conjugated equine estrogen at 0.625 mg/day, the usual dose of replacement in the United States, results in much higher concentrations of estradiol than we observed in our study (9). Several recent reports have also suggested that lower doses of estrogen could be used (10, 11). Use of lower doses might lead to fewer side effects and, perhaps, better adherence to hormone regimens.

It is also possible that nonpharmacologic interventions that either reduce or raise serum estrogen concentrations could thereby influence the risk of disease. For example, in the Women’s Health Trial, a 10- to 20-week low fat dietary intervention was associated with a 17% reduction in estradiol concentrations in healthy postmenopausal women (12). Higher intakes of lutein, a carotenoid abundant in dark green vegetables, was associated with slower rates of bone loss and reduced risk of hip fracture (13). The underlying mechanism for this relationship is unknown, but further studies delineating the effects of dietary factors as well as other lifestyle interventions like physical activity on hormone concentrations may be warranted.

However, specialized endocrine laboratories with highly sensitive assay methods were used for these studies. Assay methods at routine clinical laboratories will need to meet stricter standards to measure hormones at these very low concentrations before they can be incorporated into routine clinical practice.

Finally, the absolute level of estrogens may not be the only determinant of their biological effects. The manner in which the circulating estrogens are metabolized may also be important. The two main pathways of estrogen metabolism consist of the 2-hydroxylation and the 16α-hydroxylation pathways, with the 2-hydroxylation pathway leading to less estrogenic activity (14). Women who metabolize estrogens to the 16α pathway appear to have a higher risk of breast cancer (15) but lower risk of osteoporosis (16). Hence, future research on estrogen should also consider its metabolic pathways and include measurements of estrogen metabolites.

### References


# The Epidemiology of Cardiovascular Disease in Postmenopausal Women

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CARDIOVASCULAR disease (CVD) is the leading cause of death in the United States for all women (1, 2), and in 1993 was responsible for twice as many deaths (500,387) in females as all forms of cancer combined (250,529 deaths) (1). Rates of CVD mortality increase sharply with age in both men and women, with higher rates in men than women at all ages. Although the death rates from coronary heart disease for females declined 27.6% from 1984 to 1994, heart attack remains the single largest cause of death for US females, and death rates were 34.3% higher in black than in white women in 1993 (1).

### “Gender gap” in CVD risk

An examination of age-specific graphs of CVD mortality rates shows an apparently large gender difference at younger ages, narrowing after the age of menopause. The largest apparent increase in coronary mortality in women occurs around age 50, coinciding with the time of menopause (3). This has led to speculation that declining estrogen levels associated with menopause result in an increased risk of CVD (2). However, evidence from vital statistics data does not support the theory that menopause apart from chronological aging increases risk of CVD in women (4). The narrowing of the gender gap appears to be due in part to declining incidence rates in men rather than to increases in women (3). Moreover, as several investigators have pointed out, if one plots the rates on the log scale to measure the slope, or rate of increase, there is no sharp increase, or “bump,” in the CVD mortality rate for women at the age of menopause (3–5). In contrast, rates of breast cancer do show a menopausal effect, with nonparallel rates of increase for the 50–69 and 40–49 age groups (3). Autopsy findings also suggest that changes such as atherosclerosis occur steadily with age, with no steep increase at the age of menopause (3). CVD mortality rates differ markedly by country, and the sex advantage in CVD mortality rates appears to be lower or nonexistent in populations that have a generally low level of risk, as in Japan (6). This indicates that behavioral and environmental risk factors may play a larger role in explaining CVD mortality.
in women than differences in endogenous estrogen (7). Studies based on population statistics are limited in that menopausal status cannot be related to CVD risk on an individual level.

**CVD risk after natural menopause**

Past studies of menopause-associated changes in CVD morbidity, mortality, and risk factors are difficult to interpret in part because of inadequate adjustment for important confounding factors such as chronologic age, cigarette smoking, and obesity that are associated both with occurrence of menopause and heart disease (3, 4). Other methodological problems include misclassification of menopause status and unstable estimates due to small numbers of women with major coronary disease (3).

