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# The Association Between Metabolic Syndrome and Characteristics of Benign Prostatic Hyperplasia

A Systematic Review and Meta-Analysis

Jian-Ye Wang, MD, PhD, Yan-Yan Fu, MD, PhD, and De-Ying Kang, MD

**Abstract:** The purpose of this systematic review was to examine the association of metabolic syndrome (MS) with measures of benign prostatic hyperplasia (BPH) including prostate growth rate, prostate volume, International Prostate Symptom Score (IPSS), prostate-specific antigen (PSA) level, and maximal flow rate.

Medline, Cochrane CENTRAL, EMBASE, CBM, and Google Scholar databases were searched until March 23, 2015 using combinations of the keywords benign prostate hyperplasia/BPH, metabolic syndrome, total prostate volume, prostate growth rate, prostate specific antigen, International Prostate Symptom Score/IPSS, maximal flow rate. Cohort or case–control studies of patients with BPH and MS that reported quantitative outcomes were included. The pooled mean differences of the outcome measures were compared between patients with and without MS.

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A total of 158 potentially relevant studies were identified, and 8 were included in the meta-analysis. The 8 studies included in the meta-analysis contained a total of 3093 BPH patients, wherein 1241 had MS and 1852 did not have MS. BPH patients with MS had a significantly higher prostate growth rate (pooled mean difference = 0.67 mL/y, P < 0.001) and larger prostate volume (pooled mean difference = 6.8 mL, P = 0.010) than the BPH patients without MS. There was no significant difference in IPSS score (pooled mean difference = -1.41 mL/s, P = .345) between BPH patients with and without MS. A borderline nonsignificant difference in PSA (pooled mean difference = 0.24 mg/mL, P = 0.056) was noted between BPH patients with and without MS.

The results of this meta-analysis are consistent with literature indicating that BPH patients with MS have a higher prostate growth rate and larger prostate volume than those without MS; however, further study is necessary to determine the association of BPH and metabolic disorder elements and the potential risk of disease progression in BPH patients with MS.

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**Abbreviations:** BMI = body mass index, BPH = benign prostatic hyperplasia, CI = confidence interval, ED = erectile dysfunction, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostatic model assessment of insulin resistance, IPSS = International Prostate Symptom Score, LUTS = lower urinary tract symptoms, MS = metabolic syndrome, PSA = prostate specific antigen.

# INTRODUCTION

**B** enign prostatic hyperplasia (BPH), characterized by enlargement of the prostate gland and narrowing of the urethra, affects >50% of men older than 60 years and the majority older than 80 years, and is a major cause of lower urinary tract symptoms (LUTS).<sup>1,2</sup> LUTS can be obstructive and/or irritative, and can significantly affect quality of life.<sup>1,2</sup> BPH is the result of a nonmalignant proliferation of cells in the prostate gland, and although the etiology of the proliferation is not well understood, known factors associated with BPH are aging and androgen metabolism.<sup>3</sup> Recent evidence has also suggested that metabolic disorders, including hyperinsulinemia, dyslipidemia, and obesity may play a role in the development of prostate hyperplasia.<sup>4–7</sup>

Metabolic syndrome (MS) is a cluster of medical conditions including hypertension, impaired glucose metabolism, abdominal obesity, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C).<sup>8</sup> The underlying feature of MS is insulin resistance, and MS is associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease.<sup>8</sup> Similar to BPH, the prevalence of MS increases with age.<sup>9</sup>

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From the Department of Urology, Beijing Hospital, Ministry of Health (J-YW); MSD China, Medical Affairs Department, Beijing Office, Beijing (Y-YF); and Department of Evidence Based Medicine and Clinical Epidemiology (D-YK); West China Hospital, Sichuan University, Chengdu China (D-Y K).

Correspondence: De-Ying Kang, Department of Evidence Based Medicine and Clinical Epidemiology, West China Hospital, Sichuan University, Chengdu 610041, China (e-mail: deyingkang@126.com).

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The authors initiated the concept for the meta-analysis and are responsible for the content of the manuscript.

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J-YW contributed to conceiving and study design, providing substantive suggestions for revision or critical review, reviewing, and approving final version of the article, and all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

D-YK contributed to critical review, final version of the article, and all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Y-YF, the medical manager of MSD, contributed to conceiving and study design, interpreting the results, providing substantive suggestions for revision or critical review, reviewing and approving final version of the article, and all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

J-YW, Y-YF (the medical manager of MSD), and D-YK had no relevant conflict of interest in the work under consideration for publication, relevant financial activities outside the submitted work, intellectual property, and relationships not covered above.

Furthermore, recent evidence is suggesting a link between MS and prostatic hyperplasia and LUTS.<sup>5,10–13</sup> In contrast with results from the United States and European countries, results from Asian populations have been inconsistent.<sup>1</sup> One study indicated that MS was not clearly correlated with LUTS/BPH in Korean men in their 50s,<sup>1</sup> whereas the results of another study indicated that MS was associated with an increased total volume and annual prostate growth rate.<sup>14</sup> A recent meta-analysis indicated that patients with MS have a higher total prostate volume than those without MS, yet International Prostate Symptom Scores (IPSS) were not different between those with and without MS.<sup>15</sup>

As there are a number of different measures of determining BPH, the purpose of this meta-analysis was to examine the association of MS with measures of BPH including prostate growth rate, prostate volume, IPSS, prostate-specific antigen (PSA) level, and maximal flow rate.

# MATERIALS AND METHODS

#### Literature Search and Study Selection

This systematic review and meta-analysis was performed in accordance with MOOSE guidelines.<sup>16</sup> Medline, Cochrane, EMBASE, Google Scholar databases, and CBM were searched from inception until March 23, 2015 using combinations of the keywords: benign prostate hyperplasia/BPH, metabolic syndrome, total prostate volume, prostate growth rate, prostate specific antigen, International Prostate Symptom Score/IPSS, maximal flow rate. Inclusion criteria for the analysis were: cohort or case-controlled studies; patients had BPH with or without LUTS and were older than 18 years; compared patients with and without MS; quantitative outcomes of interest were reported. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded, as were studies in which no quantitative outcome was reported. Reference lists of relevant studies were hand-searched. Searches were conducted by 2 reviewers, and a third reviewer was consulted for resolution of disagreements.

The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, number of patients in each group, age, BMI, IPSS, and quantitative outcomes.

# Quality Assessment

The Newcastle-Ottawa scale was used to assess the quality of the included studies.<sup>17</sup> Briefly, the instrument contains 8 items categorized into 3 dimensions: selection, comparability, and exposure (outcome). A point system is used for a semiquantitative assessment of study quality.

## **Outcome Measures and Data Analysis**

The primary outcome was the association of prostate growth rate and MS, and secondary outcomes were the associations of prostate volume, PSA level, IPSS, and maximal flow rate with MS. Data reported as median and range were converted to mean and standard deviation.<sup>18</sup> Pooled mean differences were compared between groups. Heterogeneity among the studies was assessed by the Cochran Q and the  $I^2$  statistic.<sup>19</sup> If either the Q statistic value of *P* was <0.1 or  $I^2$  was >50%, a random-effects model of analysis (DerSimonian-Laird method) was used. Otherwise, a fixed-effects model (Mantel-Haenszel method) was used. Sensitivity analyses based on the leave-one-out approach were performed to evaluate the robustness of the

pooled estimates of the primary and secondary outcomes. Publication bias was not evaluated in this study because there were only 3 studies included for the primary outcome (prostate growth rate), which is insufficient to detect funnel plot asymmetry.<sup>20</sup> All analyses were performed with Comprehensive Meta-Analysis software, version 2.0 (Biostat, Englewood, NJ).

