Association between benign prostate hyperplasia and metabolic syndrome in men under 60 years old: a meta-analysis

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Abstract

Objective: To assess the potential relationship between benign prostate hyperplasia (BPH) and metabolic syndrome in men under 60 years old.

Methods: We searched the Medline, Embase, and Web of Science databases for studies of patients with metabolic syndrome and BPH using the key words 'metabolic syndrome', 'benign prostatic hyperplasia', and 'BPH'. The odds ratios (ORs) and 95% confidence intervals (95%CIs) were extracted from the included studies and the role of metabolic syndrome in BPH and its characteristics (International Prostate Symptom Score (IPSS), total prostate volume (TPV), post-void residual (PVR)) were evaluated by meta-analysis.

Results: Six comparative studies comprising 61,826 individuals were identified and included in this meta-analysis. There were significant correlations between metabolic syndrome and BPH (OR = 1.24, 95%CI = 1.19–1.29), clinical BPH (OR = 1.37, 95%CI = 1.03–1.70), and TPV (OR = 2.34, 95%CI = 1.25–3.42). However, there was no significant association between metabolic syndrome and IPSS (OR = 1.19, 95%CI = 0.35–2.04) or PVR (OR = 2.15, 95% CI = 0.95–3.34).

Conclusions: These results indicate that metabolic syndrome is significantly and positively correlated with the incidence of BPH in younger men aged <60 years. However, there was no significant relationship between metabolic syndrome and BPH-related symptoms.

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Introduction

Benign prostate hyperplasia (BPH) is characterized by increased prostate volume, a relatively narrow urethra, recurrent urinary tract infections, and lower urinary tract symptoms (LUTS). BPH is common among older men, with potentially significant impacts on their daily life.[1] The prevalence of BPH increases with age, with an increasing incidence of pathological BPH from 8% to 80% between men in their 40s and 90s, respectively.[2] However, social economic lifestyle changes have been reflected by a significant increase in the age-adjusted prevalence of BPH in past decades.[3] In addition to age, emerging evidence has suggested that other factors may also be involved in the development of BPH, including metabolic syndrome, androgen disorders, and ethnicity.[3–5] Thus although BPH has traditionally been regarded as an age-dependent disease, its incidence in the younger male population has increased in recent years, and it is therefore imperative to identify the risk factors of BPH in this young population of men under 60 years old.

Like BPH, metabolic syndrome, manifesting as obesity, low high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated triglycerides, is also an age-dependent condition. Numerous recent studies have indicated that metabolic syndrome may be involved in the development of BPH.[4,5] However, the components of metabolic syndrome could be positive or negative predictors or BPH,[6,7] and the mechanism of interaction between metabolic syndrome and BPH still needs to be elucidated.

Although some studies have examined the association between metabolic syndrome and BPH based on the overall worldwide population, regardless of age,[8,9] both age and region contribute to the incidences of metabolic syndrome and BPH, leading to potentially unreliable results in non-adjusted analyses. BPH is an age-dependent disease, and the risk factors for BPH in the young male population under 60 are still unclear.[10] We therefore performed a meta-analysis to identify the association between metabolic syndrome and BPH among men under 60.

Materials and methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).[11]

Literature search

We searched the Medline, Embase, and Web of Science databases up to 20 October 2018 for studies involving metabolic syndrome and BPH using the following keywords: 'metabolic syndrome', 'benign prostatic hyperplasia', and 'BPH'. Related references in the identified records were also reviewed for further potential inclusions. Duplicate records were removed using Mendeley Desktop Software (Elsevier, Amsterdam, The Netherlands).

Inclusion and exclusion criteria

Studies were included if the diagnosis of metabolic syndrome was based on meeting three of the following five criteria: waist circumference ≥85 cm; systolic blood pressure ≥130 mmHg and/or diastolic ≥85 mmHg and/or receiving antihypertensive treatment; HDL-C <40 mg/dL and/or receiving treatment for reduced HDL-C; elevated fasting blood sugar ≥100 mg/dL and/or drug treatment for elevated FBS; and elevated triglycerides ≥150 mg/dL and/or receiving antihypercholesterolemic treatment. Included studies were also required to provide detailed extractable information about the association between metabolic syndrome and BPH or BPH characteristics (International Prostate Symptom Score (IPSS), total prostate volume (TPV), postvoid residual (PVR)), and to be published in English. Studies were excluded if they met any of the following criteria: studies not carried out in humans; odds ratios (ORs) and 95% confidence intervals (95% CIs) could not be extracted or calculated; not original studies (e.g., reviews, letters, editorials, case reports); and records not relevant to the association between metabolic syndrome and BPH or BPH-related characteristics.

