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Metabolic syndrome is associated with prostate enlargement: a systematic review, meta-analysis, and meta-regression on patients with lower urinary tract symptom factors

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Abstract

Background: Metabolic syndrome (MetS) is defined by at least three of the following five criteria: blood pressure ⩾130/85 mmHg, fasting blood glucose ⩾5.6 mmol/l, triglycerides concentration ⩾1.7 mmol/l, waist circumference ⩾102 cm (for men), and high-density lipoprotein cholesterol concentration <1.03 mmol/l (for men). MetS has been associated with worse lower urinary tract symptoms (LUTS) and higher International Prostate Symptom questionnaire scores.

Materials and Methods: MEDLINE, Cochrane, ClinicalTrials.gov, and SCOPUS were critically appraised for all peer-reviewed manuscripts that suitably fulfilled our protocol's inclusion criteria established *a priori*. Meta-analytical and meta-regression calculations were performed in R using the Sidik–Jonkman and Hartung–Knapp random effects model and predefined covariates.

Results: A total of 70 studies ($n = 90{,}206$) were included in qualitative synthesis. From these, 60 studies focused on MetS and LUTS: 44 reported positive correlations, 5 reported negative correlations, 11 reported no association, and 10 studies focused on MetS and total prostate volume (TPV). MetS positively correlated with moderate LUTS [odds ratio (OR) = 1.56, 95% confidence interval (CI) = 1.35–1.80], severe LUTS (OR = 2.35, 95% CI = 1.82–3.03), overactive bladder (OAB; OR = 3.2, 95% CI = 1.6–5.8), and nocturia severity (OR = 2.509, 95% CI = 1.571–4.007) at multivariate analysis. A total of 30 studies ($n = 22{,}206$) were included in meta-analysis; MetS was significantly associated with higher TPV (mean differences = 4.4450 ml, 95% CI = 2.0177–6.8723), but no significant predictive factors for effect sizes were discovered.

Conclusion: Our meta-analysis demonstrates a significant association between the aggravating effects of MetS, which commonly coexists with obesity and benign prostate enlargement.

Keywords: lower urinary tract symptoms, meta-analysis, metabolic syndrome, obesity, systematic review, total prostate volume

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Introduction

Metabolic syndrome (MetS) is defined by at least three of the following five criteria: blood pressure (BP) ⩾130/85 mmHg, fasting blood glucose (FBG) ⩾5.6 mmol/l, triglycerides (TG) concentration ⩾1.7, waist circumference (WC) ⩾102 cm for men and ⩾89 cm for women, and high-density lipoprotein cholesterol (HDL-C) concentration <1.03 mmol/l for men and <1.4 mmol/l for women.[1] One of the major contributing factors to MetS is obesity; the prevalence of those with obesity has almost since 1975.[2] In England, it affects 28% of adults and it was directly associated with 1117 hospital admissions in 2018/2019.[3,4]

Body mass index (BMI) ⩾35 kg/m^2 has been positively correlated with moderate–severe lower urinary tract symptoms (LUTS) [odds ratio (OR) = 1.38, 95% confidence interval (CI) = 1.17–1.63];[5] WC ⩾42 inches (106.7 cm) was also a significant factor.[6] In addition, low-density lipoprotein cholesterol (LDL-C) concentration >7.4 mmol/l caused a fourfold increased risk of benign prostatic hyperplasia (BPH; OR = 4.00, 95% CI = 1.27–12.63, $p = 0.02$).[7] LUTS encompass a variety of bladder conditions: BPH, urinary tract infection (UTI), overactive bladder (OAB), nocturia, interstitial cystitis (IC), and bladder pain syndrome (BPS). LUTS consist of storage symptoms (urinary incontinence, urgency, frequency, and nocturia), voiding symptoms (intermittency, slow stream, hesitancy, straining to void, terminal dribble, and splitting of stream), and post-micturition symptoms (incomplete bladder emptying).[8,9] Obesity and more specifically patients with a BMI ⩾35 kg/m^2 have been positively correlated with moderate–severe LUTS (OR = 1.38, 95% CI = 1.17–1.63).[5,7] LUTS leads to worsening quality of life, sleep, and mental health in men and women.[9] LUTS severity may be quantified by the International Prostate Symptom Score (IPSS) that looks mild, moderate, and severe symptoms.[8]

This systematic review and meta-analysis aims to review all existing evidence on the association between MetS and in LUTS – more specifically, the effect of MetS on prostatic inflammation and subsequent hyperplasia in patients with LUTS and BPH. MetS is a growing problem worldwide, and its role in LUTS is unclear; LUTS etiology is not entirely understood. While studies point toward an association between MetS and LUTS, several studies reported no association at multivariate analysis.[10–13] Our aim is to provide new insight and propose therapeutic targets for MetS and LUTS.

Materials and methods

The protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and followed methods outlined in The Cochrane Handbook for Systematic Reviews of Interventions.[14] This systematic review has been registered with PROSPERO (international prospective register of systematic reviews) with registration number CRD42020223412.

Search strategy

Two reviewers conducted systematic searches of the following databases: Medical Literature Analysis and Retrieval System online (MEDLINE), SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases. The following MeSH (Medical Subject Heading) terms were used: (((((metaflammation) OR (metabolic cells)) OR (mitochondrial dna)) OR (inflammaging)) OR (metabolic syndrome)) AND (((((lower urinary tract symptoms) OR (luts)) OR (urinary tract infection)) OR (uti)) OR (interstitial cystitis)). In addition, reference lists of selected articles and other literature sources were browsed to ensure a comprehensive literature search was completed. Searches filtered results based on year of publication date (last 10 years), and the last search was carried out on 24 October 2020.

Study selection

Studies were imported into Covidence [Covidence (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org)].[15] All studies were screened for selection by two reviewers independently (of a group of five) and any conflicts were resolved by a third reviewer. Selection was completed in two stages – first by title and abstract and then by full text. Studies were selected using specific criteria which removed duplicates. Five reviewers selected studies individually, and once completed, a second reviewer selected the studies. A third reviewer resolved conflicts. Studies were screened for title and abstracts and then full text screened. Studies were included if they met the inclusion criteria: cohort studies, case-control

studies, randomized clinical trials, and cross-sectional studies (no limit on sample size, setting, follow-up period, or intervention); men and/or women aged 18 years or above; any component of MetS; any LUTS condition, for example, LUTS/BPH, OAB, detrusor overactivity (DO), and urinary incontinence (UI); and original articles. Exclusion criteria included the following: studies including children, pregnant women, bladder or prostate cancers/other forms of cancers, and animal models; editorials, letters, case reports, opinion pieces, commentaries, systematic reviews, and meta-analyses; and articles not in English.

Data extraction

Five reviewers extracted data using Covidence.[15] A second reviewer checked the data extracted. Finally, the data were exported to Microsoft Excel from Covidence. Example of columns: reference, country, study design, start date, end date, method to classify LUTS, type of LUTS, sample size, gender, population description, MetS criteria, outcome measured, summary of association of Mets and LUTS, and quality assessment. Meta-analysis and meta-regression were conducted from February 2021 to 26 April 2021.

Quality assessment

Each study was assessed for bias using the Newcastle–Ottawa scale (NOS). Studies were evaluated on eight factors, categorized into three groups: selection (including whether the cohort is representative of the population), comparability (assessed on grounds of study design and the analysis performed), and outcome (i.e. the assessment of outcome, follow-up rate, and adequacy of follow-up period). Stars were awarded per category, with a maximum of four, two, and three stars possible for the 'selection', 'comparability', and 'outcome' categories, respectively.[16] Five reviewers assessed the studies to be of poor (three stars or less), fair (four–six stars), or good (seven–nine stars) quality (NOS). A risk of bias assessment using the Quality in Prognosis Studies (QUIPS) tool was also carried out for all 30 studies included in meta-analysis.[17] The QUIPS tool assessed study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis reporting, and overall risk of bias.

Data synthesis and statistical analysis

All meta-analytical calculations were carried out by an external statistician using R statistical software (v4.0.4) with meta package (v4.18-0). The drawn forest plots were contrived using this software. Pooled ORs were calculated with 95% CIs from the extracted count data, while continuous data were used to calculate pooled weighted mean differences (MD) with 95% CI. Pooled MD with 95% CI were calculated using the inverse variance method and random-effects model with Sidik–Jonkman estimation and Hartung–Knapp adjustment for random effects model. Presence of heterogeneity was tested using the χ^2 test and quantified with the I^2 statistic ($I^2 > 75\%$ considered significant). Heterogeneity was addressed by performing meta-regression analysis using mixed-effects model with predefined predictors (sample size, study rating, year of publication, and country of study). Meta-regression analysis was performed to address heterogeneity by checking for possible association of predefined factors (sample size, study rating, year of publication, and country of study) with effect size differences. Bubble plots were generated to visualize the results of meta-regression analysis. ORs were used to compare the relative odds of LUTS in relation to MetS. $OR < 1$ suggests the intervention or exposure is associated with reduced odds of said outcome occurring. $OR = 1$ suggests no association between the outcome and intervention. $OR > 1$ suggests higher odds of an outcome occurring as an association with an intervention.[14] Any potential publication bias was assessed with Egger's test of intercept and visual evaluation of the funnel plot.

