

# Association between serum prostate-specific antigen concentrations and the risk of developing type 2 diabetes mellitus in Chinese men: A cohort study

Shao-fen Huang<sup>1,†</sup>, Ying-lin Yu<sup>2,†</sup>, Yun-feng Cui<sup>2</sup>, Yan-mei Lou<sup>3</sup>, Min-qi Liao<sup>2</sup>, Chang-yi Wang<sup>4</sup>, Shan Xu<sup>4</sup>, Hong-en Chen<sup>4</sup>, Xu-ping Gao<sup>2</sup>, Shu-hong Dai<sup>4</sup>, Xiao-lin Peng<sup>4</sup>, Dan Zhao<sup>4</sup>, Li Wang<sup>4</sup>, Zhao Ping<sup>3</sup>, Fang-fang Zeng<sup>2\*</sup>

<sup>1</sup>Shenzhen Nanshan District Shekou People's Hospital, Shekou Industrial District, Shenzhen, China, <sup>2</sup>Department of Epidemiology, School of Medicine, Jinan University, Guangzhou, China, <sup>3</sup>Department of Health Management, Beijing Xiao Tang Shan Hospital, Beijing, China, and <sup>4</sup>Department of Non-communicable Disease Prevention and Control, Shenzhen Nanshan Center for Chronic Disease Control, Shenzhen, China

## Keywords

Cohort study, Serum prostate-specific antigen, Type 2 diabetes mellitus

## \*Correspondence

Fang-fang Zeng  
Tel: +86-20-8522-6335  
Fax: +86-20-8522-1343  
E-mail address:  
zengffjnu@126.com

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## ABSTRACT

**Aims/Introduction:** The current literature suggests that men with diabetes have a lower prostate-specific antigen concentration than men without diabetes, but the causal association remains unclear. We aimed to investigate the association between serum prostate-specific antigen concentrations and the risk of type 2 diabetes mellitus in a cohort study of a Chinese population.

**Materials and Methods:** We designed a cohort study that comprised 16,811 initially non-diabetic Chinese men who received annual health checkups between 2009 and 2016. The outcome of this study was type 2 diabetes mellitus, identified by medical diagnosis, self-reportage, medication use, fasting glucose, 2-h post oral glucose or glycated hemoglobin measurements. Cox proportional hazards models were carried out to evaluate the association.

**Results:** During a median follow-up period of 3.8 years (interquartile range 1.91–5.73 years), 1,260 participants developed incident type 2 diabetes mellitus. The multivariable model, adjusted for various potential confounders, showed that serum prostate-specific antigen concentrations were inversely related to type 2 diabetes mellitus risk ( $P$  for trend = 0.014). Compared with the lowest quartile of serum prostate-specific antigen, the hazard ratio and 95% confidence intervals of type 2 diabetes mellitus risk for quartile 2–4 were 0.84 (0.66–1.07), 0.75 (0.59–0.94) and 0.77 (0.62–0.96), respectively. Subgroup analyses suggested the inverse relationship was more prominent in overweight or obese participants ( $P$  for interaction = 0.013).

**Conclusions:** High serum prostate-specific antigen concentration was associated with a low risk of type 2 diabetes mellitus in Chinese men. Future studies are required to confirm these findings and investigate underlying mechanisms.

## INTRODUCTION

There has been a global increase in the number of patients with type 2 diabetes mellitus<sup>1</sup>. Currently, there are approximately 415 million people worldwide with diabetes, >90% of whom have type 2 diabetes mellitus. This number is projected to

increase to 642 million by 2040<sup>1</sup>. The prevalence of type 2 diabetes mellitus has rapidly increased in Asian populations, and China has become a major center of the diabetes epidemic<sup>2</sup>. A national cross-sectional study carried out in 2017 suggested that 12.8% of adults living in China had diabetes, as diagnosed using criteria outlined by the American Diabetes Association, and estimated that the total number of individuals with diabetes in mainland China was 129.8 million<sup>3</sup>. Given the growing

<sup>†</sup>These authors contributed equally to this work.

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health challenge of type 2 diabetes mellitus, increased knowledge of factors that are involved in its development might enable more effective type 2 diabetes mellitus preventive strategies to be developed.

Prostate-specific antigen (PSA) is an androgen-regulated serine protease produced by prostate epithelial cells, and is a member of the tissue kallikrein enzyme family<sup>4</sup>. Serum PSA concentrations are often elevated in men with prostate cancer and other prostate diseases, and thus it is the most commonly used serum marker for prostate cancer. PSA expression is primarily androgen-regulated at the transcriptional level by the action of the androgen receptor<sup>5</sup>. A positive correlation between serum PSA and testosterone concentrations has been shown in low androgenic environments, such as in subfertile men or in those with testosterone dysfunction<sup>6–8</sup>. Low PSA concentrations have been considered to be reflective of low concentrations of bioactive circulating testosterone and indicative of hypogonadism<sup>8,9</sup>. Hypogonadism, particularly testosterone deficiency, can contribute to metabolic disorders by increasing visceral adiposity and insulin resistance<sup>10,11</sup>. Patients with hypogonadism have a higher risk of developing obesity, metabolic syndrome and type 2 diabetes mellitus<sup>11</sup>. Therefore, serum PSA, a marker of testosterone activity, might be associated with the risk of developing type 2 diabetes mellitus.