Data synthesis and analysis

The following items were extracted using a predefined table: first author (year of publication), country, study design, definition of metabolic syndrome, group (with or without metabolic syndrome), case number, mean age, body mass index (kg/m^2), IPSS, and mean prostate volume (MPV; mL). The methodological quality of each study was evaluated using the Newcastle–Ottawa Scale (NOS), including the general aspects of subject selection, comparability of groups, and clinical outcomes. The total NOS score ranged from 0 to 9, with a higher score indicating better methodological quality. Both the data extraction and quality assessment of the included studies were checked by two reviewers independently, and any disagreement was addressed through discussion with a third reviewer.

Statistical analysis

The ORs and 95% CIs for individuals with and without metabolic syndrome were extracted to evaluate the potential role of metabolic syndrome in the development of BPH and its characteristics (TPV ≥30 mL, PVR ≥39 mL, and IPSS >7). The ORs were further pooled and analyzed using Stata software, version 12.0 (StatCorp, College Station, TX, USA). Heterogeneity among the included studies was assessed using the I^2 statistic and P-value. If the I^2 value was >50% or $P < 0.05$, indicating the presence of significant heterogeneity, we preferred to calculate the pooled ORs using a random-effects model; otherwise, the analyses were performed using a fixed-effects model. A pooled result with an OR >1, with 1 not included in its 95%CI, indicated that metabolic syndrome was significantly associated with BPH and its characteristics. We used the 'trim and fill' method to detect potential unpublished studies and validate our primary conclusions. A value of $P<0.05$ was considered significant.

Results

Literature search and study selection

A total of 346 records were initially identified using the search strategy described above, of which 213 studies remained after the deletion of duplicates. After checking the titles and abstracts, 208 studies were removed because they were animal studies, editorials, case reports, reviews, or lacked data or definition criteria for metabolic

syndrome or BPH. Six studies were therefore included for further analysis,[12–17] comprising 61,826 individuals (20,176 individuals with metabolic syndrome, 41,650 individuals without metabolic syndrome). The flow chart for the study is depicted in Figure 1.

Characteristics of the included studies

The population sizes of the included studies ranged from 778 to 57,790. All the study subjects were from Asian countries (China, Korea) and all were aged under 60 years. The included studies were published from 2012 to 2018 in English. One study was prospectively designed, four studies were retrospectively designed, and the design of the remaining study was not reported. Four of the six studies used the National Cholesterol Education Program-Adult Treatment Panel III