Results

In total, 1741 studies were imported into Covidence, which removed four duplicates. Four reviewers screened 1737 studies for title and abstracts, and 1518 were excluded. Five reviewers screened the full text of the remaining 219 studies; 149 studies were excluded. Seventy studies were included in qualitative synthesis and 30 in meta-analysis (Figure 1). Three studies used the same patient cohorts and were excluded.[18–20] General characteristics of the included studies are presented in Table 1, while the outcomes measured and a summary of the association between MetS and LUTS are detailed in Table 2. A forest plot for total prostate volume (TPV) and MetS

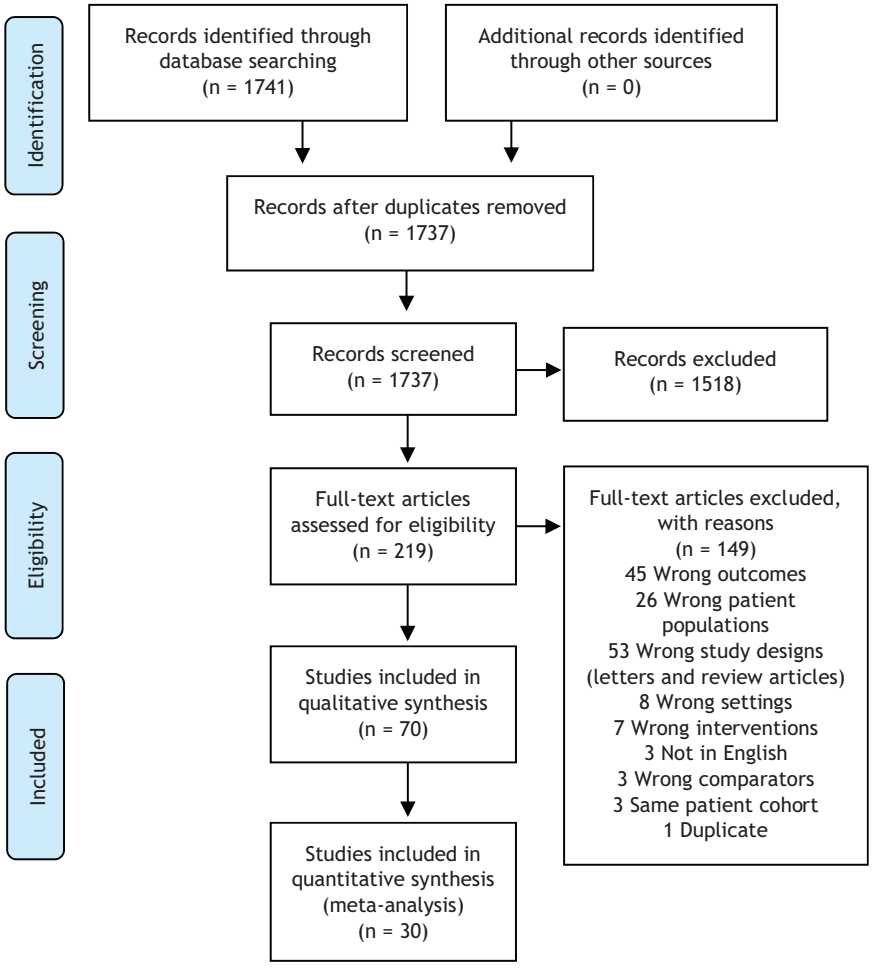

Figure 1. PRISMA flow diagram for studies assessed for eligibility from Moher *et al.*[21]

and mixed-effects model results are presented in Figure 2 and Table 3, respectively. Figure 3 represents meta-regression analysis (bubble plots) for age, study rating, and publication year. The results of the publication bias assessment – Egger's test of the intercept – are presented in Figure 4. Figure 5 represents a QUIPS Risk of Bias Assessment for the 30 studies included in meta-analysis is presented as a graph (Figure 5) and table (Table 4).

Summary of qualitative data

A total of 70 studies were included in qualitative synthesis. From these, 60 studies focused on MetS and LUTS: 44 reported positive correlations, 5 reported negative correlations, 11 reported no association, and 10 studies focused on MetS and TPV (Table 2). MetS positively correlated with moderate LUTS (OR = 1.56, 95% CI = 1.35–1.80; $p < 0.001$), severe LUTS (OR = 2.35, 95% CI = 1.82–3.03; $p < 0.001$),[66] OAB (OR = 3.2, 95% CI = 1.6–5.8, $p = 0.01$),[44] and nocturia severity (OR = 2.509, 95% CI = 1.571–4.007, $p = 0.001$)[34] at multivariate analysis. Demir *et al.*[10] reported positive correlations between MetS and LUTS (OR = 2.4, 95% CI = 1.24–4.59, $p = 0.009$); however, significance was lost at multiple logistic regression analysis. Baykam *et al.*[25] found no association between LUTS and BMI (kg/m^2); only FBG was significant at multivariate analysis ($\beta = 0.001$, $t = 3.491$, $p = 0.001$). Gao *et al.*[13] found that MetS was not associated with the severity of LUTS (multivariate: OR = 0.97; 95% CI = 0.67–1.39).

Summary of meta-analysis

Initially, data from 70 studies was extracted and a meta-analysis on MetS and LUTS, which

Table 1. General characteristics of studies included in systematic review.

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (*n*)	Sex	Population description	NOS rating
Akin *et al.*[22]	Turkey	Cohort	NCEP	OAB	OAB-V8	August 2012	December 2013	204	Female	Patients divided into two groups: patients with OAB and patients without OAB	9 – Good
Aktas *et al.*[23]	Turkey	Cohort	US NCEP-ATP III	LUTS	IPSS	January 2009	October 2009	106	Male	Patients over 50 years of age admitted to clinic with BPH-related LUTS	9 – Good
Barbosa *et al.*[24]	Brazil	Cohort	IDF, AHA, NHLBI	LUTS	IPSS	2012	2012	907	Male	All patients presenting for an institutional prostate cancer screening program in 2012 Screening for age ⩾50 and did not have urological follow-up	8 – Good
Baykam *et al.*[25]	Turkey	Cohort	NCEP-ATP III	LUTS/BPH	PRI	January 2013	March 2014	120	Male	Men over 50 years	8 – Good
Bray *et al.*[26]	The United Kingdom	Cohort	None given	OAB	ICIQ-FLUTS	Not defined		212	Female	36 control, 176 cases – all women discriminated according to ethnicity, parity, menopause, age, and BMI	8 – Good
Byun *et al.*[27]	Korea	Retrospective	NCEP-ATP III, AHA, NHLBI	BPH	TRUS, PSA	January 2005	December 2010	521	Male	Men aged who underwent TRUS; mean age was 53.8 ± 6.9 years	7 – Good
Choi *et al.*[28]	Korea	Retrospective	IDF 2009, NHLBI, WHF, IAS, IASO	BPH	TRUS, PSA	January 2007	July 2011	4111	Male	Routine checkups measuring PSA level and using TRUS; mean age was 54.0 ± 8.2 years	8 – Good
Chung *et al.*[29]	Taiwan	Cross-sectional	Ethnicity-specific for Chinese	OAB	OABSS	May 2008	November 2008	1301	Male	Diabetic male patients with or without nocturia	9 – Good
Coban *et al.*[30]	Turkey	Cohort	IDF 2005 criteria	LUTS	IPSS, QOL	May 2012	April 2013	107	Male	Presented at urology outpatients with LUTS/ED and at endocrinology outpatients for DM; sexually active patients aged ⩾44 years	9 – Good
Dagdeviren and Cengiz[31]	Turkey	Cohort	IDF 2006	OAB	OAB-V8	January 2015	September 2015	90	Female	Patients with OAB (30), patients with OAB and MetS (30), and healthy women without OAB and MetS (30)	8 – Good
Demir *et al.*[10]	Turkey	Cross-sectional	NCEP-ATP III	LUTS	IPSS-QOL	Not defined		190	Male	Male patients aged >44 years in a steady sexual relationship for the 6 months prior to study admitted to urology clinics with complaints of LUTS (from four different institutions)	8 – Good
De Nunzio *et al.*[32]	Italy	Cohort	ATP III	LUTS	IPSS	January 2009	Onward	431	Male	Patients >50 at urology outpatients with LUTS due to BPE	9 – Good

(Continued)

Table 1. (Continued)

