ORIGINAL RESEARCH

Association of Serum Testosterone and Luteinizing Hormone With Blood Pressure and Risk of Cardiovascular Disease in Middle-Aged and Elderly Men

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BACKGROUND: The age-related decline in testosterone levels is thought to be of great importance for male aging and cardiovascular diseases. However, data are controversial on whether abnormal sex hormones are linked to the presence of cardiovascular diseases and it is also uncertain how blood pressure modifies the association between testosterone levels and major cardiovascular diseases.

METHODS AND RESULTS: This is a multicenter, population-based, cross-sectional study of 6296 men conducted between 2013 and 2016. Basic information and clinical symptoms were obtained by questionnaires. Blood pressure and plasma levels of total testosterone, sex hormone–binding globulin, luteinizing hormone, and free testosterone were determined in men in a multistage random, cluster sampling in 6 provinces of China. There were 5786 Chinese men (mean [SD] age 55.0 [10.1] years) included after exclusion criteria were applied; 37.2% (2150) of them were diagnosed with hypertension. Total testosterone, free testosterone, and sex hormone–binding globulin were inversely associated with the prevalence of hypertension. Age >65 years or body mass index ≥24 negatively impacted the inverse correlation between testosterone levels and hypertension, whereas smoking and family history of hypertension strengthened the correlation. In participants with grade 2 hypertension, total testosterone was positively associated with the presence of stroke, and luteinizing hormone was also positively correlated with cardiovascular and cerebrovascular diseases.

CONCLUSIONS: Lower total testosterone could be a promising risk marker for prevalent hypertension. Both low and high levels of testosterone are associated with greater cardiovascular risk. Primary hypogonadism may be a risk marker for major cardiovascular diseases in men with severe hypertension.

Key Words: cardiovascular disease ■ hypertension ■ stroke ■ testosterone

Hypertension is a highly prevalent condition and responsible for half of the cardiovascular mortality and morbidity, causing a huge burden on the world population.[1] High blood pressure (BP) affects multiple organs and is the primary modifiable risk factor for cardiovascular disease (CVD), such as coronary heart disease, myocardial infarction, and stroke.[2] Controlling BP and preventing vascular damage are essential in lifelong hypertension treatment.[3] Generally, men are more susceptible to hypertension and CVD events than women at an early age. This sexual dimorphism may be partly explained by differences in endogenous

CLINICAL PERSPECTIVE

What Is New?

- We investigated the relationship between endogenous sex hormones, blood pressure, and major cardiovascular diseases in a multicenter, population-based study of 6296 middle-aged and elderly men, which is rarely conducted in China.
- Primary hypogonadism, characterized by increased luteinizing hormone, could potentially be a risk marker for major cardiovascular diseases in men with relatively severe hypertension.

What Are the Clinical Implications?

- Low testosterone is associated with increased risk of prevalent hypertension for men who smoke or have a family history of hypertension.
- With both low and high levels of testosterone associated with greater cardiovascular risk, an enhanced understanding of the relationship may lead to better preventive and therapeutic strategies of testosterone-related diseases.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
SBP	systolic blood pressure

sex hormone concentrations.[4,5] Testosterone confers many physiological advantages in men[6]; however, it is also associated with CVD risk in men with advancing age.[7]

Most testosterone circulates tightly bound to sex hormone–binding globulin (SHBG) or weakly bound to albumin, and free testosterone (FT) is considered a reflection of testosterone biological activity.[8] It is well recognized that with advancing age SHBG rises, while FT declines more rapidly than total testosterone (TT).[9,10] The age-related decline in testosterone level has been implicated as a possible explanation for the increased risk of hypertension, which is a predisposing factor for future incidence of CVD. Reduced SHBG level is also reported to be the predictor of metabolic syndrome, nonalcoholic fatty liver disease, and diabetes mellitus independent of testosterone.[11,12] In fact, testosterone is capable of activating both vasodilator and vasoconstrictor pathways, but it is mainly prohypertensive and more likely to induce vasoconstriction, sodium retention, and cardiac hypertrophy,[13,14] and castration attenuates BP in many animal models of hypertension.[15] On the other hand, testosterone is an anabolic hormone promoting muscle mass, fat

loss, and insulin sensitivity. Therefore, chronic testosterone deficiency is closely associated with the characteristics of metabolic syndrome such as dyslipidemia, abdominal obesity, and hypertension.[16] Thus, the relationship between testosterone and BP is multifaceted and paradoxical. That is why epidemiological studies often yield inconsistent results.

In observational studies, an inverse relationship of endogenous testosterone with BP and cardiovascular risk has been reported,[17,18] while some find no association after adjustment for body mass index (BMI).[19] Furthermore, testosterone therapy fails to improve dyslipidemia or lower BP, and its association with CVD events is somewhat conflicting.[20] In this multicenter population-based study, we aimed to explore the relationship between endogenous sex hormones, BP, and major cardiovascular and cerebrovascular diseases among Chinese middle-aged and elderly men.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

From June 2013 to August 2016, a multicenter cross-sectional investigation was conducted in the male healthcare centers of 6 regions in China. Multistage random, cluster sampling was adopted in this study. Purposive sampling was performed at the first stage to select 6 provinces of China and the cluster sampling was considered as fixed effect. The stratified random sampling was used in the second stage to select proportionally urban or rural areas from each province. In the third stage, all men aged between 35 and 80 years from the selected regions were informed to attend this study. A total of 6296 adult men from the northeast (Shanxi province, n=1127), north (Hebei, n=1093), east (Jiangsui, n=966), southwest (Guizhou, n=921), south (Guangdong, n=1038), and the center (Hubei, n=1151) of China were recruited. In our study, we excluded those who had diseases that may induce abnormal BP or hormonal alterations (n=293) (ie, malignant tumors, hypothalamus–pituitary diseases, adrenal disease, primary renal disease, thyroid diseases, secondary hypertension, diabetes mellitus, testis injury or infection, and current use of medications that may affect androgen levels). Participants with insufficient information or unfinished laboratory tests were also excluded (n=217). As a result, 5786 subjects remained for current analyses. Written informed consents were obtained from all participants. The study was approved by the Ethical Committee

Review Board of Tongji Medical College, Huazhong University of Science and Technology, China (No. 2013S073). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cross-sectional studies.

