Do Statins Affect Androgen Levels in Men? Results from the Boston Area Community Health Survey

Susan A. Hall,[1] Stephanie T. Page,[2] Thomas G. Travison,[1] R. Bruce Montgomery,[2] Carol L. Link,[1] and John B. McKinlay[1]

[1]New England Research Institutes, Watertown, Massachusetts and [2]Department of Medicine, University of Washington, Seattle, Washington

Abstract

Background: **In 2005, statins were among the most commonly used prescription medications in the United States. Some data suggest statins may affect cancer risk and/or disease severity. Because cholesterol is a required intermediate in sex steroid synthesis, it is possible that statins influence prostate cancer risk through effects on steroid hormone metabolism. We investigated whether levels of circulating androgens and their carrier protein, sex hormone–binding globulin (SHBG), varied by statin exposure among a sample of 1,812 men from a population-based epidemiologic study, the Boston Area Community Health Survey.**

Methods: **We measured serum total testosterone, free testosterone, dehydroepiandrosterone sulfate, luteinizing hormone, and SHBG. Statin exposure was collected through participant self-report and/or interviewer-recorded information. Multivariate linear models were constructed to account for potential confounding.**

Results: **The prevalence of statin use was 12.4% [95% confidence interval (95% CI), 10.3-14.9]. On average, statin users were older, had larger body mass index and more chronic illnesses, and used more medications. We found no relationship between statin use and free testosterone, dehydroepiandrosterone sulfate, or luteinizing hormone. A significant association between statin use and total testosterone was initially observed but was not robust to covariate control in a multivariate model that included age, body mass index, time since awakening, and history of cardiovascular disease and diabetes (−5.5%; 95% CI, −13.2 to 2.9%). In multivariate models adjusted similarly, SHBG levels among statin users were statistically significantly lower compared with nonusers (−10.6%; 95% CI, −18.8 to −1.6%).**

Conclusion: **In this sample, it is unlikely that statins affect circulating androgens and prostate cancer risk through a hormonal mechanism.** (Cancer Epidemiol Biomarkers Prev 2007;16(8):1587–94)

Introduction

Statins, which inhibit 3-hydroxy-3-methylglutaryl CoA, are used for lowering serum cholesterol and for other cardiovascular indications. Atorvastatin was the top-selling prescription medication in the United States from 2000 to 2005 (1). It is estimated that 6.2% of the U.S. adult population used atorvastatin in 2005 (2). Considering the U.S. Medicare population, use of any statin more than doubled in 5 years; 27.1% used a statin in 2002 compared with 11.6% in 1997 (3). Statins are indicated for use throughout a patient's life until data emerge on a more appropriate length of treatment (4). As a common and potentially prolonged drug exposure, the effects of statins on physiologic processes and noncardiovascular diseases have become an important public health concern.

Recent epidemiologic studies have focused on a potential protective effect of statins on cancer at multiple sites, although the evidence is still considered inconclusive (5). Whereas some studies show no effect of statins on prostate cancer (6, 7), a recent, large cohort study showed a substantially reduced risk of metastatic or fatal prostate cancer among statin users, with evidence of decreased risk with increasing duration of use (8). Cholesterol is a required intermediate in sex steroid synthesis, and reduction of testosterone precursors may influence the risk of progression and biology of prostate cancer by suppressing steroid hormone production. Indeed, small placebo-controlled studies have found subtle effects of statins on circulating androgen levels in men with dyslipidemia (9, 10). To date, the effect of statins on circulating androgen levels in men has not been considered in an epidemiologic study.

We investigated the hypothesis that statins lower serum androgen levels in community-dwelling men using data from the Boston Area Community Health (BACH) Survey, a population-based epidemiologic study conducted in Boston, Massachusetts. The goals of our study were (*a*) to estimate the apparent effect of statin use on serum androgen concentrations and (*b*) to determine to what extent this relationship could be explained by potential confounding factors [because chronic disease and higher body mass index (BMI) are associated with lower circulating androgens in men; refs. 11, 12] or if any observed relationship was independent of these variables.

Materials and Methods

Study Design and Data Collection. The BACH study was funded by the NIH (National Institutes of Diabetes and Digestive and Kidney Diseases) and is a population-based, cross-sectional epidemiologic study among 5,506 men and women ages 30 to 79 conducted in Boston, Massachusetts. A multistage stratified cluster sampling design was used for the purposes of recruiting equal numbers of persons to prespecified age groups (30-39, 40-49, 50-59, and 60-79), race and ethnic groups (black, white, and Hispanic), and gender. Interviews for 63.3% of eligible subjects were completed, with a resulting

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Requests for reprints: Susan A. Hall, New England Research Institutes, 9 Galen Street, Watertown, MA 02472. Phone: 617-923-7747; Fax: 617-924-0968. E-mail: shall@nerisicience.com

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study population of 2,301 men and 3,205 women composed of 1,770 blacks, 1,877 Hispanics, and 1,859 whites. Data were collected between April 2002 and June 2005 during a 2-h interview conducted by a trained, bilingual interviewer, usually in the home. Information collected included urologic symptoms, medical conditions, use of over-the-counter and prescription drugs, anthropometric and lifestyle factors related to health, socioeconomic status, and psychosocial factors. After written informed consent, a venous blood sample (20 mL) was collected. Further details of the study design are available (13). Informed consent was obtained from all participants, and all protocols and procedures were approved by New England Research Institutes' Institutional Review Board.

