

SUPPLEMENTARY DATA

Supplementary Table 1. Odds ratios for Metabolic Syndrome Across Quartiles of Testosterone, Free Testosterone and SHBG in Generation 2 Cross-Sectional Analyses (N=1407)

Variable	Successive Covariable Adjustment			
	Age +smoke	SHBG	BMI	All*
Testosterone (ng/dL)				
Q1	4.46	2.79	1.46	1.11
	(3.24-6.14)	(1.93-4.04)	(0.97-2.21)	(0.71-1.73)
	<0.0001	<0.0001	0.07	0.6
Q2	3.00	2.17	1.59	1.28
	(2.19-4.10)	(1.55-3.05)	(1.10-2.31)	(0.87-1.90)
	<0.0001	<0.0001	0.0138	0.2213
Q3	1.65	1.34	1.12	0.99
	(1.20-2.26)	(0.97-1.86)	(0.78-1.60)	(0.68-1.45)
	0.0019	0.0765	0.5359	0.9536
Q4	1.00			
Free Testosterone (pg/mL)				
Q1	1.92	2.20	1.35	1.08
	(1.40-2.64)	(1.58-3.07)	(0.93-1.96)	(0.72-1.61)
	<0.0001	<0.0001	0.1134	0.7127
Q2	1.74	1.78	1.36	1.21
	(1.28-2.37)	(1.30-2.45)	(0.96-1.93)	(0.83-1.76)
	0.0004	0.0004	0.0886	0.3141
Q3	1.16	1.25	1.12	1.00
	(0.86-1.57)	(0.92-1.71)	(0.80-1.58)	(0.70-1.45)
	0.3455	0.1567	0.5070	0.9899
Q4	1.00			
SHBG				
	Age +Smoke	Total T	BMI	All*
Q1	5.12	2.71	2.70	2.55
	(3.64-7.21)	(1.82-4.04)	(1.74-4.19)	(1.60-4.07)
	<0.0001	<0.0001	<0.0001	<0.0001
Q2	2.17	1.46	1.43	1.33

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	(1.58-2.99)	(1.03-2.07)	(0.98-2.10)	(0.88-1.99)
	<0.0001	0.0326	0.0660	0.1759
Q3	1.96	1.50	1.55	1.57
	(1.43-2.69)	(1.08-2.09)	(1.07-2.22)	(1.07-2.32)
	<0.0001	0.0156	0.0190	0.0227
Q4	1.00			

For each subsequent model after the first (which included only age and smoking), covariates were sequentially added to each following model. *In the final model, the model was adjusted for age, smoke, SHBG (Total T for SHBG as a predictor), BMI, and HOMA-IR.

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Supplementary Table 2. Odds ratios for Metabolic Syndrome Across Quartiles of Testosterone, Free Testosterone and SHBG in the Cross-Sectional Analyses of Generation 3 Validation Sample (N=1887)

Variable	Successive Covariable Adjustment			
	Age +smoke	SHBG	BMI	All*
Testosterone (ng/dL)				
Q1	8.69	5.64	2.50	1.84
	(6.1-12.4)	(3.81-8.33)	(1.63-3.84)	(1.18-2.89)
	<0.0001	<0.0001	<0.0001	0.0078
Q2	3.13	2.42	1.55	1.32
	(2.17-4.51)	(1.64-3.56)	(1.02-2.35)	(0.85-2.03)
	<0.0001	<0.0001	0.0392	0.2121
Q3	2.13	1.85	1.30	1.11
	(1.47-3.11)	(1.25-2.73)	(0.85-1.97)	(0.71-1.72)
	<0.0001	0.0021	0.2221	0.6473
Q4	1.00			
Free Testosterone (pg/mL)				
Q1	2.71	3.92	2.02	1.64
	(1.97-3.74)	(2.79-5.51)	(1.38-2.96)	(1.10-2.45)
	<0.0001	<0.0001	0.0003	0.0163
Q2	1.92	2.55	1.81	1.61
	(1.39-2.66)	(1.82-3.59)	(1.25-2.63)	(1.09-2.39)
	<0.0001	<0.0001	0.0018	0.0166
Q3	1.42	1.69	1.37	1.30
	(1.02-1.99)	(1.19-2.39)	(0.94-2.00)	(0.87-1.93)
	0.0393	0.0032	0.0992	0.1963
Q4	1.00			
SHBG				
	Age +Smoke	Total T	BMI	All*
Q1	6.11	2.77	2.35	2.12
	(4.38-8.51)	(1.92-4.00)	(1.57-3.54)	(1.38-3.26)
	<0.0001	<0.0001	<0.0001	0.0007
Q2	2.50	1.41	1.42	1.42