Perhaps the best information to date comes from large prospective studies. One such study, the Framingham Heart Study, reported that women aged 50–59 yr who had experienced natural menopause had 4 times the 10-yr incidence of coronary heart disease as premenopausal women in the same age range, but results were not adjusted for age or smoking (8). The largest of the prospective studies to date, the Nurses’ Health Study, found a somewhat higher risk of coronary heart disease in women with a natural menopause compared to the risk among premenopausal women when adjusting for age in 5-yr intervals (RR = 1.7, 95% CI: 1.1–2.8) (9). However, controlling for age in 1-yr intervals reduced the relative risk to 1.2, 95% CI: 0.8–1.9. A further risk reduction occurred after controlling for cigarette smoking (RR = 1.0, 95% CI: 0.8–1.3) (9).

As discussed below, natural menopause is associated with some changes in CVD risk factors. The lack of any abrupt change in CVD morbidity or mortality around the age of menopause may result from a relatively wide age range for the occurrence of a woman’s final menstrual period, and from the gradual decline in estrogen levels over time. In addition, any menopause-related changes in CVD risk factors may appear slowly in morbidity and mortality. Thus the occurrence of natural menopause may indicate that a woman is entering a period of increased risk for CVD, due to both chronologic aging and lower levels of estrogen (3).

**CVD risk after surgical menopause**

The evidence for a relationship between changes in CVD morbidity/mortality and menopause is much stronger for women who undergo a hysterectomy with bilateral oophorectomy (3, 4). A bilateral oophorectomy causes an abrupt drop in estrogen levels unlike the gradual decline associated with natural menopause. Fairly convincing evidence for estrogen as a factor comes from the Nurses’ Health Study (9), which showed a significantly increased risk (RR = 2.2, 95% CI: 1.2–4.2) of coronary heart disease in women who had undergone bilateral oophorectomy and hysterectomy and who had not taken exogenous estrogens. The risk was not increased for women who used estrogens after a similar procedure. Whether or not hysterectomy alone increased CVD risk is controversial, but hysterectomy may lead to subsequent ovarian failure (3).

**Menopause and coronary heart disease risk factors**

Cohort studies have demonstrated that risk factors for CVD morbidity and mortality are similar between men and women. These include older age, smoking, glucose intolerance, elevated blood pressure, an unfavorable lipid profile [elevated total or low density lipoprotein (LDL) cholesterol levels, decreased high density lipoprotein (HDL) levels, elevated triglyceride levels], sedentary lifestyle, and obesity (10). Several of these factors, such as low levels of HDL, diabetes, and hypertriglyceridemia, may be stronger predictors of CVD in women than in men (4, 10).

**Lipids and lipoproteins.** Of all the CVD risk factors, the evidence for a link with estrogen appears to be the strongest for lipids and lipoproteins (11). Results from both cross-sectional and longitudinal studies have reported a worse lipid profile in postmenopausal than in pre- or perimenopausal women (12–14), although not all have adjusted for age and smoking status, both of which are strongly related to menopause status and levels of lipids and lipoproteins. In the Healthy Women’s Study, a 5-yr prospective study of over 500 initially healthy premenopausal women, natural menopause was associated with unfavorable changes in HDL and LDL, even after adjustment for age and smoking (14).