Measurement of Androgens. The measurement of testosterone, sex hormone–binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS) in BACH has been reported previously (14). Briefly, testosterone, SHBG, and DHEAS were measured by competitive electrochemiluminescence immunoassay, whereas luteinizing hormone (LH) was measured by a sandwich electrochemiluminescence immunoassay, on the 2010 Elecsys autoanalyzer (Roche Diagnostics). For LH, the process was as follows. A biotinylated LH antibody and a LH antibody labeled with ruthenium were mixed with the serum sample. The LH in the sample was sandwiched between the ruthenium-labeled and biotinylated antibodies. Streptavidin-coated magnetic microparticles were then added to the reaction mixture to bind the biotinylated antibody. These immunocomplexes were magnetically entrapped on an electrode and the unbound reagents and sample were washed away. A chemiluminescent reaction was then electrically stimulated to generate light, the intensity being directly proportional to the amount of LH present in the sample.

Free testosterone (FT) was calculated using the mass action equations described by Sodergard et al. (15), with association constants for testosterone taken from Vermeulen et al. (16). These calculations take into account the concentrations of serum total testosterone (TT) and SHBG. The possible binding of other steroids to SHBG was disregarded. A fixed albumin concentration of 4.3 g/dL was assumed because this was not measured. The association constant of testosterone to SHBG was 1.0×10^9. The lower limits of detection were 2 ng/dL (0.07 nmol/L) for testosterone, and the day-to-day imprecision values at concentrations of 0.24, 2.75, and 7.01 ng/mL were 7.4%, 2.2%, and 1.7%, respectively; within run, the values at the same concentrations were 4.6%, 1.4%, and 1.1%. For SHBG, the lower limits of detection were 3 nmol/L and the day-to-day imprecision values at concentrations of 25, 64, and 95 nmol/L were 2.4%, 2.2%, and 2.7%, respectively. Within run, at concentrations of 14, 44, and 204 nmol/L, values were 2.1%, 2.4%, and 2.7%. For DHEAS, the lower limits of detection were 0.1 μg/dL and the day-to-day imprecision values at DHEAS concentrations of 117, 395, and 984 μg/dL were 3.6%, 4.7%, and 2.4%, respectively. Within run, at the same concentrations, values were 2.8%, 2.4%, and 1.7%. For LH, the lowest detection limit of this assay is 0.10 mIU/mL and the day-to-day imprecision values at concentrations of 0.54, 27.19, and 50.72 mIU/mL were 5.2%, 2.0%, and 2.0%, respectively. Within run, at the same concentration, values were 1.8%, 0.8%, and 0.8%. All assays used in the study have been approved by the Food and Drug Administration for clinical use. We defined clinically low TT and FT as <300 and <5 ng/dL, respectively, using Endocrine Society guidelines (17).

Medications. BACH participants were asked to gather all over-the-counter, alternative, and prescription medications in the home used over the past 4 weeks for recording of the label information by the interviewer. In addition, participants were asked separately if they were taking drugs for specific indications, such as high cholesterol and high blood pressure. Medications named in the self-reported response field and the medication inventory were in turn coded using the Slone Drug Dictionary created by the Slone Epidemiology Unit at Boston University School of Public Health (18). The coding process identifies drug components and classifies them using a modified form of the American Hospital Formulary Service Drug Pharmacologic Therapeutic Classification System (4). We defined statins as drugs included in class heading 24:06:08, which included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Because participants taking statins may also take cardiovascular medications, we captured four additional drug groups. Cardiac drugs included flecainide acetate, losartan potassium, irbesartan, valsartan, candesartan cilexetil, olmesartan medoxomil, cardiac glycosides, antiarrhythmics, β-adrenergic blockers, and slow channel (calcium) blockers. Hypotensives included angiotensin-converting enzyme inhibitors, antiadrenergics (central and peripheral), minoxidil, telmisartan, and hydralazine. Vasodilators included nitrates and nitrites, phosphodiesterase, dipyridamole, pentoxifylline, and viscus album. Finally, diuretics included thiazide, thiazide-like, loop, aldosterone inhibitors, carbonic anhydrase inhibitors, and miscellaneous diuretics.