#### **ETHICS**

This study did not involve human subjects, so informed consent was not required. In addition, no approval was required from an institutional review board.

## RESULTS

#### Literature Search and Study Characteristics

A flow diagram of study selection is shown in Supplemental Figure 1, http://links.lww.com/MD/A920. A total of 158 potentially relevant studies were identified, and 118 remained after duplicates were excluded. After screening by title and abstract, 31 articles were excluded, the reasons for which are shown in Supplemental Figure 1, http://links.lww.com/MD/A920. Nine full-text articles were assessed for eligibility, and of these, 8 were included in the meta-analysis.<sup>21–28</sup> The study by Aktas et al<sup>29</sup> was included in the qualitative synthesis, but did not include measures appropriate for the meta-analysis.

The characteristics of the included studies were summarized in Table 1. The 8 studies included in the meta-analysis contained a total of 3093 BPH patients, wherein 1241 had MS and 1852 did not have MS. The primary and secondary outcomes of the included studies are summarized in Supplemental Table 1. http://links.lww.com/MD/A920.

#### **Quality Assessment**

Results of the Newcastle-Ottawa scales assessment of the included studies are shown in Table 1. Six studies had a total score of 8 points, and 3 studies a total score of 7 points, indicating that the overall quality of the included studies was acceptable.

## Primary Outcome (Prostate growth Rate)

Three studies reported prostate growth rate data.<sup>25,27,28</sup> No significant heterogeneity was observed (Cochran Q=3.6, P=0.167;  $I^2=44.1\%$ ), and thus a fixed-effects model of analysis was performed. BPH patients with MS had a significantly higher prostate growth rate than the BPH patients without MS (pooled mean difference = 0.67 mL/y, P < 0.001; Figure 1 A). The pooled mean differences of prostate growth rate with each of the studies removed were similar (range, 0.55–0.68 mL/y), and remained statistically significant (all, P < 0.001), indicating good reliability in the pooled estimate (Figure 1B).

## **Prostate Volume**

All 8 studies reported prostate volume data.<sup>21–28</sup> Significant heterogeneity was observed (Cochran Q = 70.6, P < 0.001;  $I^2 = 90.1\%$ ), and thus a random-effects model of analysis was performed. BPH patients with MS had a significantly larger prostate volume than BPH patients without MS (pooled mean difference = 6.8 mL, P = 0.010; Figure 2A). The pooled mean differences of prostate volume with each of the studies removed were similar (range, 5.27–9.27 mL), indicating acceptable reliability in the pooled estimate (Figure 2B).