Several recent studies have assessed the association between serum PSA concentrations and diabetes, and most have observed an inverse association. In a cohort study of 778 men who were randomly chosen from the 2000–2002 baseline recruitment pool of a state-wide, large population-based cohort study in Germany, Muller *et al.*<sup>12</sup> reported that the mean PSA concentration in men with diabetes was significantly lower than that in men without diabetes. They also reported that more severe forms of diabetes were associated with lower PSA concentrations. In addition, Werny *et al.*<sup>13</sup> carried out a study of 1,308 American men in the National Health and Nutrition Examination Survey 2001–2002 and reported that geometric mean serum PSA concentrations were lower in patients with diabetes. In Asian populations, a consistent relationship between PSA concentrations and diabetes status was found in two cross-sectional surveys from Japan and a retrospective study on a Chinese population that enrolled 1,517, 14,486, and 2,032 men, respectively<sup>14–16</sup>. However, a cross-sectional study carried out on 1,339 Moroccan participants and a cohort study on 2,172 Japanese men found no significant differences in the PSA concentrations of men with and without diabetes, aside from in certain age groups<sup>17,18</sup>.

Given the inconsistency of previous findings, the association between serum PSA concentrations and type 2 diabetes mellitus requires further investigation, especially through cohort-based studies comprising relatively large sample sizes. Therefore, we carried out a prospective cohort study to explore the association between serum PSA concentrations and the risk of type 2 diabetes mellitus development in a relatively large group of Chinese men.

## METHODS

### Study population

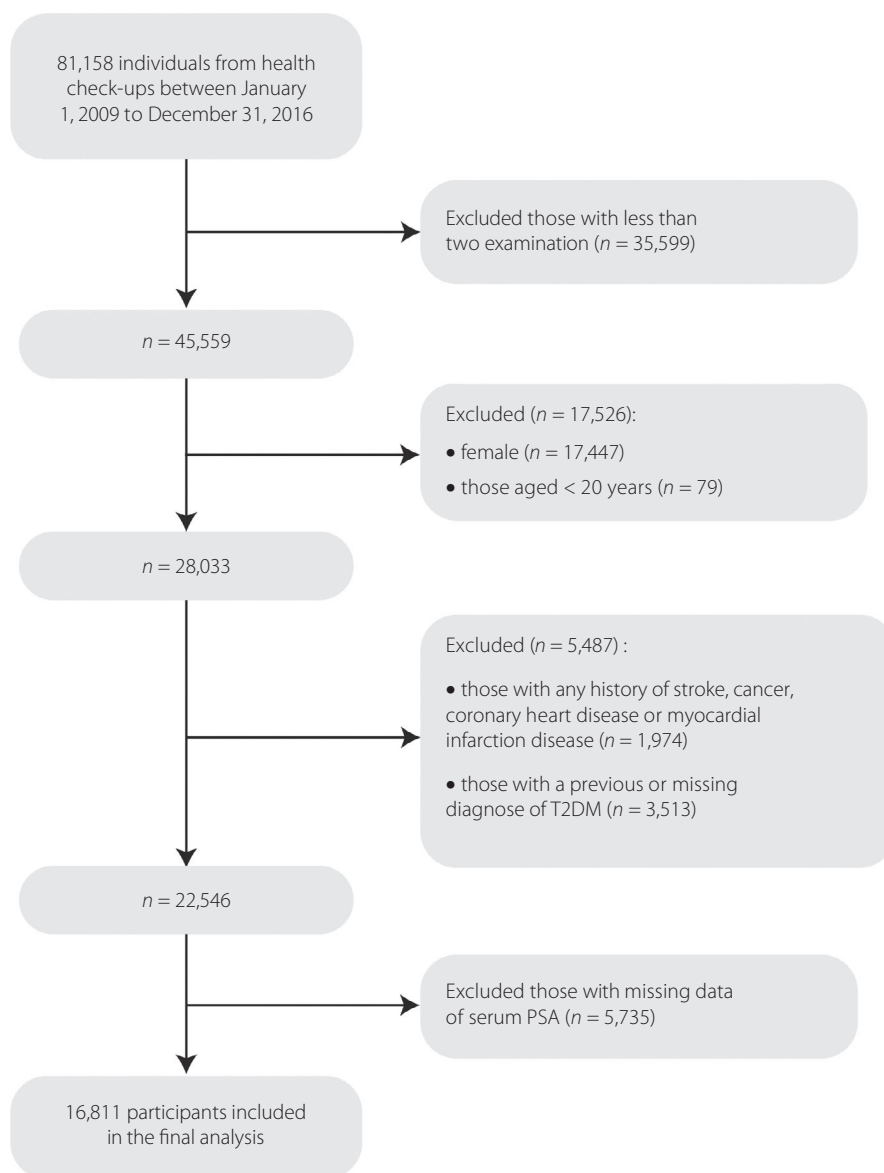
The present investigation was based on an ongoing follow-up study carried out in Xiaotangshan Hospital, Beijing, China. The design of the study has been previously described in detail<sup>19,20</sup>. Briefly, the cohort study recruited participants who underwent a routine annual or biennial health checkup at the hospital clinics. Approximately 90% of participants were government civil servants who received free annual or biennial health checkup benefits, while the remaining participants voluntarily purchased health examination plans at the medical center.