Covariates. Covariates of interest were selected based on prior studies in BACH (14) and published literature, with additional consideration of what variables might also be related to statin use for subsequent evaluation of potential confounding (8). Age and BMI, weight in kilograms divided by height in meters squared, were examined on the continuous scale. Weight and height were measured by the interviewer. Because of diurnal variation in hormone concentration (19), we also adjusted for the time interval between awakening and blood draw in all models. Categorical variables included race and ethnicity (black, white, Hispanic), type of health insurance (public only, private, none), marital status, current smoker (yes/no), alcohol use (none, <1 drink per day, 1-2 drinks per day, 3+ drinks per day), Physical Activity Scale for the Elderly score (low, 0-99; medium, 100-249; high, 250+), and socioeconomic status constructed as function of standardized income and education variables for the northeastern United States and reclassified into low, medium, and high (20, 21). Comorbidity variables were based on participant replies to the query, ''Have you ever been told by a health care provider that you have. . .?'' We included asthma, chronic lung disease, high blood pressure, cancer, kidney disease, dyslipidemia, and type I or type II diabetes as well as a composite cardiovascular disease variable that included any of the following: history of coronary artery bypass surgery or angioplasty, heart attack, angina, irregular heartbeat and/or having a pacemaker, congestive heart failure, transient ischemic attack, stroke, carotid artery surgery, intermittent claudication, surgery or angioplasty for arterial disease of the leg, pulmonary embolism, aortic aneurysm, heart rhythm disturbance, deep vein thrombosis, Raynaud's disease, or peripheral vascular disease. For depression, participants with at least five of eight symptoms on the abridged Center for Epidemiologic Studies Depression Scale were considered as having depression (22). Medication use in the four groups of medications described above was additional dichotomous variables.

Analytic Sample. Of the 2,301 men in BACH, 42 men found to be taking antiandrogen therapy (flutamide, bicalutimide, nilutamide, and finasteride), leuprolide, progestin, or ketoconazole or taking androgen therapy (testosterone and DHEA) were excluded from the analysis. We also looked for exposures to other drugs known to affect male hormone levels, such as dutasteride, but found none. Three hundred ninety-six men were missing information on blood, whereas 22 men had values 4 SDs from the mean and were considered implausible outliers and excluded. As radiation and/or chemotherapy were assumed to affect hormone levels, 29 men undergoing

current treatment for cancer were also excluded. Consequently, 1,812 men were available for the analysis. In the modeling stage, additional exclusions were made (n = 137) due to missing information on covariates and the need to nest models on the same set of participants for valid comparison of estimates, leaving 1,675 men for analysis in the preliminary models and 1,791 men in the final models.

Statistical Analysis. To account for the sampling design, all analyses including models were weighted by the inverse of the probability of selection using SUDAAN statistical software (version 9.0.0; refs. 23, 24). This allows estimates to be interpreted as representative of the Boston, Massachusetts, population. Weighted means, medians, and interquartile ranges (IQR) were calculated, stratified by statin use. The absolute difference in serum levels of each outcome by statin use can be estimated by subtraction of the means in Table 2. For example, considering the means for TT adjusted for age and time since blood draw, the difference in means comparing users with nonusers is 394.3 − 445.3 = −51 ng/dL. We modeled the effect of statin use using linear models in SUDAAN. We analyzed their natural (base e) logarithms in regression models, as hormone outcomes exhibited some right skew and data appeared approximately linear on the logarithmic scale.

Each outcome was treated individually. Because exploratory analyses revealed numerous potential confounders (Table 1) and any identified association might be spurious, a multivariate model was used to generate adjusted associations between statin use and our outcomes. The goal of model building was to identify and control for confounders of the main exposure (statin use) and the outcome using a change-in-estimate criterion (25). Because we had many covariates whose interrelationships were unknown, we chose 15% as a typical or ''middle of the road'' threshold for confounding. In an exploratory phase, candidate confounders were identified

Table 1. Characteristics of statin users (n = 237) versus nonusers (n = 1,575) among men providing blood samples in BACH Survey, 2002-2005, N = 1,812

Continuous covariates*	Statin use, yes[†], mean (SE)	Statin use, no[‡], mean (SE)
Age	57.9 (1.3)	45.5 (0.5)
BMI	29.9 (0.5)	28.5 (0.3)
Categorical covariates*	**Statin use, yes (weighted % of all statin users)**	**Statin use, no (weighted % of all nonstatin users)**
TT (<300 ng/dL)	**33.1**	**22.8**
FT (<5 ng/dL)	15.1	9.5
White race	**70.7**	**60.3**
Type of health insurance		
Private	**66.3**	**66.7**
Public	**29.0**	**16.3**
None	**4.7**	**17.0**
SES		
Low	**31.2**	**21.6**
Medium	**37.2**	**51.1**
High	**31.6**	**27.3**
Married	49.4	45.3
Current smoker	26.3	26.0
Alcohol use		
None	**38.6**	**23.8**
<1/day	**41.2**	**40.3**
1-2/day	**15.5**	**25.9**
3+/day	**4.7**	**10.0**
Physical activity (PASE score)		
Low (<100)	**39.4**	**22.9**
Medium (100-249)	**40.2**	**49.7**
High (250+)	**20.4**	**27.4**
Dyslipidemia	**90.1**	**19.5**
Cardiovascular disease[§]	**46.8**	**15.0**
High blood pressure	**60.7**	**21.1**
Diabetes	**33.8**	**5.6**
Chronic lung disease	10.3	5.3
Kidney disease	6.0	2.7
Cancer	**9.2**	**3.6**
Arthritis	**27.6**	**14.9**
Depression	16.3	13.9
Cardiac drugs	**51.7**	**7.9**
Hypotensives	**44.0**	**8.8**
Vasodilators	**23.7**	**1.7**
Diuretics	**20.3**	**5.0**

NOTE: Of 2,301 men in the BACH study, 42 men were excluded from the analysis for taking medications likely to affect androgen levels or because they were under current treatment for cancer (29 men). Three hundred ninety-six men had missing values for hormones, and 22 men had hormone values more than 4 SDs from the mean of the natural log distribution and were excluded as outliers.