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (*n*)	Sex	Population description	NOS rating
De Nunzio *et al.*[33]	Italy	Cohort	NCEP-ATP III	LUTS	IPSS, IIEF, MSHQ-EjD	January 2012	March 2016	220	Male	New patient aged >50 years with LUTS due to BPE attending outpatient clinic	9 – Good
De Nunzio *et al.*[34]	Italy	Cross-sectional	ATP III	LUTS, nocturia	IPSS	October 2009	Onward	492	Male	Men with LUTS/BPE	8 – Good
De Nunzio *et al.*[35]	Italy	Prospective cross-sectional	ATP III		IPPS	2015	Onward	227	Male	Patients with moderate–severe nocturia (voids per night), LUTS, and BPE undergoing monopolar TURP	9 – Good
Doğan *et al.*[36]	Turkey	Cross-sectional	NCEP-ATP III	LUTS	IPPS	Not defined		78	Male	78 male patients aged >40 years who consulted to urology polyclinics in Istanbul	8 – Good
Eom *et al.*[37]	South Korea	Cross-sectional	NCEP-ATP	LUTS, nocturia	IPSS	October 2003	February 2010	33,841	Male	Korean men ⩾30 years with IPSS data available and had routine health assessments	7 – Good
Eren and Horsanali[38]	Turkey	Retrospective cohort	IDF	LUTS	IPSS	January 2016	March 2018	356	Male	742 males with BPH/LUTS, 356 included in final analysis	9 – Good
Fu *et al.*[39]	China	Prospective cohort	NCEP-ATP III for Asian Americans	UI, UTI, LUTS	IPSS	April 2013	April 2016	1007	Male	Community-dwelling men with LUTS/BPH aged 45 to 78 within Beijing region; out of 1007 enrolled, 525 were carried forward	9 – Good
Gacci *et al.*[40]	Italy	Retrospective cohort	IDF, AHA, NHLBI	LUTS	IPSS, IS	January 2010	September 2011	271	Male	Consecutive patients treated with simple prostatectomy for BPH	9 – Good
Gacci *et al.*[41]	Italy	Prospective cohort	NCEP-ATP III	LUTS/BPE	IPSS, PSA, PV	January 2012	September 2013	379	Male	Patients undergone prostatectomy/ TURP for LUTS due to large BPE	8 – Good
Gao *et al.*[13]	China	Cross-sectional	2005 NCEP-ATP III	LUTS	IPSS, QOL	September 2009	December 2009	3103	Male	Non-institutionalized Chinese male individuals 17 to 88 years old	9 – Good
Haghsheno *et al.*[42]	Sweden	Cross-sectional	Not defined	LUTS, UI, BPE	IPSS, UI questionnaires	Not defined		976	Male	Random selection using national population registers; Swedish study population of 3014 men, aged 69 to 80 years, from three centers – study on Gothenburg group	8 – Good
Jeong *et al.*[43]	Korea	Retrospective cross-sectional	NCEP	Voiding, storage	IPSS	January 2006	September 2010	1506	Male	Korean men between 30 and 60 years, excluded men with prostatitis, high PSA or abnormal DRE or TRUSG findings	9 – Good
Karoli *et al.*[44]	India	Cross-sectional cohort	NCEP-ATP III	OAB	AUA-SI, IUSS, PVR	January 2012	December 2012	102	Female	Women with T2D at diabetic clinic of a medical college hospital with LUTS	9 – Good
Kim *et al.*[45]	South Korea	Retrospective cohort	NCEP-ATP III	LUTS	IPSS	2012	2014	4256	Male	Healthy native Korean men aged 40 to 65 years who voluntarily underwent a medical checkup	9 – Good

(Continued)

Table 1. (Continued)

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (*n*)	Sex	Population description	NOS rating
Kupelian *et al.*[46]	The United States	Randomized controlled trial	ATP III	LUTS	AUA-SI	April 2002	June 2005	1899	Male	A random sample of men aged 30 to 79 years	8 – Good
Kwon *et al.*[47]	Korea	Retrospective cohort	Not defined	BPO	IPSS, QOL, Qmax, PVR	March 2012	March 2016	151	Male	Patients who underwent HoLEP for BPO; patients received BPH medication at least 6 months prior to surgery	9 – Good
Lai *et al.*[48]	The United States	Observational cohort	ATP III, IDF	OAB, UI	LUTS Tool	June 2015	January 2017	920	Male, female	Patients >18 years who presented to a urologist or urogynecologist for treatment of LUTS: 456 males and 464 females	8 – Good
Lee *et al.*[49]	The United States	Retrospective cohort	Not defined	LUTS	IPSS, TRUS	January 2006	June 2008	409	Male	Men aged >40 years with moderate–severe LUTS with no previous treatment; divided into three groups according to WC	9 – Good
Lee *et al.*[11]	South Korea	Prospective cohort	NCEP-ATP III	LUTS	IPSS	2004	Onward	1520	Male	Resident within the borders of the survey area ⩾6 months; study on 328 men (aged 50–89 years) randomly selected among 1520	8 – Good
Lotti *et al.*[50]	Italy	Retrospective cohort	NCEP	Infertility	IPSS, NIHCPSI	January 2010	December 2011	187	Male	Male patients attending infertility clinic mean age 36.5	9 – Good
Martin *et al.*[51]	Australia	Cohort	Not defined	LUTS	IPSS	Not defined		1103	Male	Males aged 35 to 80 residing in the northern and western suburbs of Adelaide	7 – Good
Mitsui *et al.*[52]	Japan	Cohort	Not defined	LUTS	24-h bladder diary, IPSS, QOL	Not defined		58	Male	LUTS group: patients with IPSS ⩾8; Control group: patients with IPSS ⩾7	8 – Good
Mossa *et al.*[53]	Canada	Cohort	WHO criteria	OAB	24-h voiding diary, OABSS, ICIQ, IIQ-7	Not defined		40	Female	Women aged 50 to 80 years with clinical diagnosis of OAB (with/without treatment)	9 – Good
Nandy and Saha[54]	India	Cross-sectional	IDF 2005	LUTS	IPSS, PV	January 2014	June 2015	94	Male	Male, 50 to 65 years of age, prostate biopsy in men with serum PSA >4 ng/ml	8 – Good
Ohgaki *et al.*[55]	Japan	Cross-sectional	2005 JASSO, 2005 NCEP-ATP III, 2005 IDF	LUTS, nocturia	Japanese IPSS	April 2008	March 2009	900	Male	Japanese men who had participated in a general health checkup from April 2008 to March 2009	8 – Good
Ohgaki *et al.*[56]	Japan	Cross-sectional	Same as above	OAB	OABSS	April 2009	March 2010	1031	Male	Japanese men who visited the hospital for metabolic screening	8 – Good

(Continued)

Table 1. (Continued)

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (*n*)	Sex	Population description	NOS rating
Otunctemur *et al.*[57]	Turkey	Prospective cross-sectional	NCEP-ATP III, AHA, WHF, IAS, ASO, IDF	SUI	ICIQ, cough stress test	February 2011	January 2013	400	Female	Women who visited Okmeydani Training and Research Hospital; stratified by menopausal status	9 – Good
Ozden *et al.*[58]	Turkey	Prospective	NCEP-ATP III	LUTS/BPH	IPSS	May 2004	December 2004	93	Male	BPH patients with LUTS ⩾50 years who visited urology outpatient clinic; median age: 60 years, range: 50 to 83 years	6 – Fair
Pan *et al.*[59]	China	Retrospective cohort	NCEP-ATP III criteria for Asian Americans	LUTS/BPH	IPSS, QOL	January 2005	December 2011	1052	Male	Inpatients diagnosed with BPH and underwent TURP	9 – Good
Papaefstathiou *et al.*[60]	Greece	Cross-sectional case control	Not defined	LUTS	IPSS	December 2016	March 2017	137	Male, female	20–79 years with DM type 1, type 2, subclinical, and gestational who visited outpatient clinics and people from general population	8 – Good
Park *et al.*[61]	Korea	Prospective cohort study	NCEP-ATP III, AHA, NHLBI	Voiding symptoms, QOL, PV	IPSS, TRUS, PSA	September 2005	September 2006	348	Male	Men aged >65 years; exclusion criteria: use of medications for BPH, history of urologic surgery, pyuria	7 – Good
Park *et al.*[62]	South Korea	Cross-sectional	NCEP-ATP III	LUTS	Korean version of the IPSS	August 2011	December 2011	1224	Male	Male police officers aged 50 to 59 in Korea	9 – Good
Park *et al.*[63]	South Korea	Cross-sectional	NCEP-ATP III	LUTS	IPSS, IIEF-5, PEDT, NIHCPSI, ADAM	March 2013	September 2013	1910	Male	Healthy Korean men aged 40 to 59 years	7 – Good
Park *et al.*[64]	Korea	Cohort	NCEP-ATP III	LUTS	IPSS, IIEF, AMS	March 2015	November 2015	612	Male	Men who visited the Health Examination Center for a regular health checkup in March–June or September–November 2015	8 – Good
Park *et al.*[65]	South Korea	Retrospective cohort	Not defined	BPH/LUTS	IPSS	April 2006	May 2016	4880	Male	Men post TURP with average age 54.1 ± 8.6 years	9 – Good
Pashootan *et al.*[66]	France	Cohort	NCEP/ATP III	LUTS	IPSS	November 2009	November 2009	4666	Male	379 GPs randomly selected in France who included all male patients aged 55 to 100 years seen in consultation (2-week study)	9 – Good
Plata *et al.*[67]	Columbia	Retrospective cross-sectional	IDF, AHA NHLBI, IAS, WHF, ASO	LUTS	IPSS, IIEF	2010	2011	616	Male	All male patients aged ⩾40 years who attended outpatient urology clinic from 2010 to 2011	9 – Good
Russo *et al.*[68]	Italy	Cross-sectional	IDF	LUTS	IIEF, IPSS	January 2008	January 2013	544	Male	Patients with BPH-related LUTS	9 – Good

