



## Invited Commentary: Acne in Adolescence—Protecting the Heart but Damaging the Prostate Later in Life?

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Abbreviation: SHBG, sex hormone-binding globulin.

*Man is only man at the surface. Remove the skin, dissect, and immediately you come to machinery.*

—Paul Valery, French critic and poet (1871–1945)

Cutaneous manifestations of diseases have long helped observant clinicians to establish a diagnosis (1), but can cutaneous clues or other physical characteristics predict the risk of mortality or incident disease far into the future? For some time, researchers have linked with mixed success various physical manifestations to the risk of developing diseases, such as coronary heart disease. Among these physical markers are earlobe crease (2), arcus senilis (3), baldness (4), early hair graying (5), and facial wrinkling (6). Good reasons exist for studying the associations between physical markers and disease endpoints, because physical characteristics may help not only to elucidate underlying pathogenetic processes for diseases but also to detect persons at increased risk who would benefit by early intervention.

In this issue of the *American Journal of Epidemiology*, Galobardes et al. (7) add acne vulgaris to the list of physical characteristics that may serve as risk markers for the development of disease later in life. In a retrospective follow-up study of 11,232 men who attended Glasgow University between 1948 and 1968 and whose mortality was traced into 2004, the investigators found that participants who reported having acne during adolescence had a significantly lower risk of death from coronary heart disease and an increased, although statistically not significant, risk of death from prostate cancer. For the other causes of mortality (mortality from all causes, stroke, lung cancer, colon cancer, and external causes), no significant associations were found. This study provides an excellent example of how older epidemiologic

studies can be creatively used to generate new hypotheses about the potential pathogenetic pathways of various conditions.

Consistent with the longstanding hypothesis that endogenous sex hormones play important roles in the pathogenesis of prostate cancer and cardiovascular disease, the authors' view of acne largely as a manifestation of endogenous hormonal activity, principally androgen activity, has precedent. Although there are many reasons to believe that androgen activity may increase the risk of prostate cancer, epidemiologic studies have produced inconsistent results in linking circulating concentrations of androgens to the risk of prostate cancer (8–10). In the current study, the hazard ratio of 1.67 for mortality from prostate cancer was based on only 37–43 such deaths, and the confidence interval was wide and overlapped 1.0 considerably. Surprisingly, the authors highlighted the findings pertaining to prostate cancer in the title of their article as well as in the body of the text.

The cardiovascular findings are perhaps more interesting and noteworthy. The authors report hazard ratios of 0.74 for mortality from total cardiovascular disease and 0.67 for coronary heart disease mortality. In both instances, the confidence interval excluded unity. Adjustment for the various covariates considered by the authors had little effect on the hazard ratios. While a series of recent reviews seem to be cautiously converging on the view that androgens may exert a favorable effect on cardiovascular disease (11–13), the roles of androgens on the cardiovascular system are likely to be complex and may be sex specific. Among men, concentrations of testosterone have been inversely related to concentrations of insulin and insulin resistance (14–21), as

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**TABLE 1. Results of prospective studies of testosterone and risk of incident type 2 diabetes mellitus**

Study (reference no.)	Population	Follow-up (years)	No. of cases of diabetes	Results
Rancho Bernardo Study (34)	294 men, 233 women, aged 55–89 years	8	43*	Women: highest vs. other quartiles of free testosterone (OR† = 2.9, 95% CI†: 1.1, 8.4); men: lowest vs. other quartiles of total testosterone (OR = 2.7, 95% CI: 1.1, 6.6)
Massachusetts Male Aging Study (35)	1,156 men, aged 40–70 years	9	54	For each standard deviation decrease in free testosterone (OR = 1.58, 95% CI: 1.06, 2.29)
Multiple Risk Factor Intervention Trial (36)	12,886 men, aged 35–57 years	5	176	Low testosterone significantly associated with type 2 diabetes mellitus but not after adjustment for body mass index and fasting glucose
Swedish study of men born in 1913 (37)	659 men, aged 67 years	13	35	Low testosterone significantly associated with type 2 diabetes mellitus even after adjustment for body mass index and waist/hip ratio

\* Total of 43 cases = 26 men and 17 women.

