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Actual lowering effect of metabolic syndrome on serum prostate-specific antigen levels is partly concealed by enlarged prostate: results from a large-scale population-based study

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Objectives

To clarify the lowering effect of metabolic syndrome (MetS) on serum prostate-specific antigen (PSA) levels in a Chinese screened population.

Subjects and Methods

A total of 45 540 ostensibly healthy men aged 55–69 years who underwent routine health check-ups at Beijing Shijitan Hospital between 2008 and 2015 were included in the study. All the men underwent detailed clinical evaluations. PSA mass density was calculated (serum PSA level × plasma volume ÷ prostate volume) for simultaneously adjusting plasma volume and prostate volume. According to the modified National Cholesterol Education Programme–Adult Treatment Panel (NCEP-ATP) III criteria, patients were dichotomized by the presence of MetS, and differences in PSA density and PSA mass density were compared between groups. Linear regression analysis was used to evaluate the effect of MetS on serum PSA levels.

Results

When larger prostate volume in men with MetS was adjusted for, both PSA density and PSA mass density in men with MetS were significantly lower than in men without MetS, and the estimated difference in mean serum PSA level between men with and without MetS was greater than that before adjusting for prostate volume. In the multivariate regression model, the presence of MetS was independently associated with an 11.3% decline in serum PSA levels compared with the absence of MetS. In addition, increasing number of positive MetS components was significantly and linearly associated with decline in serum PSA levels.

Conclusion

The actual lowering effect of MetS on serum PSA levels was partly concealed by the enlarged prostate in men with MetS, and the presence of MetS was independently associated with lower serum PSA levels. Urologists need to be aware of the effect of MetS on serum PSA levels and should discuss this subject with their patients.

Keywords

prostate-specific antigen, prostate volume, metabolic syndrome, prostate cancer, screening

Introduction

Metabolic syndrome (MetS) is a complex clinical condition characterized by the coexistence of several metabolic risk factors that include central obesity, hypertension, dyslipidaemia, glucose intolerance and insulin resistance, which increase the risk of cardiovascular disease and type 2 diabetes mellitus and have been associated with increased mortality from these and other conditions [1]. In recent years, increasing evidence suggests that MetS may be involved in the development and progression of certain types of cancer as an independent aetiological factor, including cancers of the breast [2], pancreas [3], thyroid [4] and colon [5]. Meanwhile, epidemiological, histopathological, molecular pathological and clinical studies have also provided evidence of a possible role of MetS in prostate cancer (PCa) pathogenesis, and in the established mechanisms involved in this association including insulin resistance, enhanced IGF-1 pathway, sex hormone alteration and MetS-induced chronic prostatic inflammation [6].

It is reasonable and meaningful to assume that any factor that is associated with PCa would also be likely to have a corresponding impact on serum PSA levels; however, for a long time there has been conflicting evidence as to whether MetS actually affects serum PSA levels. Despite several studies reporting that serum PSA levels in men with MetS are lower

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than in men without this condition [7–9], other studies have reported that serum PSA levels were not affected by MetS [10,11]. Furthermore, a former study with a small sample size even suggested that serum PSA levels were higher in men with MetS than in men without this condition [12]. Unfortunately, data from these former studies did not consider prostate volume. Prostate volume is a factor well-known to be directly proportional to serum PSA levels [13,14], and former studies have clearly shown that MetS has a strong effect on prostate volume and prostate growth rates [15,16]; thus, serum PSA levels in men with MetS should be arithmetically higher than in men without this condition. Interestingly, even these studies did not adjust for prostate volume, the majority of the former studies did not observe higher serum PSA levels in men with MetS [7–11].

Another confounding factor involved in the association between MetS and serum PSA levels is the haemodilution effect. In a previous study, men with MetS had a larger plasma volume than men without MetS [9]. The authors used the concept of PSA mass (serum PSA level × plasma volume) to adjust for plasma volume, and found that there was no significant difference in PSA mass between men with and without MetS. The authors suggested, therefore, that the serum PSA decline in MetS may result simply from the haemodilution effect and may be unrelated to any intrinsic metabolic disturbance.