Information Collection and Laboratory Assays

The participants were given a complete noninvasive physical examination and were invited to complete the interviewer-assisted questionnaires including demographic characteristics, lifestyle habits, medication use, and family and medical history. Height, weight, and circumferences of abdomen and chest were measured and recorded by nurses. BMI was calculated as weight in kilograms divided by height in meters squared. Based on the self-reported smoking or drinking status, participants were grouped as nonsmokers, current smokers and former smokers, or nondrinkers, current drinkers, and former drinkers. In our study, participants with family history of hypertension meant maternal or/ and paternal history of primary hypertension diagnosis previously. A face-to-face interview was conducted. The questionnaire of aging men symptoms scale contained 17 questions to assess testosterone deficiency symptoms, including their physical, psychological, and sexual status.[21] All were written in simplified Chinese.

Fasting blood samples were collected from each participant between 7:00 AM and 11:00 AM. Serum TT, SHBG, and luteinizing hormone (LH) were assayed by chemiluminescent immunoassays using a Beckman Access Immunoassay System (Beckman Coulter, USA). FT was calculated by mass action equations as described by Vermeulen.[22]

Blood Pressure and Hypertension

The BP of participants was measured with an automated sphygmomanometer (Critikon Inc., USA) in the clinic by physicians after 5 minutes rest or relaxation. Repeated examinations were performed at 2-minute intervals and the mean of the recordings was used in the study. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg in the office or clinic. Classification of hypertension was based on office blood pressure measurement and we divided the participants into 4 groups (normal BP: SBP <130 mm Hg and DBP <85 mm Hg; high-normal BP: 130 ≤ SBP<139 mm Hg and/or 85 ≤ DBP<90 mm Hg, grade 1 hypertension: 140 ≤ SBP<160 mm Hg and/or 90 ≤ DBP<100 mm Hg, grade 2 hypertension: SBP ≥160 mm Hg and/or DBP ≥100 mm Hg). The diagnosis and classification of hypertension were in accordance with 2020 global hypertension practice guidelines.[23] Participants currently using antihypertensive medication were also grouped into grade 1 or 2, depending on the past diagnosis and classification by physicians.

Cardiovascular and Cerebrovascular Diseases

Generally, CVD includes the prevalence of stroke, but in our study, we separately analyzed stroke because it was cerebrovascular disease. Cardiovascular and cerebrovascular diseases of the participants were ascertained by professional cardiologists or neurologists. The CVD and stroke were self-reported with a previous medical record of hospitalization. Stroke is defined following the World Health Organization criteria, that is, participants once with a neurologic deficit of vascular origin lasting >24 hours or evidence of an ischemic infarct or hemorrhage based on neuroimaging data.[24] It should be noted that in this survey, CVD specifically included previous hospitalization for coronary artery diseases, prior myocardial infarction, history of heart failure, symptom-driven coronary revascularization, while stroke included ischemic stroke, hemorrhagic stroke, and symptom-driven cerebral revascularization.

Statistical Analysis

Continuous variables were expressed as mean±SD when normally distributed, and categorical variables were expressed as number (n) and percentage (%). Baseline data between the different groups were compared by 1-way ANOVA for continuous variables and by χ^2 test for categorical variables. Kolmogorov-Smirnov test was used to test the parameter distribution. To accommodate nonlinear associations, the sex hormone concentrations were divided into 3 groups from the lowest tertile to the highest tertile. The odds ratio was calculated to test for the presence of disease in the middle and highest tertiles of sex hormones. Binary logistic regression analyses were used to explore hormonal associations with hypertension. The restricted cubic splines were plotted to show the relationship between the odds ratio for hypertension and sex hormones. Additional trimmed analyses excluding men with hormone values in the lowest and highest 1% were performed repeatedly to rule out the possibility that outliers biased the results. Age, BMI, smoking, drinking, residence, education, occupation, marriage status, family history of hypertension, and cholesterol levels were included for multivariate models. The trend test was conducted in regression models using sex hormone tertiles as ordinal categorical variables. Tests for statistical interaction were calculated and stratified analyses were performed by age (<65 or ≥65 years), BMI (<24 or ≥24), smoking status (ever-smokers or nonsmokers), family history of hypertension (yes or no), and further stratified by 4 BP categories. All P values were adjusted for false discovery rate in multiple

hypothesis testing. R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. All P values presented were 2-tailed, $P<0.05$, or a 95% CI that did not overlap 1.0 was considered statistically significant.

RESULTS

Characteristics of the Study Subjects Stratified by BP

General characteristics of the 5786 participants are summarized in Table 1. The mean (SD) age of the overall population was 55.0 (10.1) years, 37.2% (2150) of which were diagnosed with hypertension. Higher BP was associated with advancing age and higher levels of BMI, weight, and chest and abdomen circumferences. Patients with hypertension were predisposed to have lower marriage rate, poorer education background, earn a living as a manual worker, and reside in urban areas ($P<0.001$). A higher prevalence of habitual smoking and drinking status was also found in hypertensive groups compared with normal and high-normal BP groups ($P<0.001$), indicating that the lifestyle choices can influence the BP level. Family history of hypertension presented in 25.6% of them and only 28.6% (616) of them were currently taking antihypertensive medication. The prevalence of major CVD was reported by 5.0% and stroke by 3.1% of all participants, with notably higher prevalence in hypertensive patients. Participants with hypertension had significantly higher SBP, DBP, aging men symptoms scores, cholesterol, and LH levels and lower high-density lipoprotein cholesterol and FT levels than those without hypertension. The TT and SHBG levels of those groups were also statistically different.