From 1 January 2009 to 31 December 2016, a total of 81,158 individuals who received health checkups were included in this investigation. Individuals who met the following criteria were excluded from the analysis: individuals who underwent less than two examinations ( $n = 35,599$ ); women ( $n = 17,447$ ); individuals aged <20 years ( $n = 79$ ); individuals with a history of stroke, cancer, coronary heart disease or myocardial infarction disease at baseline ( $n = 1,974$ ); individuals with pre-existing type 2 diabetes mellitus or with missing data of type 2 diabetes mellitus status ( $n = 3,513$ ); and individuals with missing data on serum PSA concentrations ( $n = 5,735$ ). Subsequently, 16,811 participants were selected for the final analysis (Fig. 1).

### Data collection

At baseline, the participants received health checkups at clinics at Xiaotangshan Hospital in Beijing, China. Trained interviewers used a detailed standard questionnaire for the collection of demographic characteristics (e.g., age, sex, marital status), lifestyle factors (e.g. smoking and drinking status), history of chronic diseases, medical histories and family histories through face-to-face interviews. Data on standing height, bodyweight and blood pressure were obtained by trained nurses after the interviews were carried out. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Individuals with a BMI of 24–27.9 kg/m<sup>2</sup> were classified as belonging to the overweight group, and those with a BMI  $\geq 28$  kg/m<sup>2</sup> were classified as belonging to the obese group<sup>21</sup>. Hypertension was defined as systolic blood pressure/diastolic blood pressure  $\geq 130/85$  mmHg or receiving anti-hypertensive drug treatment in patients with a history of hypertension<sup>22</sup>.

Blood samples were taken from the anterior cubital vein of participants after an overnight fast of >12 h. Serum lipid concentrations (total cholesterol [TC], low-density lipoprotein cholesterol, triglycerides and high-density lipoprotein cholesterol [HDL-C]) were measured by an enzymatic colorimetric assay (Type 7600; Hitachi Ltd., Tokyo, Japan). Glycated hemoglobin concentrations were measured by high-performance liquid chromatography (Bio-Rad Variant II; Bio-Rad, Munich, Germany). Concentrations of biochemical indicators (fasting plasma glucose, 2-h postprandial plasma glucose, alanine



**Figure 1** | Flowchart of participants' selection. PSA, prostate specific antigen; T2DM, type 2 diabetes mellitus.

aminotransferase [ALT], aspartate aminotransferase [AST], and  $\gamma$ -glutamyl transpeptidase [ $\gamma$ -GT]) were measured using an automatic biochemical analyzer (Olympus AU400, Tokyo, Japan). Serum PSA concentrations of blood were measured through chemiluminescent microparticle immunoassay using an Architect Total PSA Reagent Kit (Abbott Ireland Diagnostics Division, Sligo, Ireland).

#### Assessment of type 2 diabetes mellitus

All participants were required to complete follow-up questionnaires on medical records (e.g., diagnoses and hospital admissions), major health events (e.g., diagnosed type 2 diabetes mellitus) and treatment (e.g., use of antidiabetic drugs) at least

twice in two separate years. Individuals with incident type 2 diabetes mellitus were identified when any one of the following criteria were satisfied: diabetes mellitus diagnosed by a doctor; self-reported diagnosis of diabetes mellitus; use of antidiabetic medications (e.g., treatment with oral hypoglycemic agents or insulin); fasting glucose  $\geq 126$  mg/dL (7.0 mmol/L); 2-h post oral glucose tolerance test showing glucose  $\geq 200$  mg/dL (11.1 mmol/L); or HbA1c  $\geq 48$  mmol/mol (6.5%)<sup>23</sup>.

#### Statistical analysis

All analyses were carried out using R v3.6.1 (R Development Core Team, Vienna, Austria). The baseline characteristic analysis of participants was carried out using descriptive statistics with

reference to standardized serum PSA concentrations, which were divided into quartiles (Q1  $\leq 0.571$  ng/mL, Q2 0.571–0.843 ng/mL, Q3 0.843–1.26 ng/mL, Q4  $> 1.26$  ng/mL). Means  $\pm$  standard deviations or median (interquartile range) were used to describe continuous variables, and numbers and percentages were used to describe categorical variables. The differences in characteristics between serum PSA quartiles were tested by simple linear regression (continuous variables) or  $\chi^2$  statistics (categorical variables). Statistical tests were two-sided, and *P*-values  $< 0.05$  were considered to show statistical significance.

Cox proportional hazards models were carried out to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident type 2 diabetes mellitus for each quartile of PSA concentrations. There were five Cox models: model 1 was adjusted for age (continuous in years); model 2 was additionally adjusted for marital status (married and unmarried), smoking status (never, past and current), drinking status (never, past and current) and BMI (continuous in kg/m<sup>2</sup>); model 3 was further adjusted for hypertension (yes and no), family history of type 2 diabetes mellitus (yes and no); model 4 was additionally adjusted for TC (continuous in mmol/L) and HDL-C (continuous in mmol/L); model 5 was additionally adjusted fasting plasma glucose (continuous in mmol/L), AST/ALT (continuous), r-GT (continuous in U/L) and neutrophil-to-lymphocyte ratio (continuous). *P*-values for trends across serum PSA concentration quartiles were obtained by assigning quartiles as continuous variables.