As the relationships among MetS, prostate volume, plasma volume and serum PSA levels are complex and not well defined, there is a compelling need for further understanding of them. The aim of the present study, therefore, was to clarify the actual lowering effect of MetS on serum PSA levels, by using the concept of PSA mass density (serum PSA level × plasma volume ÷ prostate volume).

Subjects and Methods

Study Population

A total of 52 631 ostensibly healthy men aged 55–69 years who visited the Physical Examination Centre at Beijing Shijitan Hospital (Beijing, China) between January 2008 and December 2015 for a routine health check-up, were reviewed. Because some of these men had undergone health check-ups several times in the past years, we excluded data other than those obtained at the initial screening. The institutional review board approved the study protocol, and the dedicated informed consents were obtained from all participants before enrolling.

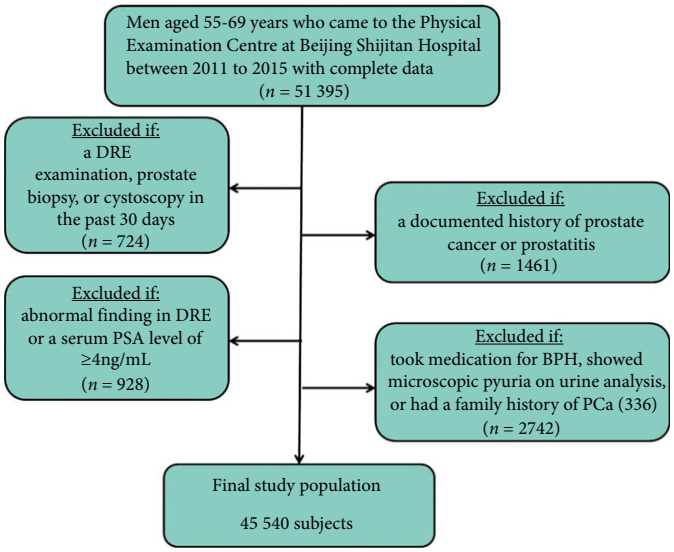
Of the 52 631 men, 1 236 were excluded for missing data, and those who had undergone a DRE (n = 415), prostate biopsy (n = 217) or cystoscopy in the past 30 days (n = 92), or had a documented history of PCa (n = 43) or prostatitis (n = 1 418) were also excluded from the study. We further excluded men for whom there were abnormal findings in the DRE (n = 213) or who had a serum PSA level of >4 ng/mL (n = 715). In addition, men who took medication (5-α reductase inhibitors) for BPH (n = 1 945), had microscopic pyuria (n = 461) on urine analysis, or had a family history of PCa (n = 336) were also excluded. The study population finally comprised 45 540 men (Fig. 1).

Data Collection

Each participant underwent a detailed clinical evaluation. The prostate volume was measured by suprapubic ultrasonography (3.5 MHz; Hitachi EUB-400, Tokyo, Japan) using the formula for an elliptical volume (height × width × length × π/6). The anthropometric measurements, including height (m), weight (kg), waist circumference (cm) and blood pressure (mmHg), were measured by nurses according to a standard protocol from the WHO [17]. Body mass index (BMI) was calculated as weight divided by the square of height. Demographic information, family history and medication history were self-reported via a standardized structural questionnaire.

Before undergoing DRE, a 10-mL 12-h fasting blood specimen was drawn for biochemical analyses when the participants had been sedentary in a sitting position for at least 15 min. Fasting blood glucose (FBG), triglyceride and high-density lipoprotein (HDL) cholesterol levels were determined by enzymatic methods using an automatic HITACHI 7020 Biochemical Analyzer (Hitachi Ltd), and serum PSA levels were determined using the monoclonal Tandem-R kit (Hybritech Inc; San Diego, CA, USA).

Fig. 1 Flow chart of selection of the included subjects. PCa, prostate cancer.



To adjust for the influence of prostate volume and plasma volume, we adopted the concept of PSA mass density, which was calculated using the following formulae: body surface area (m^2) = body weight (kg)$^{0.425}$ × height (m)$^{0.725}$ × 0.007184; plasma volume (mL) = body surface area (m^2) × 1670; PSA mass (ng) = serum PSA level (ng/mL) × plasma volume (mL); PSA mass density (ng/cm^3) = PSA mass ÷ prostate volume (mL). Formulae for PSA mass were identical to those used in the study that reported that lower serum PSA levels in men with MetS could result simply from the haemodilution effect [9].