Whether or not the unfavorable lipid changes are directly associated with declining estrogen levels is still in question. Kuller et al. (15) did not find an association with endogenous estrone and lipid levels in postmenopausal women from the Healthy Women’s Study. Women in the top quintile of estradiol levels had a more favorable lipid profile than did women with lower levels of estradiol, but in longitudinal analyses there was no consistent association between changes in estrone or estradiol and changes in lipoproteins, either for women who transitioned from peri- to postmenopause or for women who were postmenopausal throughout (15). Results from the Massachusetts Women’s Health Study, a longitudinal population-based study of women traversing the menopause, are consistent. In pre- and perimenopausal women, Longcope et al. (16) found no strong or consistent relationships between lipids and concurrent reproductive hormone levels. Longcope et al. (17) also found no association between changes in endogenous estrogen levels and changes in lipid levels. Although exogenous estrogens do result in favorable changes in lipids and lipoprotein levels (18, 19) because of the suppression of hepatic lipase activity (20), estrogens at endogenous levels may not have much impact on lipids or lipoproteins. This is consistent with findings that exogenous estrogen administered in ways that bypass the liver have little impact on lipids (16).

**Glucose and insulin.** Diabetes appears to be a strong prognostic factor for CVD in men and women, and in some studies it has a greater association with CVD in women (2, 7, 10). Diabetes is related to atherosclerosis and hence an increased risk of acute coronary ischemia, particularly in women (21). The age-adjusted relative risk for CVD is 2.3 in men and 3.7 in women (22).

Data regarding menopause status or estrogen levels and glucose and insulin levels are somewhat limited (11). Studies of natural menopause suggest no impact on either plasma
glucose or insulin concentrations (14), while others have found that menopause is associated with an increase in fasting insulin concentration (23). Exogenous estrogen may reduce plasma glucose and insulin levels (24), possibly by improving carbohydrate metabolism (11). Several studies, however, found that 2-hr insulin secretion in postmenopausal women was not different in estrogen users and non-users (19, 25).

Clotting and coagulation. As with glucose and insulin, there is little data regarding the relationship between estrogen and coagulation. Plasma levels of plasminogen activator inhibitor (PAI-1), an essential antagonist of fibrinolysis in humans, increase in women after menopause, and high levels have been associated with increased CVD risk (26). Decreased PAI-1 levels and enhancement of fibrinolytic activity has recently been demonstrated after estrogen replacement therapy, but the effect of menopause per se on PAI-1 is not yet known (26).

Circulation and vessel walls. Estrogen appears to have a favorable impact on the circulation through direct effects on vessel wall physiology and on mechanisms controlling blood flow (24). Estrogen receptors are found in the myocardium, coronary arteries, vascular smooth muscle tissues, and endothelium (27). Estrogen may act on endothelial cells to increase the relaxation response to acetylcholine, or it may act directly on vascular smooth muscle (28). In animals, estrogen administration alters the constrictor response of atherosclerotic coronary arteries (29). Estrogen also may have an impact on arterial wall mechanisms involved in formation of atherosclerotic plaques and may affect the release of vasoactive neurotransmitters involved in the control of vasoconstrictor tone (28).

Deficiency of or changes in endogenous estrogen levels are associated with conditions related to circulation, including vaginal dryness, migraine headaches, and hot flashes (28).

Exogenous estrogen appears to have a beneficial impact on blood flow (11, 30, 31). In postmenopausal women and estrogen-deficient animals, administration of estrogen increases coronary artery vascular reactivity (30, 32) and prevents acetylcholine-induced coronary vasoconstriction (30). Administration of estradiol also has a acute beneficial effect on treadmill performance in women with coronary artery disease (31). In other animal studies, administration of estradiol has led to vasodilatation, increased cardiac output, and lower systemic vascular resistance (28).

Blood pressure. Both elevated systolic and elevated diastolic blood pressures are risk factors for CVD in women, and lowering the diastolic blood pressure is associated with reductions in acute coronary events (33). Studies of natural menopause, however, have found no relationship between the menopausal transition and changes in blood pressure (14). There is also little evidence for a reduction in blood pressure after the use of estrogen estrogen replacement therapy (18).

Weight and body composition. It has been estimated that 70% of CVD in obese women and 40% in all women is due to excess weight (34). Obesity itself, however, is not an independent risk factor for CVD, but is related to CVD through other risk factors such as hypertension, elevated cholesterol, and diabetes (2). In contrast, centralized body fat, indicated by the waist-to-hip ratio, appears to be a strong predictor of incidence of CVD for both men and women (2), independent of other risk factors (35).