(NCEP-ATTIII),[18] one used the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLB) and International Diabetes Federation (IDF),[19] and the remaining study used the Abdominal Obesity and Metabolic Syndrome (AOMS) definition criteria for metabolic syndrome.[20] The ORs and 95% CIs were extracted for individuals with metabolic syndrome who satisfied at least three of the required components versus individuals without metabolic syndrome. Two of the six studies were published by Park et al.[14,15] in 2012 and 2013, focusing on the relationship between metabolic syndrome and BPH and its components, respectively. The value of metabolic syndrome in BPH or clinical BPH (cBPH) was examined in two cohorts in Zhao et al.'s study,[12] respectively. The qualities of the included studies according to the NOS scores[21] ranged from 7 to 9 (mean
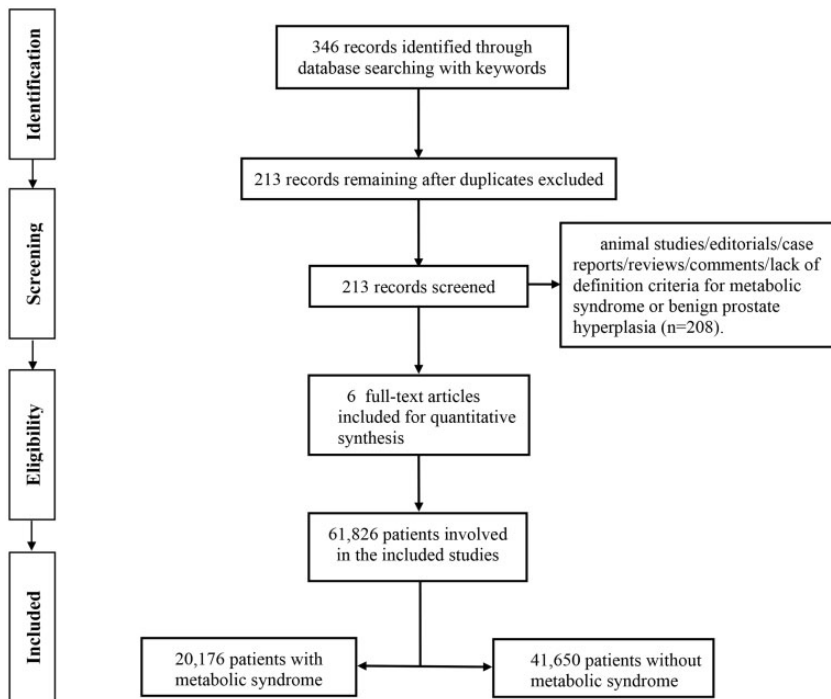

Figure 1. Flow chart for selection of included studies.

score, 8). The characteristics are detailed in Table 1.

Relationship between BPH and metabolic syndrome

Three studies including four cohorts and comprising 60,144 individuals reported the relationship between BPH and metabolic syndrome.[12–14] The pooled results indicated that metabolic syndrome was a risk factor for the development of BPH (OR = 1.24, 95%CI = 1.19–1.29), based on multivariate hazard ratios with a fixed-effects model without significant heterogeneity ($I^2 = 44\%$, $P = 0.148$) (Figure 2a). Moreover, two of the four cohorts focused on the relationship between metabolic syndrome and cBPH, defined as patients with BPH requiring treatment or with a history of medication. The pooled results derived from the random-effects model also showed that metabolic syndrome was significantly correlated with cBPH (OR = 1.37, 95%CI = 1.03–1.70) (Figure 2b).

Relationship between metabolic syndrome and TPV

Three studies including 2,906 individuals presented data on the relationship between metabolic syndrome and TPV.[15–17] The pooled results showed that metabolic syndrome was significantly correlated with higher TPV (TPV ≥30 mL vs. TPV >30 mL) (OR = 2.34, 95% CI = 1.25–3.42), based on random-effects analysis (Figure 3a).

Correlation between metabolic syndrome and PVR

The correlation between metabolic syndrome and PVR was reported in three studies involving 2,906 individuals.[15–17] The combined analysis indicated that metabolic syndrome was significantly correlated with PVR (OR = 2.15, 95% CI = 0.95–3.34),

derived from random-effects analysis (Figure 3b).

Relationship between metabolic syndrome and IPSS

Two studies including 2,128 individuals provided data to assess the relationship between metabolic syndrome and IPSS.[15,17] However, the pooled results suggested there was no significant relationship between metabolic syndrome and IPSS (IPSS >7 vs. IPSS ≤7) (OR = 1.19, 95% CI = 0.35–2.04) (Figure 3c).

Evaluation of publication bias

We used the trim and fill method to detect potential publication bias, which indicated that there were two, one, zero, one, and zero unpublished studies regarding the associations between metabolic syndrome and BPH, cBPH, TPV, PVR, and IPSS, respectively (Figure 4). However, the results derived from the trim and fill method were consistent with our previous conclusions. The results are detailed in Table 2.

Discussion

BPH has become one of the most common benign diseases affecting men worldwide. The incidence of BPH increases with age and imposes a great economic burden. BPH-related LUTS can also have significant effects on quality of life.[22] However, the specific mechanism responsible for the development of BPH remains unclear, and identifying the potential risk factors is thus an imperative issue. Recent epidemiological studies have suggested a possible association between BPH and metabolic syndrome conditions;[22,23] however, this relationship is still controversial due to heterogeneity among other factors, such as age and geographic region.[23,24] We therefore evaluated the role of metabolic syndrome in BPH in

young men under 60, taking account of age and population.