Change of Vento         Population         Number of Syndrome         Number of Prostate Volume	First Author			Definition of	Imaging Techniques						Newcastle-
Gace et al (2015) <sup>21</sup> ItalyProspectiveNCEP.ATP III <sup>4</sup> UltrasonadWith MS140 $69.7\pm7.4$ $274\pm3.5$ $20$ Cynus et al (2014) <sup>23</sup> IranCohortWH Or citeria <sup>44</sup> TransrectalWith MS $33$ $68.5\pm8.8$ $257\pm2.3$ $20$ Cynus et alIranCohortWH Or citeria <sup>44</sup> TransrectalWith MS $33$ $68.8\pm6.3$ $257\pm2.3$ $29$ Cynus et alItalyCohortNCEP.ATP IIITransrectalWith MS $33$ $68.8\pm6.3$ $29.8\pm4.3$ $9$ De Numzio et alItalyCohortNCEP.ATP IIITransrectalWith MS $33$ $68.8\pm6.3$ $29.8\pm4.3$ $9$ 2014) <sup>24</sup> ChinaCohortNCEP.ATP IIITransrectalWith MS $219$ $65.9\pm8.4$ $26.5\pm3.3$ $9$ 2014) <sup>24</sup> ChinaCohortNCEP.ATP IIITransrectalWith MS $219$ $65.9\pm8.4$ $26.5\pm3.3$ $9$ 2014) <sup>25</sup> ChinaRetrospectiveNCEP.ATP IIIUltrasonographyWith MS $84.4\pm9.82$ $23.4\pm2.56$ $11.1$ De Nunzio et alChinaRetrospectiveNCEP.ATP IIITransrectalWith MS $86.4\pm9.82$ $23.4\pm2.56$ $11.1$ CuotiChinaRetrospectiveNCEP.ATP IIITransrectalWith MS $86.4\pm9.82$ $23.4\pm2.56$ $11.1$ QuotiChinaRetrospectiveNCEP.ATP IIITransrectalWith MS $86.4\pm9.82$ $23.4\pm2.56$ $11.1$ QuotiColortNCEP.AT	(Publication Year)	Population	Study Design	Metabolic Syndrome	for Prostate Volume	Group	Number of Patients	Age, y	BMI, kg/m <sup>2</sup>	IPSS	Ottawa Scale
Cyrus et al (2014) <sup>22</sup> IranColortWHO criteria <sup>4</sup> UtrasongraphyTransrectal with MSWithout MS23868.5 ± 8.8 $25.7 \pm 2.3$ 20 $(2014)^{22}$ ColortNCEP-ATP IITransrectal ultrasongraphyWith MS7368.8 ± 6.3 $29.8 \pm 4.3$ 9 $(2014)^{23}$ ColortNCEP-ATP IIITransrectal ultrasongraphyWith MS10368.8 ± 6.3 $29.8 \pm 4.3$ 9 $(2014)^{23}$ ColortNCEP-ATP IIITransrectal ultrasongraphyWith MS23265.9 \pm 8.4 $26.5 \pm 3.3$ 9 $(2014)^{23}$ ColortNCEP-ATP IIIUltrasongraphyWith MS23265.9 \pm 8.4 $26.5 \pm 3.3$ 9 $(2014)^{23}$ ChinaRetrospectiveNCEP-ATP IIIUltrasongraphyWith MS2363.4 \pm 3.2 5.2 \pm 29.1 \pm 2.1624.1 \pm 1.2 $(2014)^{24}$ ChinaRetrospectiveNCEP-ATP IIIUltrasongraphyWith MS86 $9 \pm 7.4$ 27.4 \pm 3.523 $(2014)^{24}$ TukeyColortNCEP-ATP IIIUltrasongraphyWith MS86 $9 \pm 7.4$ 27.4 \pm 3.523 $(2014)^{25}$ TukeyColortNCEP-ATP IIITransrectalWith MS86 $9 \pm 7.4$ 27.4 \pm 3.523 $(2014)^{25}$ TukeyColortNCEP-ATP IIITransrectalWith MS86 $9 \pm 7.4$ 27.4 \pm 3.523 $(2011)^{4}$ TukeyColortNCEP-ATP IIITransrectalWith MS35 $60.41 \pm 6.75$ 24.4 \pm 3.620	Gacci et al	Italy	Prospective	NCEP-ATP III <sup>43</sup>	Ultrasound	With MS	140	$69.7 \pm 7.4$	$27.4 \pm 3.5$	$20.0\pm5.7$	8
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Cyrus et al	Iran	Cohort	WHO criteria <sup>44</sup>	Transrectal	Without MS With MS	238 47	$68.5 \pm 8.8$ $62.5 \pm 9.6$	25.7±2.3 NR	$20.5 \pm 4.8$ $16.95 \pm 8.54$	∞
	(2014) De Nunzio et al	Italy	Cohort	NCEP-ATP III	ultrasonography Transrectal	Without MS With MS	53 103	$68.8 \pm 6.3$	NR 29.8±4.3	$\begin{array}{c} 16.81 \pm 7.01 \\ 9.7 \pm 6.8 \end{array}$	×
$ \begin{array}{cccccc} (2014) \\ \mbox{Part of all constraint} & (2014)^{2} \\ \mbox{Part of all constraint} & (2014)^{2} \\ \mbox{Cohort} & (2014)^{2} \\ \mbox{Cohort} & (2014)^{2} \\ \mbox{Cohort} & (2013)^{26} \\ \mbox{Cohort} & (2010)^{27} \\ \mbox{Cohort} & (2010)^{27} \\ \mbox{Cohort} & (2010)^{26} \\ \mbox{Cohort} & $	(2014) <sup>22</sup> Zhang et al	China	Cohort	NCEP-ATP III	ultrasonography Transrectal	Without MS With MS	328 222	$65.9 \pm 8.4$ $76.93 \pm 5.85$	$26.5 \pm 3.3$ $26.18 \pm 2.78$	$9.6 \pm 7.2$ 11.18 $\pm 7.52$	∞
(2014)conot(2014)conotGacci et alItalyRetrospectiveIDF and AHA/TransrectalWith MS $634$ $71.24\pm5.93$ $24.14\pm1.20$ $18.13$ $(2013)^{26}$ TurkeyCohortNCEP-ATP IIITransrectalWith MS $86$ $69\pm7.4$ $27.4\pm3.5$ $22$ Aktas et al <sup>29</sup> TurkeyCohortNCEP-ATP IIITransrectal andWith MS $33$ $60.41\pm6.75$ $28+7.5$ $25.4\pm3.6$ $20$ Aktas et al <sup>29</sup> TurkeyCohortNCEP-ATP IIITransrectal andWith MS $33$ $60.41\pm6.75$ $28+7.5$ $28+3.6$ $29$ (2011)*Aktas et al <sup>29</sup> TurkeyCohortNCEP-ATP IIITransrectal andWith MS $33$ $60.41\pm6.75$ $28+3.6$ $29$ Coll (2011)*Aktas et al <sup>29</sup> TurkeyCohortNCEP-ATP IIITransrectal andWith MS $73$ $88+7.5$ $28+7.6$ $29+2.82$ $20.11$ Coll (2010) <sup>27</sup> CohortNote to the transpectiveModified IDF <sup>46</sup> TransebdominalWith MS $187$ $70.14\pm8.59$ $26.19\pm2.82$ $23.1.619\pm2.82$ $23.1.619\pm2.82$ $23.1.619\pm2.82$ $23.1.619\pm2.82$ $23.1.729\pm9.02$ $23.2.55\pm2.78$ $20.620-83)^{\dagger}$ $20.7.1.79\pm9.02$ $23.2.55\pm2.78$ $20.1.925\pm2.78$ $20.1.925\pm2.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.203-25.78$ $20.7.79+9.02$ $23.2.55\pm2.78$ <td>(2014) Pan et al</td> <td>China</td> <td>Retrospective</td> <td>NCEP-ATP III</td> <td>untrasonograpny Ultrasonography</td> <td>Without MS With MS</td> <td>179 418</td> <td><math>77.75 \pm 5.78</math> <math>68.44 \pm 9.82</math></td> <td><math>23.45 \pm 2.50</math> <math>28.20 \pm 2.16</math></td> <td><math display="block">\begin{array}{c} 11.20 \pm 7.96 \\ 24.80 \pm 3.93 \end{array}</math></td> <td>7</td>	(2014) Pan et al	China	Retrospective	NCEP-ATP III	untrasonograpny Ultrasonography	Without MS With MS	179 418	$77.75 \pm 5.78$ $68.44 \pm 9.82$	$23.45 \pm 2.50$ $28.20 \pm 2.16$	$\begin{array}{c} 11.20 \pm 7.96 \\ 24.80 \pm 3.93 \end{array}$	7
	(2014) <sup></sup> Gacci et al	Italy	conort Retrospective	IDF and AHA/	Transrectal	Without MS With MS	634 86	$71.24 \pm 5.93$ $69 \pm 7.4$	$\begin{array}{c} 24.14 \pm 1.20 \\ 27.4 \pm 3.5 \end{array}$	$18.58 \pm 2.87 \\ 22.5 \pm 5.7$	٢
(2011) (2011) Ultrasonography Ultrasonography Ultrasonography Vithout MS 73 NR PSS PSS $(2010)^{27}$ Cao et al Chinese Retrospective Modified IDF <sup>46</sup> Transabdominal With MS 187 70.14 \pm 8.59 26.19 \pm 2.82 23.1 (2010)^{27} cohort Cohort Ultrasonography Vithout MS 195 71.79 \pm 9.02 23.25 \pm 2.78 20.4 (2007)^{28} 59 (50-83)^{\frac{1}{12}} 2.8.7 (21.2-36.7)^{\frac{1}{12}} 2.2 (1.2007)^{28} (2007)^{28}	$(2013)^{26}$ Aktas et al <sup>29</sup>	Turkey	Cohort	NHLBI <sup>45</sup> NCEP-ATP III	ultrasonography Transrectal and	Without MS With MS	185 33	$68 \pm 7.5$ $60.41 \pm 6.75$	25.4 ± 3.6 NR	$20.9 \pm 5.7$ IPSS 0-7: 14	8
Cao et al Chinese Retrospective Modified IDF <sup>46</sup> Transabdominal With MS 187 70.14 $\pm$ 8.59 26.19 $\pm$ 2.82 23.1 (2010) <sup>27</sup> cohort Ultrasonography Without MS 195 71.79 $\pm$ 9.02 23.25 $\pm$ 2.78 20.6 Ozden et al Turkey Prospective NCEP ATP III Transrectal With MS 38 59 (50–83) <sup>†</sup> 28.77 (21.2–36.7) <sup>†</sup> 22 (1 (2007) <sup>28</sup>	(1102)				ultrasonography	Without MS	73		NR	IPSS 8–19: 16 IPSS 20–35: 3 IPSS 0–7: 19 IPSS 8–19: 50	
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(2007) Ultrasonography	Ozden et al	Turkey	Prospective	NCEP ATP III	Transrectal	Without MS With MS	195 38	71.79 $\pm$ 9.02 59 (50–83) <sup>†</sup>	$\begin{array}{c} 23.25 \pm 2.78 \\ 28.7  (21.2 {-} 36.7)^{\dagger} \end{array}$	$\begin{array}{c} 20.41 \pm 4.98 \\ 22  \left( 10{-}32 \right)^{\dagger} \end{array}$	×
Without MS 40 60 $(50-72)^{\dagger}$ 25.4 $(19.5-31.9)^{\dagger}$ 20 $(10.5-31.5)^{\dagger}$	(/ 007)				ultrasonograpny	Without MS	40	60 (50–72) <sup>†</sup>	25.4 (19.5–31.9) <sup>†</sup>	$20 \ (10 - 33)^{\dagger}$	