The shape of the association between serum PSA concentrations and type 2 diabetes mellitus was evaluated using the R smoothHR package after adjustment for the covariates described in model 5. The optimal degree of smoothing was achieved by minimizing one of the following criteria: the Akaike information criterion; the corrected Akaike information criterion; or the Bayesian information criterion. *P*-values for non-linearity were examined using a likelihood ratio test.

We also carried out subgroup analysis with respect to age ( $< 65$  years and  $\geq 65$  years), BMI ( $< 24$  kg/m<sup>2</sup>, 24–27.9 kg/m<sup>2</sup> and  $\geq 28$  kg/m<sup>2</sup>), family history of type 2 diabetes mellitus (yes and no), smoking status (never, past and current) and drinking status (never, past and current), based on model 5. The interactions between serum PSA concentrations and other covariates were also examined. To evaluate possible reverse causality, sensitivity analyses were carried out based on model 5, by excluding participants who had been followed up for  $< 1$  or 2 years.

## RESULTS

The baseline characteristics of participants, organized in terms of PSA concentration quartiles, are presented in Table 1. The cohort study comprised 16,811 men with an average age of 44.9 years (standard deviation 12.8 years) who had a negative diagnosis of diabetes at baseline. During a median follow-up period of 3.8 years (interquartile range 1.91–5.73 years), 1,260 participants developed type 2 diabetes mellitus. The number of

incident diabetes cases in each PSA concentration quartile was 346 (first quartile), 298 (second quartile), 271 (third quartile), and 345 (fourth quartile), with respective incidences of 8.2%, 7.1%, 6.4% and 8.3%. Participants with higher PSA concentrations were more likely to be older, have hypertension, have higher systolic blood pressure and have higher concentrations of 2-h postprandial blood glucose, serum TC, low-density lipoprotein cholesterol and HDL-C. In contrast, they had lower BMIs, and lower concentrations of triglycerides, ALT, AST and r-GT (all *P*  $< 0.05$ ).

Cox regression analysis showed that, after adjusting for age, increased PSA concentrations were associated with a statistically lower risk of type 2 diabetes mellitus (Q4 vs Q1, HR 0.72, 95% CI 0.62–0.84; *P* for trend  $< 0.001$ ; Table 2). Further adjustment for marital status, smoking status, drinking status and BMI slightly weakened this association (*P* for trend = 0.004). Additional adjustment for hypertension and family history of type 2 diabetes mellitus did not significantly alter this association, and a similar association was observed after further adjustments for TC and HDL-C (both *P* for trend = 0.002). With further adjustment of FBG, AST/ALT, r-GT and neutrophil-to-lymphocyte ratio, the risk persisted (*P* for trend = 0.014). Compared with the lowest quartile, the HRs (95% CI) of type 2 diabetes mellitus were 0.84 (0.66–1.07), 0.75 (0.59–0.94) and 0.77 (0.62–0.96) for serum PSA concentration quartiles Q2, Q3 and Q4, respectively. For every one-standard deviation increase in serum PSA concentration, the risk of type 2 diabetes mellitus decreased in a non-significant manner (HR 1.00, 95% CI 0.949–1.051; *P* = 0.95).

In addition, a non-linear fitting model was used to visualize the relationship between predicted serum PSA concentrations and incident type 2 diabetes mellitus, after adjustment for potential confounders in model 5 (Fig. 2). When serum PSA concentrations were within the normal range ( $< 4.0$  ng/mL), the risk of incident type 2 diabetes mellitus significantly decreased as serum PSA concentrations increased (*P* for non-linearity  $< 0.001$ ). In addition, risk factors that positively related to the risk of type 2 diabetes mellitus in the fully adjusted model were age (HR 1.04, 95% CI 1.03–1.05, *P*  $< 0.001$ , per year increase), BMI (HR 1.05, 95% CI 1.02–1.08, *P*  $< 0.003$ , per kg/m<sup>2</sup> increase), fasting plasma glucose (HR 7.14, 95% CI 5.72–8.93, *P*  $< 0.001$ , per mmol/L increase), hypertension (HR 1.23, 95% CI 1.03–1.47, *P* = 0.021, yes vs no), family history of type 2 diabetes mellitus (HR 1.41, 95% CI 1.07–1.86; *P* = 0.014, yes vs no) and neutrophil-to-lymphocyte ratio (HR 1.12, 95% CI 1.00–1.26, *P* = 0.045).

We subsequently carried out subgroup analyses with respect to age, BMI, family history of type 2 diabetes mellitus, smoking status and drinking status (Table 3). The analysis showed statistically significant interactions between BMI ( $< 24$  kg/m<sup>2</sup>, 24–27.9 kg/m<sup>2</sup> or  $\geq 28$  kg/m<sup>2</sup>) and serum PSA concentrations in model 5 (HRs for Q4 vs Q1 1.29, 0.82 and 0.65; *P* for interaction = 0.013; Table 3). However, there were no significant interactions found between serum PSA concentrations and age,