This meta-analysis evaluated six high-quality studies regarding the role of metabolic syndrome in the development of BPH and its related characteristics (TPV ≥ 30 mL, PVR ≥ 39 mL, and IPSS >7). The pooled results indicated that metabolic syndrome could be a potential risk factor for the development of BPH or cBPH. We also performed meta-analyses to assess the influence of metabolic syndrome on BPH-related characteristics, and showed that patients with metabolic syndrome were more likely to have a TPV ≥ 30 mL. However, the pooled results showed no significant association between metabolic syndrome and the BPH-related symptoms IPSS >7 and PVR ≥ 39 mL. Indeed, not all men with BPH present with clinical symptoms. The current results were based on primary data for men under 60, and represent the first meta-analysis to evaluate the association between metabolic syndrome and BPH in this young male population. Although the risk factors for the initiation of BPH in young people remain unclear, these results may provide a new direction for managing BPH in younger men.

Although numerous previous studies have reported the potential association between metabolic syndrome and BPH,[25] the mechanisms underlying this relationship still need to be identified. Hyperinsulinemia and insulin resistance induced by metabolic syndrome may promote the initiation and progression of BPH,[26] and recent studies[27] indicated that prostatic inflammation induced by metabolic syndrome may contribute to the development and progression of BPH. Although there are various potential mechanisms, Vignozzi et al.[28] proposed a '3-hit' hypothesis to interpret the relationship between BPH and metabolic syndrome: metabolic syndrome conditions can induce prostatic inflammation (1-hit), sustain the inflammation (2-hits), and

cause sex steroid abnormalities (3-hits), thus promoting remodeling and enlargement of the prostate.

Other studies that investigated the role of metabolic syndrome in BPH did not meet the criteria for inclusion in the current meta-analysis. Most of these related studies[29] also indicated that metabolic syndrome was a significant risk for BPH or its characteristics. However, Yang et al.[30] demonstrated that metabolic syndrome may have favorable effects on BPH-related symptoms in healthy middle-aged men. Two previous meta-analyses[9,31] evaluated the association between BPH and metabolic syndrome based on the overall population, and both concluded that metabolic syndrome was a key link in the development and progression of BPH. BPH is an age-dependent disease, and metabolic syndrome conditions differ among populations with different lifestyles and diet habits. Nevertheless, the previous meta-analyses did not account for the impact of age, and did not specifically investigate the association between BPH and metabolic syndrome in a young population. In contrast, the current meta-analysis included the most recent studies of the relationship between BPH and metabolic syndrome in men under 60, and demonstrated a role for metabolic syndrome in the development of BPH in this population.

There were some unavoidable limitations in this meta-analysis. First, although we adopted strict inclusion and exclusion criteria, there was still significant heterogeneity among the studies, especially with regard to the associations between metabolic syndrome and cBPH, TPV, and IPSS, which were pooled analyses using a random-effects model. Moreover, most of the included studies were retrospective, and may thus have included patient-selection bias. Finally, few studies focused on the association between metabolic syndrome and BPH in young Asian populations, and

Table 1. Characteristics of included studies.

Reference	Country	Design	Definition of metabolic syndrome	Measurement of prostate volume	Group	Case number	Mean age, years (range)	Checkpoints	Mean IPSS (range)	NOS
Park et al.[14]	Korea	Retrospective	NCEP-ATTIII	Transrectal ultrasound	With Mets	355	54 (52,56)	BPH	10 (5–15)	8
					Without Mets	869	54 (52,56)		10 (5–15)	
Kwon et al.[17]	Korea	NA	NCEP-ATTIII	Trans-rectal ultrasound	With Mets	208	54 (52–56)	TPV, PVR	14 (10,19)	7
					Without Mets	570	54 (52–56)		14 (10,19)	
Park et al.[15]	Korea	Retrospective	NCEP-ATTIII	Transrectal ultrasound	With Mets	355	54 (52,56)	TPV, PVR, IPSS	10 (5–15)	8
					Without Mets	869	54 (52,56)		10 (5–15)	
Yin et al.[16]	China	Retrospective	Abdominal obesity and metabolic syndrome	Transrectal ultrasound	With Mets	253	50–59	TPV, PVR, IPSS	NA	9
					Without Mets	651	50–59		NA	
Zhao et al.[12]	China	Prospective	AHA/NHLB, IDF	Suprapubic ultrasound	With Mets	258	54 (51,58)	BPH, cBPH	2 (1,4)	8
					Without Mets	872	52 (49,57)		2 (1,4)	
Yoo et al.[13]	Korea	Retrospective	NCEP-ATTIII	NA	With Mets	19102	50 (50–60)	cBPH	NA	8
					Without Mets	38688	50 (50–60)		NA	

