Sex Hormone–Binding Globulin, but Not Testosterone, Is Associated Prospectively and Independently With Incident Metabolic Syndrome in Men

The Framingham Heart Study

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OBJECTIVE—The association between total testosterone and metabolic syndrome has prompted speculation that low testosterone contributes to the pathophysiology of metabolic syndrome in men. We determined whether testosterone or sex hormone–binding globulin (SHBG) is independently associated with the risk of metabolic syndrome.

RESEARCH DESIGN AND METHODS—Cross-sectional relationships of hormone levels with metabolic syndrome were assessed in a sample of men in generation 2 of the Framingham Heart Study (FHS) who did not receive testosterone or androgen-deprivation therapy (n = 1,625) and confirmed in a validation sample of men in FHS generation 3 (n = 1,912). Hormone levels in generation 2 examination 7 were related prospectively to incident metabolic syndrome 6.6 years later at examination 8. Testosterone was measured using liquid chromatography–tandem mass spectrometry, SHBG was measured by immunofluorometric assay, and free testosterone was calculated. Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria.

RESULTS—Cross-sectionally, testosterone and SHBG were more strongly associated with metabolic syndrome than free testosterone in the training sample. SHBG, but not testosterone or free testosterone, was significantly associated with metabolic syndrome after adjusting for age, smoking, BMI, and insulin sensitivity (homeostasis model assessment of insulin resistance [HOMA-IR]). These findings were confirmed in a validation sample. Longitudinally, SHBG at examination 7, but not testosterone or free testosterone, was associated with incident metabolic syndrome at examination 8 after adjusting for age, smoking, BMI, and HOMA-IR. Multivariable analyses suggested that age, BMI, and insulin sensitivity independently affect SHBG and testosterone levels and the risk of metabolic syndrome and its components.

CONCLUSIONS—SHBG, but not testosterone, is independently associated with the risk of metabolic syndrome. These data do not reveal an independent prospective relationship between testosterone and metabolic syndrome in men.

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Epidemiological studies have reported that low total testosterone levels are associated with an increased risk of metabolic syndrome in men (1–8). Circulating testosterone levels also have been associated with individual components of metabolic syndrome, such as insulin resistance (9,10), visceral adiposity (10), hypertension (11), and dyslipidemia. These epidemiological observations have led to speculation that testosterone deficiency contributes to the pathophysiology of metabolic syndrome and that diagnostic evaluation for androgen deficiency and testosterone therapy might be indicated in men with metabolic syndrome (12,13).

Circulating testosterone is partly bound to sex hormone–binding globulin (SHBG) with high affinity, and testosterone levels are strongly related to SHBG concentrations. SHBG levels also have been associated with the risk of metabolic syndrome in men (1–4,8). However, we do not know whether the observed association between total testosterone and metabolic syndrome reflects an independent influence of testosterone on the risk of metabolic syndrome or primarily an association of SHBG with this disorder. The relationship of free testosterone and metabolic syndrome has been inconsistent or weak (1–8), suggesting that SHBG may be the primary determinant of the apparent relationship between total testosterone and metabolic syndrome.

This issue has therapeutic implications; if low testosterone levels are causally related to metabolic syndrome, then testosterone therapy of men with low testosterone levels might be expected to prevent or ameliorate metabolic syndrome, as has been suggested (12–14). If SHBG is the primary determinant of this apparent relationship between total testosterone and metabolic syndrome, as we hypothesize, then efforts should be directed at remediable factors, such as obesity and insulin resistance that regulate

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SHBG as well as the risk of metabolic syndrome.