Definition of Metabolic Syndrome

We defined MetS using the criteria established by the joint statement in 2009 of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity [1]. According to that report, MetS was diagnosed as the simultaneous occurrence of at least three of the following five risk factors: waist circumference ≥90 cm; triglyceride levels ≥150 mg/dL or drug treatment for elevated triglyceride levels; HDL cholesterol <40 mg/dL or drug treatment for low HDL cholesterol; elevated blood pressure (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment with a history of hypertension); and FBG levels ≥100 mg/dL or drug treatment for elevated FBG level.

Statistical Analysis

Continuous variables are presented as means ± SD and categorical variables as numbers and percentages. Values were compared between the groups using an independent *t*-test for continuous variables and a chi-squared test for categorical variables. Linear regression analysis was used to evaluate the effect of MetS and other factors on serum PSA levels, and only the significant factors in univariate analysis were selected for the multivariate regression model. In addition, for MetS, a cluster of metabolic risk factors, we explored the associations of serum PSA levels with the number of positive MetS components as a continuous variable (with values ranging from 0 to 5) to investigate whether the cumulative effect of MetS affected serum PSA levels, by using the ANOVA trend analysis. Data were analysed using SPSS software version 13.0 for windows (SPSS Inc., Chicago, IL, USA), and two-tailed *P* values <0.05 were taken to indicate statistical significance.

Results

Table 1 shows the baseline characteristics of the study population. Among the 45 540 men, the mean ± SD age was 59.4 ± 3.2 years. The overall prevalence of MetS in the entire cohort was 32.2% (14 685/45 540), and 86.7% of men fulfilled at least one positive component of MetS. The age, weight, height, BMI, body surface area, plasma volume, prostate volume and IPSS score were significantly greater in men with MetS than in men without MetS (independent *t*-test, all $P < 0.005$). With regard to each of the MetS components, the criterion for hypertension was fulfilled in 61.2% of men and was the most common of the MetS components, followed by large waist circumference (46.0%), elevated triglyceride levels (34.6%), elevated FBG levels (31.2%), and low HDL cholesterol levels (21.7%). Notably, the individual prevalence of the MetS component was significantly higher in men with MetS than in men without MetS (chi-squared test, all $P < 0.001$).

Table 2 shows the comparisons of serum PSA levels and PSA modifications between men with and without MetS. The mean serum PSA level in men with MetS was slightly but significantly lower than that in men without MetS (1.11 ± 0.79 vs 1.21 ± 0.76 ng/mL; $P = 0.026$), and the difference in mean serum PSA level between men with and without MetS was 0.10 ng/mL. When prostate volume was adjusted for, the mean PSA density in men with MetS was significantly lower than that in men without MetS (0.047 ± 0.038 vs 0.059 ± 0.038 ng/mL^2; $P < 0.001$), and the estimated difference in mean serum PSA level between men with and without MetS rose to 0.275 ng/mL after multiplying by the mean prostate volume (0.012 ng/mL^2 × 22.9 mL). When further adjusting for plasma volume, although there was no difference in PSA mass between men with and without MetS (3670.8 ± 2330.9 vs 3562.9 ± 2572.8 ng; $P = 0.453$), the PSA mass density was still significantly lower in men with MetS than in men without MetS (150.32 ± 119.95 vs 178.24 ± 116.47 ng/mL; $P < 0.001$), and the estimated difference in mean serum PSA level between men with and without MetS was 0.206 ng/mL after multiplying by the mean prostate volume and dividing by the mean plasma volume (27.92 ng/mL × 22.9 mL ÷ 3108.6 mL).

As shown in Table 3, in univariate regression analysis, age, BMI, plasma volume, prostate volume, IPSS score, the presence of MetS and central obesity were significant factors that affected serum PSA levels (all $P < 0.005$). In the multivariate regression model, BMI, plasma volume, prostate volume and the presence of MetS were independent factors that affected serum PSA levels (all $P < 0.005$). Specifically, BMI, plasma volume and the presence of MetS were inversely associated with serum PSA levels, whereas prostate volume was directly associated with serum PSA levels. The predictive model of serum PSA level was PSA = 0.984 − 0.023 BMI − 0.394 plasma volume + 0.012 prostate volume − 0.137 MetS. When BMI, plasma volume and prostate volume were held constant, the presence of MetS was independently associated with a 11.3% decline in serum PSA levels compared with men without MetS ($PSA_{MetS} - PSA_{Non\text{-}MetS} = -0.137$;

Table 1 Baseline characteristics of the study population.