IPSS, International Prostate Symptom Score; Mets, metabolic syndrome; NCEP-ATIII, National Cholesterol Education Program-Adult Treatment Panel III; BPH, benign prostate hyperplasia; TPV, total prostate volume; PVR, postvoid residual; NA, not assessed; AHA/NHL B, American Heart Association/National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; cBPH, clinical benign prostate hyperplasia.
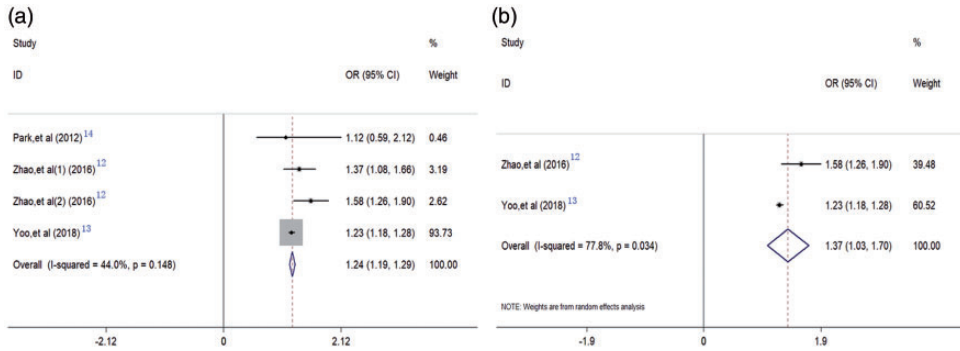
Figure 2. Forest plots evaluating the associations between benign prostatic hyperplasia (BPH) and metabolic syndrome. BPH and metabolic syndrome (a); clinical BPH and metabolic syndrome (b). OR, odds ratio; CI, confidence interval.
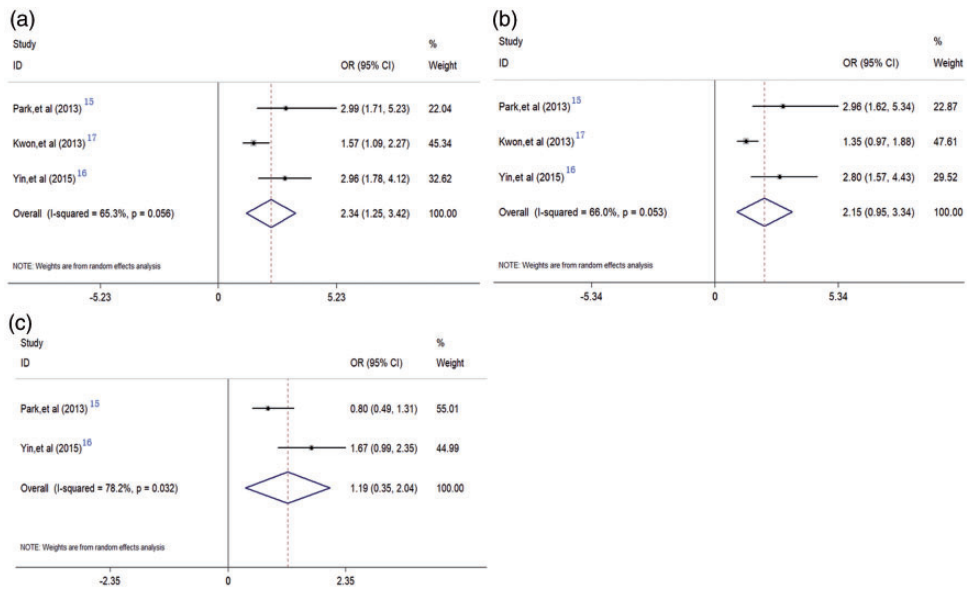