(Continued)

Table 1. (Continued)

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (*n*)	Sex	Population description	NOS rating
Russo *et al.*[69]	Italy	Cross-sectional	IDF	LUTS/BPH	IPSS	January 2009	January 2013	448	Male	Men with LUTS	8 – Good
Russo *et al.*[70]	Italy	Prospective cohort	IDF	LUTS/BPH, BOO	Not specified	January 2012	June 2014	264	Male	13.8% (32/232) patients affected by MetS, 13.8% (32/232) affected by NAFLD, 42.7% (99/232) affected by MetS and NAFLD	8 – Good
Russo *et al.*[71]	Italy	Cross-sectional	IDF	BPE	DRE, IPSS	January 2015	January 2017	224	Male	224 patients (46 MetS, 178 non-MetS)	9 – Good
Saratlija Novakovic *et al.*[72]	Croatia	Case control	AHA	OAB	OAB-V8	March 2016	May 2016	114	Male, female	57 MetS (27 men and 30 women) 57 controls (28 men and 29 women)	8 – Good
Telli *et al.*[12]	Turkey	Retrospective cohort	SEMT criteria	LUTS	IPSS	February 2009	April 2013	354	Male	74 patients with IPSS 0–7; 97 patients with IPSS 8–19; 66 patients with IPSS 20–35; 117 healthy controls	9 – Good
Uzun and Zorba[73]	Turkey	Cross-sectional	2006 IDF	OAB, UUi, frequency, nocturia	OAB-V8	May 2009	September 2010	313	Female	30–70 years, female patients who applied to the policlinics with OAB symptoms or other urologic complaints	9 – Good
Vanella *et al.*[74]	Italy	Cohort	IDF	LUTS/BPH, BOO	IPSS	January 2012	June 2019	132	Male	Patients affected by moderate–severe LUTS due to BOO, secondary to clinical BPH, and who underwent TURP	9 – Good
Xia *et al.*[75]	China	Cross-sectional	IDF	PSA	IPSS	October 2014	August 2015	506	Male	Men >45 years who underwent routine physical examinations were recruited consecutively	6 – Fair
Yang *et al.*[76]	Taiwan	Prospective cohort	NCEP-ATP III	LUTS	IPSS, QOL, Qmax	January 2010	December 2010	708	Male	Men ⩾45 years (mean, 55.6 ± 9.72 years) who voluntarily underwent a self-paid medical checkup at the Health Management Center of the National Taiwan University Hospital	9 – Good
Yang *et al.*[77]	Taiwan	Cohort	NCEP-ATP III	LUTS	PV, Chinese version of IPSS	Not defined		616	Male	Males ⩾40 years recruited from a self-paid medical checkup at the Health Management Center in National Taiwan University Hospital	9 – Good
Yee[78]	Hong Kong, China	Cross-sectional	Not defined	LUTS	IPSS	January 2013	September 2015	1176	Male	Male subjects ⩾18 years, referred to a tertiary center urology clinic for LUTS, elevated PSA, or hematuria; 966/1176 included	8 – Good
Yeh *et al.*[79]	Taiwan	Cross-sectional cohort	NCEP-ATP III	LUTS	IPSS, QOL	March 2008	August 2009	764	Male	Males who lived in Kaohsiung city and aged >40 years	9 – Good

(Continued)

Table 1. (Continued)

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (*n*)	Sex	Population description	NOS rating
Yim *et al.*[80]	Korea	Retrospective cohort study	NCEP-ATP III, AHA, NHLBI	PV	TRUS, PSA, DRE	March 2009	June 2010	968	Male	Men aged 30–49 years who underwent TRUS of prostate for a routine health checkup	7 – Good
Yoon *et al.*[81]	Korea	Prospective	NCEP-ATP III	LUTS	IPSS, PVR, KHQ, OAB questionnaire	Not defined		92	Male, female	Prospective multicenter clinical trial including patients aged 20 to 75 years; patients who successfully completed trial: aged 35 to 75 years (median = 61, mean = 60.0 ± 9.0)	8 – Good
Zacche *et al.*[82]	The United Kingdom	Prospective cohort	NCEP-ATP III, IDF, MHLW	OAB, DO, SUI, rUTI, bladder pain	KHQ, PPIUS	October 2012	January 2015	840	Female	Out of 840 enrolled, 704 had OAB, 305 had DO, 88 had stress UI, 26 had recurrent UTIS, 12 had voiding difficulties, and 10 had bladder pain	8 – Good
Zamuner *et al.*[83]	Brazil	Cross-sectional	2001 NCEP-ATP III	LUTS	IPSS	Not defined		490	Male	Unselected and consecutive 490 male adults (mean age = 58 ± 9 years) from urologic clinics at community hospital	9 – Good
Zhang *et al.*[84]	China	Cross-sectional	NCEP-ATP III	BPH	IPSS	February 2009	March 2012	401	Male	BPH patients older than 60 years	9 – Good
Zhao *et al.*[85]	China	Cross-sectional	NCEP-ATP III criteria for Asian Americans	LUTS	Chinese IPSS	October 2014	December 2014	530	Male	Elderly male residents who had IPSS >7	9 – Good
Zhao *et al.*[86]	China	Cohort	Modified NCEP-ATP III	LUTS	TRUS, IPSS, Qmax	October 2014	August 2015	551	Male	Aged ⩾45 years with moderate–severe LUTS due to BPE recruited by consecutive routine physical examination programs	9 – Good
Zorba *et al.*[87]	Turkey	Retrospective cross-sectional	NCEP-ATP III, IDF, IDF-AHA	LUTS	IPSS	Not defined		807	Male	Men aged 46 to 89 with LUTS due to BPE (PV > 30 ml and IPSS >7)	5 – Fair

ADAM, androgen deficiency in aging males; AHA, American Heart Association; AMS, Aging Male Symptom scale; ATP III, Adult Treatment Panel III; AUA-SI, American Urological Association Symptoms Index; BMI, body mass index; BOO, bladder outlet obstruction; BPE, benign prostatic enlargement; BPH, benign prostatic hyperplasia; BPO, benign prostatic obstruction; DM, diabetes mellitus; DO, detrusor overactivity; DRE, digital rectal examination; ED, erectile dysfunction; HoLEP, Holmium laser enucleation of the prostate; IAS, International Atherosclerosis Society; IASO, International Association for the Study of Obesity; ICIQ, International Consultation on Incontinence Questionnaire; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms; IDF, International Diabetes Federation; IIEF, International Index of Erectile Function; IIEF-5, Internal Index of Erectile Function–5; IIQ-7, Incontinence Impact Questionnaire; IPSS, International Prostate Symptom Score; IPSS-QOL, International Prostate Symptom Score Quality of Life; IS, Inflammatory Score; IUSS, Indevus Urgency Severity Scale; JASSO, Japan Society for the Study of Obesity; KHQ, King's Health Questionnaire; LUTS, lower urinary tract symptoms; MetS, metabolic syndrome; MHLW, Japan's Ministry of Health Labour and Welfare; MSHQ-EjD, Male Sexual Health Questionnaire ejaculatory dysfunction; NAFLD, non-alcoholic fatty liver disease; NCEP, The National Cholesterol Education Program; NHLBI, National Heart, Lung, and Blood Institute; NIHCPSI, National Institutes of Health Chronic Prostatitis Symptom Index; NOS, Newcastle–Ottawa scale; OAB, overactive bladder; OABSS, overactive bladder symptom score; OAB-V8, Overactive Bladder–Validated 8-Question awareness tool; PEDT, Premature Ejaculation Diagnostic Tool; PPIUS, Patient Perception of Intensity of Urgency Scale; PRI, Prostatic Resistive Index; PSA, prostate-specific antigen; PV, prostate volume; PVR, post-void residual volume; Qmax, peak urinary flow; QOL, quality of life; rUTI, recurrent urinary tract infection; SEMT, Society of Endocrinology and Metabolism of Turkey; SUI, stress urinary incontinence; T2D, type 2 diabetes; TRUS, transrectal ultrasound; TURP, transurethral resection of the prostate; UTI, urinary tract infection; WC, waist circumference; WHF, World Heart Federation; WHO, World Health Organization.

Table 2. Outcomes measured and summary of MetS and LUTS association.