Characteristics	Overall (*n* = 45 540)	MetS (*n* = 14 685)	Non-MetS (*n* = 30 855)	*P*
Age, years	59.4 ± 3.2	60.0 ± 3.2	59.1 ± 3.1	<0.001†
Weight, kg	73.8 ± 10.8	80.4 ± 10.4	70.6 ± 9.5	<0.001†
Height, cm	171.8 ± 5.2	172.3 ± 5.3	171.6 ± 5.1	0.01†
BMI, kg/m^2	25.0 ± 3.1	27.0 ± 2.9	24.0 ± 2.7	<0.001†
Body surface area, m^2	1.86 ± 0.14	1.94 ± 0.14	1.83 ± 0.13	<0.001†
Plasma volume, mL	3108.6 ± 235.9	3233.4 ± 228.2	3049.1 ± 215.5	<0.001†
Prostate volume, mL	22.9 ± 7.5	25.6 ± 9.1	21.6 ± 6.3	<0.001†
IPSS	9.5 ± 7.8	11.1 ± 7.9	8.7 ± 7.7	<0.001†
SBP*, mmHg	132.3 ± 15.0	142.0 ± 13.6	127.7 ± 13.3	<0.001†
DBP*, mmHg	80.7 ± 10.0	84.4 ± 10.1	79.0 ± 9.5	<0.001†
Elevated blood pressure, *n* (%)				
Negative	17 688 (38.8)	1 181 (8.0%)	16 507 (53.5%)	<0.001‡
Positive	27 852 (61.2)	13 504 (92.0)	14 348 (46.5)	–
Waist circumference*, cm	88.6 ± 8.4	91.6 ± 8.1	87.1 ± 8.1	<0.001†
Large waist circumference, *n* (%)				
Negative	24 585 (54.0)	4 554 (31.0)	20 031 (64.9)	<0.001‡
Positive	20 955 (46.0)	10 131 (69.0)	10 824 (35.1)	–
Triglycerides*, mg/dL	150.6 ± 118.1	214.4 ± 164.2	120.2 ± 70.0	<0.001†
Elevated triglycerides, *n* (%)				
Negative	29 832 (65.4)	5 395 (36.7)	24 437 (79.2)	<0.001‡
Positive	15 708 (34.6)	9 290 (63.3)	6 418 (20.8)	–
FBG*, mg/dL	99.2 ± 23.1	110.4 ± 30.1	93.8 ± 16.3	<0.001†
Elevated FBG level, *n* (%)				
Negative	31 350 (68.8)	5 610 (38.2)	25 740 (83.4)	<0.001‡
Positive	14 190 (31.2)	9 075 (61.8)	5 115 (16.6)	–
HDL cholesterol*, mg/dL	48.6 ± 11.6	42.0 ± 10.3	51.7 ± 10.9	<0.001†
Low HDL cholesterol level, *n* (%)				
Negative	35 673 (78.3)	7 128 (48.5)	28 545 (92.5)	<0.001‡
Positive	9 867 (21.7)	7 557 (51.5)	2 310 (7.5)	–
Number of metabolic components*, *n* (%)				
0	–		6 072 (13.3)	–
1	–		11 451 (25.1)	–
2	–		13 332 (29.3)	–
3	–	9 042 (19.9)		–
4	–	4 851 (10.7)		–
5	–	792 (1.7)		–

*BMI, body mass index; DBP, diastolic blood pressure; MetS, metabolic syndrome; SBP, systolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein. *MetS was defined according to the modified National Cholesterol Education Programme–Adult Treatment Panel (NCEP–ATP) criteria [1]. P were calculated by independent t-test† and chi-squared test‡.*

Table 2 Comparisons of serum prostate-specific antigen (PSA) levels and PSA modifications between men with and without metabolic syndrome.