**Table 1** | Characteristics of the study population according to quartiles of serum prostate-specific antigen

	Quartiles of serum PSA				P trend
	Q1 (n = 4213)	Q2 (n = 4199)	Q3 (n = 4248)	Q4 (n = 4151)	
Person-years of follow up	15768.37	14969.48	15464.66	15837.15	
T2DM, n (%)	346 (8.2)	298 (7.1)	271 (6.4)	345 (8.3)	0.82
Age (years)	43.3 (12.16)	42.5 (11.11)	43.9 (11.60)	49.8 (14.6)	<0.001
Married, n (%)	3585 (94.4)	3501 (94.5)	3583 (94.6)	3616 (97.0)	<0.001
BMI (kg/m <sup>2</sup> )	26.5 (3.37)	26.1 (3.26)	25.9 (3.15)	25.7 (2.95)	<0.001
Family history of T2DM, n (%)	244 (5.8)	262 (6.2)	225 (5.3)	231 (5.6)	0.07
Smoking status, n (%)					
Never	1893 (44.9)	1850 (44.1)	1897 (44.7)	1808 (43.6)	0.03
Past	1056 (25.1)	1116 (26.6)	1065 (25.1)	1218 (29.3)	
Current	1264 (30.0)	1233 (29.4)	1286 (30.3)	1125 (27.1)	
Drinking status, n (%)					
Never	1419 (33.7)	1369 (32.6)	1391 (32.7)	1540 (37.1)	0.31
Past	627 (14.9)	661 (15.7)	671 (15.8)	607 (14.6)	
Current	2167 (51.4)	2169 (51.7)	2186 (51.5)	2004 (48.3)	
SBP (mmHg)	122.6 (14.72)	122.6 (14.92)	122.8 (14.83)	124.5 (15.39)	<0.001
DBP (mmHg)	77.6 (10.04)	77.4 (10.16)	77.4 (10.16)	77.8 (10.04)	0.39
Hypertension, n (%)	1244 (29.5)	1174 (28.0)	1249 (29.4)	1498 (36.1)	<0.001
FPG (mmol/L)	5.3 (0.51)	5.3 (0.53)	5.3 (0.52)	5.4 (0.52)	0.26
2h_PPG (mmol/L)	6.4 (1.40)	6.3 (1.38)	6.3 (1.37)	6.5 (1.41)	0.004
HbA1c (%)	5.44 (0.39)	5.42 (0.38)	5.45 (0.38)	5.47 (0.37)	0.07
Total cholesterol (mmol/L)	4.9 (0.95)	4.9 (0.93)	4.9 (0.92)	5.0 (0.94)	0.03
LDL-c (mmol/L)	3.0 (0.75)	3.1 (0.74)	3.1 (0.75)	3.1 (0.75)	<0.001
HDL-c (mmol/L)	1.2 (0.28)	1.2 (0.27)	1.3 (0.27)	1.3 (0.28)	<0.001
Triglycerides (mmol/L)	2.0 (1.67)	1.9 (1.53)	1.8 (1.39)	1.8 (1.39)	<0.001
AST (U/L)	23.9 (12.80)	23.0 (9.74)	22.6 (8.40)	22.6 (9.65)	<0.001
ALT (U/L)	30.3 (24.76)	28.7 (21.34)	27.7 (18.13)	25.7 (17.32)	<0.001
AST/ALT	0.8 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	<0.001
r-GT (U/L)	27.0 (19.0–43.0)	27.0 (19.0–41.1)	26.6 (18.3–41.0)	25.2 (18.0–39.0)	<0.001
NLR	1.78 (0.70)	1.77 (0.66)	1.78 (0.68)	1.84 (0.72)	<0.001

Continuous variables are expressed as the mean (standard deviation) or median (interquartile range); categorical variables are shown as the number and its proportion. Serum prostate-specific antigen (PSA) values were divided into four quartiles (Q): Q1  $\leq 0.571$  ng/mL, Q2 0.571–0.843 ng/mL, Q3 0.843–1.26 ng/mL and Q4  $>1.26$  ng/mL. 2h\_PPG, 2 hours postprandial plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; r-GT,  $\gamma$ -glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

family history of type 2 diabetes mellitus, smoking status, and drinking status with respect to type 2 diabetes mellitus incidence.

In the sensitivity analysis that excluded participants with  $<1$  year of follow up, the strength of the negative association between serum PSA concentrations and the risk of incident type 2 diabetes mellitus decreased in model 5 in a manner that was weakly statistically significant, compared to the original analyses (Q4 vs Q1, HR 0.81, 95% CI 0.63–1.03; *P* for trend = 0.049; Table S1). After excluding individuals who had been followed up for fewer than 2 years, the negative association between PSA and type 2 diabetes mellitus was not significant (Q4 vs Q1, HR 0.82, 95% CI 0.62–1.09; *P* for trend = 0.079; Table S2).

## DISCUSSION

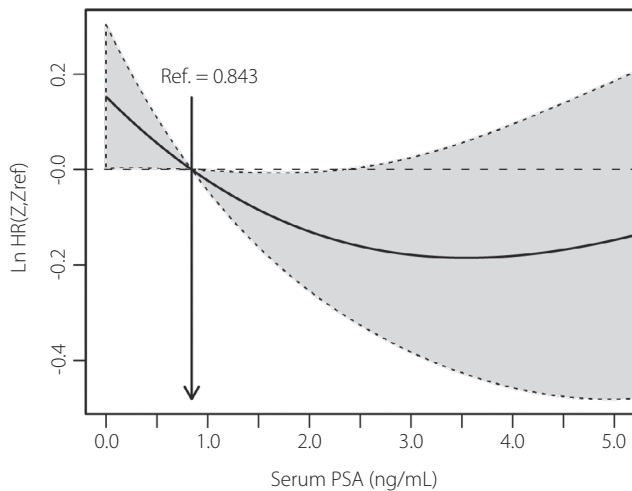
In the present study, we first used a prospective cohort design to investigate the association between serum PSA concentrations and the risk of developing type 2 diabetes mellitus. Our results showed that serum PSA concentrations were inversely associated with the incidence of type 2 diabetes mellitus, and that this association was more apparent in overweight or obese participants.

