	50–84	1234	Past 14% Current 10%	8	All CVD (194) CVD death (48) MI (51)	1.76 ($P < 0.01$) ^c 1.94 ($P > 0.05$) ^c 1.87 ($P > 0.05$) ^c	
Eaker and Castelli (29)	50–59 60–69	695 602	15% 8%	10	CHD no angina (35) (51)	0.26 (0.06–1.22) ^{c,d} 1.68 (0.71–4.00) ^{c,d}	0.4 ($P > 0.05$) ^c 2.2 ($P > 0.05$) ^c
Bush <i>et al.</i> (30)	40–69	2270	26%	8.5	CVD death (50)	0.34 (0.12–0.81)	0.37 (0.16–0.88)
Petitti <i>et al.</i> (31)	18–54	6093	Ever 44%	10–13	CVD death	0.9 (0.2–3.3)	0.6 (0.3–1.1)
Criqui <i>et al.</i> (32)	50–79	1868	39%	12	CHD death (87)	0.75 (0.45–1.24)	0.99 (0.59–1.67)
Henderson <i>et al.</i> (33)	40–101 (median = 73)	8807	Past 43% Current 14%	4.6	MI deaths (149)	Past 0.62 (0.43–0.90) Current 0.47 (0.20–2.00) Ever 0.59 (0.42–0.82)	No change No change No change
Croft and Hannaford (34)	20–60	Nested	Ever 6.5%	19	MI (9)	0.8	0.8 (0.3–1.8)
Avila <i>et al.</i> (37)	50–64	24 900	Current 14%	5	MI (120)	0.7 (0.4–1.3)	0.7 (0.4–1.4)
Sullivan <i>et al.</i> (38)	?	2268	Ever 10.5%	10	Death		0.16 (0.04–0.66)

^a The crude odds ratio and confidence intervals are derived from data given in the text.^b The results based on the analysis of Eaker and Castelli (29) are not included in the quantitative overview.^c This includes high-density lipoprotein cholesterol in the regression analysis.^d These results are taken as the average of findings using examinations 11 and 12 as baseline.**Table 5** Prospective studies without internal controls

Study	Age at baseline	Number	Percentage estrogen use of baseline	Follow-up (years)	Endpoints (number of cases)	Age-adjusted relative risk and 95% CI
Burch <i>et al.</i> (22)	Mean about 48	737	100	13.4	Fatal CHD (9)	0.43 (0.20–0.81) ^a
McMahon (23)	49	1891	100	12	CHD death (estimated 33)	0.30 (0.21–0.42)
Hunt <i>et al.</i> (36)	60% 45–54	4544	100	Up to 19 median 3.5	CHD death (20)	0.48 (0.29–0.74)

^a The crude odds ratio and confidence intervals are derived from data given in the text.

defined on the baseline questionnaire and was not updated. Adjustment for several CHD risk factors did not appreciably change the results.

A cohort of 6093 women, ages 18 to 54 from the Kaiser Permanente Medical Program, was followed for an average of 10 to 13 years.³¹ The mortality rate from cardiovascular disease was slightly lower among estrogen users, with a relative risk of 0.9, 95% confidence intervals, 0.2–3.3. After adjustment for a variety of cardiovascular risk factors including age, hypertension,

obesity, and smoking, the apparent benefit was more marked, with a relative risk of 0.6, 95% confidence interval, 0.3–1.1. Estrogen use was defined at the baseline in 1968–1972 and was updated through 1977, but not thereafter.

In contrast to all other cohort studies, Wilson *et al.*²⁸ from the Framingham Heart Study reported an increase in risk for cardiovascular disease associated with estrogen use. A participant was classified as an estrogen user if that was included on the medication form during an 8-year period, between biennial

examinations 8 and 12. Follow-up began at the end of that 8-year interval for 1,234 women who were postmenopausal and 50 years of age or older. Of these, 302 had used estrogens at some time. They were followed for an additional 8 years. After adjustment for age, hypertension, obesity, total cholesterol, HDL-C, smoking, and alcohol consumption, the relative risk for all cardiovascular disease among ever users of estrogen was 1.8 compared with never users. This endpoint included CHD, angina pectoris, intermittent claudication, transient ischemic attack, MI, congestive heart failure, and coronary and sudden death. The apparent elevation in risk was not statistically significant when only MI was considered.