Here, we investigated the relationship between total and free testosterone as well as SHBG with metabolic syndrome cross-sectionally in community-dwelling men in the Framingham Heart Study (FHS) and confirmed these associations in a validation sample. We also longitudinally evaluated the association of these hormones with incident metabolic syndrome. Previous studies measured testosterone levels using immunoassays (1–7) that lack accuracy in the low range (15). We measured total testosterone by liquid chromatography–tandem mass spectrometry (LC-MS/MS), the method with the highest accuracy and specificity (15). We adjusted the analyses for factors that independently affect metabolic syndrome and testosterone levels, such as age, BMI, smoking, and insulin sensitivity index (homeostasis model assessment of insulin resistance [HOMA-IR]). We also determined whether testosterone levels were associated with metabolic syndrome after adjusting for SHBG. We hypothesized that the apparent relationship between total testosterone and metabolic syndrome is driven mostly by the association of SHBG with metabolic syndrome.

RESEARCH DESIGN AND METHODS

The Boston University Institutional Review Board approved the study. All subjects provided written consent.

Study sample

In 1971, the offspring of the original FHS participants and the spouses of the offspring (FHS generation 2) were enrolled into the Framingham Offspring Study (16) and have since completed eight examinations at 4- to 8-year intervals. Generation 2 men who attended examination 7 (1998–2001) were eligible for inclusion in cross-sectional analyses (n = 1,625). The validation sample included children of the offspring cohort (generation 3) who attended examination 1 (n = 1,912). Men receiving testosterone or androgen-deprivation therapy for prostate cancer and those missing testosterone or data necessary for defining metabolic syndrome were excluded, resulting in a sample size of 1,407 subjects for the cross-sectional analyses of the training sample and 1,887 subjects for the validation sample (Fig. 1).

To determine whether hormone levels were associated with incident metabolic syndrome, the men of generation 2 who had hormone measurements at examination 7 were examined, on average, 6.6 years later (2005–2008) at examination 8. We excluded men who were receiving testosterone or androgen-deprivation therapy for prostate cancer or those who had missing testosterone or other data necessary for defining metabolic syndrome at either examination 7 or examination 8. We also excluded men who reported metabolic syndrome at examination 7 (n = 668). Hence, 618 men were available to prospectively examine the association between hormone levels at examination 7 and incident metabolic syndrome at examination 8 (Fig. 1).

Hormone measurements

Total testosterone and SHBG levels were measured in generation 2 at examination 7 and in generation 3 at examination 1. Samples were obtained after an overnight fast between 7:00 and 9:00 A.M. and stored at −80°C. Total testosterone was measured by LC-MS/MS (17) with a sensitivity of 2 ng/dL and interassay coefficients of variation (CVs) of 7.8, 5.9, and 3.5% at testosterone concentrations of 250, 500, and 1,000 ng/dL, respectively.

SHBG levels were measured using an immunofluorometric assay (DELFIA-Wallac, Turku, Finland) with a sensitivity of 2.5 nmol/L (17). Interassay CVs were 8.3, 7.9, and 10.9%, and intra-assay CVs were 7.3, 7.1, and 8.7%, respectively, in the low, medium, and high pools. Free testosterone was calculated using a law-of-mass-action equation whose dissociation constants and assumptions have been published (17).

Metabolic syndrome

Metabolic syndrome was defined using modified Adult Treatment Panel III criteria (18), which defines metabolic syndrome by the presence of at least three of the following: waist circumference >40 inches (102 cm); HDL cholesterol <40 mg/dL; triglycerides ≥150 mg/dL; high blood pressure defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or on antihypertensive treatment; and fasting glucose ≥100 mg/dL or on diabetes treatment.

Other variables

HOMA-IR was calculated as follows: ([insulin] × [fasting glucose × 0.055]/22.5). The men who reported smoking during the past year were categorized as smokers. High-sensitivity C-reactive protein (hsCRP) was measured using a published assay (19).