Abbreviations: PASE, Physical Activity Scale for the Elderly; SES, socioeconomic status.

*Data were missing on covariates as follows: BMI (5), insurance status (6), socioeconomic status (97), marital status (10), alcohol use (2), activity (15), dyslipidemia (13), high blood pressure (6), diabetes (1), chronic lung disease (2), kidney disease (7), and arthritis (7). Bold indicates that the P value for a χ^2 test of independence was <0.05. Comorbidities are any history of the condition, self-reported by the participant as diagnosed by a health care provider.

† Overall weighted prevalence of statin use is 12.4% (95% CI, 10.3-14.9). All analyses were weighted by the inverse of the probability of being sampled. Thirteen statin users were on other cholesterol medications: bile acid sequestrants (1), fibric acid derivatives (4), and ''miscellaneous'' cholesterol medications (8).

‡ Thirty nonstatin users were on other cholesterol medications: fibric acid derivatives (17) and miscellaneous cholesterol medications (13).

§As defined by any history of coronary artery bypass surgery or angioplasty, heart attack, angina, having a pacemaker, congestive heart failure, transient ischemic attack, stroke, carotid artery surgery, intermittent claudication, surgery or angioplasty for arterial disease of the leg, pulmonary embolism, aortic aneurysm, heart-rhythm disturbance, deep vein thrombosis, Raynaud's disease, or peripheral vascular disease.

using a submodel approach. To determine the structure of the final model, a full model was fit, and using backward selection, only those covariates that induced a 15% change in the β coefficient for the statins/outcome estimate were included in the final model (unless borderline and clinically relevant). Our final model was then compared with a minimal model (adjusted only for age and elapsed awake time before blood draw) to consider the effect of the covariates and to judge important confounders. A third set of models containing estimates adjusted for all variables found to confound any association between statins and the five outcomes was estimated.

For interpretation in the tables, natural logarithms were transformed for interpretation as percentage change in serum levels of androgens, SHBG, and LH among men exposed versus unexposed to statins. To enhance interpretability, we back transformed estimates of the regression variables obtained from analysis of log outcome values using the antilog (again, base e) and converted them to model-estimated percentage increases in outcomes per unit increase in predictors. Therefore, for an estimated regression variable β, we obtained (and report) the quantity $100 \times (e^{\beta} - 1)$. With respect to statin use specifically, the resulting estimate may therefore be interpreted as the approximate percentage difference in mean testosterone concentrations between statin users and nonusers, as one example. Confidence intervals (CI) were obtained by applying a similar transformation to the 95% confidence limits for β.

Results

The mean age of our sample of male BACH participants was 47.0 (SE, 0.5) and the mean BMI was 28.6 (SE, 0.3). The prevalence of statin use was 12.4%. Statin users (73.4%) were using atorvastatin followed by simvastatin (16.4%), pravastatin (5.1%), lovastatin (2.7%), fluvastatin (1.9%), and rosuvastatin (1.3%; two men were using two types; thus, percentages do not sum up to 100%). The majority (88.3%) of our statin exposure information was recorded in the drug inventory and was also self-reported by the participant; 1.2% appeared in the inventory but was not self-reported, whereas 10.6% was self-reported only. Table 1 presents characteristics of all statin users compared with nonusers. Statin users were different on most covariates. Users were on average 12.5 years older, had a higher BMI, and were more likely to have clinically low TT and comorbid diseases, such as diabetes, high blood pressure, and cardiovascular disease, compared with nonusers. Accordingly, statin users were also more likely to be taking cardiac medications, hypotensives, vasodilators, and diuretics than were nonstatin users.

Table 2 presents calculated means (crude means and means adjusted for age and time since awakening), medians, and IQRs for outcomes of interest. Considered crudely, means and medians were lower among statin users than nonusers for TT, FT, and DHEAS, whereas crude means and medians were higher for statin users for SHBG and LH. Differences in crude means were substantial for TT, FT, and DHEAS. Considering adjusted means, differences were most substantial for TT and SHBG. Figure 1 represents the distribution of hormone variables on the natural log scale by age, stratified by statin use. The fact that statin users are older is reflected in the relative placement of the black versus the gray dots. Although the tail ends of the age frequencies are small in frequency and should be interpreted with caution, there is a suggestion that any statin effect for testosterone and SHBG is more profound at younger ages. For LH and FT, there were no substantial differences between the groups. For DHEAS, there was a suggestion that statins may be associated with lower DHEAS in older men, but at younger ages, an effect was absent.