† OR, odds ratio for type 2 diabetes mellitus; CI, confidence interval.

well as to obesity (22, 23) and central adiposity (16, 21, 23–27). Indeed, small clinical trials have found that treatment with testosterone decreased visceral fat and improved insulin sensitivity in obese men (28) and men with low concentrations of testosterone (29). In contrast, high concentrations of androgens have been associated with dyslipidemia, hypertension, and insulin resistance in women (30, 31). In a cross-sectional study of 143 women aged 60 years or less from New Zealand, those with polycystic ovarian syndrome had more extensive coronary heart disease on angiography than did women with normal ovaries (32). In a cohort of 253 Swedish women aged 54–60 years (31), low concentrations of sex hormone-binding globulin (SHBG), a marker of androgenicity, were associated with increased overall mortality (32 events) and risk of myocardial infarction (12 events) during 12 years of follow-up. The relation between the concentration of SHBG and the 12-year incidence of myocardial infarction was U shaped. In a study of diabetic women ( $n = 120$ ) and men ( $n = 123$ ) from Wisconsin who were followed for 5 years, however, plasma concentrations of SHBG or other sex hormones were not significantly associated with coronary heart disease mortality (33).

Data from relatively few prospective studies indicate that testosterone may differentially affect the risk of type 2 diabetes mellitus in men and women (table 1) (34–37). In the Massachusetts Male Aging Study, low concentrations of testosterone predicted incidence of diabetes. The odds ratio for future diabetes was 1.58 for a decrease of one standard deviation in the concentration of free testosterone (4 ng/dl) and 1.89 for a decrease of one standard deviation in the concentration of SHBG (16 nmol/liter), both significant findings (35). Men with concentrations of serum dehydroepiandrosterone sulfate (DHEAS) in the lowest quartile at baseline (<1.6 µg/ml) were significantly more likely to develop coronary heart disease during the follow-up (adjusted odds ratio = 1.60, 95 percent confidence interval: 1.07, 2.39),

independently of known coronary risk factors (38). In the Rancho Bernardo cohort, the one prospective study that included both women and men, highly significant and *opposite* predictive roles for plasma testosterone were observed in the sexes (34). The odds ratio of developing type 2 diabetes mellitus among women with a concentration of bioavailable testosterone in the highest quartile was 2.9 (95 percent confidence interval: 1.1, 8.4) compared with women with lower concentrations, while men with concentrations of testosterone in the lowest quartile had a risk of type 2 diabetes mellitus nearly triple that of men with higher concentrations. Taken together, accumulating evidence indicates that androgens may exhibit a sexual dimorphism with respect to coronary heart disease risk, with elevated concentrations in women and lower concentrations in men increasing the risk.

On an a priori basis, one might assume that the associations between the different expressions of androgen activity (acne, alopecia, hirsutism, and shaving frequency) and coronary heart disease risk should be reasonably congruent. Thus, the lack of concordance in the association between acne and coronary heart disease risk in this study and that between alopecia and coronary heart disease risk reported in other studies are perplexing and difficult to explain. Previous studies are reasonably consistent in reporting that alopecia is associated with an increased risk of cardiovascular disease, especially in younger men (39). Perhaps in the case of alopecia, the associations do not reflect an effect of excess androgen activity but rather another physiologic mechanism. Alternatively, these markers may not reflect androgen pathophysiology and instead capture some other interrelated mechanisms with which sex hormones are associated (possibly through genetic linkage). An evaluation of a possible interaction between body mass index and acne would have been of interest as well, because of the likely interactions between steroid hormone and adipocyte cytokines.

As in any epidemiologic study, a critical assessment of the dependent, exposure, and confounding variables is needed. Incidence, mortality, or both are the main types of endpoints used in prospective studies. Incidence and mortality may often yield similar results, especially in situations where mortality is high and relatively rapid after a diagnosis. When survival rates are high, however, those who died may have had more severe disease and may have been less representative of the larger group of participants who developed the disease. If an exposure is more prevalent among fatal cases of a disease than among nonfatal cases, a measure of association based on fatal cases should produce higher estimates than one based on all incident cases. For example, data from the Surveillance, Epidemiology, and End Results Program in the United States show that the 5-year survival rate for prostate cancer among White men increased from 50 percent during 1960–1963 to 100 percent during 1995–2000 (40). Case-fatality rates for cardiovascular disease have been declining in many countries including Scotland (41).

In the Glasgow Alumni Cohort Study, mortality was determined through the use of an administrative database. Although the authors do not provide statistics about the validity of these records, outcomes based on information from death certificates and administrative databases are used commonly and successfully in epidemiologic studies. Unless there is reason to believe that the inherent misclassification of using such records differed by exposure status, the measures of association should be largely unaffected. By reporting in greater detail the associations for the other covariates such as age, smoking, and systolic blood pressure, the authors could have lent additional credence to the mortality data.