Reference	Outcome measured	Summary of association of Mets and LUTS
Akin *et al.*[22]	MetS on OAB using NC and WC measurements	Statistically significant association between MetS and OAB ($p < 0.001$). OAB is positively associated with BMI, WC, NC ($p < 0.001$), TG, HDL-C, BP, MetS, and age.
Aktas *et al.*[23]	MetS, ED, and LUTS in BPH patients	MetS presence was not found to be associated with the severity of LUTS ($p = 0.144$). Significant difference between ED groups concerning MetS presence ($p = 0.032$).
Barbosa *et al.*[24]	LUTS and MetS and androgenetic alopecia in Latin American population	MetS were associated with moderate/severe LUTS and storage symptoms (and low testosterone): WHR ≥ 1 (LUTS, $p < 0.001$; storage, $p < 0.001$; voiding, $p = 0.093$), cardiovascular event (LUTS/storage/voiding, $p < 0.001$).
Baykam *et al.*[25]	Prostatic IR and cardiovascular system risk factors in patients with BPH	Prostatic RI level is significantly related to MetS ($N = 58$, $p < 0.001$). Univariate analysis: $p < 0.001$. Multivariate analysis: $p = 0.045$ ($p < 0.05$ is significant). PRI: 0.74 ± 0.068; PRI and CVS ($N = 55$, $p < 0.001$); PRI and smokers ($N = 92$, $p = 0.002$); PRI and HC ($p = 0.006$).
Bray *et al.*[26]	KODAMA and PAM clustering	Associations between metabolites and LUTS as per metabolome studies.
Byun *et al.*[27]	Effect of MetS on PV, PV measured using TRUS (ALOKA, Prosound-α5sv)	PV and MetS: $B = 2.284$; 95% CI = 1.737–2.831; $p < 0.0001$. PV positively correlated with WC ≥ 90 cm ($p < 0.0001$), SBP ($p = 0.002$), DBP ($p < 0.0001$), TG ($p < 0.0001$), low HDL-C ($p < 0.0001$), FBG ($p < 0.0001$). Each increase in the number of MetS components increases PV by 2.28 ml.
Choi *et al.*[28]	Effect of MetS on PSA	MetS group had significantly larger PV ($p < 0.001$) and lower level of mean serum PSA levels ($p = 0.006$) compared with non-MetS. Multivariate analysis of PV and PSA; $B = 0.020$; 95% CI = 0.018–0.022; $p < 0.001$. PSA and MetS: $B = -0.038$; 95% CI = −0.074 to −0.002; $p = 0.036$.
Chung *et al.*[29]	Patient characteristics and diabetes-related complications to risk of nocturia were evaluated	OAB is an important predictor of nocturia in T2DM patients. Obesity, HT, stroke, and chronic kidney disease were associated with nocturia after adjusting for age, DM duration, and OAB presence. Severe nocturia elevates mortality risk.
Coban *et al.*[30]	BP, FBG, serum lipid profile, TG, total cholesterol, BMI, PSA	No association between IPSS scores between patients with/without MetS ($p = 0.6$); IIEF-5 scores lower in MetS group ($p = 0.03$) (ED).
Dagdeviren and Cengiz[31]	OAB, MetS, and serum nerve growth factors	Oxidative stress, proinflammatory status, and sympathetic overactivity, (MetS) elevated serum NGF levels in women with OAB ($p = 0.001$). NGF, pg/ml: group 1 (OAB), 416.3 ± 49.6; group 2 (OAB and MetS), 476.7 ± 111.0; group 3 (healthy), 292.9 ± 84.4.
Demir *et al.*[10]	Obesity, high FBG, and HT as risk factors for severe LUTS development; MetS role in pathogenesis of ED and LUTS	MetS incidence increased with severe LUTS (26% *versus* 46%, $p = 0.009$). Severe LUTS positively associated with WC <102 cm ($p < 0.05$), BP $>130/85$ mmHg ($p < 0.05$), FBG >6.1 mmol/l ($p < 0.01$).
De Nunzio *et al.*[32]	BPS, LUTS, MetS	MetS associated with an increased risk of storage symptoms in patients with BPE.
De Nunzio *et al.*[33]	MetS and EjD in patients of LUTS and BPE	MetS not associated with EjD evaluated with the MSHQ-EjD-SF.
De Nunzio *et al.*[34]	IPSS, age, BMI, smoker status, PV, PSA, FBG, TG, HDL-C, LDL-C	MetS and smoking doubled risk of moderate/severe nocturia in patients with LUTS and BPE. Multivariate analysis: age (OR: 1.067 per year, 95% CI = 1.036–1.098; $p = 0.001$), PV (OR = 1.011 per ml, 95% CI = 1.003–1.019; $p = 0.006$), MetS (OR = 2.509, 95% CI = 1.571–4.007; $p = 0.001$), and smoking (OR = 1.690, 95% CI = 1.061–2.693; $p = 0.027$) associated with nocturia severity.

(Continued)

Table 2. (Continued)

Reference	Outcome measured	Summary of association of Mets and LUTS
De Nunzio *et al.*[35]	PV, pre-op voiding and post-op voiding, LUTS, MetS	MetS and smoking increased risk of moderate/severe persistent nocturia after TURP in patients with LUTS/BPE.
Doğan *et al.*[36]	LUTS/BPH and MetS incidence and severe ED	MetS criteria did not correlate with IPSS except for TG ($r = 0.298$, $p < 0.01$). Weakly negative association between age and IIEF scores ($r = -0.377$, $p < 0.001$). IIEF scores decreased with aging. MetS criteria not correlated with IIEF scores.
Eom *et al.*[37]	LUTS, HOMA-IR, MetS	LUTS negatively correlated with MetS (age-adjusted, $p = 0.045$); increasing the number of MetS strengthened correlation ($p < 0.01$), especially voiding symptoms in early compensatory stage. MetS, IR, and hyperinsulinemia lowered IPSS-T, storage and voiding symptoms, and QOL.
Eren and Horsanali[38]	NAFLD, PSA level, IPSS, PV, Qmax, PVR	NAFLD was an independent predictive factor for IPSS, PV, Qmax, PVR, and IIEF-5 score. MetS only correlated with IIEF-5. NAFLD better than MetS in identifying high risk of LUTS.
Fu *et al.*[39]	PV, Qmax, and biological parameters	MetS, especially DM and HT, may increase BPH deterioration in community-dwelling middle-aged/older men. MetS positively correlated with IPSS, Qmax, and PV ($p < 0.05$) after 3-year follow-up. BPH deteriorated rapidly MetS group, compared with non-MetS group ($p < 0.05$).
Gacci *et al.*[40]	PV, prostatic AP diameter and intraprostatic IS, glandular disruption	MetS positively correlated with PV, intraprostatic IS, and prostatic AP diameter; MetS is a predictor of prostate inflammation and BPH. Positive association between MetS and prostatic AP diameter supports the lower uroflowmetric parameters observed in MetS patients.
Gacci *et al.*[41]	Effect of MetS and each MetS component on prostate growth in men surgically treated for BPE	Metabolic factors involved in pathogenesis of LUTS/BPH. Persistent storage LUTS after TURP/OP associated with obesity in men. WC correlated with persistent pre-op urinary symptoms after surgical treatment of BPE.
Gao *et al.*[13]	Association between LUTS severity and MetS and its components	MetS is not associated with LUTS. Reduced incidence of MetS in moderate–severe storage and voiding symptoms. Aging correlated with LUTS, and men ⩾60 years had a twofold increased likelihood of moderate–severe LUTS.
Haghsheno *et al.*[42]	Association of LUTS and UI with MetS, association between LUTS and BPE	No association between LUTS or UI and major MetS components. Serum serotonin was negatively associated with LUTS and UI. FBG and serum adiponectin were positively associated with LUTS. The data confirm BPE potentially causes LUTS.
Jeong *et al.*[43]	Effect of MetS on PV	Positive correlation between MetS and PV, even in young males. For men <60 years, obesity and DM were significant risk factors for BPE.
Karoli *et al.*[44]	Prevalence of bladder dysfunction on women with chronic complications of T2D	MetS positively correlated with moderate LUTS (OR = 2.6, 95% CI = 0.98–4.12, $p = 0.02$) and OAB (OR = 3.2, 95% CI = 1.6–5.8, $p = 0.01$). Among its components, only HT associated (LUTS: OR = 2.4, 95% CI = 1.67–3.87; OAB: OR = 1.82, 95% CI = 1.0–3.12, $p = 0.53$) Peripheral neuropathy (OR = 3.2, 95% CI = 2.13–4.8, $p = 0.001$) and nephropathy (OR = 1.46, 95% CI = 0.87–2.62, $p = 0.03$) positively correlated with moderate LUTS.
Kim *et al.*[45]	Effect of MetS on moderate–severe LUTS in middle-aged men	MetS had favorable effects on odds of having moderate–severe LUTS in middle-aged men with enlarged PV. Increasing the number of MetS components (HT and hypertriglyceridemia in particular) reduced likelihood of moderate-to-severe LUTS development.