To consider the effect of statins on androgens adjusted for relevant covariates, multivariate linear models for all androgens are presented in Table 3. All models include age and elapsed time between awakening and blood draw. Because our examination of the statin and outcome relationships in Table 2 (considering adjusted means) and Fig. 1 showed the strongest effects for TT and SHBG, we focus on these in the discussion below. For TT and SHBG, baseline models yield evidence of substantial differences considering statin users and nonusers of comparable age (Table 3, column 1). However, the significance of the difference in TT was not resistant to control for covariates (Table 3, columns 2 and 3) and the magnitude of the difference was substantially reduced. In the model-building process, covariates found to be confounders by our

Table 2. Weighted summary statistics for serum androgen levels by 4-wk history of statin use (yes versus no) among men providing blood samples in BACH Survey, 2002-2005, *N* = 1,812

Outcome	Estimates	Total (N = 1,812)	Statin use, yes (n = 237)	Statin use, no* (n = 1,575)	P †
TT (ng/dL)‡	Adjusted mean (SE)	439.1 (7.8)	394.3 (16.0)	445.3 (8.1)	0.004
	Crude mean (SE)	439.1 (7.8)	382.1 (14.2)	447.2 (8.6)	0.0005
	Median (IQR)§	417.3 (248.9)	362.3 (186.1)	423.5 (255.7)	
FT (ng/dL)‡	Adjusted mean (SE)	9.1 (0.2)	8.6 (0.3)	9.2 (0.2)	0.11
	Crude mean (SE)	9.1 (0.2)	7.4 (0.2)	9.4 (0.2)	<0.0001
	Median (IQR)	8.6 (4.6)	7.3 (2.9)	8.9 (4.6)	
SHBG (nmol/L)	Adjusted mean (SE)	33.7 (0.6)	28.8 (1.8)	34.4 (0.6)	0.01
	Crude mean (SE)	33.7 (0.6)	35.3 (1.5)	33.5 (0.7)	0.15
	Median (IQR)	29.9 (19.1)	33.8 (19.5)	29.5 (19.1)	
DHEAS (μg/mL)‖	Adjusted mean (SE)	2.0 (0.1)	1.9 (0.1)	2.1 (0.04)	0.06
	Crude mean (SE)	2.0 (0.1)	1.4 (0.1)	2.1 (0.1)	<0.0001
	Median (IQR)	1.9 (1.5)	1.1 (1.0)	2.0 (1.5)	
LH (IU/L)	Adjusted mean (SE)	5.4 (0.1)	5.6 (0.4)	5.3 (0.1)	0.98
	Mean (SE)	5.4 (0.1)	6.1 (0.4)	5.3 (0.1)	0.18
	Median (IQR)	4.7 (2.8)	5.0 (3.0)	4.7 (2.8)	

NOTE: Adjusted means and SEs are adjusted for age and the time between awakening and having blood drawn. Of 2,301 men in the BACH study, 42 men were excluded from the analysis for taking medications likely to affect androgen levels or because they were under current treatment for cancer (29 men). Three hundred ninety-six men had missing values for hormones, and 22 men had hormone values more than 4 SDs from the mean of the natural log distribution and were excluded as outliers.

*n for nonusers of statins was 1,575 for TT and 1,574 for the other four hormones.

† P value for t test of differences in means (on natural log scale) comparing statin use with no use.

‡ Metric units in nanograms per deciliter can be divided by 28.84 to obtain Systeme International units, nanomoles per liter.

§ IQR (calculated as the 75% percentile minus the 25% percentile).

‖ Metric units in micrograms per deciliter can be multiplied by 0.02714 to obtain Systeme International units, micromoles per liter.