Various scales to grade the severity of acne exist (42–44). These were not available to the authors who had to rely instead on a relatively crude measure of acne. Some questions remain about the manner in which acne was assessed during a student's visit to the health services. Although the authors note that a history of acne was obtained from a questionnaire, greater detail about whether students had to run down a checklist of conditions or whether there was a specific question about acne would have been helpful. As the authors point out, no additional information about the acne was solicited from the students. Thus, it is not clear whether students had acne at the time of the visit or had experienced it earlier in their life. The prevalence of acne was 18.0 percent in the Glasgow Alumni Cohort Study, and the authors assumed that the presence of acne probably represented severe acne. Perhaps as likely is the possibility that acne may have represented a more complete clinical spectrum of this skin condition. The percentage of adolescents who have acne may be as high as 90 percent (45). In a study from Hamburg, Germany, the prevalence of acne diagnosed during a dermatologic examination was 61.7 percent among participants aged 14–19 years and 64.0 percent among participants aged 20–29 years (46). Furthermore, 75.4 percent of all participants aged 1–87 years had no acne, 21.7 percent had moderate acne, and 2.9 percent had severe acne. In another study of New Zealand senior high school students, 91 percent of male participants and 79 percent of female participants had acne based on a physical examination, and 6.9 percent of males and 1.1 percent of females had severe acne (47).

Because the effect sizes reported by Galobardes et al. (7) were modest, a key issue is how these authors controlled for potential confounders. Selecting an appropriate set of confounding variables can make or break an epidemiologic analysis. The authors seem to have approached their discussion about the possible impact of confounders they were unable to include in their analyses by assuming that candidate confounders had to confound simultaneously any association between acne and the various outcomes. However, such an assumption depends on a correct understanding of the specific causal model that cannot be readily verified. A variable may well confound only the relation of acne to a particular outcome but not to another outcome, and a different confounder could do the opposite. Consequently, we are reluctant to endorse the authors' conclusion that "... confounding does not explain the pattern of mortality observed in our study" (7, p. 1099).

Given the multiple outcomes in the analysis of the Glasgow Alumni Cohort Study, different sets of confounding variables may have been needed. The authors adjusted for the date of the examination, measures of socioeconomic status, the number of siblings, height, body mass index, smoking status, and systolic blood pressure. With regard to cardiovascular disease, several key risk factors were not included, notably, concentrations of lipids and diabetes. Additional risk factors that might have been considered are family history of cardiovascular disease, inflammatory parameters, alcohol use, and dietary nutrients or patterns. Some and perhaps all of these variables were probably not collected. Even if data had been available for these variables, their inclusion may not have altered the findings in a meaningful way.

The authors discuss and dismiss several potential sources of confounding: socioeconomic status and smoking status that they did adjust for, diet, use of antibiotics, and unspecified behavioral factors. Although the relation between diet and acne continues to be controversial (48), we are less willing to dismiss dietary factors as possible confounders. Diets are complex, and their actions on organ systems need not be uniform. For example, increased intake of alpha-linolenic acid may protect against cardiovascular disease (49) but also may increase the risk of prostate cancer (50). However, a particular dietary factor need not both lower the risk of cardiovascular disease and increase the risk of prostate cancer.

Because this study was conducted among men only, future studies should include more diverse populations including women, so that the potential sexual dimorphism in the effects of androgens on cardiovascular risk can be evaluated. A better definition of acne is clearly desirable, and including experts in this field to develop study questionnaires or to conduct examinations deserves serious consideration. A more precise definition of endpoints that includes incidence as well as mortality will help to minimize misclassification from this source. Including a proper set of potential confounding variables is also critical in the evaluation of any association between acne and health outcomes. If androgen activity is reflected in the severity of acne (perhaps less so in men than in women), examining severity as a predictor of health outcomes should also be attempted, especially in

women. If the genesis of conducting studies of the associations between acne status and future risk of disease is to evaluate the possible role of endogenous sex hormones, we submit that it would be most fruitful to directly and comprehensively assess sex-hormone status or activity and their related gene variants in prospective studies with samples of blood and DNA.

At present, despite much biologic research on the effects of these hormones on the vascular system, no clear relation has yet been firmly established between endogenous sex hormones and coronary heart disease risk. The scientific issues related to estrogen offer a case in point for this complexity. Although low estrogen levels had long been proposed as an explanation for the dramatic rise in coronary heart disease risk after menopause (51), coronary heart disease risk was demonstrated to increase significantly in postmenopausal women given exogenous estrogen therapy in later randomized trials (52), suggesting that higher estrogen levels may actually increase risk. Constrained by the prevailing knowledge and technology at the time of its development and inception, this study, like almost all epidemiologic studies, is subject to various limitations, especially when viewed critically through a scientific magnifying loop many years later. Building on previous research, however, a new generation of epidemiologic studies will expand the boundaries of our knowledge about the links between sex hormones and disease.

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