(Continued)

Table 2. (Continued)

Reference	Outcome measured	Summary of association of Mets and LUTS
Kupelian *et al.*[46]	Relationship between LUTS (using AUA-SI) and MetS	MetS positively correlated with LUTS. Men with mild–severe LUTS (AUA-SI 2-35) had an increased incidence of MetS (compared AUA-SI 0 or 1) (multivariate OR = 1.68, 95% CI = 1.21–2.35). MetS positively correlated with voiding symptom score ⩾5 (multivariate adjusted OR = 1.73, 95% CI = 1.06–2.80) but not for storage symptom score ⩾4.
Kwon *et al.*[47]	Effect of MetS on patient outcomes who underwent HoLEP for BPO	MetS correlated with reduced postoperative symptom improvement. LUTS after surgery is possibly a systemic disorder because of multiple metabolic risk factors.
Lai *et al.*[48]	Relationship between MetS (central and general obesity, dyslipidemia) and OAB, any UI, SUI, UUI, urgency, frequency, and nocturia	Higher WC correlated with higher incidence of UI (OR = 1.16 per 10 cm increase, $p = 0.008$) and UUI (OR = 1.24 per 10 cm increase, $p = 0.001$) in both sexes, and SUI in females (OR = 1.27 per 10 cm increase, $p = 0.008$). WC positively correlated with incidence of nocturia and OAB (OR = 1.25/10 cm increase, $p = 0.003$) in females, but not males. Dyslipidemia with nocturia >2 (OR = 1.46, $p = 0.035$).
Lee *et al.*[49]	Obesity (WC) and metabolic dysfunction: hypertension, dyslipidemia, and T2D	Obesity increased male pelvic dysfunction risk especially when accompanied by other MetS components. High WC correlated with worsened voiding. Number of MetS components increased in patients with higher WC. WC positively correlated with PV, serum PSA, and IPSS.
Lee *et al.*[11]	Biological, medical, psychological, social, lifestyle, and economic factors linked to MetS and LUTS severity	MetS not correlated with moderate/severe LUTS. Multivariate analysis: moderate/severe LUTS risk correlated with age and ED.
Lotti *et al.*[50]	Effect of MetS on prostate abnormalities in infertile men	Increasing the number of MetS components increases total and transitional zone prostate enlargement and prostate-related-inflammatory signs. Positive correlations established between number of MetS components and seminal IL-8 (marker for inflammation of prostate).
Martin *et al.*[51]	Age, LUTS, insomnia, OA, RA, thyroid function, MetS, androgen levels, socioeconomic	Storage LUTS positively associated with increased abdominal fat mass, plasma glucose, low HDL-C, OSA risk, and retirement. Frequency (12.3%), nocturia (9.9%), and urgency (8.1%) were the most common storage symptoms. Weak stream (8.5%), intermittency (5.4%), incomplete emptying (5.1%), and straining (2.4%) were the most common voiding symptoms.
Mitsui *et al.*[52]	Metabolomics analysis of LUTS patients	Metabolomics analysis identified 60 metabolites from patient plasma. Multivariate analysis: increased glutamate and decreased arginine, asparagines, and inosine monophosphate associated with LUTS in males.
Mossa *et al.*[53]	Urinary metabolites	No significant difference in questionnaires or voiding diary between MetS and non-MetS in OAB group. OAB symptoms' severity remains unchanged following OAB discovery irrespective of underlying pathology.
Nandy and Saha[54]	LUTS including PV, MetS	Positive association between PV with MetS and its four components: BP, FBG, TG, and HDL-C <2.2 mmol/l (no correlation with WC). MetS (and its components) may increase prostatic enlargement and LUTS risk.
Ohgaki *et al.*[55]	Relationship of presence of the MetS with each IPSS or age group was investigated	MetS negatively correlated with storage symptoms in middle-aged men. In young and older men, LUTS was observed equally in those with and without the MetS. Aging correlated with an increased rate of moderate–severe LUTS (except for post-micturition symptom) irrespective of MetS.
Ohgaki *et al.*[56]	OABSS and the presence of MetS was also evaluated	MetS did not show a clear association with OAB. In middle-aged men, MetS negatively correlated with OAB rate. In elderly men, MetS negatively correlated with total OABSS. Irrespective of MetS, aging correlated with increased rates of moderate–severe OAB.

(Continued)

Table 2. (Continued)

Reference	Outcome measured	Summary of association of Mets and LUTS
Otunctemur *et al.*[57]	Serum total and HDL-C, TG, and glucose levels	WC and FBG correlated with SUI. SUI was more prevalent in pre- and postmenopausal women with MetS ($p = 0.001$ and $p < 0.001$). DM is an independent risk factor for UI.
Ozden *et al.*[58]	MetS and annual prostatic growth rates of BPH patients	MetS increases prostate growth [rate (ml/year), $p = 0.018$] in BPH patients. MetS and total PV (ml): $p = 0.07$. No correlation between MetS and IPSS ($p = 0.167$).
Pan *et al.*[59]	Effect of MetS on LUTS in a Chinese male population with BPH	MetS correlated with an increased risk of total volume and annual growth rate of prostate. MetS and its components are associated with LUTS in patients with BPH.
Papaefstathiou *et al.*[60]	Effect of DM on LUTS on men and women with LUTS	Moderate/severe LUTS more prevalent in women with DM with an OR of 3061 (95% CI = 1.131–8.286) compared with women without DM. Male groups: no statistical significance. In women with DM, only HbA1c levels correlated independently with moderate/severe LUTS presence ($p = 0.024$, OR = 2,729, 95% CI = 1,144–6,509).
Park *et al.*[61]	Relationship between the MetS and LUTS in a community-based elderly population	No significant differences were found in the mean IPSS or QOL between the MetS and non-MetS groups. Age, PSA level, and total prostate and transitional zone were not significantly different between the two groups.
Park *et al.*[62]	LUTS/BPH assessment and MetS assessment; TPV calculated TRUS and gland examined using digital rectal examination; Qmax and PVR were also assessed	LUTS/BPH incidence positively correlated with the number of MetS components, albeit IPSS and QOL were not significantly different between MetS and non-MetS groups. IPSS >7 and Qmax <15 ml/s ratio was unrelated to MetS or the number of MetS components. TPV and PVR were significantly higher in MetS patients. Increasing the number of positive MetS components increased the OR in relation to TPV >30 ml and PVR >50 ml (after adjusting for age and/or TT).
Park *et al.*[63]	Ability of anthropometric index and symptom scores of five widely used questionnaires to detect men's health problems	No association between LUTS and MetS ($p = 0.395$, OR = 0.919, 95% CI = 0.756–1.117), obesity, or WHR. Logistic regression analysis: age and total PV were independent predictors of LUTS. MetS was the only significant negative predictive factor for chronic prostatitis symptoms ($p = 0.022$, OR = 0.747, 95% CI = 0.581–0.959).
Park *et al.*[64]	Impact of metabolic status on associations of serum vitamin D with hypogonadism and LUTS/BPH	Clinical usefulness of vitamin D for hypogonadism or LUTS/BPH treatment varies according to metabolic status. Vitamin D levels positively correlated with TT but not with PV or IPSS.
Park *et al.*[65]	Effect of MetS on BPH and LUTS in Asian population	MetS variables were strongly associated with BPH/LUTS. Reduction of fat mass and LDL-C levels could prevent BPH/LUTS development in healthy Korean men within 5 years. BMR (kcal/day) declined with LUTS presence ($p = 0.023$). BMR is a predictor of BPH/LUTS ($p < 0.001$).
Pashootan *et al.*[66]	Correlation between MetS and its individual components, and the severity of LUTS	MetS associated with treated LUTS ($p < 0.001$). MetS positively correlated with LUTS severity ($p < 0.001$) for overall IPSS, voiding and storage scores ($p < 0.001$). Multivariate analysis: each component of MetS (except HDL-C) was an independent risk factor of high IPSS and of LUTS treatment. MetS positively correlated with PV.
Plata *et al.*[67]	Prevalence of MetS was determined, and LUTS and ED were assessed	MetS correlated with LUTS but not ED. Specific components such as diabetes were associated to both. Bivariate analysis between IIEF/IPSS and MetS.
Russo *et al.*[68]	Effect of insulin resistance on LUTS	IR accounted for higher IPSS (19.0 *versus* 15.0; $p < 0.01$), IPSS storage (6.0 *versus* 5.0; $p < 0.01$), IPSS voiding (12.0 *versus* 9.0; $p < 0.01$), TPV (54.8 *versus* 36.5; $p < 0.01$), and lower IIEF-EF (17.0 *versus* 20.0; $p < 0.01$) and TT (3.83 *versus* 4.44; $p < 0.01$). IR was an independent predictor of severe LUTS (IPSS ⩾ 20) (OR = 2.0, $p < 0.01$).