		S	tatisti	ics for	each s	udy							
Study name	Differe in mea	nce Stand	ard L or l	lower. limit	Upper limit	p-Value	Relat weig	tive tht	Differ	ence in	means	and 9	5% CI
Pan (2014)	0.69	0.03	3 (	0.62	0.76	< 0.001	85.	6	T	1	T	T	с Г.
Cao (2010)	0.58	0.09	9 (	0.41	0.75	< 0.001	12.	3				- 4	
Ozden (2007)	0.36	0.21	ı -	-0.05	0.77	0.088	2.1	i			-	-	-
Pooled estimate	0.67	0.03	3 (	0.61	0.73	< 0.001							
(Fixed)									-1.00	-0.50	0.00	0.50	1.00
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A Study name Pan (2014) Cao (2010) Ozden (2007)	Point 0.55 0.68 0.68	Statistics Standard error 0.08 0.03 0.03	with st Lowe limi 0.39 0.62 0.62	tudy r er U it 1 9 ( 2 ( 2 (	remove pper imit 0.71 0.75 0.74	d -Value <0.001 <0.001 <0.001	Diffe	erence with	in me study	ans (9: remov	5% CI) ed	)	
A Study name Pan (2014) Cao (2010) Ozden (2007) Pooled estimate	Point 0.55 0.68 0.68 0.67	Statistics Standard error 0.08 0.03 0.03 0.03 0.03	with st Lowe 0.39 0.62 0.62	tudy r er U it 1 9 ( 2 ( 2 ( 1 (	remove pper imit 0.71 0.75 0.74 0.73	d -Value <0.001 <0.001 <0.001 <0.001	Diffe	erence with	in me study	ans (9:	5% CI) ed	)	
A Study name Pan (2014) Cao (2010) Ozden (2007) Pooled estimate (Fixed)	Point 0.55 0.68 0.68 0.67	Statistics           Standard           error           0.08           0.03           0.03           0.03	with st Lowe limi 0.39 0.62 0.62 0.61	tudy r er U it 1 9 ( 2 ( 1 (	remove pper imit 0.71 0.75 0.74 0.73	d 	Diffe	erence with	in me study	ans (9: remov	5% CI) ed	) )	

FIGURE 1. Meta-analysis for prostate growth rate. (A) Pooled estimate. (B) Sensitivity analysis.

PSA

Six studies reported PSA data.<sup>21,23–25,27,28</sup> Significant heterogeneity was observed (Cochran Q=11.8, P=0.038;  $I^2=57.5\%$ ), and thus a random-effects model of analysis

was performed. BPH patients with and without MS had a borderline nonsignificant difference in PSA (pooled mean difference = 0.24 ng/mL, P = .056; Figure 3A). The pooled mean differences of PSA with each of the studies removed



FIGURE 2. Meta-analysis for prostate volume. (A) Pooled estimate. (B) Sensitivity analysis.

		5	statis	stics for	each s	tudy								
Study name	Differe in me	ence Stand ans erre	lard or	Lower limit	Uppe limit	r p-Valu	ie Re w	lative eight	Diffe	rence	in m	eans	and 95	5% CI
Gacci (2015)	0.70	0 0.2	5	0.21	1.19	0.005	1	13.9	1	Т		1-	- <b>1</b>	
De Nunzio (2014)	-0.2	0 0.2	0	-0.59	0.19	0.313	1	17.7		- 1		ŀ.		
Pan (2014)	0.10	0.1	0	-0.09	0.29	0.297	1 2	26.6		- 1				
Zhang (2014)	0.30	0 0.2	1	-0.10	0.70	0.146	5 1	17.0		- 1		ł≡	-	
Cao (2010)	0.8	0 0.3	7	0.08	1.52	0.030	)	8.5		- 1		-		-
Ozden (2007)	0.20	0 0.2	2	-0.22	0.62	0.354	1 1	16.3		- 1	-		-	
Pooled estimate	0.24	4 0.1	3	-0.01	0.49	0.056	5		1	- 1				
(Random)									-2.00	-1.0	0 0	.00	1.00	2.00
									Fevou	rs M	S	I	evours	no MS
A														
		Statistics	with	study 1	remove	ed	Di	fferen	ce in n	ieans	(95%	CD		
Study name	Point	Standard error	Lo lii	wer U mit J	pper imit	p-Value	D	wit	h study	y rem	oved			
Gacci (2015)	0.15	0.11	-0	.07	0.37	0.180			-	-	1			
De Nunzio (2014)	0.32	0.13	0.	.07	0.57	0.011				-	H-			
Pan (2014)	0.31	0.17	-0	.03	0.65	0.077				-	H- 1			
Zhang (2014)	0.24	0.15	-0	.06	0.54	0.116			-		+			
Cao (2010)	0.18	0.12	-0	.05	0.42	0.130				-	-			
Ozden (2007)	0.26	0.15	-0	.04	0.56	0.089			1	_	+			
Pooled estimate	0.24	0.13	-0	.01	0.49	0.056								
(Random)							-1.00	-0.5	0.0	00	0.50	1.0	00	
							Fevou	rs MS		F	evour	s no	MS	

В

FIGURE 3. Meta-analysis for prostatic specific antigen. (A) Pooled estimate. (B) Sensitivity analysis.

were similar (range, 0.15–0.32 ng/mL), which indicated an acceptable reliability in the pooled estimate (Figure 3B).

# IPSS

All 8 studies reported IPSS data.<sup>21–28</sup> Because significant heterogeneity was observed between studies (Cochran Q = 250.8, P < 0.001;  $I^2 = 97.2\%$ ), a random-effects model of analysis was performed. There was no significant difference in IPSS score between BPH patients with and without MS (pooled mean difference = 1.58, P = .202; Figure 4A). The pooled mean differences of IPSS with each of the studies removed were similar and remained statistically nonsignificant (all, P > 0.05), which indicated a good reliability in the pooled estimate (Figure 4B).

# **Maximal Flow Rate**

Four studies reported maximal flow rate data.<sup>21,24–26</sup> Because significant heterogeneity was observed between studies (Cochran Q = 297.8, P < 0.001;  $I^2 = 99.0\%$ ), a random-effects model of analysis was performed. There was no difference in maximal flow rate between BPH patients with and without MS (pooled mean difference = -1.41 mL/s, P = 0.345; Figure 5A). The pooled mean differences of maximal flow rate with each of the studies removed were similar (range, -1.92 to -0.27 mL/s) and remained statistically nonsignificant (all, P > 0.05), indicating good reliability in the pooled estimate (Figure 5B).

# Subgroup Analysis By Region (Asia And Europe)

Subgroup analyses by region (Asia and Europe) for prostate volume, PSA, IPSS, and maximal flow rate were performed to reduce the heterogeneity among the included studies. Four studies from Asia<sup>22,24,25,27</sup> reported prostate volumes for patients with and without MS, and the mean differences of prostate volume showed no obvious heterogeneity (Q = 3.2, df = 3, P = 0.360;  $I^2 = 6.7\%$ ); thus, a fixed-effects model was used. The pooled estimate showed that patients with MS had higher prostate volume than those without MS (pooled mean difference = 11.96, 95% confidence interval [CI]: 10.94–12.98, P < .001). Three studies from Europe<sup>21,23,26</sup> reported prostate volumes for patients with and without MS, and the mean differences of prostate volume showed obvious heterogeneity (Q = 5.9, df = 2, P = 0.053;  $I^2 = 66.1\%$ ); thus, a random-effects model was used. The pooled estimate showed no significant difference in prostate volume between patients with and without MS (Figure 6A).

Three studies from Asia<sup>24,25,27</sup> reported PSA for patients with and without MS, and the mean differences of PSA showed minor heterogeneity (Q = 3.9, df = 2, P = 0.146;  $I^2 = 48.1\%$ ); thus, a fixed-effects model was used. The pooled estimate showed that patients with MS had higher PSA than those without MS (pooled mean difference = 0.17, 95% CI: 0.00– 0.34, P = 0.044). Two studies from Europe<sup>21,23</sup> showed obvious heterogeneity (Q = 7.9, df = 1, P = 0.005;  $I^2 = 87.3\%$ ); thus, a random-effects model was used. The pooled estimate showed no significant difference in PSA between patients with and without MS (Figure 6B).