Statistical analyses

Descriptive statistics for continuous variables and percentages for dichotomous variables were generated. Cross-sectional associations among sex hormones and metabolic syndrome were assessed using multiple logistic regression. Models were adjusted for age and smoking because

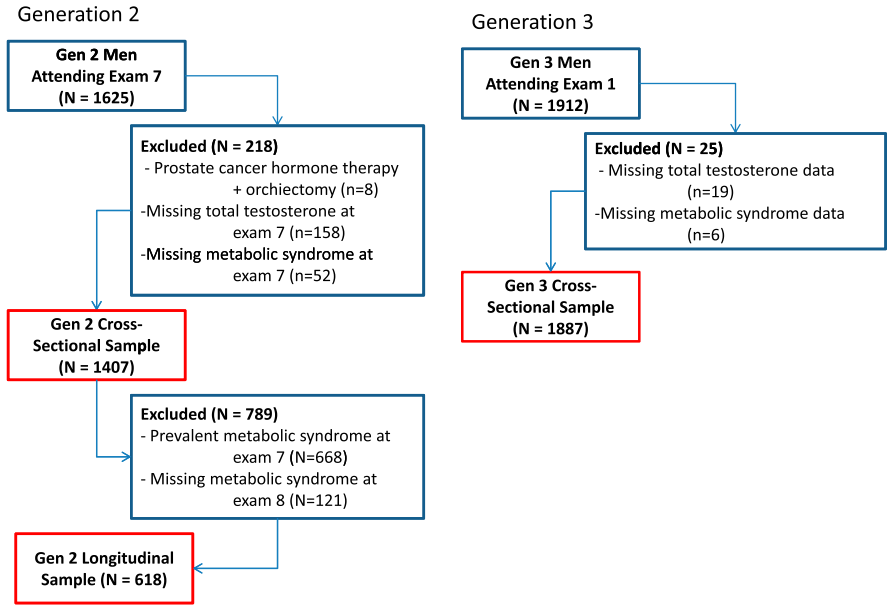

Figure 1—*Strobe diagram illustrating the selection of the generation 2 cross-sectional and longitudinal samples and the generation 3 cross-sectional validation sample. (A high-quality color representation of this figure is available in the online issue.)*

these variables were significantly associated with testosterone levels. To determine whether the association of total testosterone with metabolic syndrome was influenced by SHBG, we adjusted the analyses for SHBG. In additional models, BMI and HOMA-IR were added sequentially.

We used multiple logistic regression to examine the relationship between sex hormone levels at examination 7 and incident metabolic syndrome at examination 8 in men free of metabolic syndrome at examination 7, adjusting for age and smoking. Additional models to examine the association between total and free testosterone at examination 7 with incident metabolic syndrome at examination 8 were generated after sequential adjustment for age, smoking, SHBG, BMI, and HOMA-IR. Statistical significance level was set at two-sided $P < 0.05$.

RESULTS

Baseline characteristics

The original sample for cross-sectional analyses included 1,407 men of generation 2 who attended examination 7, had nonmissing total testosterone, and were not receiving testosterone or androgen-deprivation therapy (Fig. 1). The validation sample included 1,887 men of generation 3 who attended examination 1, had nonmissing testosterone, and were not receiving androgen-deprivation therapy.

For longitudinal analyses, of 1,625 men in generation 2 who attended examination 7, we excluded those who had missing testosterone or metabolic syndrome data, those who received hormonal treatment for prostate cancer, and those who had metabolic syndrome at examination 7; the remaining 618 men constituted the analytic sample for longitudinal analyses. Men who were excluded did not differ from those who were included in longitudinal analyses (not shown).

Men in the original sample were, on average, 61.1 years old with mean total testosterone, free testosterone, and SHBG levels of 586 ± 227 ng/dL, 87 ± 32 pg/mL, and 58 ± 27 nmol/L, respectively (Table 1). A total of 47.5% of men in the sample had metabolic syndrome at baseline, 51.8% had abdominal adiposity, 57.3% had fasting glucose >100 mg/dL, 61.4% had hypertension, 33.1% had hypertriglyceridemia, and 36.0% had low HDL cholesterol. In contrast, the men in the validation sample were, on average, younger and had higher total and free testosterone levels and a lower prevalence of metabolic syndrome and all of its components. Because men with metabolic syndrome at examination 7 were excluded from longitudinal analyses, the sample used for longitudinal analyses had a lower prevalence of cardiovascular disease, hypertension, abdominal adiposity, impaired fasting glucose, hypertriglcyeridemia, and low HDL cholesterol.