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	(1.78-3.51)	(0.98-2.03)	(0.96-2.12)	(0.93-2.17)
	<0.0001	0.0064	0.0817	0.1030
Q3	2.08	1.51	1.40	1.54
	(1.48-2.91)	(1.06-2.15)	(0.95-1.06)	(1.02-2.34)
	<0.0001	0.0236	0.0934	0.0403
Q4	1.00			

For each subsequent model after the first model (which included only age and smoking), covariates were sequentially added to each following model. *In the final model, the model was adjusted for age, smoke, SHBG (Total T for SHBG as a predictor), BMI, and HOMA-IR.

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Supplementary Table 3. Odds ratios for Metabolic Syndrome Across Quartiles of Testosterone, Free Testosterone and SHBG in Gen 2 Longitudinal Analyses (N=618)

Variable	Successive Covariable Adjustment			
	Age +smoke	SHBG	BMI	All*
Testosterone (ng/dL)				
Q1	1.71	0.99	0.74	0.64
	(1.01-2.88)	(0.53-1.86)	(0.38-1.44)	(0.33-1.27)
	0.0448	0.9707	0.3710	0.2020
Q2	1.40	0.96	0.82	0.71
	(0.83-2.39)	(0.54-1.73)	(0.45-1.50)	(0.38-1.32)
	0.2106	0.9027	0.5111	0.2739
Q3	1.14	0.87	0.83	0.77
	(0.66-1.97)	(0.49-1.55)	(0.46-1.48)	(0.42-1.41)
	0.6341	0.6409	0.5201	0.3984
Q4	1.00			
Free Testosterone (pg/mL)				
Q1	1.04	1.08	0.77	0.68
	(0.60-1.79)	(0.62-1.86)	(0.43-1.38)	(0.38-1.24)
	0.8938	0.7981	0.3831	0.2121
Q2	1.07	1.10	0.94	0.91
	(0.62-1.82)	(0.64-1.88)	(0.54-1.64)	(0.52-1.59)
	0.8179	0.7403	0.8364	0.7414
Q3	1.28	1.38	1.21	1.15
	(0.76-2.13)	(0.82-2.33)	(0.70-2.06)	(0.66-1.99)
	0.3546	0.2234	0.4978	0.6233
Q4	1.00			
SHBG				
	Age +Smoke	Total T	BMI	All*
Q1	2.56	2.60	2.44	2.73
	(1.45-4.50)	(1.33-5.10)	(1.21-4.90)	(1.33-5.62)
	0.0012	0.0054	0.0123	0.0064
Q2	2.20	2.23	2.28	2.39

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	(1.28-3.81)	(1.22-4.07)	(1.22-4.27)	(1.25-4.57)
	0.0046	0.0089	0.0096	0.0082
Q3	1.16	1.17	1.20	1.31
	(0.65-2.07)	(0.64-2.14)	(0.65-2.24)	(0.69-2.49)
	0.6089	0.6042	0.5588	0.4139
Q4	1.00			

For each subsequent model after the first model (which included only age and smoking), covariates were sequentially added to each following model. *In the final model, the model was adjusted for age, smoke, SHBG (Total T for SHBG as a predictor), BMI, and HOMA-IR.