A reanalysis of the Framingham data demonstrated that the results were sensitive to the choice of the baseline examination. Eaker *et al.* state that 'after careful analysis of the data, it was evident that the relationships observed between estrogen use or nonuse and cardiovascular disease were present only for examination 12'.²⁹ The second analysis²⁹ was limited to CHD without angina, and considered two time periods instead of just one (i.e., using examination 12 and examination 11 as the baseline for assessing estrogen use for the subsequent 10-year follow-up). Taking the average of the findings using the two baselines, there was a nonsignificant protective effect among women ages 50 to 59 with a relative risk of 0.4 (0.1–2.3). Among older women, there was a nonsignificant adverse effect, with a relative risk of 1.8 (0.5–6.9). Both Framingham analyses presented findings adjusted for HDL-C, which is probably inappropriate as that is the most plausible mechanism of action for estrogen. For the overview, we used the results reported by Wilson *et al.* Because no standard error or confidence interval was given for MI, we assumed that the nonsignificant relative risk of 1.87 from the multivariate analysis for MI had a *P* value of 0.10.

There has been only one clinical trial of estrogen use and coronary disease.²⁵ Eighty-four pairs of women matched for age and medical condition were randomly assigned to take 2.5 mg conjugated estrogen daily and 10 mg Medroxyprogesterone for 7 days a month or placebos. The women were all residents of a long-term chronic care hospital. After 10 years of follow-up, the relative risk for estrogen users was 0.3 (0.1–2.8) for fatal and nonfatal MI. With only four MIs in this small trial, the results, while intriguing, are difficult to interpret on their own.

In a recent study, Sullivan *et al.*³⁸ assessed the survival of women with serious, moderate, or no coronary stenosis on angiography according to estrogen use. Estrogen users had a substantially reduced mortality rate, particularly among those with more severe coronary disease.

Results of the quantitative overview

Of the 31 studies evaluated, 2 were null (relative risk between 0.9 and 1.1) and 4 showed an adverse trend. In none of the latter was the adverse effect statistically significant. The relative risk for all studies ranged from 0.16 to 4.25. Of the 25 studies that found a reduced risk of CHD among estrogen users, 12 were statistically significant.

Figure 1 shows the relative risks for each study according to its weight, based on its precision. The first analysis included all studies, whenever possible using estimates for ever use. This yielded a summary relative risk of 0.56, with estimated 95% confidence intervals of 0.50–0.61. Because the estimate of the

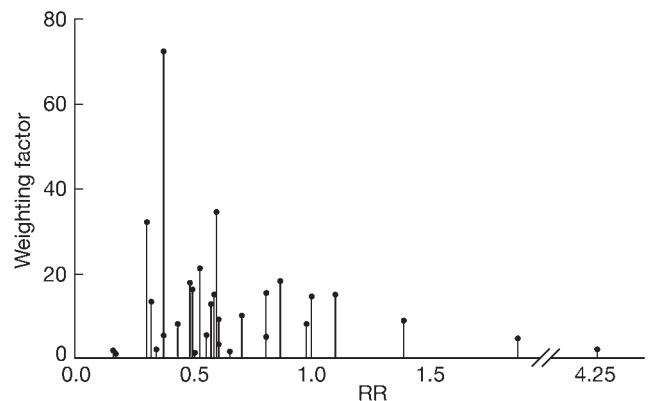


Figure 1 The relative risk from each of 31 studies of estrogen use and coronary heart disease is shown with its weighting factor, which is proportional to the precision (i.e., to the inverse of the variance of each estimate)