Cross-sectional analyses

In cross-sectional analyses of the original sample, total as well as free testosterone levels were significantly negatively associated with the risk of metabolic syndrome after adjusting for age and smoking; the association of metabolic syndrome was stronger with total than with free testosterone (Table 2). For each SD decrease in total and free testosterone levels, the odds of prevalent metabolic syndrome were increased by 83 and 25%, respectively, after adjusting for age and smoking (Table 2). The men in the lowest quartile of total testosterone had 4.5 times the odds of having prevalent metabolic syndrome than men in the highest quartile ($P < 0.0001$) (Fig. 2*A*) (Supplementary Table 1). The men in the lowest quartile of free testosterone had 1.9 times the odds of having metabolic syndrome than those in the highest quartile ($P < 0.0001$).

In addition to age and smoking, total and free testosterone levels were associated with SHBG, BMI, HOMA-IR, and hsCRP levels. SHBG levels also were related to age, smoking, BMI, and HOMA-IR. Accordingly, in sensitivity analyses, we adjusted the analyses sequentially for these covariates in addition to age and smoking. The associations of total and free testosterone with the risk of metabolic syndrome were attenuated after adjusting for SHBG and BMI sequentially; the association was substantially weakened when

Table 1—*The characteristics of the analytic samples*

	Generation 2 cross-sectional sample	Generation 3 cross-sectional sample	Generation 2 longitudinal sample
n	1,407	1,887	618
Age (years)	61.1 (9.5)	40.3 (8.8)	59.1 (9.3)
Total testosterone (ng/dL)	585.9 (226.8)	646.1 (224.5)	649.4 (238.6)
Free testosterone (pg/mL)	86.5 (31.9)	125.4 (45.42)	92.0 (31.7)
SHBG (nmol/L)	58.3 (26.7)	39.8 (17.9)	62.3 (26.3)
BMI (kg/m^2)	28.8 (4.5)	28.0 (4.7)	27.0 (3.7)
Cancer	132 (9.4)	27 (1.4)	54 (8.7)
Prevalent cardiovascular disease	248 (17.6)	44 (2.3)	63 (10.2)
Hypercholesterolemia	465 (33.1)	368 (19.5)	150 (24.3)
Smoker	175 (12.4)	346 (18.4)	74 (12.0)
Metabolic syndrome	668 (47.5)	520 (27.6)	
Elevated blood pressure	864 (61.4)	695 (36.8)	239 (38.7)
Triglycerides ≥150 mg/dL	465 (33.1)	565 (29.9)	69 (11.2)
HDL <40 mg/dL	506 (36.0)	546 (28.9)	84 (13.6)
Abdominal adiposity (waist circumference >102 cm)	729 (51.8)	631 (33.4)	164 (26.5)
Glucose ≥100 mg/dL and/or diabetes treatment	806 (57.3)	642 (34.0)	205 (33.2)
Number of metabolic syndrome factors			
0	151 (10.7)	528 (28.0)	
1	232 (16.5)	465 (24.6)	
2	356 (25.3)	374 (19.8)	
3	359 (25.5)	275 (14.6)	
4	196 (13.9)	184 (9.8)	
5	113 (8.0)	61 (3.2)	

Data are *n* (%) unless otherwise indicated. Baseline characteristics of the three analytic samples. To convert total testosterone from ng/dL to nmol/L (SI units), multiply the value in ng/dL by 0.0347; to convert free testosterone from pg/mL to pmol/L (SI units), multiply the value in pg/mL by 3.47. To convert triglycerides from mg/dL to mmol/L, multiply triglyceride level in mg/dL by 0.01129. To convert HDL cholesterol from mg/dL to mmol/L, multiply the HDL cholesterol level in mg/dL by 0.02586. To convert glucose concentrations from mg/dL to mmol/L, divide the glucose concentration in mg/dL by 18.

the analyses were adjusted for all covariates (i.e., age, smoking, SHBG, BMI, and HOMA-IR) simultaneously. Free testosterone was no longer significantly associated with prevalent metabolic syndrome after adjusting for BMI and HOMA-IR (Table 2). Additional adjustment for hsCRP had little effect on the strength of association of hormone levels with metabolic syndrome (not shown).