Association Between Sex Hormones and Hypertension

Table S1 demonstrates the crude odds ratio and 95% CI for prevalent hypertension. The associations between odds ratio for prevalent hypertension and TT, FT, SHBG, and LH levels are shown in Figure (A). The FT level varied with TT in a nonlinear way in both hypertensive and normal participants (Figure [B]). The FT was curtailed in <7.25 and >36.15 mmol/L of TT while it soared between (7.25, 36.15) of TT in the hypertension group. FT levels in the normal cohort fluctuated in concert with those of hypertension. We further made adjustment in multivariate models (shown in Table 2). In model 1, TT, FT, and SHBG remained negatively associated with the prevalence of hypertension. After adjusting for covariates, all these inverse associations were attenuated. In model 3, increase of TT remained significantly associated with the decreased odds for

hypertension. The inverse association between FT and hypertension was notable but P for trend was statistically insignificant, while the relationship between SHBG and hypertension was eliminated. It should be noted that none of the associations between LH tertiles and the odds of prevalent hypertension was significant after adjustment.

Stratified Analyses by Age, BMI, Smoking Status, and Family History for Hypertension Risk

To explore the potential roles of age, BMI, smoking status, and family history of hypertension in modifying the association between sex hormones and hypertension risk, we further conducted stratified analyses. As shown in Table 3, we found that TT, FT, and SHBG in participants aged >65 years showed no significant associations with hypertension. In contrast, in participants aged <65 years, the TT and SHBG concentrations were negatively and significantly related to the risk of prevalent hypertension. A similar situation occurred in the subgroup of BMI ≥24, which is considered to be overweight in China.[25] The TT, FT, and SHBG of those participants showed no significant association with prevalent hypertension while in the group of BMI <24, the negative relationship persisted among TT, FT, and hypertension. Similarly, when we stratified analyses by smoking status or family history of hypertension in the adjusted model, the inverse association remained significant only in participants who ever smoked or had a family history of hypertension. Additionally, LH showed no significant association with prevalent hypertension in the subgroups. Interactions of sex hormones and the 4 factors on hypertension risk are shown in Table 3.

Association Among Sex Hormones and CVD and Stroke in Different BP Categories

There were 291 and 180 men reported with previous CVD and stroke, respectively. The adjusted associations between sex hormones and cardiovascular or cerebrovascular diseases are shown in Table S2. To explore whether BP categories could affect the association between sex hormones and major CVD, we stratified all participants by BP levels as shown in Table 4. We found significant inverse association of TT with the presence of CVD in the normal-high BP group and grade 1 hypertension group. The LH level was found to be positively and significantly related to the risk of CVD in the grade 2 hypertension group, while the rest remained insignificant after adjustment. With respect to stroke, negative association of TT, FT, and SHBG with the prevalence of stroke

Table 1. Demographic and Clinical Characteristics of All Men, Stratified by BP (n=5786)

Characteristics	All Subjects (n=5786)	Normal BP (n=2130)	High-Normal BP (n=1506)	Grade 1 Hypertension (n=1350)	Grade 2 Hypertension (n=800)	P Value
Age, mean (SD), y	55.0 (10.1)	53.1 (10.1)	53.7 (9.8)	57.0 (9.8)	59.4 (9.3)	<0.001
BMI, mean (SD), kg/cm^2	24.2 (4.3)	23.2 (3.7)	24.7 (5.5)	24.8 (3.7)	25.2 (3.8)	<0.001
Height, mean (SD), cm	164.4 (6.9)	164.1 (7.2)	164.8 (7.2)	164.7 (6.6)	164.1 (6.4)	0.004
Weight, mean (SD), kg	65.6 (11.7)	62.6 (10.8)	66.8 (11.6)	67.4 (11.8)	68.0 (12.2)	<0.001
Chest circumference, mean (SD), cm	90.7 (7.8)	88.7 (7.2)	91.3 (7.3)	92.2 (8.3)	92.5 (8.2)	<0.001
Abdomen circumference, mean (SD), cm	85.9 (11.3)	82.7 (9.9)	86.8 (11.4)	88.2 (12.2)	88.9 (11.0)	<0.001
Married, no. (%)	5405 (93.4%)	2010 (94.4%)	1424 (94.5%)	1246 (92.3%)	725 (90.6%)	<0.001
Education, no. (%)						<0.001
0–8 y	2038 (35.2%)	687 (32.3%)	499 (33.1%)	501 (37.1%)	351 (43.9%)	
≥9 y	3748 (64.8%)	1443 (67.7%)	1007 (66.9%)	849 (62.9%)	449 (56.1%)	
Occupation, no. (%)						0.0530
Professional worker	989 (17.1%)	391 (18.4%)	267 (17.7%)	202 (15.0%)	129 (16.1%)	
Manual worker	4797 (82.9%)	1739 (81.6%)	1239 (82.3%)	1148 (85.0%)	671 (83.9%)	
Residence, no. (%)						0.0213
Urban	841 (14.5%)	307 (14.4%)	188 (12.5%)	222 (16.4%)	124 (15.5%)	
Rural	4945 (85.5%)	1823 (85.6%)	1318 (87.5%)	1128 (83.6%)	676 (84.5%)	
Smoking status, no. (%)						<0.001
Nonsmokers	1730 (29.9%)	670 (31.5%)	541 (35.9%)	346 (25.6%)	173 (21.6%)	
Former smokers	1408 (24.3%)	456 (21.4%)	332 (22.1%)	385 (28.5%)	235 (29.4%)	
Current smokers	2648 (45.8%)	1004 (47.1%)	633 (42.0%)	619 (45.9%)	392 (49.0%)	
Drinking status, no. (%)						<0.001
Nondrinkers	1558 (26.9%)	689 (32.4%)	382 (25.3%)	324 (24.0%)	163 (20.3%)	
Former drinkers	2371 (41.0%)	850 (39.9%)	614 (40.8%)	561 (41.6%)	346 (43.3%)	
Current drinkers	1857 (32.1%)	591 (27.7%)	510 (33.9%)	465 (34.4%)	291 (36.4%)	
Family history of hypertension, no. (%)	1479 (25.6%)	433 (20.3%)	381 (25.3%)	393 (29.1%)	272 (34.0%)	<0.001
CVD, no. (%)	291 (5.0%)	71 (3.3%)	78 (5.2%)	85 (6.3%)	57 (7.1%)	<0.001
Stroke, no. (%)	180 (3.1%)	36 (1.7%)	32 (2.1%)	67 (5.0%)	45 (5.6%)	<0.001
SBP, mean (SD), mm Hg	132.6 (21.1)	113.6 (8.9)	129.0 (6.6)	145.5 (6.2)	167.9 (19.0)	<0.001
DBP, mean (SD), mm Hg	84.6 (12.6)	74.6 (6.5)	84.4 (6.9)	91.3 (10.8)	99.9 (13.3)	<0.001
AMS score, mean (SD)	29.9 (9.5)	29.2 (8.9)	29.6 (9.3)	30.5 (10.1)	31.5 (10.2)	<0.001
Triglyceride, mean (SD), mmol/L	1.91 (1.89)	1.81 (2.05)	1.97 (1.92)	1.95 (1.72)	1.98 (1.62)	<0.001
HDL, mean (SD), mmol/L	1.66 (0.52)	1.67 (0.53)	1.65 (0.63)	1.64 (0.50)	1.64 (0.52)	<0.001
Cholesterol, mmol/L	5.47 (1.15)	5.38 (1.10)	5.47 (1.15)	5.53 (1.12)	5.60 (1.32)	0.073
Hormone levels						
TT mean (SD), nmol/L	16.25 (6.67)	16.8 (6.18)	15.81 (5.8)	15.99 (8.65)	16.07 (8.65)	<0.001
SHBG mean (SD), nmol/L	44.69 (22.95)	47.05 (23.69)	42.66 (22.08)	44.07 (22.81)	43.31 (22.81)	<0.001
LH mean (SD), IU/L	6.33 (5.08)	6.15 (4.75)	6.07 (5.51)	6.54 (5.6)	6.94 (5.6)	<0.001
FT mean (SD), nmol/L	0.28 (0.09)	0.29 (0.09)	0.29 (0.11)	0.28 (0.09)	0.27 (0.09)	<0.001