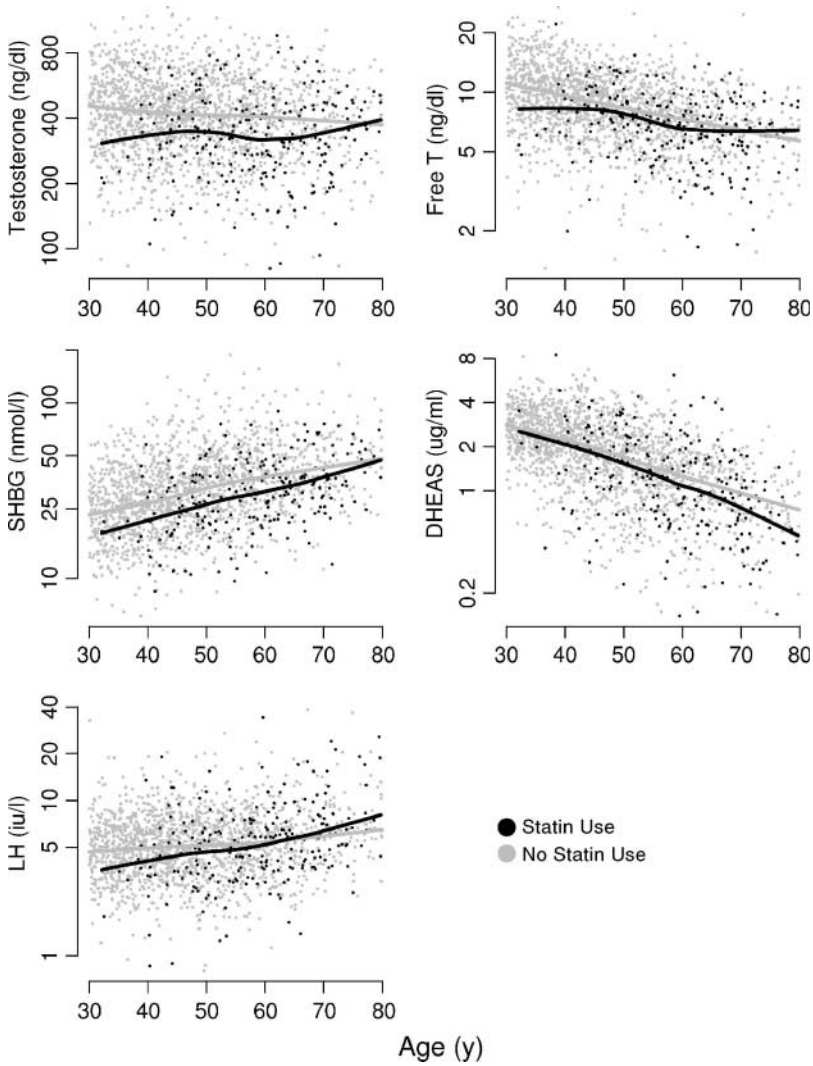

Figure 1. Age trends in serum hormone concentrations by statin use. Differences are most pronounced for TT and SHBG. Regression lines were estimated using locally weighted regression smoothing.

definition were age, BMI, cardiovascular disease, and diabetes. Conversely, the observed difference in the SHBG baseline model was robust to covariate control and remained of substantial magnitude. Covariates included in the most parsimonious model predicting mean SHBG were age, BMI, and diabetes (Table 3, column 2). We also fit a model with a full set of potential confounders (defined as confounding even one of the associations between androgens and statin use and including age, BMI, cardiovascular disease, diabetes, high blood pressure, race, use of alcohol, smoking, use of hypotensives, use of vasodilators, and use of cardiac medications) to both SHBG and TT and found similar results (Table 3, column 3) with respect to the magnitude and the significance of the association observed in the more parsimonious model.

For TT, more than one combination of covariates (i.e., diabetes plus cardiovascular disease or else BMI alone) reduced the TT difference to nonsignificance; adjusting for all covariates simultaneously did not affect the estimate much more (Fig. 2). Conversely, SHBG differences did not change substantially when the same covariates were added and remained statistically significant (Fig. 2).

Discussion

Our study results revealed that 237 (12.4%) men in BACH took a statin drug in the prior 4 weeks and that statin users were quite different than nonusers with respect to factors known to affect testosterone (including age, BMI, and the presence of chronic disease; ref. 11). Consistently, substantial unadjusted differences in mean testosterone were present but did not stand up to covariate control. Of a larger candidate list examined, BMI, cardiovascular disease, and diabetes were the most important. We found that statin use was associated with lower levels of SHBG in our models and that these findings were robust when additional covariates were added, but age was the most important. Compared with the unadjusted mean, controlling for age and time since awakening changed the direction of effect on SHBG and increased its magnitude, and further changes on the main effect through addition of covariates were minimal. We did not find an effect of statins on FT, DHEAS, or LH in any of our models.

Placebo-controlled intervention trials examining the effect of statin use on serum testosterone have reported mixed results. Dobs et al. (26) found that 12 weeks of daily treatment with 80 mg simvastatin lowered serum TT by 13.6% (compared with 1.5% in the placebo-treated group; $P = 0.09$) and bioavailable testosterone by 10.2% (versus an increase of 1.3% in the placebo group; $P = 0.03$) in men with dyslipidemia. Similarly, Hyyppa et al. (10) noted a significant decline in serum testosterone after 12 weeks of treatment with 20 mg of daily simvastatin. In contrast, low-dose simvastatin (20 and 40 mg daily) and pravastatin treatment did not alter serum androgen or gonadotropin levels in two subsequent trials (9, 27). Our study of population-based study of community-dwelling men may better reflect the influence of statins on androgen levels

Table 3. Linear regression model coefficients for percentage change in serum androgen levels for statin users versus nonusers among men in the BACH Survey, 2003-2005, *n* = 1,791

Outcome	Transformed β coefficient (%), minimally adjusted model* (95% CI)	Transformed β coefficient (%), parsimonious model† (95% CI)	Transformed β coefficient (%), full model‡ (95% CI)
TT (ng/dL)	**−11.7 (−19.4 to −3.4)**	−5.5 (−13.2 to 2.9)	−4.8 (−12.8 to 4.0)
FT (ng/dL)	−5.7 (−12.6 to 1.6)	1.8 (−6.4 to 10.6)	2.2 (−6.1 to 11.2)
SHBG (nmol/L)	**−12.4 (−21.1 to −2.8)**	**−10.6 (−18.8 to −1.6)**	**−11.5 (−19.0 to −3.2)**
DHEAS (μg/mL)	−13.5 (−26.2 to 1.5)	−8.4 (−20.9 to 6.0)	−7.1 (−19.3 to 6.9)
LH (IU/L)	1.1 (−11.3 to 15.2)	−7.1 (−17.6 to 4.7)	−6.8 (−17.0 to 4.8)

NOTE: Modeling was conducted using outcomes on the natural log scale and estimates were untransformed for interpretation as estimated percentage change in androgen levels for statin use versus nonuse. Twenty-one men were excluded from the analysis because of missing data on covariates (necessary for comparison of minimally versus fully adjusted models).