	Overall *n* = 45 540	MetS *n* = 14 685	No MetS (*n* = 30 855	*P**
PSA, ng/mL	1.18 ± 0.78	1.11 ± 0.79	1.21 ± 0.76	0.026
Prostate volume, mL	22.9 ± 7.5	25.6 ± 9.1	21.6 ± 6.3	<0.001
PSA density, ng/mL^2	0.055 ± 0.039	0.047 ± 0.038	0.059 ± 0.038	<0.001
Plasma volume, mL	3108.6 ± 235.9	3233.4 ± 228.2	3049.1 ± 215.5	<0.001
PSA mass, ng	3636.0 ± 2411.2	3670.8 ± 2330.9	3562.9 ± 2572.8	0.453
PSA mass density, ng/mL	169.24 ± 118.29	150.32 ± 119.95	178.24 ± 116.47	<0.001

*MetS, metabolic syndrome. *P values were calculated by independent t-test.*

equivalent formulae, mean PSA $_{MetS}$ = 0.887 × mean PSA $_{Non\text{-}MetS}$).

Finally, when the number of positive MetS components was treated as a continuous variable, the mean PSA level was significantly and linearly decreased as each component of MetS was added, after the adjustment for age, BMI, plasma volume and prostate volume (*P* for trend <0.001; Fig. 2).

Discussion

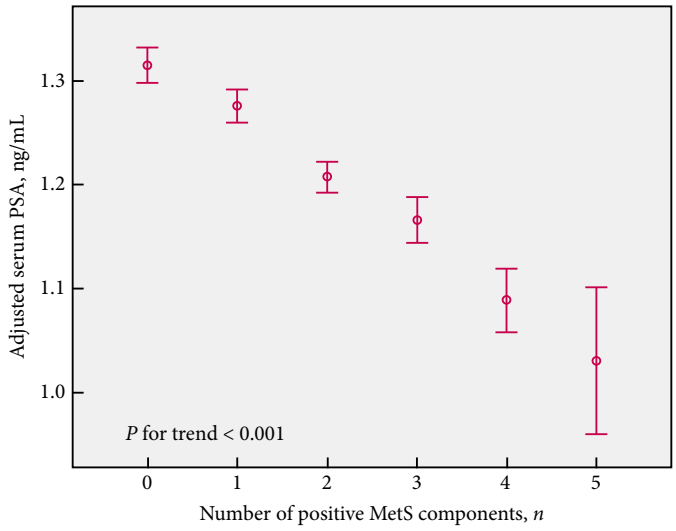
Data from this large-scale population-based study in China showed that MetS had a lowering effect on serum PSA levels when prostate volume and plasma volume were simultaneously considered. These results have potential public health significance because an increasing number of Chinese middle-aged men have MetS [18], as reflected in the present

Table 3 Multivariate regression analysis of metabolic syndrome and other factors that affect serum prostate-specific antigen (PSA) levels.

Characteristics	*B*	SE	*t*	95% CI	*P*
Univariate regression analysis					
Age	0.028	0.007	4.310	0.015, 0.041	**<0.001**
BMI	−0.012	0.007	−1.846	−0.025, −0.001	**0.045**
Plasma volume	−0.344	0.088	−3.903	−0.516, −0.171	**<0.001**
Prostate volume	0.013	0.003	4.603	0.007, 0.018	**<0.001**
IPSS	0.013	0.003	4.865	0.008, 0.018	**<0.001**
MetS*	−0.100	0.045	−2.232	−0.187, −0.012	**0.026**
Hypertension*	0.064	0.043	1.503	−0.020, 0.148	0.133
Central obesity*	−0.122	0.042	−2.923	−0.204, −0.040	**0.004**
Hypertriglyceridaemia*	−0.090	0.044	−3.231	−0.237, 0.056	0.318
Hyperglycaemia*	−0.055	0.045	−1.226	−0.154, 0.033	0.220
Low HDL cholesterol*	−0.099	0.050	−3.604	−0.281, 0.083	0.276
Multivariate regression analysis					
Age	0.014	0.008	1.850	−0.001, 0.029	0.064
BMI	−0.023	0.012	−1.993	−0.046, −0.001	**0.046**
Plasma volume	−0.394	0.146	−2.691	−0.680, −0.107	**0.007**
Prostate volume	0.012	0.004	3.213	0.005, 0.019	**0.001**
IPSS	0.004	0.004	1.088	−0.003, 0.011	0.277
Metabolic syndrome*	−0.137	0.051	−2.684	−0.237, −0.037	**0.007**
Central obesity*	−0.093	0.057	−1.620	−0.205, 0.020	0.105