The relationship between diabetes and serum PSA concentrations has been previously explored in several cross-sectional and cohort studies. Muller *et al.*<sup>12</sup> carried out a cohort study of 778 men aged 50–74 years who were randomly chosen from the baseline of a state-wide, large population-based cohort study carried out in 2000–2002 in Germany. They discovered that

**Table 2** | Cox proportional hazards model analysis for association of serum prostate-specific antigen with the incidence of type 2 diabetes mellitus

	Quartiles of serum PSA (ng/mL)				P trend
	Q1	Q2	Q3	Q4	
PSA (ng/mL) †	0.43 (0.34–0.51)	0.70 (0.64–0.77)	1.02 (0.92–1.12)	1.73 (1.45–2.43)	
Cases/person-years	346/15768.37	298/14969.48	271/15464.66	345/15837.15	
Model 1	1.00	0.95 (0.82–1.11)	0.78 (0.67–0.92)	0.72 (0.62–0.84)	<0.001
Model 2	1.00	0.98 (0.83–1.15)	0.85 (0.72–1.00)	0.81 (0.69–0.95)	0.004
Model 3	1.00	0.97 (0.82–1.14)	0.84 (0.71–0.99)	0.80 (0.68–0.94)	0.002
Model 4	1.00	0.97 (0.82–1.14)	0.84 (0.71–0.99)	0.80 (0.68–0.93)	0.002
Model 5	1.00	0.84 (0.66–1.07)	0.75 (0.59–0.94)	0.77 (0.62–0.96)	0.014

Q1–Q4, serum prostate-specific antigen (PSA) values were divided into four quartiles: ≤0.571 ng/mL, 0.571–0.843 ng/mL, 0.843–1.26 ng/mL, >1.26 ng/mL. Model 1: adjusted for age. Model 2: model 1 + marital status (yes or no), smoking status (never, past and current), drinking status (never, past and current) and body mass index (kg/m<sup>2</sup>). Model 3: model 2 + hypertension and family history of type 2 diabetes mellitus. Model 4: model 3 + total cholesterol (mmol/L) and high-density lipoprotein cholesterol (mmol/L). Model 5: model 4 + fasting plasma glucose (mmol/L), aspartate aminotransferase/alanine aminotransferase, γ-glutamyl transpeptidase (U/L) and neutrophil-to-lymphocyte ratio. †Data are shown as the median (interquartile range).



**Figure 2** | Non-linear regression of the dependence of risk of type 2 diabetes mellitus on serum prostate-specific antigen (PSA) level with adjustments for potential confounders as in model 5 (restricted to the interval between 0 and 5.0 ng/mL; log hazard ratio [Ln HR], with 95% confidence limits; reference = 0.843 ng/mL [median of serum PSA values]).

the age-adjusted mean PSA in men with diabetes was 17% lower than that in men without diabetes. Furthermore, they reported that men with more severe forms of diabetes tended to have lower PSA concentrations.

Werny *et al.*<sup>13</sup> analyzed data from 1,308 American men in the National Health and Nutrition Examination Survey 2001–2002, and found that men with self-reported diabetes had geometric mean PSA concentrations that were 21.6% lower than those without diabetes. A similar association was found in a retrospective analysis of 2,032 participants in a Chinese population: PSA concentrations were 22.8% lower in men who had diabetes than in those who did not<sup>16</sup>.

Fukui *et al.*<sup>14</sup> compared the serum PSA concentrations of 224 Japanese men with diabetes with those of 1,293 healthy men aged 40–79, and observed that men aged 50–79 who had diabetes had lower serum PSA concentrations than those who did not have the disease. In addition, Kobayashi *et al.*<sup>15</sup> carried out a study comprising 14,486 Japanese men with a median age of 52 years, and found that predicted geometric mean PSA concentrations were 11.9% lower in men with diabetes than in those without the disease.

However, a cross-sectional study comprising 1,339 participants from Morocco found no significant differences in PSA concentrations between men with and without diabetes (with vs without diabetes: 1.31 ± 0.04 ng/mL vs 1.36 ± 0.03 ng/mL; *P* = 0.380), except in men aged 50–59<sup>18</sup>. Similarly, a cohort study of 2,172 Japanese men aged 35–69 years found no statistically significant differences in PSA concentrations between men with diabetes and those without diabetes (with vs without diabetes: 1.05 ng/mL vs 1.14 ng/mL; *P* = 0.095), but found that the diabetes was associated with a reduction of PSA levels in men aged 60–69<sup>17</sup>. These inconsistencies in the relationship between PSA concentrations and type 2 diabetes mellitus could be due to the limited sample sizes and differences in populations in the above-described studies.

The present prospective cohort study observed that serum PSA concentrations were inversely associated with the risk of type 2 diabetes mellitus, which is consistent with the findings of most previous studies. We found that the highest PSA quartile had a 23% lower risk of type 2 diabetes mellitus when the lowest quartile was used as a reference (HR 0.77, 95% CI 0.62–0.96; *P* for trend = 0.014).