SHBG levels were significantly negatively associated with the risk of metabolic syndrome; each SD decrease in SHBG was associated with 78% higher odds of prevalent metabolic syndrome after adjusting for age and smoking (Table 2). Men in the lowest quartile of SHBG had nearly five times the odds of having prevalent metabolic syndrome than those in the highest quartile (Fig. 2*A*) (Supplementary Table 1). Unlike total and free testosterone, the association of SHBG with the risk of metabolic syndrome persisted after adjusting for age, smoking, testosterone, BMI, and HOMA-IR.

Validation analysis

The results of the cross-sectional analyses in the original sample were confirmed by analyses of the validation sample (Table 2) (Supplementary Table 2). Total and free testosterone levels in generation 3 were negatively associated with the odds of having metabolic syndrome after adjusting for age and smoking; this association was attenuated after adjusting for SHBG and attenuated further after additional adjustments for BMI and HOMA-IR. Free testosterone was not significantly associated with metabolic syndrome after adjusting for age, smoking, BMI, and HOMA-IR.

Longitudinal analyses

Neither total nor free testosterone at examination 7 was significantly associated with incident metabolic syndrome at examination 8 regardless of whether total and free testosterone levels were considered as continuous variables or categorized in quartiles (Table 2) (Fig. 2*A*) (Supplementary Table 3). Only SHBG at examination 7 was significantly associated with incident metabolic syndrome at examination 8 (Table 2). The association of SHBG with incident metabolic syndrome persisted after adjusting for age, smoking, BMI, and HOMA-IR (Fig. 2*A*). The men in lower quartiles of SHBG levels had progressively higher risk of incident metabolic syndrome than men in the highest quartile, even

Table 2—*The relationship between hormone levels and prevalent metabolic syndrome in men of the FHS, with adjustment for covariates*

	Testosterone: covariable adjustment			
	Age and smoking	Age, smoking, and SHBG	Age, smoking, SHBG, and BMI	Age, smoking, SHBG, BMI, and HOMA
Total testosterone				
Generation 2 cross-sectional	1.83 (1.62–2.06); $P < 0.0001$	1.54 (1.33–1.77); $P < 0.0001$	1.22 (1.04–1.42); $P < 0.02$	1.11 (0.94–1.31); $P < 0.22$
Generation 2 longitudinal	1.20 (1.00–1.45); $P < 0.05$	0.96 (0.76–1.22); $P < 0.76$	0.85 (0.66–1.09); $P < 0.20$	0.81 (0.63–1.04); $P < 0.10$
Generation 3 cross-sectional	2.50 (2.17–2.87); $P < 0.0001$	2.13 (1.82–2.48); $P < 0.0001$	1.52 (1.29–1.80); $P < 0.0001$	1.36 (1.14–1.63); $P < 0.0007$
Free testosterone				
Generation 2 cross-sectional (without SHBG)	1.25 (1.12–1.41); $P < 0.0001$		1.04 (0.92–1.18); $P < 0.55$	0.98 (0.85–1.12); $P < 0.75$
Generation 2 cross-sectional (with SHBG)		1.34 (1.19–1.51); $P < 0.0001$	1.11 (0.97–1.26); $P < 0.13$	1.03 (0.90–1.19); $P < 0.68$
Generation 2 longitudinal (without SHBG)	1.05 (0.87–1.27); $P < 0.67$		0.93 (0.76–1.14); $P < 0.47$	0.89 (0.73–1.09); $P < 0.27$
Generation 2 longitudinal (with SHBG)	1.05 (0.87–1.27); $P < 0.64$	1.06 (0.87–1.28); $P < 0.57$	0.94 (0.77–1.15); $P < 0.58$	0.91 (0.74–1.11); $P < 0.34$
Generation 3 cross-sectional (without SHBG)	1.55 (1.37–1.76); $P < 0.0001$		1.22 (1.06–1.40); $P < 0.004$	1.15 (0.99–1.32); $P < 0.06$
Generation 3 cross-sectional (with SHBG)		1.82 (1.60–2.08); $P < 0.0001$	1.39 (1.20–1.61); $P < 0.0001$	1.27 (1.09–1.48); $P < 0.002$