Demographic and clinical characteristics of all men, stratified by blood pressure. AMS indicates aging men symptoms; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; FT, free testosterone; HDL, highdensity lipoprotein cholesterol; LH, luteinizing hormone; SBP, systolic blood pressure; SHBG, sex hormone–binding globulin; and TT, total testosterone.

was significant in the normal BP group, whereas in the grade 2 hypertension group, an unexpected positive relationship between TT and stroke was found. In addition, the LH level was also positively associated with the odds of stroke in the grade 2 hypertension group.

DISCUSSION

This is a multicenter population-based study in China with participants from diverse cultural and socioeconomic backgrounds. We conducted detailed subgroup analyses and explored the association among
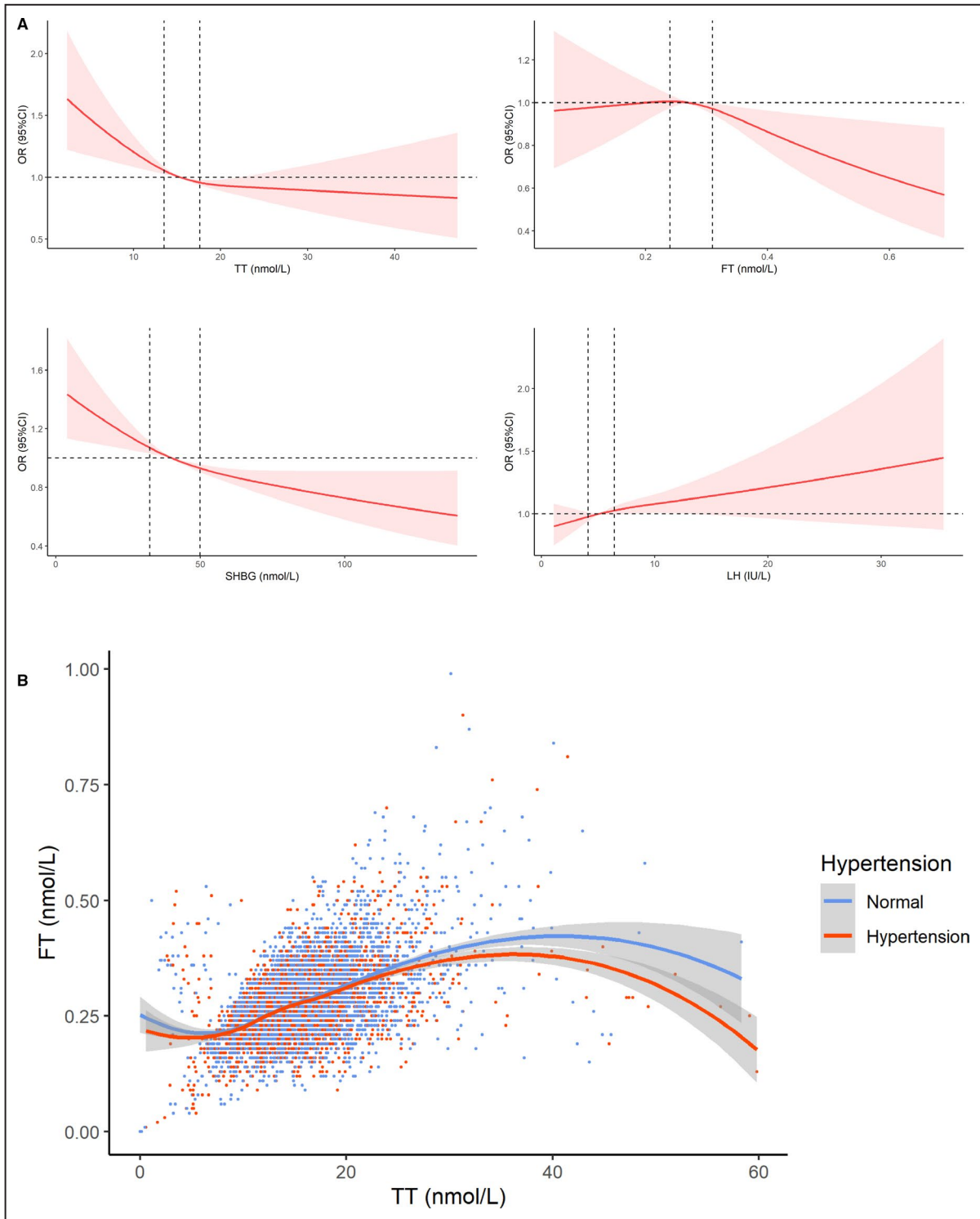
Figure. Relationships between prevalent hypertension and sex hormones.
A, The restricted cubic splines for the association between hypertension and endogenous sex hormone concentrations in 5786 men. The lines represented the adjusted ORs based on restricted cubic splines for TT, FT, SHBG, and LH levels. Adjustment factors were age, BMI, smoking, drinking, residence, education, occupation, marriage status, family history of hypertension, and cholesterol level. The vertical dotted lines give the tertile ranges of the sex hormone distribution. Shaded areas indicated 95% CI. **B**, The scatter plot portraying FT and TT levels among individuals. BMI indicates body mass index; FT, free testosterone; LH, luteinizing hormone; OR, odds ratio; SHBG, sex hormone–binding globulin; and TT, total testosterone.