The potential mechanisms linking the relationship between serum PSA concentrations and the risk of type 2 diabetes mellitus are still unclear. PSA expression is mainly activated by androgens and regulated by the androgen receptor, which binds to androgen response elements that are present in a specific promoter and enhancer of the PSA gene<sup>5</sup>.

**Table 3** | Subgroup analyses of variables in relation to quartiles of prostate-specific antigen with the incidence of type 2 diabetes mellitus

	Incidence of diabetes% (cases/n)	Quartiles of serum PSA				<i>P</i> trend	<i>P</i> interaction
		Q1	Q2	Q3	Q4		
Age (years)							0.121
<65	6.69 (1039/15537)	1.00	0.73 (0.56–0.95)	0.71 (0.55–0.91)	0.76 (0.59–0.99)	0.026	
≥65	17.35 (221/1274)	1.00	1.91 (1.03–3.54)	1.08 (0.59–2.00)	1.44 (0.87–2.37)	0.429	
BMI (kg/m <sup>2</sup> )							0.013
18–23.9	3.42 (137/4010)	1.00	1.61 (0.69–3.78)	1.01 (0.40–2.50)	1.29 (0.60–2.77)	0.825	
24.0–27.9	7.08 (599/8461)	1.00	0.91 (0.65–1.27)	0.84 (0.60–1.17)	0.82 (0.60–1.11)	0.178	
≥28	12.30 (512/4164)	1.00	0.68 (0.46–1.00)	0.67 (0.47–0.97)	0.65 (0.45–0.95)	0.018	
Family history of T2DM							0.739
No	6.73 (428/6364)	1.00	0.85 (0.57–1.27)	0.77 (0.53–1.13)	0.80 (0.56–1.16)	0.206	
Yes	12.27 (118/962)	1.00	1.95 (0.99–3.86)	1.26 (0.58–2.73)	0.85 (0.40–1.83)	0.411	
Smoking status							0.314
Never	7.20 (536/7448)	1.00	0.81 (0.55–1.18)	0.68 (0.47–0.99)	0.93 (0.66–1.31)	0.559	
Past	8.08 (360/4455)	1.00	0.98 (0.62–1.53)	0.86 (0.55–1.33)	0.84 (0.56–1.24)	0.321	
Current	7.42 (364/4908)	1.00	0.83 (0.54–1.28)	0.76 (0.50–1.16)	0.58 (0.38–0.89)	0.012	
Drinking status							0.088
Never	7.85 (449/5719)	1.00	0.88 (0.58–1.35)	0.80 (0.53–1.19)	0.95 (0.66–1.36)	0.765	
Past	7.33 (188/2566)	1.00	0.46 (0.23–0.90)	0.71 (0.40–1.27)	0.53 (0.29–0.98)	0.089	
Current	7.31 (623/8526)	1.00	0.97 (0.70–1.34)	0.74 (0.53–1.04)	0.72 (0.51–0.99)	0.017	

All the data were adjusted for the covariates in model 5. Q1–Q4, serum prostate-specific antigen (PSA) values were divided into four quartiles: ≤0.571 ng/mL, 0.571–0.843 ng/mL, 0.843–1.26 ng/mL and >1.26 ng/mL. BMI, body mass index; T2DM, type 2 diabetes mellitus.

Several studies have reported a positive correlation between serum PSA concentrations and testosterone concentrations in relatively low androgenicity environments, but this correlation is absent at higher concentrations of testosterone<sup>6–8</sup>. These observations were further supported by the proposed “saturation” model<sup>24</sup>. In subfertile individuals, testosterone was observed to be strongly correlated with PSA concentration, with a correlation coefficient of 0.354 ( $P < 0.001$ ); a positive correlation between the short androgen receptor gene CAG-repeat length and PSA concentrations has also been observed<sup>6</sup>. A cross-sectional study of 2,291 men with sexual dysfunction found that there was an approximately linear association between PSA concentrations and low testosterone concentrations ( $<8$  nmol/L;  $R^2 = 0.034$ ;  $P < 0.001$ )<sup>7</sup>. The findings also showed that low PSA concentrations could be regarded as a biological consequence of severe hypogonadism<sup>7</sup>. Another study of 2,967 patients with sexual dysfunction found that PSA concentrations as low as  $0.612 \pm 0.022$  ng/mL could accurately predict hypogonadism (testosterone concentrations of  $<8$  nmol/L;  $P < 0.0001$ ), and that low PSA concentrations were associated with hypogonadism-related features and comorbidities<sup>8</sup>. Given that low PSA concentrations might reflect lower levels of androgen receptor stimulation and reduced concentrations of bioactive testosterone, serum PSA concentrations are considered a reliable biochemical marker of testosterone deficiency and might represent the hypogonadism status of an individual<sup>8,9</sup>.

There is compelling evidence from observational studies and meta-analyses to support the association of hypogonadism with metabolic disorders<sup>10,11</sup>, and its utility for the prediction of the

risk of developing incident metabolic syndrome and type 2 diabetes mellitus<sup>11</sup>. Increased lipoprotein lipase activity induced by testosterone deficiency results in increased development of visceral adipose tissue, further leading to the development of obesity and insulin resistance and worsening pre-existing metabolic conditions<sup>10,11</sup>. Testosterone replacement therapy in patients with testosterone deficiency and obesity or/and type 2 diabetes mellitus improves insulin sensitivity and increases lipolysis through the enhancing the protective effects of pancreatic  $\beta$ -cells and decreasing inflammation in adipose tissue<sup>10,25</sup>. Therefore, the inverse association between serum PSA concentrations and incident type 2 diabetes mellitus is attributable to the effects of testosterone on metabolism. Further studies are required to clarify the potential mechanisms linking the relationships between PSA concentrations, testosterone activity, and the development of type 2 diabetes mellitus.