*BMI, body mass index; HDL, high-density lipoprotein; MetS, metabolic syndrome. *Metabolic syndrome was defined as the modified National Cholesterol Education Programme–Adult Treatment Panel (NCEP-ATP) criteria [1]. Bold indicates statistically significant values.*

Fig. 2 Adjusted mean serum prostate-specific antigen (PSA) level according to the number of positive metabolic syndrome (MetS) components. The mean serum PSA level was adjusted for age, body mass index, plasma volume and prostate volume. White circle indicates mean. Lower and upper bar indicates 95% CI.



study population, in which the prevalence of MetS was 32.2%. To our knowledge, this is the first study focusing on the effect of MetS on serum PSA levels in a Chinese-screened population.

Despite the important implications for PCa detection, there has been conflicting evidence with regard to the effect of MetS on serum PSA levels. In fact, several studies reported that men with MetS had lower serum PSA levels compared with men without MetS [7–9]. A preliminary study firstly showed that the presence of MetS was inversely associated with serum PSA levels (0.75 vs 0.80 ng/mL; $P = 0.043$), and that an increasing number of positive MetS components was significantly associated with a linear decline in serum PSA levels (P for trend <0.001), although data from this study were not analysed after adjustment for demographic variables, and the sample size was small [7]. Another study reported that serum PSA levels were significantly affected by some components of MetS (obesity, diastolic blood pressure, HDL cholesterol level and FBG level); however, this study suggested that an increasing number of positive MetS components was associated with a linear increase and not a decline in serum PSA levels ($P < 0.001$ between groups) [8]. Notably, a former study, also using routine check-up data, reported that serum PSA levels of men with MetS were slightly lower than those of men without MetS (1.119 vs 1.081 ng/mL; $P = 0.001$); however, after adjustment for age and plasma volume, the significance of this difference disappeared (1.113 vs 1.093 ng/mL; $P = 0.10$) [9]. The authors suggested, therefore, that the serum PSA decline associated with MetS may result simply from the haemodilution effect and may be unrelated to any intrinsic metabolic disturbance. None of these studies, however, included prostate volume as a confounding factor.

In the present study, although the mean serum PSA level in men with MetS was slightly lower than that in men without MetS ($P = 0.026$), the lowering effect of MetS on serum PSA levels became more prominent after the adjustment for prostate volume ($P < 0.001$), and the estimated difference in

mean serum PSA level between men with and without MetS was greater than that before adjustment (0.275 ng/mL after adjustment vs 0.10 ng/mL before adjustment). When plasma volume was further adjusted for, although there was no significant difference in PSA mass between men with and without MetS, the PSA mass density in men with MetS was still significantly lower than in men without MetS ($P < 0.001$), and the estimated difference in mean serum PSA level between men with and without MetS was again greater than that before adjustment for prostate volume (0.206 ng/mL after adjustment vs 0.10 ng/mL before adjustment). These specific results imply that the total amount of serum PSA derived from per prostate volume (mL) is lower in men with MetS than in men without MetS, and indicate that the actual lowering effect of MetS on serum PSA levels is partly concealed by the enlarged prostate in men with MetS.

At the level of prostate *per se*, serum PSA levels are under androgenic influence; thus, a plausible explanation for the lower PSA levels in men with MetS in the present study may be the inverse association between MetS and testosterone levels. In the past few years, evidence has shown that MetS-related metabolic disorders, namely lower sex hormone-binding globulin, enhanced activity of aromatase and a low-grade inflammation state may directly influence the clearance, conversion and synthesis of testosterone [19–21]; therefore, a lower serum PSA level might be attributable to the underlying differences in testosterone levels. In this context, the present study also showed that increasing number of positive MetS components was significantly and linearly associated with decline in serum PSA levels, after adjustment for age, BMI, plasma volume and prostate volume (P for trend <0.001), which was further in accordance with findings that testosterone levels decreased gradually with greater number of MetS components [22]. The present results should not be simply interpreted, however, as a rejection of the haemodilution effect on serum PSA levels previously reported [9], rather, we emphasize that the actual lowering effect of MetS on serum PSA levels should be greater combined with the haemodilution effect because, in multivariate regression analysis in the present study, both the presence of MetS and plasma volume were independently associated with lower PSA levels.