	SHBG: covariable adjustment		
	Age and smoking	Age, smoking, and total testosterone	Age, smoking, total testosterone, and BMI	Age, smoking, total testosterone, BMI, and HOMA
Generation 2 cross-sectional	1.78 (1.57–2.02); $P < 0.0001$	1.38 (1.19–1.61); $P < 0.0001$	1.38 (1.16–1.62); $P < 0.0002$	1.41 (1.18–1.69); $P < 0.0002$
Generation 2 longitudinal	1.48 (1.19–1.85); $P < 0.0004$	1.52 (1.16–1.99); $P < 0.003$	1.48 (1.12–1.96); $P < 0.006$	1.53 (1.15–2.04); $P < 0.004$
Generation 3 cross-sectional	2.02 (1.77–2.30); $P < 0.0001$	1.45 (1.26–1.68); $P < 0.0001$	1.38 (1.17–1.61); $P < 0.0001$	1.32 (1.11–1.56); $P < 0.002$

Data are odds ratio (95% CI); *P* value. Odds ratios quantify the relationship between a 1-SD difference in hormone (testosterone or SHBG) values and prevalent (cross-sectional) or incident (longitudinal) metabolic syndrome. Moving left to right, each column depicts this odds ratio controlling first for age and smoking and then models adding other hormone factors, BMI, and HOMA in succession as covariables.