Table 2. Associations of Sex Hormones in Tertiles With Hypertension in Men

Sex Hormones	Adjusted OR (95% CI)		
	Model 1	Model 2	Model 3
TT, nmol/L			
T1 (<13.53)	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2 (13.53–17.62)	0.86 (0.75–0.99)*	0.86 (0.75–1.00)	0.91 (0.78–1.05)
T3 (>17.62)	0.79 (0.69–0.90)*	0.78 (0.68–0.89)*	0.84 (0.73–0.97)*
P for trend	0.026	0.008	0.045
FT, nmol/L			
T1 (<0.24)	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2 (0.24–0.31)	0.90 (0.79–1.03)	0.96 (0.84–1.10)	0.97 (0.85–1.11)
T3 (>0.31)	0.77 (0.67–0.88)*	0.84 (0.73–0.97)*	0.86 (0.75–0.99)*
P for trend	<0.001	0.088	0.165
SHBG, nmol/L			
T1 (<32.5)	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2 (32.5–49.9)	0.94 (0.82–1.07)	0.96 (0.84–1.09)	0.97 (0.85–1.11)
T3 (>49.9)	0.82 (0.72–0.95)*	0.86 (0.75–0.98)*	0.96 (0.84–1.09)
P for trend	0.044	0.110	0.436
LH, IU/L			
T1 (<4.13)	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2 (4.13–6.45)	0.98 (0.87–1.11)	1.02 (0.90–1.15)	1.01 (0.89–1.14)
T3 (>6.45)	1.08 (0.94–1.24)	1.05 (0.91–1.22)	1.04 (0.89–1.20)
P for trend	0.280	0.464	0.610

Multivariate logistic regression analyses for adjusted OR of sex hormone levels in tertiles associated with prevalent hypertension. T1 was the lowest tertile of hormones and set as the reference group. T2 was the middle tertile and T3 was the highest tertile. Model 1 was adjusted for age; Model 2 was adjusted for age, BMI, smoking, and drinking; Model 3 was adjusted for age, BMI, smoking, drinking, residence, education, occupation, marriage status, family history of hypertension, and cholesterol level. BMI indicates body mass index; FT, free testosterone; LH, luteinizing hormone; OR, odds ratio; SHBG, sex hormone–binding globulin; and TT, total testosterone.

*Indicates the association is statistically significant.

sex hormones, BP, and CVD. We found that TT, FT, and SHBG were inversely associated and LH was positively associated with the prevalent hypertension in middle-aged and elderly men, but after adjustment, association remained most significant between TT and hypertension. Furthermore, this association may be affected by some major characteristics such as age, BMI, smoking status, and family history of hypertension. Also, in the grade 2 patients with hypertension, LH became positively related to the risk of CVD while TT was also positively associated with the presence of stroke. The biological mechanism remains to be explored further and testosterone therapy requires prudent consideration.

Hypertension is considered to be the most crucial risk factor of CVD, which deserves extensive attention globally.[3] However, it has a high underdiagnosis rate and low awareness among elderly respondents in rural areas with poor education background. The general characteristic analysis of our participants revealed that socioeconomic status can heavily affect the risk of prevalent hypertension. In addition to the traditional risk factors such as advanced age, overweight, and

unhealthy smoking and drinking habits, we found the factors of manual workers with poor education background, unmarried status, and urbanized lifestyle may also increase the risk of prevalent hypertension. It was reported that elevated depressive symptoms were correlated with cardiovascular risk.[26] Aging men symptoms scores demonstrated the overall mental, physiological, and sexual states of men, and the aging men symptoms scores were positively associated with the risk of hypertension. In the human body, blood vessels and heart muscle cells have receptors that latch onto testosterone. Testosterone plays an essential role in regulating BP by activating both vasoconstriction and vasorelaxation, while FT is a derived measure as the metabolically active fraction with certain limitations.[27] SHBG, the major circulating protein that binds to and transports steroid sex hormones, also has cardiometabolic effects.[28] In our study, after adjustment for conventional cardiovascular risk factors, an inverse association remained significant only between TT and hypertension.