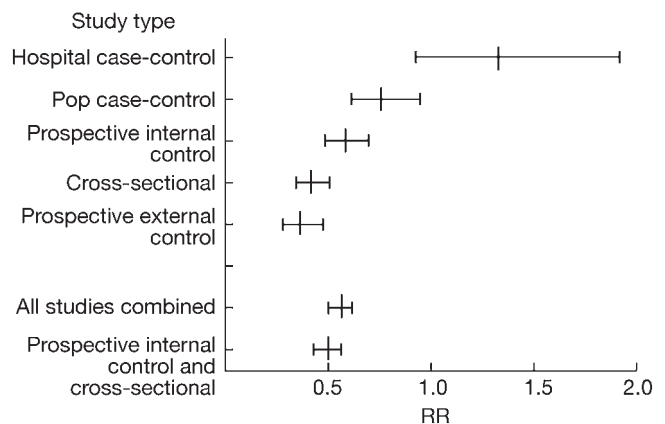


Figure 2 Summary relative risks and 95% confidence interval estimates for studies of estrogen use and risk of coronary disease, by study design. There was significant ($P < 0.001$) heterogeneity by study design

standard error for the summary relative risk requires the assumption that the same quantity is being measured (clearly untenable here), the confidence intervals should be taken only as a rough guide to the precision rather than as strict 95% intervals.

The summary relative risk estimate ignores a highly significant ($P < 0.001$) heterogeneity by groups of study design. Figure 2 shows the weighted summary relative risks and confidence intervals by study design. In contrast to the other designs, the hospital-based case-control studies tended to show a nonsignificant trend towards an adverse effect of estrogens, with a summary relative risk of 1.33 (0.93–1.91). All other designs show significant reductions in risk. The hospital-based studies, with an inherent tendency to underestimate benefit, show the highest relative risk. The population-based case-control studies, with less bias, but still with the difficulties of control selection and participation, and recall bias, had a relative risk of 0.76 (0.61–0.94). The cohort studies without internal controls show the greatest apparent benefit, relative risk of 0.36 (0.28–0.47); this is likely to be biased toward an overestimate. The most plausible estimates are provided by the cohort studies with internal controls, with a relative risk of 0.58 (0.48–0.69),

Table 6 Risk factor profile of estrogen users and nonusers

Prevalence (%) of coronary risk factors by estrogen use			Mean level or prevalence of risk factor by estrogen use		
Variable	Nurses' Health Study [Stampfer <i>et al.</i> (27)]		Characteristic	Lipid Research Clinics [Bush <i>et al.</i> (30)]	
	Never	Current		Nonuser	User
Maternal MI	11	11	Age	53	54
Paternal MI	23	25	Systolic BP	128	129
Smoking	38	35	Diastolic BP	80	80
Hypertension ^a	18	18	BMI kg/m ²	26	25
High cholesterol ^a	5	6	Cholesterol	235	235
Diabetes ^a	3	2	Smoking (%)	31	33
BMI > 24.6 kg/m ²	42	32	Regular exercise	10	12
			Alcohol use (%)	79	82
	Leisure World Study [Henderson <i>et al.</i> (33)]			Framingham Study [Wilson <i>et al.</i> (28)]	
	Never	Ever		Nonuser	User
Prevalent CHD	14	15	Smoking	0.22	0.27
Hypertension	41	42	Systolic BP	142	139
Smoking	8	8	Relative weight	123	119
BMI ≥ 35 kg/m ²	24	28	Alcohol (oz/week)	2.1	2.2
Sedentary ^b	36	35			

^a By self-report.^b Exercise <0.5 hr/day.

and the cross-sectional angiography studies, with a relative risk of 0.41 (0.34–0.50). The summary estimate combining these two designs is 0.50 (0.43–0.56).

Discussion

Although the findings from the epidemiologic studies are not completely consistent, the preponderance of the evidence strongly suggests that women taking postmenopausal estrogen therapy are at decreased risk for CHD. The consistency of the findings is more apparent in the better designed and analyzed studies.

A positive association does not necessarily imply causality. Physicians and patients decide upon estrogen therapy, and in many instances the health status of the patient has an important influence, so perhaps estrogen use is merely a marker rather than a cause of good health. One way to assess this is to evaluate the risk profile of estrogen users and nonusers. In the Nurses' Health Study²⁷ the distribution of coronary risk factors was quite similar among current and never users of estrogens.²⁷ Generally similar findings were observed in other studies (see Table 6). Moreover, multivariate analyses yielded the same results as age-adjusted analyses in most studies,^{27,30,20,13,33,34} suggesting lack of confounding by known risk factors. In others,^{18,14,5,17,32} the relative risk estimates increased slightly after multivariate analysis. In general, the change was modest; the largest difference was in the hospital case-control study of Rosenberg *et al.*⁵ where the relative risk increased from 0.71 to 0.97. In contrast, Petitti *et al.*³¹ found that multivariate control revealed a stronger protective effect, which could occur only if estrogen users had a somewhat higher underlying risk; the estimate changed from 0.9 to 0.6. Szklo *et al.*⁸ and Rosenberg

*et al.*⁷ also found a decrease in the relative risk following multivariate analysis. Thus, the findings are inconsistent. In some populations, the risk factor profiles of users and nonusers are similar, and in others they vary somewhat in either direction. There are thus substantial data to suggest that no more than a fraction of the benefit of estrogen can be explained by selection of healthier women for its use.