(Continued)

Table 2. (Continued)

Reference	Outcome measured	Summary of association of Mets and LUTS
Russo *et al.*[69]	Presence of NAFLD using FLI and US confirmation	Patients with MetS and FLI ⩾40 had twofold the risk of moderate–severe LUTS than those with only MetS.
Russo *et al.*[70]	Presence inflammatory infiltrate from TURP resections in patients with MetS and NAFLD	Patients with BPH/LUTS and metabolic aberration exhibited greater prostatic inflammation. Coexistence of MetS and NAFLD exerted a greater detrimental effect on prostate.
Russo *et al.*[71]	Serum PSA, FBG, HDL-C, LDL-C, and total cholesterol, and TG levels were recorded	Patients with MetS had increased IPP ($p < 0.01$), TPV ($p < 0.01$), and TZV ($p = 0.02$). MetS was positively correlated with prostate size and with TZV and IPP, supporting the association between metabolic alterations and clinical increase in PV.
Saratlija Novakovic *et al.*[72]	Association between OAB and MetS	Participants with MetS had a higher frequency of urinary symptoms.
Telli *et al.*[12]	Height, weight, and WC (2 cm above umbilicus); BMI was computed according to Quetelet index (kg/m^2)	No significant difference in MetS and its components including BMI ($p = 0.452$), FBG ($p = 0.291$), TG ($p = 0.307$), LDL cholesterol ($p = 0.069$), and total cholesterol ($p = 0.337$) between the IPSS severity and control groups.
Uzun and Zorba[73]	Relevance of MetS in etiopathogenesis of OAB in female patients	MetS correlates highly with OAB in female patients ($p = 0.002$). Large WC, high BMI, low HDL-C, and HT positively correlate with OAB.
Vanella *et al.*[74]	Pathological characterization of prostatic inflammatory infiltrates	Alteration of serum TG and HDL-C significantly impairs HO-1 and HO-2 levels in BPH patients. Prostate metaflammation is inversely related to intraprostatic HO-1 levels, serum HDL-C, and positively with TG.
Xia *et al.*[75]	Effect of MetS on PSA	When simultaneously adjusting for age, BMI, prostate volume, and HDL-C, serum insulin levels and SHBG levels were inversely correlated with serum PSA levels ($p = 0.049$ and $p = 0.004$, respectively), and testosterone levels were positively correlated with serum PSA levels ($p = 0.039$).
Yang *et al.*[76]	Age, height, weight, BP, WC, and basic serum biochemistry profiles and serum PSA	MetS group had reduced mean IPSS-T compared with non-MetS group (6.85 ± 6.52 *versus* 7.89 ± 6.63; $p = 0.05$), and reduced severity of weak urinary stream during voiding (0.95 1.50 *versus* 1.24 1.60; $p = 0.021$), furthermore experienced lower severity of IPSS grading ($p = 0.014$).
Yang *et al.*[77]	Correlations of PV with MetS, metabolic components, and body composition indices	Raised WC was the independent predictor of PV in subjects with LUTS. Subjects with large PV were older (56.5 *versus* 52.7 years) and had higher PS (1.73 *versus* 0.96 ng/ml), higher IPSS score (8.37 *versus* 6.16), and higher body fat, body mass, and WC (all $ps < 0.05$). In multivariate analysis, age, serum PSA, WC, fatness, and body fat mass were significantly correlated with PV of study subjects.
Yee *et al.*[78]	Urinary symptoms severity of LUTS in correlation with cardiovascular risk factors; correlation between Framingham risk score, cardiovascular risk factors, and severity of LUTS investigated	Severity of LUTS and storage symptom significantly increases Framingham risk score and cholesterol. Multinomial logistic regression analysis: LUTS and Framingham score ($p = 0.008$), total cholesterol (OR = 1.318; $p = 0.010$), and age (OR = 1.032; $p = 0.006$). Framingham risk score associated with storage symptoms ($p < 0.0001$) but not voiding symptoms.
Yeh *et al.*[79]	Influence of MetS and its components, lifestyle, and PV on LUTS in elderly males	MetS or any MetS components did not correlate with LUTS severity. Age, cigarette smoking, alcohol consumption, physical activity, and PV significantly correlated with LUTS severity at univariate analysis. Aging, cigarette smoking, lack of regular exercise, and larger PV were independent predictors for moderate/severe LUTS at multivariate analysis.

(Continued)

Table 2. (Continued)

Reference	Outcome measured	Summary of association of Mets and LUTS
Yim *et al.*[80]	Relationship between parameters of MetS and PV in men <50 years of age	PV was not significantly larger in the MetS group than in the non-MetS group. Groups with abnormal FBG and WC had larger PV than normal groups.
Yoon *et al.*[81]	Effect of tamsulosin on LUTS and MetS patients	No correlation between MetS and PV [TRUS (gm)] ($p = 0.92$), PSA ($p = 0.49$), and IPSS ($p = 0.30$). MetS significantly correlated with OAB-Q ($p < 0.01$).
Zacche *et al.*[82]	Relationship between MetS components and OAB in women with LUTS	Obesity correlated with OAB/DO in female patients. However, other components of MetS not associated with OAB/DO. When the outcome DO was considered, BMI (OR = 1.06, 95% CI = 1.03–1.08, $p < 0.001$) was the only independent predictor at multivariate analysis. Obesity was the only independent risk factor for OAB (OR = 1.09, 95% CI = 1.05–1.13) and DO (OR = 1.06, 95% CI = 1.03–1.08).
Zamuner *et al.*[83]	Correlation among male LUTS, MetS, PV, and age	Association of male LUTS, PV, and MetS might be coincidental and related to an older age. Only age remained as an independent factor for LUTS after multivariate analysis.
Zhang *et al.*[84]	Effect of simvastatin and atorvastatin (statins) in elderly male patients with BPH and MetS	MetS, BMI, low HDL-C level, increased serum insulin, and especially IR are considered risk factors for prostate enlargement. BPH patients split into MetS ($N = 222$) and non-MetS ($N = 179$).
Zhao *et al.*[85]	IPSS score for LUTS, MetS	MetS positively correlated with LUTS severity ($p < 0.001$) and voiding scores ($p < 0.001$); individual MetS components were independent risk factors for severe LUTS (IPSS > 19, all $ps < 0.001$). Increasing number of MetS components (all $ps < 0.05$) increased percentage of subjects with ⩾1 predictors for clinical BPH progression. After adjusting for age and serum testosterone level, the MetS were independently associated with the presence of TPV ⩾31 cm^3 (OR = 17.030, 95% CI = 7.495–38.692).
Zhao *et al.*[86]	Effect of MPV on patients with BPH/LUTS	Number of positive MetS components, CRP, MPV, and parameters of BPH/LUTS are correlated. Chronic inflammation is a key factor and elevated MPV may predict MetS-induced inflammation in BPH/LUTS progression.
Zorba *et al.*[87]	Most effective MetS definition that can be used in patients with BPE/LUTS	In the patients with MetS according to each of the three definitions, the IPSS, the storage and voiding symptom scores, PV, PSA, and PVR were significantly higher.

AP, Antero-posterior; AUA-SI, American Urological Association Symptoms Index; BMI, body mass index; BMR, basal metabolic rate; BP, blood pressure; BPE, benign prostatic enlargement; BPH, benign prostatic hyperplasia; BPO, benign prostatic obstruction; BPS, bladder pain syndrome; CI, confidence interval; CRP, C-reactive protein; CVS, cardiovascular system; DBP, diastolic blood pressure; DM, diabetes mellitus; DO, detrusor overactivity; ED, erectile dysfunction; FBG, fasting blood glucose; FLI, fatty liver index; HbA1c, hemoglobin A1C; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HO, heme oxygenase; HoLEP, Holmium laser enucleation of the prostate; HOMA-IR, Homeostatic Model Assessment - Insulin Resistance; HT, hypertension; IIEF, International Index of Erectile Function; IIEF-EF, International Index of Erectile Dysfunction – Erectile Dysfunction; IIEF-5, Internal Index of Erectile Function–5; IL-8, Interleukin 8; IPP, Inflatable Penile prosthesis; IPSS, International Prostate Symptom Score; IPSS-T, International Prostate Symptom Score Total; IR, insulin resistance; IS, inflammatory score; KODAMA, knowledge discovery by accuracy maximization; LDL-C, low-density lipoprotein cholesterol; LUTS, lower urinary tract symptoms; MetS, metabolic syndrome; MPV, Mean Platelet Volume; NAFLD, non-alcoholic fatty liver disease; NC, neck circumference; NGF, nerve growth factor; OA, osteoarthritis; OAB, overactive bladder; OAB-Q, overactive bladder-questionnaire; OABSS, overactive bladder symptom score; OP, Open Prostatectomy; OR, odds ratio; OSA, obstructive sleep apnea; PAM, partition around medoids; PRI, prostatic resistive index; PSA, prostate-specific antigen; PV, prostate volume; PVR, post-void residual volume; Qmax, peak urinary flow; QOL, quality of life; RA, Rheumatoid Arthritis; RI, Resistive Index; SBP, systolic blood pressure; SHBG, Sex Hormone Binding Globulin; SUI, stress urinary incontinence; T2D, type 2 diabetes; T2DM, type 2 diabetes mellitus; TG, triglycerides; TPV, total prostate volume; TRUS, transrectal ultrasound; TT, total testosterone; TURP, transurethral resection of the prostate; TZV, transition zone volume; UI, Urinary Incontinence; UUI, urinary urgency incontinence; WC, waist circumference; WHR, waist-hip ratio.

included 33 studies, was conducted; this generated 16 forest plots. the following outcomes *versus* MetS were evaluated: International Prostate Symptom Score Total (IPSS-T), IPSS voiding, IPSS storage, International Prostate Symptom Score Quality of Life (IPSS-QOL), TPV (ml), prostate-specific antigen (PSA; ng/ml), uroflowmetry Qmax (ml/s); and post-void residual