As with blood pressure, there appears to be little association between natural menopause and body weight per se (14, 36, 37). The menopause transition may, however, be associated with a change in body composition, with an increased waist-to-hip ratio occurring at the time of the menopause (36).

Behavioral factors. Key behavioral factors affecting CVD risk in women are cigarette smoking and physical activity (2, 10). There is a strong positive, dose-response relationship between cigarette smoking and the risk of fatal CVD, and smoking may modify the effect of other risk factors, such as diabetes, high blood pressure, and adverse lipid profiles (38). Smoking is also associated with an earlier age at menopause (39).

The impact of exercise on CVD is less well-established in women than in men (2). Recently, a 7-yr follow-up of women from the Iowa Women’s Health Study found an inverse association between higher physical activity levels and mortality, most strongly for CVD mortality (40).

Ongoing studies of CVD and menopause

Currently in progress are two large prospective studies that may provide some answers to the magnitude of the impact of the menopause on CVD risk. These are The Women’s Health Initiative, which is studying the impacts of factors such as HRT and diet in very large groups of women who are already postmenopausal, and The Study of Women’s Health Across the Nation (SWAN), which is recruiting and following somewhat younger women, who are initially premenopausal or still early in the perimenopausal transition. These women will be closely followed as they transition through menopause, and their levels of estrogen, lipids, glucose, and clotting factors will be measured longitudinally to assess the impact of the menopausal transitions and the decline in estrogen levels.

References

Does Estrogen Have a Role in the Prevention of Cardiovascular Disease?

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PREVENTIVE cardiology can point to a proud tradition of evidence-based practice. In particular, random allocation of clinical trials was required before accepting the benefits of antihypertension or cholesterol lowering therapies. Demonstration of the association of high blood pressure or high blood cholesterol with coronary heart disease (CHD), and that drugs lowered these risk factors, were deemed insufficient; we also wanted to know that treatment lowered CHD events and did so without increasing the risk of non-coronary events (1–4). This tradition is not being upheld in the case of estrogen. In actuality, we do not currently know whether estrogen will prevent cardiovascular disease, and we will not know until the large clinical trials now underway are completed. Despite this lack of certainty, most physicians in the United States are convinced that estrogen works, are advised to prescribe it for prevention of CHD, and are doing so in increasing numbers (5). Numerous articles on this topic in the scientific literature encourage this trend, and the supposed benefits of estrogen are widely touted by written and electronic news media. Respected bodies responsible for putting out practice guidelines have also succumbed to the lure of estrogen for the prevention of CHD (6, 7). While these guidelines pay lip service to the need for clinical trials, they nonetheless take an encouraging stance towards estrogen treatment especially for women at high risk of CHD. The purpose of this contribution is to offer reasons why a more cautious attitude toward the widespread use of long-term estrogen might be in order.

Evidence that estrogen may prevent CHD

Physicians have some justification for believing in estrogen therapy. Taken at face value, the flood of observational studies, together with studies of intermediate mechanisms, may appear convincing. Indeed, it is quite possible that these studies are correct in their prediction of benefit. But it is at least equally possible that they are wrong. The studies may appear convincing. Indeed, it is quite possible that these studies are correct in their prediction of benefit. But it is at least equally possible that they are wrong. The studies may be wrong even to the extent that there may be no benefit whatsoever for CHD prevention, or that any benefit is insufficient to offset the adverse effects.

Observational studies. A large number of observational studies have suggested that women who have ever taken estrogen appear to have a 30–50% lower risk of CHD than women who have never used estrogens (8, 9). Benefit appears to be strongest in current users (8, 10). Fewer studies have data on estrogen use in combination with a progestin, but apparent risk reductions are similar to those for estrogen alone (10–12). The data for stroke are less consistent (13). For all types of strokes combined there appears to be no net effect, although in the Nurses’ Health Study there was a significant