Four studies from Asia<sup>22,24,25,27</sup> and 3 from Europe<sup>21,23,26</sup> reported IPSS data, and obvious heterogeneity was present in both groups (Asia: Q = 104.7, P < 0.001,  $I^2 = 97.1\%$ ; Europe: Q = 5.2, P = 0.075;  $I^2 = 61.4\%$ ); thus, random-effects models were used. For both Asia and Europe, the pooled estimate of included studies showed no significant difference in IPSS between patients with and without MS (Figure 6C).

Two studies from Asia<sup>24,25</sup> reported maximal flow rate data, and there was obvious heterogeneity among studies

		Stati	stics for	each st	udy						
Study name	Differenc	e Standard	Lower	Upper	p-Value	Relativ	ve Diff	ference	e in mea	ins and	1 95% Cl
	in means	error	limit	limit		weigh	t				
Gacci (2015)	-0.50	0.55	-1.58	0.58	0.362	13.0		- 1			1 1
Cyrus (2014)	0.20	1.55	-2.84	3.24	0.897	11.0		- I		<u> </u>	
De Nunzio (2014)	0.10	0.80	-1.47	1.67	0.901	12.6		- I	_ — <b>Q</b>	H .	
Pan (2014)	6.20	0.21	5.79	6.61	< 0.001	13.3		- I			
Zhang (2014)	0.00	0.78	-1.52	1.52	1.000	12.7		- I	-	<u>–</u>	
Gacci (2013)	1.60	0.74	0.14	3.06	0.031	12.7		- I	- F		
Cao (2010)	2.70	0.48	1.75	3.65	0.000	13.1		- I			
Ozden (2007)	2.00	1.28	-0.51	4.51	0.119	11.7		- I	Ť		tΙ
Pooled estimate	1.58	1.24	-0.85	4.01	0.202		1		-		1 1
(Random)							-8.00	-4.0	0.0	0 4.	00 8.0
							Fevo	urs M	s	Fevo	urs no M
A											
A	St	atistics wit	h study 1	removed	ł	Differ	ence in	means	(95% (	<b>CI)</b>	
A Study name	Si Point St	atistics wit	h study : ower U	removed Jpper	i Value	Differ	ence in vith stu	means dy rem	(95% ( noved	CI)	
A Study name	St Point <sup>St</sup>	atistics wit andard Le error li	h study : ower U imit I	removed Jpper limit l	d p-Value	Differ	ence in vith stue	means dy rem	(95% ( noved	CI)	
A Study name Gacci (2015)	<b>St</b> <b>Point St</b> 1.90	atistics wit andard Lo error li 1.23 -0	h study p ower U imit 1 0.50	removed Jpper limit 4.31	d p-Value 0.121	Differ	ence in vith stu	means dy rem	(95% ( noved	св) -	
A Study name Gacci (2015) Cyrus (2014)	<b>Point St</b> 1.90 1.75	atistics wit andard Le error li 1.23 1.32	h study p ower U imit 1 0.50 0.83	removed Upper limit 4.31 4.33	<b>h</b> <b>p-Value</b> 0.121 0.183	Differ V	ence in vith stue	means dy rem	(95% ( noved	cı) -	
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014)	50 Point 51 1.90 1.75 1.80	atistics witi andard Lo error li 1.23 1.32 1.32	h study 1 ower U imit 1 0.50 0.83 0.79	removed Jpper limit 4.31 4.33 4.38	d 0.121 0.183 0.174	Differ	ence in vith stu	means dy rem	(95% ( noved	CI) 	
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014)	<b>Solution</b> <b>Point</b> <b>Solution</b> <b>Solution</b> <b>1.90</b> <b>1.75</b> <b>1.80</b> <b>0.89</b>	atistics witi andard La error li 1.23 1.32 1.32 0.59	h study p ower U imit 1 0.50 0.83 0.79 0.27	removed limit 4.31 4.33 4.38 2.04	<b>h</b> 0.121 0.183 0.174 0.131	Differ	ence in vith stud	means dy rem	(95% ( noved	cī) 	
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014) Zhang (2014)	<b>St</b> <b>Point St</b> 1.90 1.75 1.80 0.89 1.81	atistics wit andard Le error li 1.23 -( 1.32 -( 1.32 -( 0.59 -( 1.32 -(	h study p ower U imit 10.50 0.83 0.79 0.27 0.77	removed Jpper limit 4.31 4.33 4.38 2.04 4.39	<b>p-Value</b> 0.121 0.183 0.174 0.131 0.168	Differ	ence in vith stue –	means dy rem	(95% ( noved	CI) 	
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014) Zhang (2014) Gacci (2013)	<b>St</b> <b>Point St</b> 1.90 1.75 1.80 0.89 1.81 1.58	atistics wit andard Le error li 1.23 -( 1.32 -( 1.32 -( 0.59 -( 1.32 -( 1.32 -( 1.37 -	h study p ower U imit 100.50 0.83 0.79 0.27 0.77 1.12	removed imit 4.31 4.33 4.38 2.04 4.39 4.27	<b>p-Value</b> 0.121 0.183 0.174 0.131 0.168 0.251	Differ	ence in vith stue - -	means dy rem	(95% ( noved	cī) 	
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014) Zhang (2014) Gacci (2013) Cao (2010)	St           Point         St           1.90         1.75           1.80         0.89           1.81         1.58           1.40         1.40	atistics with andard La error li 1.23 1.32 0.59 1.32 1.32 1.37 - 1.51 -	h study p ower U imit 0.50 0.83 0.79 0.27 0.77 1.12 1.56	removed Jpper limit 4.31 4.33 4.38 2.04 4.39 4.27 4.37	Image: block of the state of the s	Differ	ence in vith stud - -	means dy rem	(95% ( noved		
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014) Zhang (2014) Gacci (2013) Cao (2010) Ozden (2007)	St           Point         St           1.90         1.75           1.80         0.89           1.81         1.58           1.40         1.53	atistics with andard Le error li 1.23 1.32 0.59 1.32 1.37 - 1.51 - 1.34 -	h study p ower U imit 0.50 0.79 0.27 0.77 1.12 1.56 1.10	removed Jpper limit 4.31 4.33 4.38 2.04 4.39 4.27 4.37 4.15	P-Value 0.121 0.183 0.174 0.131 0.168 0.251 0.353 0.255	Differ	ence in vith stud - - - -	means dy rem	(95% ( noved		
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014) Zhang (2014) Gacci (2013) Cao (2010) Ozden (2007) Pooled estimate	<b>Point St</b> 1.90 1.75 1.80 0.89 1.81 1.58 1.40 1.53 1.58	atistics with         andard       Le         error       li         1.23       -1         1.32       -1         0.59       -1         1.32       -1         1.37       -         1.37       -         1.34       -         1.34       -	h study p ower U imit 20.50 0.83 0.79 0.27 0.77 1.12 1.56 1.10 0.85	removed Jpper limit 4.31 4.33 4.38 2.04 4.39 4.27 4.37 4.15 4.01	P-Value 0.121 0.183 0.174 0.131 0.168 0.251 0.255 0.202	Differ	ence in vith stud	means dy rem	(95% ( noved		
A Study name Gacci (2015) Cyrus (2014) De Nunzio (2014) Pan (2014) Zhang (2014) Gacci (2013) Cao (2010) Ozden (2007) Pooled estimate (Random)	St           Point         St           1.90         1.75           1.80         0.89           1.81         1.58           1.40         1.53           1.58         1.58	atistics with         andard       Le         error       li         1.23       -4         1.32       -4         0.59       -4         1.32       -4         1.37       -1         1.37       -1         1.34       -1         1.34       -1	h study p ower U imit 20.50 0.83 0.79 0.27 0.77 1.12 1.56 1.10 0.85	removed jpper limit 4.31 4.33 4.38 2.04 4.39 4.27 4.37 4.15 4.01	<b>p-Value</b> 0.121 0.183 0.174 0.131 0.168 0.251 0.353 0.255 0.202	Differ	ence in vith stud	means dy rem	(95% ( noved	CI) 	

FIGURE 4. Meta-analysis for International Prostate Symptom Score (IPSS). (A) Pooled estimate. (B) Sensitivity analysis.