One might argue that because estrogen users see physicians more often, silent or nearly silent infarctions might be diagnosed more readily than among nonusers. This seems unlikely to have a material impact because the degree of protection is similar for fatal and nonfatal MI. Also, if such a bias were present, it would tend to attenuate rather than exaggerate any benefit from estrogens.

Current users of estrogens appeared to enjoy greater protection than past users.^{5,7,12,14} Only the study of Adam *et al.*¹⁵ found a (nonsignificantly) higher risk, but this was based on only two cases among current users. Only two of the prospective studies directly compared current and past use. Henderson *et al.*³³ observed a relative risk of 0.47 for current use and 0.62 for past use. Stampfer *et al.*²⁷ reported a relative risk of 0.30 for current use and 0.59 for past use. A summary of these two yielded a relative risk of 0.37 (0.21–0.65) for current use and 0.61 (0.45–0.84) for past use. In all three cross-sectional studies, the use was current. In many of the cohort studies, current use was defined at baseline and not updated, leading to misclassification of the exposure variable which attenuated the relative risk. The difference in effect of current or recent use and past use may partly explain the greater apparent protection in the cross-sectional studies.

Few studies have examined the effect of duration of estrogen use on CHD risk. Both Henderson *et al.*³³ and Stampfer *et al.*²⁷

observed no effect of duration. Specific estrogen preparations have generally not been studied. Most studies were in the United States where oral conjugated estrogens (specifically Premarin) were by far the most common form of estrogen used.

Few reports have provided data on the effects of different doses. Ross *et al.*¹³ found a nonsignificant trend for greater protection from doses of 0.625 mg/day of conjugated estrogens compared with 1.25 or more. However, Henderson *et al.*,³³ in a prospective study in the same population, found no effect of dose; neither did Stampfer *et al.*²⁷

Age has been suggested as a possibly important modifier of the estrogen effect, especially since a trend toward benefit was observed in the Framingham study for younger but not older women. Stampfer *et al.*²⁷ and Bush *et al.*³⁵ observed a benefit at all ages in their studies. Sullivan *et al.*¹⁸ found slightly greater protection among younger women, while Gruchow *et al.*¹⁹ found the opposite; in both studies, all age groups experienced an apparent benefit. Henderson *et al.*³³ observed substantial benefit in a population with a median age of 73.

The effect of type of menopause was investigated in several studies. Gruchow *et al.*¹⁹ and Henderson *et al.*³³ found no differences. Bain *et al.*¹⁴ found a protective effect only among those with bilateral oophorectomy in a fairly young population (under age 55); in all other studies, a benefit was observed regardless of type of menopause, but the magnitude of protection was greater among those with a surgical menopause.^{8,20,27,35}

Several studies have observed more protection from estrogens among non-smokers or light smokers.^{13,18,33} Wilson *et al.*²⁸ observed no effect among nonsmokers and an adverse affect of estrogens among smokers. Criqui *et al.*³² observed the opposite, with a benefit only among current smokers, and an adverse effect among past smokers.

A plausible biological mechanism for the protective effect of estrogen is its impact on the lipid profile. Among postmenopausal women, estrogens lower the levels of LDL-C and raise the concentration of HDL-C.³⁹ In their review, Bush and Miller found that on average, 0.625 mg/day of conjugated estrogens led to a 10% increase in HDL and a 4% increase in LDL.³⁹ A 1 mg/dl increase in HDL is associated with approximately a 3–5% decrease in risk for coronary disease, and 1 mg/dl decrease in LDL is associated with about a 2% decline in risk; hence, the changes induced by estrogen could lead to a relatively large decrease in risk.⁴⁰ Estrogens have other effects on the cardiovascular system which may play important roles in mediating this protective effect [reviewed in (41)].

