Evidence from over 30 epidemiologic studies indicates that postmenopausal women who take estrogen are at lower risk for coronary heart disease. A recent meta-analysis of all published studies found a 35 percent decrease in coronary disease (relative risk (RR) = 0.65, 95 percent confidence interval (CI) 0.60–0.70) for women who had ever used hormones compared with never users (1). Furthermore, the data suggest that most of this apparent protection is among the current hormone users; the summary relative risk for those studies that separately examined current use was 0.49 (95 percent CI 0.43–0.56) (1). Nonetheless, this consistent finding from observational studies does not prove cause and effect. It is widely recognized that women who choose to use estrogen may also make other choices that could be associated with reduced rates of heart disease (2-5).

In this issue of the Journal, Matthews et al. (6) contribute to a growing body of literature that finds in the general population, women who are prescribed hormones often are healthier than women who are not given estrogen replacement therapy (ERT) (2, 7). In a prospective study of randomly selected premenopausal women in Pennsylvania, Matthews et al. observed a better cardiovascular risk factor profile prior to ERT among the women who subsequently took hormones at menopause than among women who did not take hormones; ERT users were better educated, had higher high density lipoprotein (HDL) cholesterol, more physical activity, and greater alcohol intake than nonusers, as well as lower apolipoprotein B, blood pressure, weight, and fasting insulin levels. Based on these differences among the subsequent hormone users and nonusers in their study population, the authors suggest that the apparent benefit of hormones on cardiovascular disease may in fact be attributable largely to prior, advantageous characteristics of the women who are prescribed ERT.

Similar arguments have been propounded recently by Posthuma et al. (3), Sturgeon et al. (5), and Vandenbroucke (4).

Posthuma et al. (3) reviewed studies of ERT that reported data on both cardiovascular disease and cancer. In addition to a decreased risk of cardiovascular disease, there also were lower risks of cancer in many of these studies (summary RR = 0.83, 95 percent CI 0.71–0.96). Posthuma et al. reason that, because hormones do not generally protect against cancer, the decrease in cancer rates must reflect the selection of healthy women for estrogen therapy; they suggest that at least 20 percent of the reduced risk of cardiovascular disease reported in observational studies should be subtracted based on the extent of protection noted for cancer.

Sturgeon et al. (5) examined mortality data from a prospective study that updated information on hormone use on an annual basis. They reported lower mortality among current hormone users than among never users, but a higher rate of mortality for women who had recently stopped taking estrogens, which largely diminished as years since hormone use increased. They explain these results by hypothesizing that women discontinue hormone use when symptoms of a fatal disease develop, again leaving only healthy women as current hormone users.

Most of these arguments are not new. It is quite likely that, in general, hormone users are healthier than nonusers. The more important question is how and to what extent the differences affect our interpretation of studies of ERT and heart disease. That is, should we believe that the overall 50 percent decrease in the risk of coronary disease found for current hormone users represents a true protective effect of hormones, or merely reflects biases characteristic of observational epidemiologic studies? In the absence of randomized trials that remove self-selection as an issue, we must rely on indirect evidence to address the concerns raised by Matthews et al. (6), as well as others. We
must consider the following: whether an assessment of a decrease in cancer is an appropriate method for estimating the degree of bias in cardiovascular outcomes; if differences in risk factor profiles in general population samples reflect those in the epidemiologic studies of estrogen and heart disease; and the biologic basis for a potential protective effect of estrogen.

Posthuma et al. (3) suggest that an overall relative risk of 0.83 (95 percent CI 0.71–0.96) for cancer and hormone use indicates a 20 percent bias in observational studies of cardiovascular disease and ERT. First, many of the studies from which Posthuma et al. extract their data on cancer are mortality studies, which likely suffer from the problem described by Sturgeon et al. (5); that is, most people who die of cancer are diagnosed prior to their death and immediately discontinue hormone use. Thus, it would be surprising if Posthuma et al. did not observe such a decrease in cancer risk. Furthermore, the confidence interval around the summary estimate produced by Posthuma et al. is, in fact, closely compatible with their prior hypothesis of no relation between hormones and cancer, although it is possibly too early to hypothesize on the effect of hormones on cancer. While it seems that breast cancer is increased by postmenopausal hormones (8), in recent reports, colon cancer, also common in women, appears to be reduced among hormone users (9). The selective factors leading women with cancer to discontinue (or never initiate) hormone use are unrelated to selection for cardiovascular disease risk factors. So, examination of cancer rates in epidemiologic studies is not appropriate for quantifying potential biases in the studies of hormones and heart disease. Better means are provided by many of the investigators who have explored the relation between ERT and coronary disease and who have considered the relevant differences in subjects who take and do not take hormones.