Figure 3. Forest plots evaluating the relationships between metabolic syndrome and benign prostatic hyperplasia (BPH)-related characteristics. Metabolic syndrome and total prostate volume (a); metabolic syndrome and postvoid residual (b); and metabolic syndrome and International Prostate Symptom Score (c).

the number of relevant studies included in this meta-analysis was therefore limited, and publication bias was also unavoidable. However, we performed a trim and fill analysis to identify potential unpublished studies, and further analyzed the results with

both fixed- and random-effects models to validate our conclusions.

In conclusion, this study represents the first meta-analysis to evaluate the relationship between BPH and metabolic syndrome among men aged under 60. Metabolic
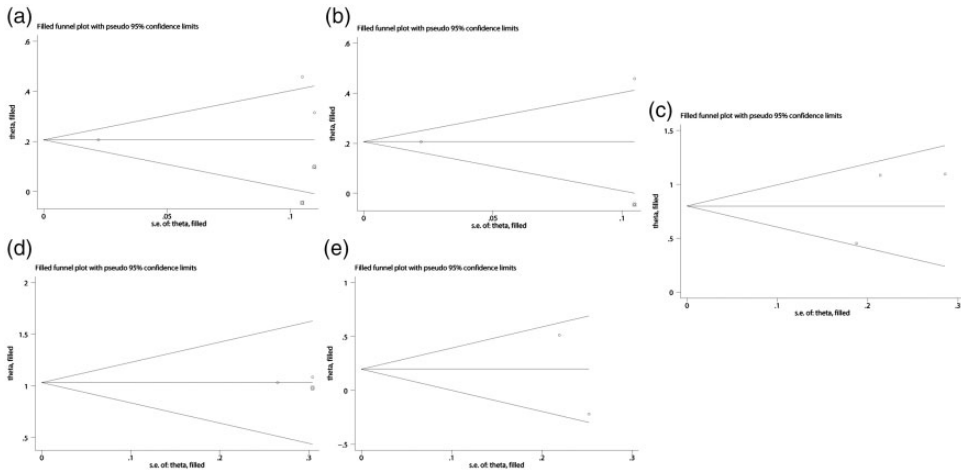
Figure 4. 'Trim and fill' results identifying potential unpublished studies for benign prostatic hyperplasia (BPH) and metabolic syndrome (a), clinical BPH and metabolic syndrome (b), total prostate volume and metabolic syndrome (c), postvoid residual and metabolic syndrome (d), and International Prostate Symptom Score and metabolic syndrome (e). Circles indicate included studies and squares indicate possible unpublished studies. s.e., standard error.

Table 2. Trim and fill results derived from fixed- and random-effects models.

Groups	Fixed model (OR, 95%CI)	P value	Random model (OR, 95%CI)	P value
Mets vs. BPH	1.229 (1.181, 1.279)	<0.001	1.229 (1.076, 1.404)	0.002
Mets vs. cBPH	1.229 (1.179, 1.281)	<0.001	1.229 (0.996, 1.516)	0.054
Mets vs. TPV	2.223 (1.734, 2.848)	<0.001	2.343 (1.491, 3.684)	<0.001
Mets vs. PVR	2.804 (2.021, 3.890)	<0.001	2.804 (2.021, 3.890)	<0.001
Mets vs. IPSS	1.216 (0.879, 1.683)	0.237	1.169 (0.570, 2.395)	0.670

Mets, metabolic syndrome; BPH, benign prostate hyperplasia; cBPH, clinical benign prostate hyperplasia; TPV, total prostate volume; PVR, postvoid residual; IPSS, International Prostate Symptom Score; OR, odds ratio; CI; confidence interval.

syndrome was significantly correlated with the development of BPH, cBPH, and TPV, but not with BPH-related symptoms such as IPSS and PVR. Further large-scale randomized controlled trials are required to validate the association between metabolic syndrome and BPH in younger men.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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