Strengths of the present study include the large study sample size, and the use of standardized demographic and laboratory assessment, clearly documented questionnaires and the rigorous exclusion criteria. Most importantly, only men aged 55–69 years were included. The European Randomized Study of Screening for Prostate Cancer (ERSPC) [23] showed that there was the strongest evidence of benefit outweighing harms for men in this age range with regard to PSA-based screening (risk reduction of 21% in disease-specific mortality). This recommendation for PSA screening was further adopted by the most up-to-date AUA guideline for early detection of PCa (Standard; Evidence Strength Grade B) [24].

The present study also has some limitations. Because serum PSA levels were determined simultaneously with clinical evaluation, we were unable to confirm that the presence of MetS lowered serum PSA levels in the same person over time. In addition, because prostate biopsy was not included as a part of our health check-up programme, we cannot definitively exclude the presence of PCa. Because the mechanism of serum PSA elevation in PCa is totally different from that in benign conditions [25], the present results may be biased by undiagnosed PCa; however, there is no reason to believe that the presence of PCa would dramatically change the direction of the association between MetS and serum PSA levels. We excluded men with serum PSA levels >4 ng/mL; theoretically, the effect of MetS on serum PSA levels may even be greater in men with higher serum PSA levels.

The present results show that the presence of MetS was independently associated with a 11.3% decline in serum PSA levels. Arithmetically, the magnitude of this lowering effect of MetS on serum PSA levels is approximately estimated by 0.55 ng/mL when serum PSA level is 4.0 ng/mL, a threshold universally adopted as an indication for prostate biopsy [26]. Based on our results, it is worth noting that the impact of MetS on early detection of PCa probably extends beyond disease pathogenesis itself. In this context, although most previous studies suggested that MetS was directly associated with high grade and more advanced PCa, data on the association between MetS and PCa risk are controversial [6,27–29]. To date, researchers have partially attributed this phenomenon to differences in study sample size, baseline characteristics or length of follow-up. Otherwise, because most prostate biopsies are prompted by and PCa is detected by elevated serum PSA levels in asymptomatic men, it can also be speculated that the lowering effect of MetS on serum PSA levels may lead to the delayed detection of PCa in men with MetS, as fewer men with MetS have elevated serum PSA levels and consequently fewer men with MetS would be prompted to undergo prostate biopsy.

Ever since Whitmore et al. [30] first conceived of the PCa paradox of whether cure was possible when it was necessary and whether cure was necessary when it was possible, one important question surrounding the PSA-based screening is whether PCa detected by elevated serum PSA levels is biologically consequential [31]. Given that studies have shown that men with MetS were more likely to have high grade and more aggressive PCa, were at greater risk of biochemical recurrence after radical prostatectomy and were more likely to die from the PCa [27,29], and that a substantial number of PCa cases were indeed biologically consequential at low serum PSA levels [32], it could be further speculated that the correct interpretation of serum PSA levels in men with MetS

might even be important for the early detection of 'clinically significant' PCa in a screening setting, although future confirmation through prostate biopsy is required.

In conclusion, data from this large-scale population-based study in China showed that the actual lowering effect of MetS on serum PSA levels was partly concealed by the enlarged prostate in men with MetS, and the presence of MetS was independently associated with lower serum PSA levels. Given the high prevalence of MetS and the important ramifications for disease detection, urologists need to be aware of the effect of MetS on serum PSA levels and to discuss this subject with their patients. Future studies are needed to verify with prostate biopsy whether the presence of MetS indeed affects the detection rates of PCa.

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Conflict of Interest

The authors of this manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interested in the subject matter or materials discussed in this manuscript.

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Abbreviations: BMI, body mass index; FBG, fasting blood glucose; HDL, high-density lipoprotein; MetS, metabolic syndrome; PCa, prostate cancer.