Matthews et al. (6) and previous studies (2, 7) have found in general population samples that estrogen users have a better cardiovascular disease risk factor profile than nonusers. However, such variations reflect sociologic heterogeneity, and are not biologic phenomena. We would expect hormone users in the general population to be of higher socioeconomic status than nonusers; they can afford medical care. Studies that have compared rates of heart disease in women who take hormones to rates in the general population (10, 11) have found extremely low relative risks (ranging from 0.3–0.4), partly reflecting these socioeconomic and health disparities. Yet, such socioeconomic variation may not be present in a study that consists entirely of registered nurses or women who live in a specific retirement community. For example, in both the Nurses' Health Study (12) and the Leisure World Study (13), few important risk factor differences have been found in estrogen users compared with nonusers.

Thus, when Matthews et al. estimate, based on their study population, that 11.5 percent of the difference in heart disease rates between hormone users and nonusers could be due to preexisting characteristics (i.e., higher HDL cholesterol levels), we should modify their claim to more accurately suggest that 11.5 percent of the reduction found in other general population studies may be due to preexisting characteristics. It is not instructive to apply results found in general populations to those reported by the unique (and more homogeneous) populations used in most large epidemiologic studies.

The results from several studies have been adjusted for a large number of risk factors (12–14); these adjustments often have only a modest effect on the benefits seen among estrogen users, again indicating similar risk factor status for hormone users and nonusers. In the Leisure World Study (13), the age-adjusted relative risk of all-cause mortality was 0.80 (95 percent CI 0.70–0.87) for estrogen users compared with nonusers; after further adjustment for high blood pressure, history of angina, myocardial infarction or stroke, alcohol use, smoking, body mass index, and age at menopause, the relative risk was virtually the same (RR = 0.79, 95 percent CI 0.71–0.88). Matthews et al. argue that adjustment for variables such as educational status may not in fact control for confounding, and that risk factors prior to menopause are ignored by investigators who contribute to the literature on ERT and cardiovascular disease. However, it is well known that education is merely a proxy for more specific variables related to heart disease, and in some of the largest studies, the Nurses' Health Study (12), the Leisure World Study (13), and the Lipid Research Clinics Program Follow-up study (14), the authors do adjust for many of the specific factors examined by Matthews et al., including alcohol intake, physical activity, high blood pressure, and body mass index. In particular, while body mass index appeared to explain much of the difference between hormone users and nonusers in Matthews et al.'s study, and estrogen users in the general population often are leaner than nonusers (7), there are not such striking disparities in many other study populations. In the Lipid Research Clinics Program Follow-up study, the mean body mass index for estrogen users was 24.7 and for nonusers it was 25.7; addition of body mass index to a model including age, blood pressure, smoking, and total cholesterol only changed the relative risk estimate from 0.44 to 0.47. An analysis restricted solely to women in the Nurses' Health Study who were free from major coronary disease risk factors,
including obesity, still revealed approximately a 50 percent decrease in the risk of heart disease for current estrogen users. In addition, factors that predate menopause are often considered. The multivariate estimates from the Nurses' Health Study are adjusted for lifetime history of hypertension, high cholesterol, and diabetes, past cigarette smoking, past oral contraceptive use, and family history of myocardial infarction.

Compliance with use of estrogen has also been considered as a marker for low risk of heart disease (2, 15), suggesting to some that the behavioral characteristics of hormone users are more important to their decreased risk of coronary disease than the estrogen that they are taking. This argument is based on findings from clinical trials, where subjects who were compliant placebo takers had a better outcome than noncompliant subjects on placebo (16). In the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial (17), a substantial number of women with a uterus had discontinued estrogen use by the end of 3 years, which suggests that the long-term “compliant” users are a selected group.