In nearly all of the epidemiological studies, the use of progestins was uncommon. Progestins are now often recommended to reduce or eliminate the excess risk of developing endometrial cancer due to unopposed estrogen. Unfortunately, most progestins tend to lower HDL-C and raise LDL-C. Although one can devise regimens in which some of the estrogen benefit on lipids remains apparent, it is nonetheless attenuated by the addition of most progestins. An important challenge in this area is to develop a progestin regimen or formulation that will maintain protection of the uterus, yet not impair the benefits of estrogen on lipids.

Conclusion

The preponderance of evidence from the epidemiologic studies strongly supports the view that postmenopausal estrogen

therapy can substantially reduce the risk for coronary heart disease. The consistency of the findings is more apparent in the prospective cohort and angiographic studies. The summary relative risk from those studies was 0.50 (95% CI 0.43–0.56). This effect is unlikely to be explained by confounding factors or selection.

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Commentary: Hormones and heart disease: do trials and observational studies address different questions?

Meir Stampfer

By 1990, the number of epidemiological studies of postmenopausal hormone use and coronary heart disease (CHD) was sufficient to justify a quantitative assessment of the evidence. Divergent views of the potential effect of postmenopausal hormones on cardiovascular risk were common. On the one hand, the observation that premenopausal women had substantially lower risk for cardiovascular disease led many to suspect that oestrogens might be protective. On the other hand, the experience of higher risk for cardiovascular disease (though not coronary atherosclerosis) with the early oral contraceptive agents, combined with the adverse experience of oestrogen in men in the Coronary Drug Project, led many to believe that it was harmful. The drug labelling for postmenopausal hormones carried warnings of risk for an increase in cardiovascular disease.

Observational data from epidemiological studies were remarkably consistent in showing that postmenopausal hormone users tended to be at lower cardiovascular disease risk than non-users. The epidemiological studies summarized in the review at the time were augmented by additional observational studies that followed.¹ In the review, we recognized the possibility that this association might not represent cause and effect but could perhaps be due to confounding or biased ascertainment of endpoints. However, the latter explanation seemed implausible. Since women taking hormones were under closer medical scrutiny, it seemed likely that borderline cases would be more rather than less likely to be diagnosed. The potential for confounding seemed more plausible because oestrogen users tended to be healthier (i.e. at lower cardiovascular risk) in several studies. However, this was not universally true, and depended on the population under study. Moreover, adjustment for a wide array of known confounders had only a modest impact on the relative risk estimates, suggesting that residual confounding would have to be quite substantial to account for the remaining association.

The studies included in this review, along with other data from a variety of sources, provided some of the impetus for the Women's Health Study Initiative trial of postmenopausal hormones.

Presumably, this review was chosen for retrospective scrutiny and reflection because of the apparent differences in the results of the Women's Health Initiative (WHI) Trial² and the observational studies of postmenopausal hormones and CHD. A variety of explanations for these apparent differences have been

offered many of which we considered in the review. The most speculative suggestion (which we did not consider in the review) was suggested by Col and Pauker;³ without providing any evidence, they hypothesize that misdiagnosis of CHD endpoints in a biased manner led to an apparent protective effect of hormone therapy. According to this scenario, silent infarctions would be preferentially diagnosed among non-users of oestrogen, and epidemiological investigators would systematically code CHD less often among oestrogen users because of the expectation that it would be protective. Such an explanation defies logic. Only 3% of non-fatal infarctions in the WHI were silent infarctions so even systematic misdiagnosis in observational studies could not have yielded findings of the magnitude observed. Moreover, the expectation of lower risk among oestrogen users followed rather than preceded the results of the observational studies. At the time most of those studies were conducted, that expectation was absent. Moreover, most of the epidemiological studies had strict criteria for endpoints such that systematic miscoding, of the magnitude required, would be virtually impossible.

Another unlikely explanation is that the differences are due to confounding by socio-economic status between hormone users and non-users.⁴ This suggestion ignores the findings from studies that did adjust for differences in socio-economic status. Typically, such adjustment had little impact.⁵ Moreover, several of the influential observational studies were conducted in relatively homogeneous strata of socio-economic status or employment category, such as the Leisure World Study and the Nurses' Health Study.