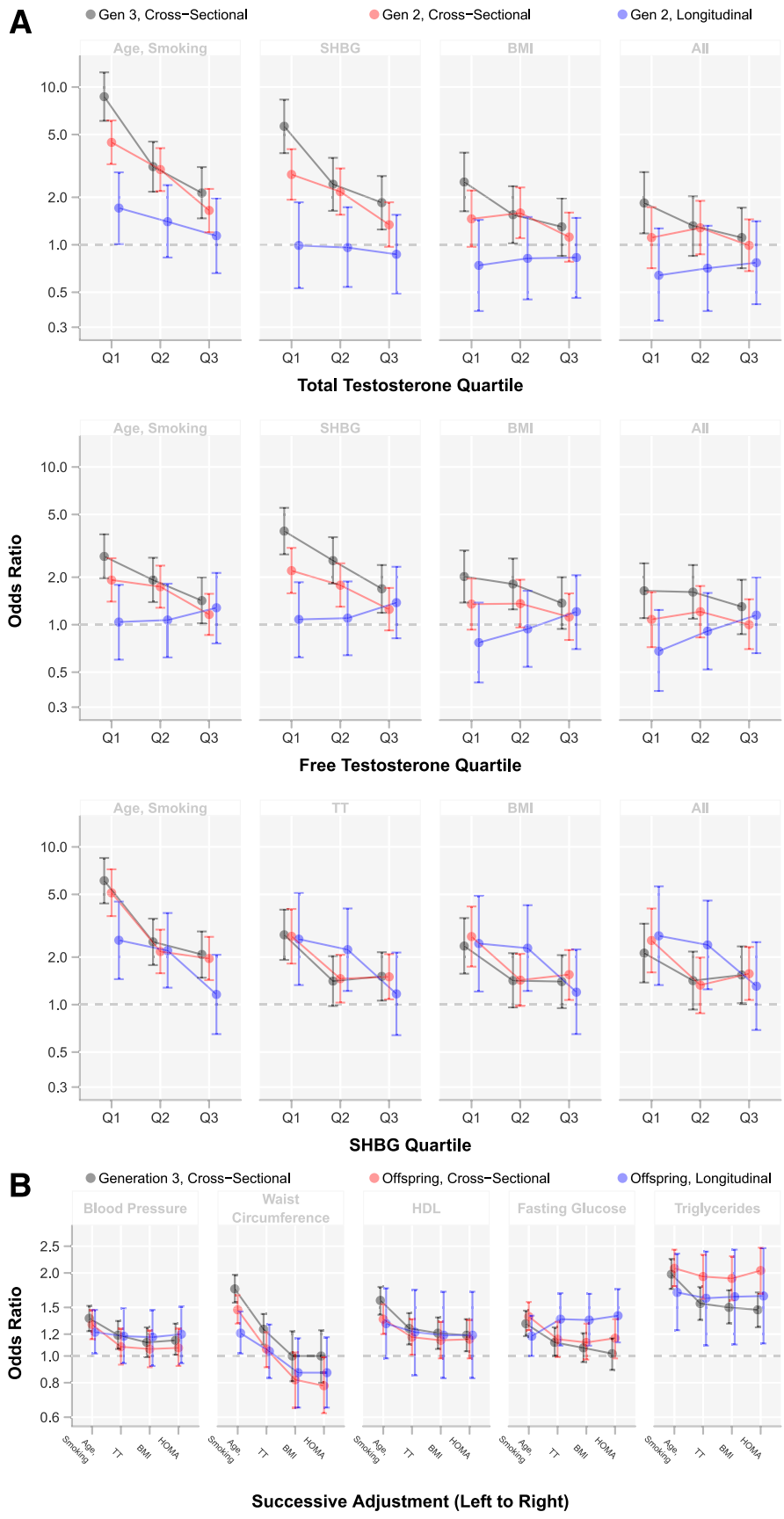

Figure 2—A: *Odds ratios expressing the association between hormone quartiles and the metabolic syndrome. For each measure (total testosterone, free testosterone, and SHBG) the highest quartile (Q4) is the reference group with which the other three quartiles (Q1, Q2, and Q3) are* after adjusting for total testosterone, BMI, and HOMA-IR.

Association of SHBG with components of metabolic syndrome

SHBG levels were significantly associated with each individual component of metabolic syndrome in both the original and the validation samples, although the association was generally stronger for abdominal adiposity and high triglycerides than for other components (Fig. 2*B*) (Supplementary Tables 4–6). The association of SHBG with individual components of the metabolic syndrome was attenuated after a multivariable adjustment for age, BMI, and HOMA-IR.

CONCLUSIONS—Our analyses reveal that SHBG, but not testosterone, is an independent predictor of incident metabolic syndrome. Consistent with a large body of published data (1–9), our cross-sectional analyses also revealed a significant association of total and free testosterone levels with prevalent metabolic syndrome. However, the association of total testosterone and SHBG with prevalent metabolic syndrome was stronger than that of free testosterone. Furthermore, the cross-sectional association of total testosterone with metabolic syndrome was attenuated substantially when the analyses were adjusted for SHBG, age, BMI, and insulin sensitivity. Likewise, the association of free testosterone with metabolic syndrome was no longer significant after adjusting for age, BMI, and insulin sensitivity. In longitudinal analyses, neither total nor free testosterone was significantly associated with incident metabolic syndrome. Only SHBG was significantly associated both cross-sectionally and longitudinally with the risk of metabolic syndrome, independent of testosterone levels.

SHBG has been reported to be associated with incident diabetes (20) and fracture risk (21). Polymorphisms of the *SHBG* gene also have been linked with diabetes (20,22). These observations, when viewed together with our data, highlight the importance of SHBG as an independent predictor of metabolic disorders, such as diabetes and metabolic syndrome.

Our study has several strengths. The FHS cohort included community-dwelling men over a wider age range (aged 19–95 years) than has been included in other studies, which were focused mostly on older men. The findings from the original

sample were confirmed in a separate validation sample. The longitudinal analyses lend additional strength to our inferences. Furthermore, the progressive decrease in odds ratios as hormone levels increased from the first to the fourth quartile suggests robust dose-response relationships in these associations. We adjusted our analyses for potential confounders, including age, BMI, smoking, and insulin sensitivity. We measured testosterone levels using LC-MS/MS, the reference method for testosterone measurements (15).