		St	atistics for	each st	udy						
Study name	Differen in mean	ce Standa Is erroi	rd Lower limit	wer Upper p-Value Ro nit limit w		Relative weight	Differ	Difference in means		and 95	% CI
Gacci (2015)	0.10	0.38	-0.64	0.84	0.792	24.9					
Pan (2014)	-4.70	0.13	-4.95	-4.45	< 0.001	25.3			T		
Zhang (2014)	-0.30	0.36	-1.01	0.41	0.408	25.0					
Gacci (2013)	-0.70	0.43	-1.54	0.14	0.104	24.8					
Pooled estimate	-1.41	1.50	-4.35	1.52	0.345						
(Random)							-8.00	-4.00	0.00	4.00	8.00
							Fevour	s no MS	5	Fevo	urs MS
A											
	S	tatistics w	ith study	removed	1	Differen		ana (05	04 CD		
Study name	Point S	tandard error	Lower U limit	opper limit F	p-Value	wit	h study	remove	d		
Gacci (2015)	-1.92	1.69	-5.23	1.40	0.257			- 1	1		
Gacci (2015) Pan (2014)	-1.92 -0.27	1.69 0.22	-5.23 -0.71	1.40 0.17	0.257 0.230			-			
Gacci (2015) Pan (2014) Zhang (2014)	-1.92 -0.27 -1.78	1.69 0.22 1.78	-5.23 -0.71 -5.28	1.40 0.17 1.72	0.257 0.230 0.318			_			
Gacci (2015) Pan (2014) Zhang (2014) Gacci (2013)	-1.92 -0.27 -1.78 -1.65	1.69 0.22 1.78 1.83	-5.23 -0.71 -5.28 -5.22	1.40 0.17 1.72 1.93	0.257 0.230 0.318 0.367			_			
Gacci (2015) Pan (2014) Zhang (2014) Gacci (2013) Pooled estimate	-1.92 -0.27 -1.78 -1.65 -1.41	1.69 0.22 1.78 1.83 1.50	-5.23 -0.71 -5.28 -5.22 -4.35	1.40 0.17 1.72 1.93 1.52	0.257 0.230 0.318 0.367 0.345			-			
Gacci (2015) Pan (2014) Zhang (2014) Gacci (2013) Pooled estimate (Random)	-1.92 -0.27 -1.78 -1.65 -1.41	1.69 0.22 1.78 1.83 1.50	-5.23 -0.71 -5.28 -5.22 -4.35	1.40 0.17 1.72 1.93 1.52	0.257 0.230 0.318 0.367 0.345	-6.00 -3.0	00 0.00		6.00		

FIGURE 5. Meta-analysis for maximal flow rate. (A) Pooled estimate. (B) Sensitivity analysis.