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Supplementary Table 4. Cross-sectional association of SHBG with the Individual Components of the Metabolic Syndrome in the Framingham Heart Study Generation 2 Sample (N=1407)

	Adjusted for age and smoking	Adjusted* for Total T	Adjusted* for BMI	Adjusted* for HOMA
Elevated Blood Pressure	1.30 (1.15-1.47) <0.0001	1.08 (0.93-1.26) 0.32	1.06 (0.91-1.24) 0.44	1.07 (0.92-1.26) 0.38
Elevated Waist Circumference	1.47 (1.31-1.66) <0.0001	1.06 (0.91-1.22) 0.47	0.82 (0.65-1.03) 0.08	0.78 (0.62-0.99) 0.04
Low HDL Cholesterol	1.36 (1.20-1.54) <0.0001	1.17 (1.01-1.36) 0.04	1.14 (0.98-1.33) 0.09	1.15 (0.98-1.35) 0.08
Elevated fasting glucose or diabetes medication	1.39 (1.24-1.57) <0.0001	1.15 (0.99-1.33) 0.07	1.12 (0.97-1.31) 0.12	1.16 (0.98-1.36) 0.08
Elevated Triglycerides	2.08 (1.79-2.43) <0.0001	1.94 (1.61-2.33) <0.0001	1.91 (1.59-2.30) <0.0001	2.04 (1.68-2.47) <0.0001

Odds ratios per 1 SD difference in SHBG are shown, along with 95% confidence intervals and p-values
 *Moving left to right, covariates were sequentially added to the previous model

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Supplementary Table 5. Cross-sectional association of SHBG with the Individual Components of the Metabolic Syndrome in the Framingham Heart Study Generation 3 Sample (N=1887)

	Adjusted for age and smoking	Adjusted* for Total T	Adjusted* for BMI	Adjusted* for HOMA
Elevated Blood Pressure	1.37 (1.23-1.52) <0.0001	1.19 (1.06-1.34) 0.004	1.12 (0.99-1.27) 0.06	1.15 (1.01-1.31) 0.04
Elevated Waist Circumference	1.75 (1.56-1.97) <0.0001	1.25 (1.10-1.42) 0.0008	1.00 (0.81-1.23) 0.99	1.00 (0.80-1.24) 0.96
Low HDL Cholesterol	1.59 (1.41-1.78) <0.0001	1.26 (1.10-1.43) 0.0006	1.21 (1.06-1.38) 0.004	1.19 (1.04-1.36) 0.01
Elevated fasting glucose or diabetes medication	1.31 (1.18-1.46) <0.0001	1.12 (1.00-1.27) 0.06	1.07 (0.95-1.21) 0.27	1.02 (0.89-1.16) 0.82
Elevated Triglycerides	1.99 (1.75-2.25) <0.0001	1.55 (1.35-1.78) <0.0001	1.50 (1.31-1.73) <0.0001	1.47 (1.27-1.70) <0.0001

Odds ratios per 1 SD difference in SHBG are shown, along with 95% confidence intervals and p-values

*Moving left to right, covariates were sequentially added to the previous model

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Supplementary Table 6. Prospective association of SHBG with the Individual Components of the Metabolic Syndrome in the Framingham Heart Study Generation 2 Sample (N=618)

Odds ratios per 1 SD difference in SHBG are shown, along with 95% confidence intervals and

	Adjusted for age and smoking	Adjusted* for Total T	Adjusted* for BMI	Adjusted* for HOMA
Elevated Blood Pressure	1.22 (1.02-1.47) 0.0333	1.18 (0.94-1.49) 0.1641	1.17 (0.92-1.47) 0.1982	1.20 (0.94-1.51) 0.1386
Elevated Waist Circumference	1.21 (1.02-1.45) 0.0340	1.04 (0.83-1.30) 0.75	0.87 (0.65-1.16) 0.34	0.87 (0.65-1.17) 0.36
Low HDL Cholesterol	1.31 (0.98-1.76) 0.07	1.22 (0.85-1.74) 0.29	1.19 (0.83-1.71) 0.34	1.19 (0.83-1.71) 0.34
Elevated fasting glucose or diabetes medication	1.18 (1.00-1.40) 0.06	1.36 (1.09-1.69) 0.006	1.35 (1.09-1.68) 0.007	1.40 (1.12-1.75) 0.003
Elevated Triglycerides	1.70 (1.24-2.35) 0.001	1.62 (1.09-2.39) 0.02	1.64 (1.10-2.43) 0.01	1.65 (1.11-2.46) 0.01

p-values

*Moving left to right, covariates were sequentially added to the previous model