However, it is unclear to what extent these findings from drug therapy trials can be extended to the interpretation of observational studies where the subjects themselves have chosen to use medication. It is possible, for example, that clinical trial participants with symptoms of preclinical disease may selectively stop taking their randomly assigned regimen, perhaps explaining part of the apparent benefit of compliance. Furthermore, although few studies have specifically examined this issue, there does not consistently appear to be a greater protection against heart disease in long-term ERT users compared with short-term users (12), indicating that the long-term “compliant” women do not have a substantially different health profile than short-term users.

Yet, Matthews et al. point out that it is primarily the current hormone users, regardless of duration, who seem to be protected against heart disease. Thus, again, it may be attributes of the women who choose to take ERT and not the hormone itself which is beneficial. This ignores a substantial body of experimental data which support an immediate effect of current, but not past, estrogen use on heart disease. Improved blood flow was noted in a study that lasted just 2.5 months (18), and reduced arterial impedance and decreased symptoms (20). Sack et al. (21) also found that estrogen’s antioxidant properties were eliminated almost immediately after cessation of estrogen use. In fact, these findings suggest that many investigations, which generally combine current and past hormone use, have underestimated the effect of hormones on heart disease to an extent dependent on the proportion of current and past users in the population studied.

Furthermore, considerable biologic data from clinical trials in both animals and women support a benefit of estrogen use on numerous factors related to cardiovascular disease, substantiating the results of observational studies in women. In a series of randomized trials of ovariectomized monkeys given estrogen or placebo, monkeys on estrogen had 50 percent less atherosclerosis (22), a 70 percent reduction in low density lipoprotein (LDL) uptake in the coronary arteries (23), and vasodilation after acetylcholine infusion (24). Impedance to blood flow is reduced in women after estrogen use (18, 19, 25), and Sack et al. (21) reported that women who were given estrogen for 3 weeks had a 16 percent prolongation of the lag time of LDL oxidation (p < 0.01 compared with pretreatment). Finally, as Matthews et al. note, in the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) Trial (17), women randomized to estrogen had higher HDL and lower LDL cholesterol levels than women on placebo; for women who took unopposed oral conjugated estrogen, there was an average 14.5 mg/dl decrease in LDL and a 5.6 mg/dl increase in HDL. A 1 mg/dl decrease in LDL is associated with approximately a 2 percent decrease in risk of coronary disease, and 1 mg/dl increase in HDL is associated with about a 3 percent decline in risk (26); hence, this average LDL change translates to a 29 percent reduction in coronary disease risk and the HDL increase would mean a 16.8 percent reduction in risk. In addition, the PEPI trial was analyzed by intention to treat. Given the substantial number of women who stopped taking estrogen during the trial, the above figures underestimate the actual benefit of estrogen for women who maintain its use; thus, this trial predicts, with no possibility for selection bias, much of the reduced risk of heart disease reported in observational studies.

Finally, while it is not surprising that Sturgeon et al. (5) found that women appear to stop taking estrogen before their deaths, other investigators have recognized and appropriately designed their analyses to accommodate this issue. In analyses of cancer mortality, women with a cancer diagnosis at baseline must be excluded in order to avoid this problem. In addition, studies with updated hormone use, such as the one analyzed by Sturgeon et al. (5), must deal with the
further complication of how to handle women diagnosed with cancer during the follow-up periods. In the Nurses’ Health Study, breast cancer mortality (8) was examined as a nested case-control study, with follow-up for cases ending at their diagnosis of breast cancer and controls chosen who were alive at the cases’ diagnosis date. This seems the best way, methodologically, to avoid bias due to medical practice and the treatment of women with diagnosed disease prior to their death.

In summary, it seems clear that, in general population samples, hormone users are at decreased risk of cardiovascular disease, regardless of the apparent benefits of estrogen. But, the better health status of hormone users may mean less in many of the epidemiologic studies that provide the data on estrogen and heart disease; adjustment for health differences usually shows only a modest bias. Clinical trials of ERT are currently underway and are necessary; however, it will be several years before their outcome is known. Findings from observational studies, in conjunction with abundant biologic evidence, lend support to a causal relation between estrogen and heart disease.

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