Our study also has some limitations. Epidemiologic studies can define associations but not causality. The FHS population is largely white and of European ancestry; therefore, our findings may not be generalizable to other races/ethnicities. We did not have sex hormones measured at examination 8 to evaluate the relationship between age-related changes in testosterone and SHBG levels and incident metabolic syndrome. We did not measure estradiol and are unable to assess the possible role of aromatization on these outcomes. Testosterone levels are affected by pulsatile, diurnal, and circannual rhythms, and single samples ignore rhythmic hormone secretion. Our analyses show that single, early-morning SHBG levels, obtained in a manner similar to that used by physicians in clinical practice, were associated with incident metabolic syndrome. The FHS cohort was younger and healthier than some other epidemiologic studies, resulting in lower rates of metabolic syndrome.

These data have clinical implications and suggest that previously reported relationships between testosterone and metabolic syndrome should be interpreted cautiously (1–8). Our data do not support the notion that low testosterone is independently related to metabolic syndrome. However, on the basis of the CIs obtained in the regressions of testosterone on incident metabolic syndrome, we cannot exclude the possibility of effects as high as an odds ratio of 1.45 for total testosterone in the age-adjusted model and 1.04 in the fully adjusted model (1.27 and 1.09, respectively, for free testosterone). Testosterone levels are strongly associated with SHBG levels; because of this colinearity between testosterone and SHBG, it is not surprising that total testosterone also is associated with metabolic syndrome. Our findings assert that prevention strategies should focus on factors such as such as adiposity, insulin resistance, and inflammation, which may affect SHBG levels as well as the risk of metabolic syndrome rather than on testosterone therapy.

We do not know whether SHBG is a marker of metabolic syndrome or whether it is causally linked to metabolic syndrome. Additional research is needed to determine whether SHBG is an early predictor of metabolic syndrome and its components or whether it should be considered as an additional component of the metabolic risk assessment. The mechanistic basis of the relationship between SHBG and metabolic syndrome is poorly understood. SHBG can modulate the bioavailability and the biologic effects of testosterone and estradiol on the target tissues (23). SHBG-bound testosterone can be internalized by endocytosis through the megalin receptor (24). SHBG may have testosterone-independent actions (23); it has been reported to regulate the growth of prostate cancer cells and to interact with estrogen receptor.

Our multivariable analyses, consistent with previous reports, suggest that age and BMI independently affect the risk of metabolic syndrome as well as the circulating concentrations of SHBG and total and free testosterone. SHBG levels are independently associated with the risk of metabolic syndrome as well as with total and free testosterone levels. Our analyses suggest that age, BMI, and insulin sensitivity, rather than testosterone, may be the independent pathophysiologic determinants of the risk of metabolic syndrome; among these, BMI and insulin sensitivity are potentially modifiable risk factors. Insulin is known to inhibit hepatic SHBG production (25). Age, BMI, and insulin sensitivity could independently affect SHBG, testosterone, and metabolic risk. Although caution is warranted because of the colinearity and bidirectionality of some of these relationships, overall, our analyses do not reveal an independent prospective relationship between testosterone and incident metabolic syndrome.

compared. Moving left *to* right*, panels express estimates obtained from models with successive inclusions of variables listed in the title for each panel. The bars that do not intersect with the dotted line corresponding to the odds ratio of 1 are statistically significant.* B*: Odds ratios quantifying the association between low SHBG and components of the metabolic system, by FHS cohort. Line segments read* left *to* right *track change in the estimated effect with addition of successive covariates to multivariate models. The bars that do not intersect with the dotted line corresponding to the odds ratio of 1 are statistically significant. TT, total testosterone.*

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S.B. wrote the manuscript. G.K.J. and M.P. performed the analyses and wrote portions of the manuscript. R.D., A.D.C., and R.S.V. reviewed the manuscript and contributed to discussion. T.G.T. performed the analyses and wrote portions of the manuscript.

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