As mentioned above, the possibility for confounding by known or suspected coronary risk factors was discussed at some length in the review. At that time, we concluded that, although in general, hormone users tended to be healthier, the differences were insufficient to explain the magnitude of the reduction in subsequent disease incidence for hormone users. Specifically, adjustment for numerous coronary risk factors in observational studies resulted in only modest changes in the point estimates for the relative risk. Some have argued that subtle differences, such as willingness to take medication, would define a particularly healthy subgroup. While the possibility of such confounding cannot be ruled out, such logic would suggest that compliance to any medication would identify a group at low risk for heart disease. However, the observational studies that found lower risk for hormone use did not uniformly find low risk for all manner of medications.

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A second line of evidence also suggests that confounding factors are unlikely to provide the whole explanation for findings from observational studies compared with trials. Observational studies actually have found results virtually identical to the WHI trial for all other endpoints. For example, when the Nurses' Health Study and other observational studies reported a lower risk for colon cancer among oestrogen users,⁶ the findings were greeted with intense skepticism and disbelief. However, a protective effect was confirmed in the WHI, and the relative risk estimates were nearly identical. More important, the Nurses' Health Study reported an increase in risk of stroke⁷ of almost identical magnitude as later observed in the trial. Stroke shares many risk factors with CHD and is also closely linked with a variety of socio-economic status indicators. Hence, if confounding were present to the extent that would explain the apparent divergence for CHD, how could one account for the consistent relative risk estimates for stroke?

These observations, and other data, suggest an alternative explanation for the different results. Specifically, the observational studies reflected common clinical practice whereby women were typically initiated on postmenopausal hormones at the time of menopausal symptoms. Thus, the vast majority of hormone use began at a relatively young age, close to the time of menopause. In contrast, two-thirds of the participants in the WHI began the trial at age ≥ 60 . Do the differences in age matter? Experimental data suggests that they do.⁸ Monkeys randomized to postmenopausal hormones at the time of oophorectomy had substantially reduced coronary atherosclerosis compared with those given placebo. In contrast, however, when hormone use was begun 2 years after surgical menopause (equivalent to about 6 human years) no such protection was observed.⁹ In a rabbit model, oestrogens had either a beneficial or adverse effect depending on the state of the arteries. Animals with healthy arteries showed a protective effect of oestrogen, but in those with damaged arteries, the effect was adverse.¹⁰ Data in humans support these differences. The effect of oestrogen on acetylcholine-induced vasodilation differs markedly according to the presence or absence of coronary atherosclerosis.¹¹ Randomized trials of women with CHD did not show any benefit of oestrogen (indeed, they tended to show harm), but a trial in younger postmenopausal women demonstrated a reduction in progression of atherosclerosis in the treated group compared with those given placebo.¹¹ Thus, perhaps the differing results from the observational studies and the WHI trial may be attributed to the differences in populations. The results of the WHI trial themselves support such an explanation. The WHI found a trend toward lower risk with decreasing time since menopause; among women <10 years since menopause (65 total cases), the relative risk of CHD with hormone therapy versus placebo was 0.89 (95% CI: 0.55, 1.46); for 10–19 years since menopause, it was 1.22, and for 20+ years, 1.71.¹ This trend is statistically significant ($P = 0.036$).

An important limitation of most observational studies was the inability to capture possible acute effects of postmenopausal hormones.⁷ The increase in CHD events in WHI was

concentrated in the initial year after starting hormones. This short-term effect would tend to be missed in observational studies, even with fairly frequent updating of exposure. This effect probably led to a modest overestimate of the apparent benefit of hormones for CHD in the observational studies.

Although biological differences offer a plausible explanation for the apparently divergent findings from the observation findings and WHI, from a clinical perspective, this may not matter. For the oestrogen-progestin combination, the increased risk of breast cancer is now well established from observational studies¹² and the WHI trial. Thus, even if such therapy were proven to be protective for women at a young age, it still would not balance the excess risk due to breast cancer. In particular, many safe options are available for reducing risk of CHD, but few are available for breast cancer prevention. Overall, from a clinical perspective, it would not make sense to employ long-term oestrogen with progestin for chronic disease prevention.

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