Our stratification analysis based on BMI showed that the inverse relationship between serum PSA concentrations and the risk of type 2 diabetes mellitus was particularly strong in individuals with higher BMIs. Specifically, a statistically significant interaction was observed between serum PSA concentrations and BMI ( $P$  for interaction = 0.013). Previous studies suggested that obese men have significantly lower PSA concentrations than non-obese men due to higher plasma volumes and decreased androgenic activities<sup>26–29</sup>, but obese men have similar or higher PSA mass than non-obese men<sup>26,27</sup>. Similarly, in the current study, we found that participants with higher PSA concentrations had a lower BMI ( $P < 0.001$ ; Table 1). After adjusting for BMI and other potential confounders in our Cox

regression models, the inverse association between serum PSA concentrations and the risk of type 2 diabetes mellitus remained statistically significant, indicating that the association was independent of obesity.

As BMI is considered to be a strong risk factor for diabetes, it is difficult to explain the significantly negative relationship between PSA concentrations and the risk of type 2 diabetes mellitus that we observed in participants with higher BMI. Although the combined association of BMI and serum PSA concentrations with the risk of diabetes has not been widely explored, some studies have reported the combined association of BMI and diabetes with PSA concentrations. Based on the 2001–2002 National Health and Nutrition Examination Survey, Werny *et al.*<sup>13</sup> used age-adjusted models to show that men without diabetes who had a BMI <25 kg/m<sup>2</sup> had significantly higher geometric mean PSA concentrations than those who had been living with diabetes for >10 years and had a BMI ≥25 kg/m<sup>2</sup> (40.8% reduction; *P* = 0.001).

In another study, Kobayashi *et al.*<sup>15</sup> detected a similar age-adjusted combined association of diabetes and BMI with PSA concentrations in men without diabetes and with a BMI <25 kg/m<sup>2</sup> than in men with diabetes and a BMI ≥ 30 kg/m<sup>2</sup>. Further studies are required to investigate this relationship and show the mechanisms responsible for these associations.

In sensitivity analyses that excluded participants who had been followed up for <1 year, we observed that the strength of the negative association between serum PSA concentrations and the risk of developing type 2 diabetes mellitus decreased, but remained statistically significant. After excluding participants who had been followed up for fewer than 2 years, we found that this negative association was in a non-significant manner, which might be attributed to a decreased sample size after the exclusion. In addition, the association might have weakened as a result of the bi-directional causal relationship between testosterone concentrations and metabolic disruption. That is, testosterone deficiency leads to the development of metabolic disorders due to an increase in visceral adipose tissue and insulin resistance, which in turn further reduce testosterone concentrations through insulin resistance- and pro-inflammatory cytokine-mediated decreases in sex hormone-binding globulin, creating a vicious cycle<sup>11,25</sup>. However, the negative association between serum PSA concentrations and the risk of developing type 2 diabetes mellitus remained statistically significant after the exclusion of individuals who had been followed up for <1 year, further confirming the causative association of baseline serum PSA concentrations with the risk of type 2 diabetes mellitus development.

The strengths of the present study arise from: its prospective design, which was intended to delineate the relationship between PSA and type 2 diabetes mellitus; the large sample size, which added confidence to the association estimation; the reliability of the data, which were collected by well-trained nurses; the use of mixed models, which adjusted for potential confounders; and carrying out several sensitivity analyses.

However, some limitations of the present study remain to be addressed. First, selection bias could not be completely avoided, as most of participants were middle-aged civil servants of the government of Beijing, China. Thus, the results might not be representative of other ethnic or age groups. Second, serum PSA concentrations were measured only once at baseline, which might have influenced the accuracy of our risk estimations. Additionally, we failed to account for the association between changes in serum PSA concentrations and the risk of developing type 2 diabetes mellitus. Third, serum PSA concentrations differ according to the method by which they are determined, which might explain the dissimilarities between the findings of this current study and other previously published studies. Finally, although we corrected for several confounding factors, insufficient adjustments for unknown or poorly collected confounders (e.g., eating habits and exercise status) might have affected the outcomes.

In conclusion, our prospective cohort study found that there was an inverse association between serum PSA concentrations and the risk of incident type 2 diabetes mellitus, especially in men with a higher BMI. Serum PSA concentrations are a common biochemical index recorded during health checkups, and thus might be used as a biomarker for clinical risk prediction of incident type 2 diabetes mellitus, and to guide type 2 diabetes mellitus screening procedures for individualized medicine. This will improve prevention of type 2 diabetes mellitus and reduce its burden on the population. Additional prospective studies comprising larger sample sizes are required to validate this association in other populations, and further experimental investigation is required to determine the exact mechanisms that are involved.

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## DISCLOSURE

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Cox proportional hazards model analysis for association of serum PSA with the incidence of type 2 diabetes mellitus excluding participants with <1 year of follow up.

**Table S2** | Cox proportional hazards model analysis for association of serum prostate-specific antigen with the incidence of type 2 diabetes mellitus excluding participants with <2 years of follow up.