In the subgroup analyses, we found that inverse association of testosterone level with the risk of prevalent

Table 3. Stratified Analyses by Age, BMI, Smoking Status, and Family History for Hypertension Risk

Variables		Age		BMI	
		<65 y (n=4747)	≥65 y (n=1039)	<24 y (n=2956)	≥24 y (n=2813)
TT, nmol/L	T1	Reference	Reference	Reference	Reference
	T2	0.92 (0.79–1.08)	1.08 (0.81–1.44)	0.89 (0.74–1.08)	0.93 (0.77–1.13)
	T3	0.80 (0.69–0.94)*	1.16 (0.82–1.65)	0.71 (0.58–0.86)*	0.85 (0.70–1.04)
$P_{interaction}$		0.03		0.12	
FT, nmol/L	T1	Reference	Reference	Reference	Reference
	T2	1.02 (0.89–1.17)	0.92 (0.68–1.23)	0.86 (0.71–1.04)	1.08 (0.91–1.27)
	T3	0.99 (0.85–1.17)	1.10 (0.82–1.47)	0.73 (0.61–0.89)*	1.15 (0.94–1.41)
$P_{interaction}$		0.52		<0.01	
SHBG, nmol/L	T1	Reference	Reference	Reference	Reference
	T2	0.93 (0.79–1.09)	1.09 (0.81–1.46)	1.06 (0.87–1.30)	0.94 (0.78–1.15)
	T3	0.82 (0.70–0.96)*	1.11 (0.77–1.58)	0.88 (0.71–1.08)	0.86 (0.71–1.05)
$P_{interaction}$		0.18		0.93	
LH, IU/L	T1	Reference	Reference	Reference	Reference
	T2	1.05 (0.91–1.20)	0.90 (0.66–1.22)	0.98 (0.82–1.18)	1.07 (0.90–1.27)
	T3	1.04 (0.89–1.23)	1.03 (0.77–1.39)	1.08 (0.88–1.33)	1.05 (0.85–1.29)
$P_{interaction}$		0.89		0.87	
Variables		Smoking Status		Family History of Hypertension	
		Ever (n=4056)	Never (n=1730)	Yes (n=1479)	No (n=4307)
TT, nmol/L	T1	Reference	Reference	Reference	Reference
	T2	0.79 (0.64–0.96)	1.10 (0.84–1.46)	0.86 (0.74–1.01)	1.06 (0.83–1.36)
	T3	0.72 (0.59–0.88)*	1.15 (0.85–1.54)	0.72 (0.61–0.84)*	1.12 (0.84–1.50)
$P_{interaction}$		0.02		0.01	
FT, nmol/L	T1	Reference	Reference	Reference	Reference
	T2	0.94 (0.77–1.15)	1.10 (0.83–1.46)	0.93 (0.79–1.09)	1.03 (0.78–1.36)
	T3	0.84 (0.68–1.04)	1.15 (0.86–1.55)	0.81 (0.68–0.95)*	0.93 (0.70–1.23)
$P_{interaction}$		0.15		0.35	
SHBG, nmol/L	T1	Reference	Reference	Reference	Reference
	T2	0.88 (0.73–1.08)	1.04 (0.83–1.31)	0.97 (0.83–1.14)	1.02 (0.78–1.34)
	T3	0.74 (0.61–0.91)*	1.03 (0.81–1.33)	0.85 (0.72–1.00)	0.93 (0.71–1.23)
$P_{interaction}$		0.05		0.66	
LH, IU/L	T1	Reference	Reference	Reference	Reference
	T2	0.93 (0.76–1.14)	1.10 (0.83–1.45)	0.97 (0.83–1.14)	1.03 (0.78–1.35)
	T3	0.83 (0.67–1.03)	1.13 (0.84–1.53)	0.87 (0.73–1.02)	0.94 (0.72–1.25)
$P_{interaction}$		0.09		0.78	

Adjusted odds ratios for hypertension in subgroup analyses. The model adjusted for age, BMI, smoking, drinking, residence, education, occupation, marriage status, family history of hypertension, and cholesterol level. Each group adjusted for the other covariates except itself. $P_{interaction}$ represented the P values of Interaction analyses between sex hormones and age, BMI, smoking status, and family history for hypertension risk. BMI indicates body mass index; FT, free testosterone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; and TT, total testosterone.

*Indicates the association is statistically significant.

hypertension remained notable only in participants aged <65 years or BMI <24, but not in the older or overweight men. It suggested that lower testosterone primarily had negative impacts on the relatively young or low-normal weight population, yet the role of testosterone was attenuated in advanced age and overweight men because age-related decline and metabolic disorders played a major part. In fact, low testosterone is a key factor in the pathogenesis of obesity, while weight gain leads to decreased testosterone.[29,30] Furthermore, in participants who ever smoked or had a family history of hypertension, the inverse association of testosterone with hypertension was more pronounced. This interesting and novel discovery may be explained by potential synergistic or additive effects of those factors. That is, habitual smoking or familial genetic factor might aggregate the impact testosterone deficiency had on hypertension and high BP-induced

Table 4.   Association of Sex Hormones With CVD and Stroke in Different BP Categories

