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Endogenous Sex Hormones and Cardiovascular Disease Incidence in Men

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Background: Data suggest that endogenous sex hormones (testosterone, dehydroepiandrosterone sulfate [DHEA-S], and estradiol) influence cardiovascular disease (CVD) risk factors and vascular function. Yet, prospective studies relating sex hormones to CVD incidence in men have yielded inconsistent results.

Objective: To examine the association of circulating sex hormone levels and CVD risk in men.

Design: Prospective cohort study.

Setting: Community-based study in Framingham, Massachusetts.

Participants: 2084 middle-aged white men without CVD at baseline.

Measurements: The authors used multivariable Cox regression to relate baseline levels of testosterone, DHEA-S, and estradiol to the incidence of CVD (coronary, cerebrovascular, or peripheral vascular disease or heart failure) during 10 years of follow-up.

Results: During follow-up, 386 men (18.5%) experienced a first CVD event. After adjustment for baseline standard CVD risk factors, higher estradiol level was associated with lower risk for CVD (hazard ratio per SD increment in log estradiol, 0.90 [95% CI, 0.82 to 0.99]; $P = 0.035$). The authors observed effect modification by age: Higher estradiol levels were associated with lower CVD risk in older (median age >56 years) men (hazard ratio per SD increment, 0.86 [CI, 0.78 to 0.96]; $P = 0.005$) but not in younger (median age ≤56 years) men (hazard ratio per SD increment, 1.11 [CI, 0.89 to 1.38]; $P = 0.36$). The association of higher estradiol level with lower CVD incidence remained robust in time-dependent Cox models (updating standard CVD risk factors during follow-up). Serum testosterone and DHEA-S levels were not statistically significantly associated with incident CVD.

Limitations: Sex hormone levels were measured only at baseline, and the findings may not be generalizable to women and nonwhite people.

Conclusions: In the community-based sample, a higher serum estradiol level was associated with lower risk for CVD events in older men. The findings are consistent with the hypothesis that endogenous estrogen has vasculoprotective influences in men.

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Male sex is an independent risk factor for cardiovascular disease (CVD) (1). Scientists have postulated that the 5- to 10-year lag period in CVD incidence in women (compared with men) may be related to differences in endogenous sex hormones (2–7). Indeed, substantial evidence suggests that sex hormones (testosterone, estrogen, and dehydroepiandrosterone sulfate [DHEA-S]) influence traditional and newer CVD risk factors (2–7). Interest in the role of sex hormones in the pathogenesis of CVD has been rekindled by the observation that men with genetic defects of estrogen synthesis (8) or action (9) develop premature atherosclerosis. In addition, genetic variation in estrogen receptor-α has been associated with prevalent CVD (10, 11), and androgen and estrogen receptor expression in coronary arteries has been reported to influence coronary atherosclerosis in men (12).

In contrast to the aforementioned data, prospective studies relating circulating sex hormone levels to incident CVD in men have been inconclusive. For example, low serum testosterone levels have been associated with greater progression of subclinical atherosclerosis in 2 previous investigations (13, 14), but other studies have reported no association of testosterone levels with CVD events (15–21). On a parallel note, low DHEA-S levels have been linked to greater CVD risk in some studies (18, 22–24) but not in other studies (13, 20, 25–29). Investigations relating serum estradiol levels to CVD risk in men have generally found no statistically significant association (15–20). Some previous investigations were limited by modest sample sizes (14, 17, 18, 22, 25, 26); an insufficient number of CVD events (15–18, 22, 23, 26); and, in some instances, a retrospective study design (17–21, 25, 26). In addition, some reports (15, 22, 24) focused on CVD death (they did not evaluate nonfatal CVD events). Thus, a large prospective community-based study relating sex hormones to CVD risk with adequate power to detect modest potential associations is needed. Accordingly, we evaluated the associations of serum levels of sex hormones that were measured at a routine baseline examination with CVD incidence in a prospectively assembled cohort of participants.

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Web-Only
Appendix Table
Conversion of figure and tables into slides