*Models were adjusted for age and time between awakening and blood draw. Estimates with CIs in bold exclude 1.00.

†Models were adjusted for preselected confounders found to be important (defined as causing a 15% change in β coefficient for the main effect of statin use on androgens) in a backward selection process. Estimates from the most parsimonious model that controlled confounding are presented in this column. For TT, the model includes age, time since participant woke, BMI, history of cardiovascular disease, and history of diabetes. For FT, the model includes age, time since participant woke, BMI, smoking, history of cardiovascular disease, history of diabetes, race, use of vasodilators, and use of cardiac medications. For SHBG, the model includes age, time since participant woke, BMI, and history of diabetes. For DHEAS, the model includes age, time since participant woke, BMI, history of cardiovascular disease, diabetes, high blood pressure, race, use of alcohol, use of hypotensives, and cardiac medications. For LH, the model includes age, time since participant woke, history of diabetes, race, use of vasodilators, and use of cardiac medications.

‡Models in this column were adjusted for all of the covariates listed above.

in ''real world'' settings, and the generalizability of BACH is known (13).

We found a relationship between SHBG and statin use even after controlling for BMI and other covariates, including diabetes and cardiovascular disease. SHBG levels were ~11% lower in statin users versus nonstatin users in the multivariate analyses (Table 3). To examine the potential for residual confounding by central adiposity, we also examined the effect of waist circumference but did not find its inclusion with or substitution for BMI in our SHBG models meaningfully changed the results. Although we cannot rule out a direct effect of statins on SHBG metabolism in this study, intervention trials have not shown an effect of statins on SHBG levels in men with dyslipidemia (26). A more likely explanation for this finding is the effect of circulating insulin on SHBG production. Insulin is a negative regulator of SHBG production in the liver (28, 29). Ninety percent to 95% of adults with diabetes are insulin resistant and have high levels of circulating insulin (30). It is likely that, even after controlling for the presence of diabetes, which may or may not be adequately treated, statin users have higher circulating insulin levels than nonstatin users. Higher insulin levels would drive down SHBG levels in these individuals. Consistent with this explanation, low levels of SHBG have been associated with the development of type 2 diabetes and the metabolic syndrome (31-35). It is possible, however, that statins have direct effects on SHBG metabolism in some men. Bataille et al. (36) have suggested that SHBG may be directly involved in lipid metabolism because SHBG was an independent, positive predictor of HDL levels in men at risk for cardiovascular disease even after controlling for fasting insulin levels. The relationship between SHBG, statins, and cholesterol metabolism warrants further investigation.

Cholesterol is a required intermediate in androgen synthesis in the testis and adrenal glands, and reducing the available substrate for testosterone and dihydrotestosterone production might suppress circulating androgen levels. Despite the lack of effects of statins on serum androgen levels in this study, we cannot rule out the possibility that statins may modulate steroid synthesis in prostate tissues. Several groups have shown that, in men treated with agents that modulate serum testosterone, tissue androgen levels are relatively unchanged (37-39). The mechanisms by which prostatic tissue maintains tissue androgens may include metabolism of adrenal androgens or *de novo* synthesis from cholesterol (40). In patients