	Normal BP	High-Normal BP	Grade 1 Hypertension	Grade 2 Hypertension
CVD	(n=71)	(n=78)	(n=85)	(n=57)
TT, nmol/L				
T1	Reference	Reference	Reference	Reference
T2	0.67 (0.34–1.35)	0.64 (0.37–1.09)	0.89 (0.54–1.48)	1.09 (0.57–2.04)
T3	0.97 (0.54–1.81)	0.47 (0.26–0.84)*	0.50 (0.27–0.89)*	0.73 (0.33–1.50)
FT, nmol/L				
T1	Reference	Reference	Reference	Reference
T2	0.88 (0.49–1.55)	0.79 (0.45–1.38)	1.05 (0.63–1.77)	1.03 (0.54–1.95)
T3	1.19 (0.64–2.15)	0.63 (0.34–1.15)	0.65 (0.34–1.19)	0.71 (0.32–1.47)
SHBG, nmol/L				
T1	Reference	Reference	Reference	Reference
T2	0.69 (0.34–1.39)	0.77 (0.44–1.36)	1.05 (0.63–1.78)	1.03 (0.54–1.94)
T3	0.98 (0.54–1.88)	0.65 (0.35–1.20)	0.65 (0.34–1.19)	0.70 (0.32–1.45)
LH, IU/L				
T1	Reference	Reference	Reference	Reference
T2	1.17 (0.65–2.12)	1.88 (1.10–3.24)	0.93 (0.53–1.60)	1.42 (0.70–2.93)
T3	1.04 (0.55–1.99)	1.72 (0.93–3.17)	1.51 (0.88–2.56)	2.23 (1.10–4.63)*
Stroke	(n=36)	(n=32)	(n=67)	(n=45)
TT, nmol/L				
T1	Reference	Reference	Reference	Reference
T2	0.51 (0.23–1.07)	0.94 (0.43–2.09)	0.85 (0.42–1.67)	1.86 (0.83–4.44)
T3	0.26 (0.08–0.67)*	0.39 (0.13–1.01)	1.13 (0.63–2.05)	2.71 (1.22–6.44)*
FT, nmol/L				
T1	Reference	Reference	Reference	Reference
T2	0.50 (0.23–1.06)	1.14 (0.51–2.60)	1.12 (0.62–2.00)	1.23 (0.57–2.70)
T3	0.26 (0.08–0.66)*	0.50 (0.17–1.36)	0.81 (0.40–1.58)	1.09 (0.47–2.53)
SHBG, nmol/L				
T1	Reference	Reference	Reference	Reference
T2	0.51 (0.23–1.07)	1.14 (0.51–2.61)	1.13 (0.63–2.03)	1.27 (0.59–2.78)
T3	0.27 (0.09–0.69)*	0.50 (0.17–1.36)	0.83 (0.41–1.63)	1.14 (0.51–2.55)
LH, IU/L				
T1	Reference	Reference	Reference	Reference
T2	0.77 (0.35–1.62)	1.46 (0.63–3.42)	1.80 (1.00–3.27)	1.93 (0.85–4.67)
T3	0.55 (0.20–1.34)	1.61 (0.64–3.98)	1.04 (0.50–2.09)	2.96 (1.30–7.18)*

Adjusted odds ratios for the presence of CVD and stroke according to tertiles of sex hormones stratified by different BP categories. The lowest tertile (T1) was set as the reference group. The multivariable model was adjusted for age, BMI, smoking, drinking, residence, education, occupation, marriage status, family history of hypertension, and cholesterol level. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; FT, free testosterone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; and TT, total testosterone.

*Indicates the association is statistically significant.

vascular damage. It also indicated that for participants who ever smoked or had a family history of hypertension, low testosterone was associated with increased risk of hypertension. Thus, they should be extra cautious when test results indicate they have testosterone deficiency.

We further evaluated the relationship between sex hormones, BP categories, and cardiovascular diseases. Testosterone was found to be inversely associated with the presence of CVD, especially in normal-high BP and grade 1 hypertension groups, while in other groups it displayed a suggestive level of association. It is in line with the investigations showing that low testosterone is associated with increased CVD risks, such as myocardial infarction, coronary heart disease, atherosclerosis, and even all-cause mortality in some studies,[31–33] although some consider it is not significantly relevant.[34,35] Interestingly, LH was positively associated with the odds of CVD in the grade 2 hypertension group, suggesting that men with severe

hypertension with hypergonadotrophic hypogonadism appeared to have an increased prevalence of CVD. In fact, few studies explore the relationship between gonadotrophins and CVD in men. It is reported that men with hypergonadotrophic hypogonadism are more susceptible to ischemic heart disease than those with hypogonadotrophic hypogonadism,[36] the underlying mechanism of which is unclear. LH might theoretically exert a direct effect on the vascular tissue or heart through the LH receptor in extragonadal sites.[37]

In terms of previous stroke, TT, FT, and SHBG presented an inverse association with the prevalence of stroke in the normal BP group. This is consistent with some investigations.[38,39] In contrast, other studies demonstrate that TT and SHBG are not associated with the risk of stroke in elderly men,[40] nor with the ischemic changes on magnetic resonance imaging of the brain.[41] Additionally, novel positive association of LH with stroke was found significant only in patients with the highest grade of BP, indicating LH could be a promising biomarker for patients with relatively severe hypertension. Apart from this, we found that a positive correlation existed between TT and the presence of stroke in the grade 2 hypertension group. The biological mechanism underlying this association was unclear. There remained a possibility that elevated testosterone could be a part of a causal chain through relationships with other stroke risk factors that we had not considered or that were difficult to detect, such as atrial fibrillation, carotid atherosclerosis, or thrombosis, causing a higher susceptibility to stroke. Higher BP may predispose men to atrial fibrillation. The latter is also affected by sex hormones. Two prospective studies have reported that higher testosterone levels contribute to atrial fibrillation incidence in men, and it may be explained by adverse atrial remodeling.[42,43] Additionally, the formation of carotid atherosclerotic plaque followed by plaque rupture may precipitate embolism and stroke events.[44,45] Limited and conflicting evidences exist on testosterone and risk of stroke. It is also reported that higher FT is associated with increased mortality.[46] Thus, we suggested that the relationship of testosterone with stroke may be U-shaped rather than linear, with both low and high levels associated with greater cardiac risk. Testosterone may more likely serve as a marker than the cause of stroke, and other unmeasured factors also contribute to stroke.

The synthesis of testosterone by testicular Leydig cells in response to LH may decrease slightly with increasing age. Testosterone levels are generally lower in aging men with chronic comorbidities and metabolic disorders.[47] It can be indistinguishable whether low testosterone is the cause of their illness or just a byproduct. Low testosterone has been linked to various cardiac risk factors, but that does not necessarily prove it causes CVD incidence. In contrast, clinical trials regarding the benefits and risks of testosterone therapy are controversial.[48–50] It has raised concern that testosterone administration might increase the risk of CVD outcomes. Testosterone treatment used in the cohort of veterans with comorbidities is associated with increased risk of ischemic stroke.[51] It is possible that testosterone promoted platelet aggregation, coronary plaque formation, and affected salt and water retention, endothelium inflammation, or through other mechanisms that might render some men susceptible to adverse CVD outcomes.[52] In fact, increased testis volume is found to be a positive predictor of incident CVD events.[53] The decline in testosterone level with aging may be an adaptive response, as an indicator of underlying comorbidities.[54] Therefore, exogenous testosterone administration may cause consequences by interrupting the whole body homeostasis in some circumstances.