Subgroup			Stati	stics for	each stu	dy			
by area	Study name	Difference in means	Standar d error	Lower limit	Upper limit	p-Value	Relative weight	Differen	ace in means and 95% CI
Asia	Cyrus (2014)	11.00	5.37	0.47	21.53	0.041	0.9		
	Pan (2014)	11.70	0.55	10.61	12.79	0.000	88.6		
	Zhang (2014)	12.90	2.12	8.74	17.06	0.000	6.0		
	Cao (2010)	16.10	2.49	11.22	20.98	0.000	4.4		
	Pooled estimate	11.96	0.52	10.94	12.98	0.000			
	(Fixed)						-25	.00 -12.50	0.00 12.50 25.00
	G : (2015)	0.50	5.(2	20.54	1.54	0.000	22.5	Fevours MS	Fevours no MS
Europe	Gacci (2015)	-9.50	5.65	-20.54	1.54	0.092	42.5	-	
	Gacci (2013)	-3.30	2.10	2 10	12 10	0.117	43.9		
	Pooled estimate	-1.90	3.55	-2.10	5.05	0.107	35.1		
	(Random)	1.90	5.00	0.05	5.05	0.572			
	()						-25	.00 -12.50	0.00 12.50 25.00
A								revours MS	revours no Mis
Subgroup			Stati	stics for	each stu	dy		84	
by area	Study name	Difference	Standar	Lower	Upper	p-Value	Relative	Differen	ice in means and 95% CI
	D (2014)	in means	d error	limit	limit	P 0.007	weight		
Asia	Pan (2014)	0.10	0.10	-0.09	0.29	0.297	17.9		
	$Z_{nang}(2014)$	0.30	0.21	-0.10	0.70	0.146	10.8		
	Pooled estimate	0.30	0.08	0.00	0.34	0.030	5.5		
	(Fixed)	0.17	0.00	0.00	0.54	0.044		I I	
	(1.000)							Fevours MS	Eevours no MS
Europe	Gacci (2015)	0.70	0.25	0.21	1.19	0.005	48.5	1 1	
	De Nunzio (2014)	-0.20	0.20	-0.59	0.19	0.313	51.5		
	Pooled estimate	0.24	0.45	-0.65	1.12	0.599			
	(Random)							1 1	100 100 200
								-2.00 -1.00 Fevours MS	Fevours no MS
В									
Subgroup	Study name	Difference	Stati	stics for	each stu	dy	Delativo	Differen	ace in means and 95% CI
Subgroup by area	Study name	Difference	Stati Standar d error	stics for Lower limit	each stu Upper limit	dy p-Value	Relative	Differen	ice in means and 95% CI
Subgroup by area Asia	Study name	Difference in means 0.20	Stati Standar d error 1.55	stics for Lower limit -2.84	each stu Upper limit 3.24	<b>b</b> <b>p-Value</b> 0.897	Relative weight 21.5	Differen	nce in means and 95% CI
Subgroup by area Asia	Study name Cyrus (2014) Pan (2014)	Difference in means 0.20 6.20	Stati Standar d error 1.55 0.21	stics for Lower limit -2.84 5.79	each stu Upper limit 3.24 6.61	<b>p-Value</b> 0.897 0.000	Relative weight 21.5 26.8	Differen	nce in means and 95% CI
Subgroup by area Asia	Study name Cyrus (2014) Pan (2014) Zhang (2014)	Difference in means 0.20 6.20 0.00	Stati Standar d error 1.55 0.21 0.78	stics for Lower limit -2.84 5.79 -1.52	each stu Upper limit 3.24 6.61 1.52	dy p-Value 0.897 0.000 1.000	<b>Relative</b> weight 21.5 26.8 25.3	Differen	ice in means and 95% CI
Subgroup by area Asia	<b>Study name</b> Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010)	Difference in means 0.20 6.20 0.00 2.70	Standar d error 1.55 0.21 0.78 0.48	stics for Lower limit -2.84 5.79 -1.52 1.75	each stu Upper limit 3.24 6.61 1.52 3.65	dy p-Value 0.897 0.000 1.000 0.000	Relative weight 21.5 26.8 25.3 26.3	Differer	nce in means and 95% CI
Subgroup by area Asia	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate	Difference in means 0.20 6.20 0.00 2.70 2.42	Stati           Standar           d error           1.55           0.21           0.78           0.48           1.61	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73	each stu Upper limit 3.24 6.61 1.52 3.65 5.57	dy           p-Value           0.897           0.000           1.000           0.000           0.133	<b>Relative</b> weight 21.5 26.8 25.3 26.3	Differen	nce in means and 95% CI
Subgroup by area Asia	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random)	Difference in means 0.20 6.20 0.00 2.70 2.42	Stati           Standar           d error           1.55           0.21           0.78           0.48           1.61	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73	each stu Upper limit 3.24 6.61 1.52 3.65 5.57	dy p-Value 0.897 0.000 1.000 0.000 0.133	Relative weight 21.5 26.8 25.3 26.3	Differen	the in means and 95% CI
Subgroup by area Asia	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random)	Difference in means 0.20 6.20 0.00 2.70 2.42	Stati           Standar           d error           1.55           0.21           0.78           0.48           1.61	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73	each stu Upper limit 3.24 6.61 1.52 3.65 5.57	dy p-Value 0.897 0.000 1.000 0.000 0.133	Relative weight 21.5 26.8 25.3 26.3 39.0	Differen -8.00 -4.00 Fevours MS	the in means and 95% CI
Subgroup by area Asia Europe	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random) Gacci (2015) De Nunzio (2014)	Difference in means 0.20 6.20 0.00 2.70 2.42 -0.50 0.10	Stati           Standar           d error           1.55           0.21           0.78           0.48           1.61           0.55           0.80	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73 -1.58 -1.47	each stu Upper limit 3.24 6.61 1.52 3.65 5.57 0.58 1.67	dy p-Value 0.897 0.000 1.000 0.000 0.133 0.362 0.901	Relative weight 21.5 26.8 25.3 26.3 39.0 29.5	Differen -8.00 -4.00 Fevours MS	the in means and 95% CI
Subgroup by area Asia Europe	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random) Gacci (2015) De Nunzio (2014) Gacci (2013)	Difference in means 0.20 6.20 0.00 2.70 2.42 -0.50 0.10 1.60	Stati Standar d error 1.55 0.21 0.78 0.48 1.61 0.55 0.80 0.74	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73 -1.58 -1.47 0.14	each stu Upper limit 3.24 6.61 1.52 3.65 5.57 0.58 1.67 3.06	dy p-Value 0.897 0.000 1.000 0.000 0.133 0.362 0.901 0.031	Relative weight 21.5 26.8 25.3 26.3 39.0 29.5 31.5	Differen -8.00 -4.00 Fevours MS	the in means and 95% CI
Subgroup by area Asia Europe	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random) Gacci (2015) De Nunzio (2014) Gacci (2013) Pooled estimate	Difference in means 0.20 6.20 0.00 2.70 2.42 -0.50 0.10 1.60 0.34	Stati Standar d error 1.55 0.21 0.78 0.48 1.61 0.55 0.80 0.74 0.64	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73 -1.58 -1.47 0.14 -0.92	each stu Upper limit 3.24 6.61 1.52 3.65 5.57 0.58 1.67 3.06 1.60	dy p-Value 0.897 0.000 1.000 0.000 0.133 0.362 0.901 0.031 0.599	Relative weight 21.5 26.8 25.3 26.3 26.3 39.0 29.5 31.5	Differen -8.00 -4.00 Fevours MS	ace in means and 95% CI
Subgroup by area Asia Europe	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random) Gacci (2015) De Nunzio (2014) Gacci (2013) Pooled estimate (Random)	Difference in means 0.20 6.20 0.00 2.70 2.42 -0.50 0.10 1.60 0.34	Stati           Standar           d error           1.55           0.21           0.78           0.48           1.61           0.55           0.80           0.74           0.64	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73 -1.58 -1.47 0.14 -0.92	each stu Upper limit 3.24 6.61 1.52 3.65 5.57 0.58 1.67 3.06 1.60	dy p-Value 0.897 0.000 1.000 0.000 0.133 0.362 0.901 0.031 0.599	Relative weight 21.5 26.8 25.3 26.3 39.0 29.5 31.5	Differen -8.00 -4.00 Fevours MS	the in means and 95% CI
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Subgroup by area Asia Europe C Subgroup by area Asia Europe	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random) Gacci (2015) De Nunzio (2014) Gacci (2013) Pooled estimate (Random)  Study name Pan (2014) Zhang (2014) Pooled estimate (Random)  Gacci (2015) Gacci (2013) Pooled estimate (Fixed)	Difference in means 0.20 0.00 2.70 2.42 -0.50 0.10 1.60 0.34 Difference in means -4.70 -0.30 -2.51 0.10 -0.70 -0.25	Stati Standar d error 1.55 0.21 0.78 0.48 1.61 0.55 0.80 0.74 0.64 Standar d error 0.13 0.36 2.20 0.38 0.43 0.28	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73 -1.58 -1.47 0.14 -0.92 stics for Lower limit -4.95 -1.01 -6.82 -0.64 -1.54 -0.81	each stu Upper limit 3.24 6.61 1.52 3.65 5.57 0.58 1.67 3.06 1.60 each stu Upper limit -4.45 0.41 1.80 0.84 0.144 0.31	dy p-Value 0.897 0.000 0.000 0.000 0.133 0.362 0.901 0.031 0.599 dy p-Value 0.000 0.408 0.253 0.792 0.10 0.380	Relative weight 21.5 26.3 25.3 26.3 39.0 29.5 31.5 31.5 <b>Relative</b> weight 50.3 49.7 56.3 43.7	Differen -8.00 -4.00 Fevours MS -8.00 -4.00 Differen -8.00 -4.00 Fevours no MS -8.00 -4.00	the in means and 95% CI
Subgroup by area Asia Europe C Subgroup by area Asia Europe	Study name Cyrus (2014) Pan (2014) Zhang (2014) Cao (2010) Pooled estimate (Random) Gacci (2015) De Nunzio (2014) Gacci (2013) Pooled estimate (Random)  Study name Pan (2014) Zhang (2014) Pooled estimate (Random)  Gacci (2015) Gacci (2013) Pooled estimate (Fixed)	Difference in means 0.20 6.20 0.00 2.70 2.42 -0.50 0.10 1.60 0.34 Difference in means -4.70 -0.30 -2.51 0.10 -0.70 -0.25	Stati           Standar           d error           1.55           0.21           0.78           0.48           1.61           0.55           0.80           0.74           0.64           Stati           Stati           0.13           0.36           2.20           0.38           0.43           0.28	stics for Lower limit -2.84 5.79 -1.52 1.75 -0.73 -1.58 -1.47 0.14 -0.92 stics for Lower limit -4.95 -1.01 -6.82 -0.64 -1.54 -0.81	each stu Upper limit 3.24 6.61 1.52 3.65 5.57 0.58 1.67 3.06 1.60 <b>each stu</b> Upper limit -4.45 0.41 1.80 0.84 0.144 0.31	dy p-Value 0.897 0.000 0.000 0.000 0.133 0.362 0.901 0.031 0.599 dy p-Value 0.000 0.408 0.253 0.792 0.10 0.380	Relative weight           21.5           26.3           25.3           26.3           39.0           29.5           31.5           Relative weight           50.3           49.7           56.3           43.7	Differen -8.00 -4.00 Fevours MS -8.00 -4.00 Fevours MS Differen -8.00 -4.00 Fevours no MS	tee in means and 95% CI

FIGURE 6. Subgroup analysis by area (Asia and Europe) (A) prostate volume (B) PSA (C) IPSS, and (D) maximal flow rate.