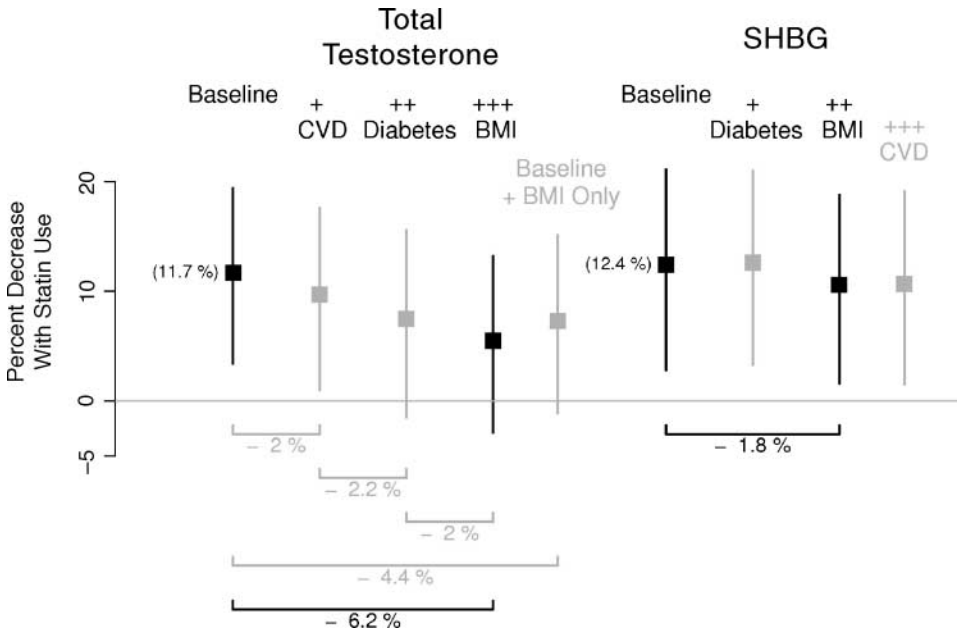

Figure 2. Changes in the apparent effect of statin use when other factors are included. *Black,* baseline models (adjusting only for age and time since awakening) as well as final fitted models; *gray,* successive intermediate models. Baseline models reveal apparent differences across statin use in both TT and SHBG concentrations. Successive addition of covariates reveals that adding either the combination of history of diabetes and cardiovascular disease (*CVD*; **A**) or BMI (**B**) to the baseline model is sufficient to reduce the magnitude and statistical significance of the apparent effect on TT. The apparent effect on SHBG, on the other hand, is robust to statistical control of all factors displayed.

undergoing androgen deprivation therapy to treat prostate cancer, statins could influence disease progression via effects on residual androgen production, which might help explain the association between prostate cancer severity and statin use observed in Platz et al. (8). Other mechanisms through which statins may influence prostate cancer severity have also been proposed (41), as statins have been shown to lower prostate-specific antigen in small studies (42), including increasing prostate epithelial cell sensitivity to apoptosis (43). Further studies examining the effect of statin use on androgen levels in the setting of prostate cancer therapy are warranted.

Our statin users were different from nonusers and were more likely to be older, with larger BMI, and to have other common comorbidities and to be on other medications. Other comorbidities and medications were more prevalent among male statin users than nonusers in the Health Professionals Follow-Up Study and in a recent study of U.S. veterans (8, 44). The BACH study is a population-based, racially and ethnically diverse sample representative of Boston and provides information on a wide range of behavioral, medication, and anthropometric variables, including factors that have an important influence on testosterone. For testosterone, our results suggest it is important to use an enriched data source to eliminate ''confounding by indication.'' Simplistically, this may occur when persons who receive a particular drug are more likely to have a disease that is in turn related to the outcome under study compared with those not on the drug. In this case, men receiving statins were more likely to have cardiovascular disease and higher BMI, both of which also affect testosterone levels regardless of statin exposure (11, 12). However, unlike textbook examples of confounding, many relationships likely exist between our covariates, outcomes, and exposure and are not currently well understood. These relationships are difficult to disentangle in a cross-sectional study, such as BACH, but our results suggest it is critical to study relevant covariates.

There are strengths and limitations to our ascertainment of statin use in this study. We did not consider dose, and as such, our study does not examine dose response or address any effects associated with duration of use. As a cross-sectional study, however, duration of use may be more important for an outcome, such as cancer, compared with hormone levels from a one-time blood draw. Our data captured both drugs from self-reported medications field and interviewer-recorded drug names from the drug inventory. A strength of our study is that most our statin exposure information was reflected in a drug inventory. In-home drug inventory collection methods have been found to correspond well with a ''gold standard'' of external pharmacy records (45). In addition, we had the ability to measure other medications and include them in our analyses, lending more confidence that our findings are not due to a medication correlated with statin use. Our relatively small sample of 237 statin users and the preponderance of atorvastatin limited our ability to consider hydrophobic subtypes of statins (atorvastatin, simvastatin, lovastatin, and fluvastatin) versus other types that have recently been investigated for effects within the statin class (46-48). *In vitro* data suggest that particular statins may be more effective cell cycle inhibitors in prostate cancer cell lines (49). Recent studies in breast cancer have suggested that the effect of statins on hormone-sensitive cancers may be variable depending on their degree of hydrophobicity (50, 51). However, a meta-analysis did not show any significant differences between hydrophilic and nonhydrophilic statins on cancer risk (52). Additionally, an intervention trial comparing low-dose simvastatin and pravastatin effects on serum androgens failed to find a difference between statin types (9), and so this issue may be less important in our data.

Our statistical models impose a linear shape on our data and added covariates impose further multidimensionality. We transformed our data to better fit the linear model and repeating the models using untransformed data showed generally similar results with respect to the magnitude and direction of effect. The number of statin users made examination of subgroups limited, and we therefore were limited in our ability to consider interactions among our covariates, many of which are correlated with one another.

In summary, in this population-based study, we found that statins were used commonly and users were very different by age and occurrence of comorbid illness and use of other medications than nonusers. After adjusting for these covariates, our data are consistent with the conclusion that statins are unlikely to have a clinically significant effect on circulating androgen levels in our sample of community-dwelling men.

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