Our study was subject to certain limitations. First, because of the retrospective nature of this cross-sectional study, it neither addressed the temporality of observed associations nor examined the causal relationship between exposure and outcome. Second, although we adjusted for major risk factors and excluded patients with diabetes mellitus, other confounding factors such as atrial fibrillation, atherosclerosis, or specific drug use cannot be fully adjusted because of unavailable information. Third, the relatively small sample size of CVD may yield impaired statistical power, especially for subgroup analysis. Also, there was a possibility of underestimation of CVD attributed to asymptomatic or subclinical conditions. Fourth, it lacked sufficient CVD risk prediction strategies and additional data for further interpretation. We need a larger sample size with more laboratory indicators in a longitudinal study to validate the relationship in hypertensive patients. Future research is warranted to understand how testosterone differentially affects the specific subgroups and how risk might be effectively reduced.

In conclusion, our findings indicate high BP is associated with decreased TT, FT, and SHBG in middle-aged and elderly men. Thus, lower TT could be a promising marker for prevalent hypertension. Age >65 years or overweight could attenuate the inverse association between testosterone and hypertension. However, those who smoke or have a family history of hypertension should be extra cautious when testing reveals testosterone deficiency. Furthermore, primary hypogonadism, which is characterized by increased LH, could potentially be a risk marker for major CVDs in men with relatively severe hypertension. An enhanced understanding of those associations may lead to better preventive and therapeutic strategies of testosterone-related diseases.

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SUPPLEMENTAL MATERIAL

Table S1 Univariate analysis of risk factors for hypertension by logistic regression.

variables	Crude OR (95% CI)	p-value
Age 35-49 (n=1928)	Reference	
Age 50-59 (n=1866)	1.82(1.58-2.09)	P<0.001
Age 60-69 (n=1517)	2.66(2.30-3.07)	P<0.001
Age 70-80 (n=475)	3.43(2.79-4.22)	P<0.001
Reside urban	Reference	
Reside rural	0.82(0.71-0.95)	0.010
Education 0-8 years	Reference	
Education ≥9 years	0.74(0.66-0.82)	P<0.001
Occupation brain worker	Reference	
Occupation manual worker	1.21(1.05-1.40)	0.008
Non-smokers	Reference	
Former smokers	1.83(1.58-2.13)	P<0.001
Current smokers	1.44(1.26-1.64)	P<0.001
Non-drinkers	Reference	
Former drinkers	1.36(1.19-1.56)	P<0.001
Current drinkers.	1.51(1.31-1.74)	P<0.001
Married (yes vs. no)	0.65(0.53-0.80)	P<0.001
CVD (yes vs. no)	1.65(1.30-2.10)	P<0.001
Stroke (yes vs. no)	2.88(2.13-3.93)	P<0.001
Family history of hypertension(yes vs. no)	1.29(1.14-1.45)	P<0.001
BMI	1.08(1.06-1.09)	P<0.001
Chest Circumference, cm	1.05(1.04-1.06)	P<0.001
Abdomen Circumference, cm	1.04(1.03-1.05)	P<0.001
AMS score	1.017(1.011-1.022)	P<0.001
Triglyceride (mmol/l)	1.02(0.98-1.07)	0.319
Cholesterol (mmol/l)	1.11(1.03-1.19)	0.006
HDL (mmol/l)	0.90(0.76-1.06)	0.230
TT (nmol/L)	0.991(0.983-0.999)	0.045
SHBG (nmol/L)	0.997(0.995-0.999)	0.022
LH (IU/L)	1.02(1.01-1.03)	P<0.001
FT (nmol/L)	0.23(0.13-0.43)	P<0.001

Univariate logistic Regression Analyses for crude odds ratio of basic characteristics and laboratory parameters associated with prevalent hypertension. Categorical variables used the first as reference group while the others were calculated as continuous variables. TT, total testosterone; FT, free testosterone; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; BMI, body mass index; AMS, aging males' symptoms; HDL, high density lipoprotein cholesterol. CVD, cardiovascular disease.

Table S2. Associations of sex hormones with CVD and stroke risk in men.

	CVD	P-value	stroke	P-value
TT continuous	1.002(0.984-1.018)	0.796	0.970(0.943-0.996)*	0.033
TT tertiles				
T1	Reference		Reference	
T2	0.988(0.734-1.328)	0.937	0.876(0.590-1.307)	0.512
T3	1.216(0.913-1.623)	0.181	0.875(0.604-1.282)	0.486
FT continuous	0.195(0.045-0.789)*	0.025	0.041(0.005-0.263)*	0.0009
FT tertiles				
T1	Reference		Reference	
T2	0.926(0.698-1.230)	0.595	0.841(0.596-1.187)	0.324
T3	0.761(0.563-1.028)	0.076	0.570(0.385-0.835)*	0.004
SHBG continuous	0.944(0.883-1.006)	0.085	0.849(0.771-0.929)*	0.005
SHBG tertiles				
T1	Reference		Reference	
T2	0.871(0.655-1.156)	0.341	0.831(0.586-1.175)	0.297
T3	0.800(0.596-1.070)	0.134	0.653(0.446-0.946)*	0.026
LH continuous	1.014(0.993-1.031)	0.140	1.010(0.982-1.032)	0.422
LH tertiles				
T1	Reference		Reference	
T2	1.095(0.828-1.445)	0.522	1.344(0.961-1.879)	0.083
T3	1.379(1.021-1.852)*	0.034	1.081(0.715-1.607)	0.706

Multivariate logistic Regression Analyses for adjusted odds ratio of sex hormone levels associated with CVD and stroke. It is adjusted for age, BMI, smoking, drinking, residence, education, occupation, marriage status, family history of hypertension, cholesterol level. The asterisk * indicates the association is statistically significant.