 $(Q = 130.9, P < 0.001; I^2 = 99.2)$ ; thus, a random-effects model was used. Two studies from Europe<sup>21,26</sup> reported maximal flow rate data, and minor heterogeneity was present (Q = 1.9,  $P = 0.163; I^2 = 48.5\%$ ); thus, a fixed-effects model was used. For both Asia and Europe, the pooled estimates showed no significant difference in maximal flow rate between patients with and without MS (Figure 6D).

# DISCUSSION

This study aimed to evaluate the association of MS with characteristics of BPH. The results showed that BPH patients with MS had a significantly higher prostate growth rate and larger prostate volume than those without MS. However, IPSS and maximal flow rate were not different between BPH patients with and without MS, and a borderline nonsignificant difference in PSA between patients with and without MS was seen. Subgroup analysis by region, however, indicated that Asian patients with MS had a larger prostate volume and PSA than those without MS, but this finding was not present in European patients. Although there have been other studies examining the association between MetS and BPH, this was the first to provide a comprehensive examination of MS and various measures of BPH.

Epidemiological studies have indicated a possible association between MS and prostatic conditions,<sup>30,31</sup> and some studies have shown a increased prostate growth and larger prostate volume in BPH patients with MS than those without.<sup>4–6</sup> It has also been reported that MS is associated with an increased risk of LUTS as a result of prostatic enlargement.<sup>7,32</sup> Age-related changes in androgens have been generally accepted to be the primary factor involved in the pathogenesis of BPH.<sup>33</sup>

Although it is becoming apparent that there is an association with metabolic derangements and BPH, the mechanisms by which the derangements of MS may led to prostatic hyperplasia and LUTS remain to be fully elucidated. Some studies have suggested that insulin resistance and hyperinsulinemia are possible causative factors of BPH in patients with MS.<sup>5,34–38</sup> Other authors have suggested that chronic inflammation is the causative link between MS and LUTS and BPH. A recent systematic review of the literature by He et al<sup>39</sup> suggested that the proinflammatory state present in patients with MS results in inflammatory cell infiltration of prostatic and adipose tissue with subsequent tissue remodeling and overgrowth. Prostate tissue specimens of patients with BPH have been shown to have elevated levels of inflammatory cells,<sup>39</sup> and prostate volume and IPSS have been directly correlated with the level of inflammation in patients with BPH/LUTS.39

In another recent meta-analysis, Gacci et al<sup>15</sup> included 8 studies which enrolled 5403 patients, of which 1426 had MS. Patients with MS had a significantly higher total prostate volume as compared with those without MS (+1.8 mL, 95% CI: 0.74–2.87; P < 0.001); however, there was no difference in IPSS or LUTS subdomain scores between the groups. Metaregression analysis showed that differences in total prostate volume were significantly higher in older and obese patients in contrast to those with low HDL-C concentrations. The study did not examine other measures such as prostate growth rate or maximal flow. In the present study, the report by Aktas et al<sup>29</sup> did not include outcome measures appropriate for the metaanalysis. The study examined the relationship between MS, erectile dysfunction (ED), and LUTS in 106 patients with BPH, account off 31.1% (33) to whom had MS. The analysis showed a significant difference between ED groups with respect to the presence of MS (P = 0.032), but MS was not associated with the severity of LUTS (P = 0.144), nor was there a correlation between ED and LUTS severity (P = 0.303).

Other studies have examined the association of MS with various measures of BPH. In a study of 401 elderly Chinese men, Zhang et al<sup>24</sup> found that body mass index (BMI), waist circumference, fasting glucose, glycosylated hemoglobin, triglyceride, fasting insulin, and insulin resistance assessed by homeostasis model assessment of insulin resistance (HOMA-IR) were higher and HDL-C was lower in BPH patients with MS than in those without MS. Furthermore, patients with MS had a significantly larger prostate volume (P = 0.000) and longer duration of LUTS (P = 0.006), and prostate volume was positively correlated with BMI (P = 0.000), fasting insulin (P = 0.001), HOMA-IR (P = 0.003) and inversely correlated with HDL-C (P = 0.000). In another study of 764 Chinese males older than 40 years, multivariate analysis showed that aging, cigarette smoking, lack of regular exercise, and larger prostate volume were independent predictors for moderate/severe LUTS, and risk factors for LUTS were influenced by the presence of MS.<sup>40</sup> Ozden et  $al^{28}$  studied 78 patients with BPH and LUTS and found that those with MS had significantly higher median body weight, BMI, serum glucose, serum triglyceride, and PSA levels, but lower HDL-C level, compared with BPH patients without MS. The median annual total prostate growth rate (1.0 mL/y), and median annual transitional zone prostate growth rate (1.25 mL/y) were significantly higher in patients with MS than those without (0.64 mL/y and 0.93 mL/y, respectively, both P < 0.05). Interestingly, a study of only Chinese patients by Zou et al<sup>41</sup> found that patients with MS had a significantly higher PSA level than those without MS, which is similar to the subgroup analysis of Asian patients in our study. Thus, race may be a factor contributing to the different results in different studies.

Measures of clinical progression of BPH include quality of life, urinary retention, and risk of surgical intervention. However, these factors were not examined in the current analysis because of the 9 included studies, of which only 2 reported results of acute urinary retention, only 2 studies reported quality of life results, and only 1 study mentioned of risk of surgical intervention. Of the articles that reported rate of acute urinary retention, Pan et al<sup>25</sup> found acute urinary retention in 82% of patients with MS and in 17% of patients without MS, and Cao et al<sup>27</sup> reported a rate of 26.2% in patients with MS and 10.3% in patients without MS. Overall, the rate of acute urinary retention had tendency to be higher in patients with MetS than those without MS. As to quality of life, De Nunzio et al<sup>23</sup> reported no difference in quality of life between patients with and without MS. Pan et al,<sup>25</sup> however, reported that patients with MS had significantly higher IPSS quality of life score  $(4.94 \pm 1.06)$  than did patients without MS  $(3.31 \pm 0.95)$  (*P* < 0.001).

There are limitations of this analysis that have to be considered. The definition of MS used varied between the studies, and the number of available studies and data were limited. We did not examine characteristics of MS such as BMI and waist circumference, nor the mechanisms by which MS is associated with BPH examined. Five studies used transrectal ultrasonography, 1 study used transabdominal and transrectal ultrasonography, 1 study used transabdominal ultrasonography, and 2 studies used ultrasonography without mention of the site. Study has shown that the results from transabdominal ultrasonography are not consistent with those from transrectal sonography when used to measure prostate volume,<sup>42</sup> and this may have led to bias in the measurement of prostate volume.

In conclusion, the results of this meta-analysis are consistent with literature indicating that BPH patients with MS have a higher prostate growth rate and larger prostate volume than those without MS. However, measures of LUTS were not different between patients with and without MS. Further study is necessary to elucidate the association of BPH and metabolic disorder elements and the potential risk of disease progression in BPH patients with MS.

# ACKNOWLEDGMENT

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