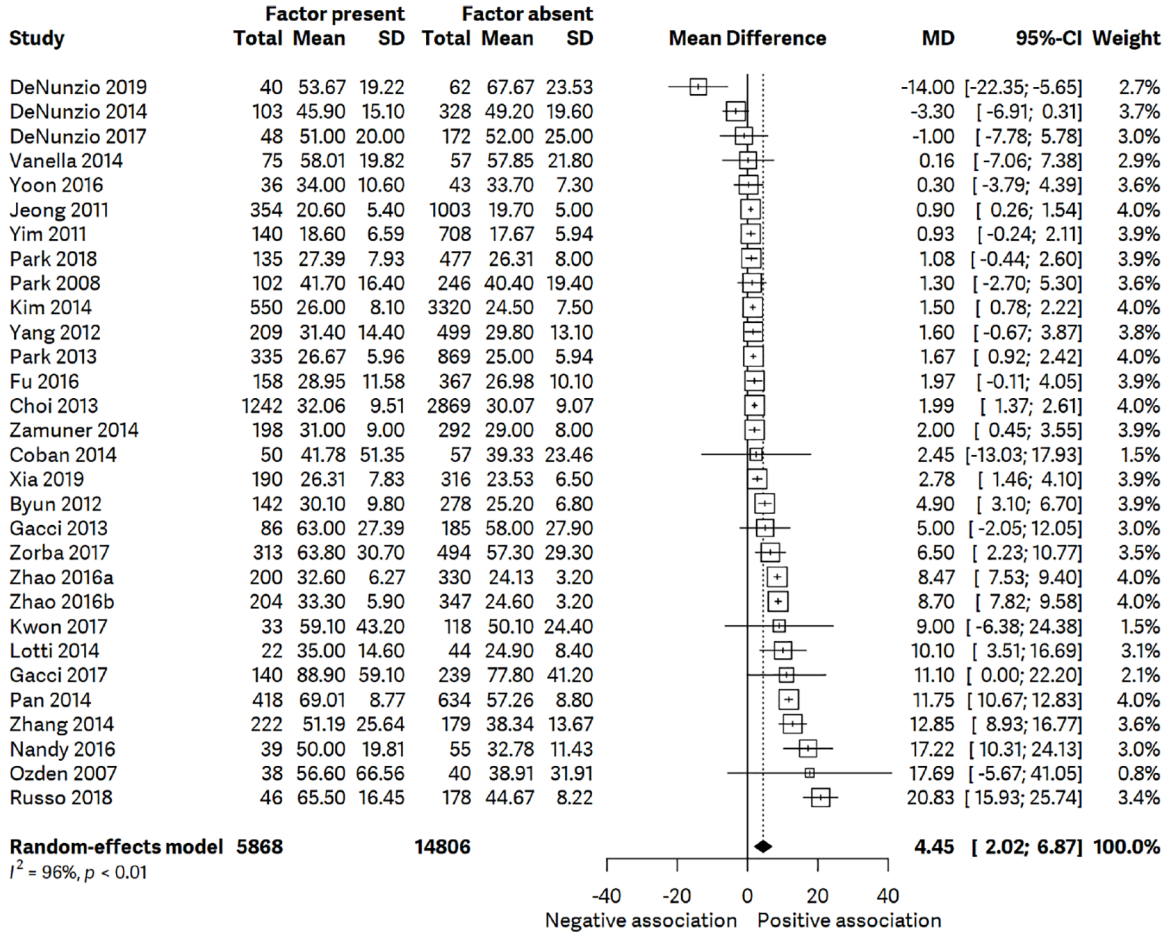

Figure 2. Forest plot for TPV and MetS. Number of studies combined: $k = 30$ ($n = 22{,}206$). MD = 4.4450; 95% CI = 2.0177–6.8723; $t = 3.75$; $p = 0.0008$. Quantifying heterogeneity: tau^2 = 37.0851 [18.9614; 71.7320]; tau = 6.0898 [4.3545; 8.4695]. I^2 = 96.3% [95.4%; 96.9%]; $H = 5.17$ [4.67; 5.72]. Test of heterogeneity: Q = 774.09; degrees of freedom (df) = 29; $p < 0.0001$. Details on meta-analytical method: inverse variance method; Sidik–Jonkman estimator for tau^2; Q-profile method for confidence interval of tau^2 and tau; Hartung–Knapp adjustment for random effects model.

volume (PVR; ml). Furthermore, forest plots for IPSS severity and each MetS component were generated; results were not significant; however, heterogeneity was relatively low in some plots. Given that TPV proved significant, we explored this further and systematically searched for studies on TPV and MetS (10 additional studies were identified). We generated another forest plot for TPV and MetS (total of 30 studies), which proved highly significant, albeit heterogeneity was high: I^2 96.3% [95.4%; 96.9%]. Results are presented in Figure 2. Due to the high heterogeneity, a meta-regression analysis was performed to test the impact of covariates on heterogeneity. Meta-regression analysis was performed for predictors, age, country, study rating, and publication year; results were not significant ($p > 0.05$); therefore, predictors had no effect on heterogeneity (Figure 3; Table 3). An Egger's test of the intercept was performed to test for publication bias; the test revealed a symmetric inverted funnel shape indicating a 'well-behaved' data set, in which publication bias is unlikely (intercept 1.073, 95% CI = –1.71 to 3.86, $t = 0.754$, $p = 0.4570147$; Figure 4). A risk of bias assessment was also performed, as shown in Figure 5 and Table 4, with an overall high risk of bias in most studies.

Discussion

Associations between LUTS and MetS have long since been contentious with clinical mechanisms and remain poorly understood. This meta-analysis sought to review all current published data in

Table 3. Mixed-effects model results.

Predictor	tau^2	SE	tau	I^2 (%)	H^2	R^2 (%)
Age	38.1733	10.5718	6.1785	98.51	66.97	0.00
Country	34.7069	10.8136	5.8913	98.54	68.71	6.41
Study rating	38.3850	10.6182	6.1956	98.54	68.66	0.00
Publication year	38.2500	10.5839	6.1847	98.51	67.07	0.00
	Estimate	**SE**	***T* value**	***p* value**	**CI lower bound**	**CI upper bound**
Intercept	1.0058	7.6215	0.1320	0.8959	−14.6061	16.6177
Age	0.0569	0.1244	0.4575	0.6508	−0.1979	0.3118
	Estimate	**SE**	***T* value**	***p* value**	**CI lower bound**	**CI upper bound**
Intercept	2.0000	5.7414	0.3483	0.7307	−9.8770	13.8770
China	5.6969	6.2062	0.9179	0.3682	−7.1415	18.5353
India	15.2200	8.7718	1.7351	0.0961	−2.9259	33.3659
Italy	1.7171	6.2024	0.2768	0.7844	−11.1136	14.5478
South Korea	−0.0747	6.0441	−0.0124	0.9902	−12.5778	12.4285
Taiwan	−0.4000	8.1601	−0.0490	0.9613	−17.2805	16.4805
Turkey	5.0225	7.4533	0.6739	0.5071	−10.3958	20.4408
	Estimate	**SE**	***T* value**	***p* value**	**CI lower bound**	**CI upper bound**
Intercept	5.2487	9.4392	0.5561	0.5826	−14.0865	24.5840
Study rating	−0.0960	1.1249	−0.0853	0.9326	−2.4003	2.2083
	Estimate	**SE**	***T* value**	***p* value**	**CI lower bound**	**CI upper bound**
Intercept	−367.3341	915.8520	−0.4011	0.6914	−2243.3719	1508.7037
Publication year	0.1846	0.4546	0.4059	0.6879	−0.7467	1.1158

CI, 95% confidence interval; H^2, unaccounted variability/sampling variability; I^2, residual heterogeneity/unaccounted variability; R^2, amount of heterogeneity accounted for; SE, standard error; tau, square root of estimated tau^2 value; tau^2, estimated amount of residual heterogeneity. Age: QE (df 28) = 370.3469, $p < 0$, $p < 0.0001$. Coefficient 2: $F(df1\ 1, df2\ 28) = 0.2093$, $p = 0.6508$. Country: QE (df 23) = 256.8090, $p < 0.0001$. Coefficients 2:7: $F(df\ 16, df\ 223) = 1.3679$, $p = 0.2691$. Study rating: QE (df 28) = 750.9320, $p < 0.0001$. Coefficient 2: $F(df1\ 1, df2\ 28) = 0.0073$, $p = 0.9326$. Publication year: QE (df 28) = 625.5066, $p < 0.0001$. Coefficient 2: $F(df1\ 1, df2\ 28) = 0.1648$, $p = 0.6879$. QE: test for residual heterogeneity; coefficient: test of moderators.

order to highlight any significant findings to date. Our meta-analysis ($k = 30$, $n = 22{,}206$) on TPV and MetS indicated significant results confirmed a significant association (MD = 4.4450, 95% CI = 2.0177–6.8723, $t = 3.75$; $p = 0.0008$). However, heterogeneity was high ($tau^2 = 37.0851$ [18.9614; 71.7320], $I^2 = 96.3\%$ [95.4%; 96.9%], $H = 5.17$ [4.67; 5.72]). Meta-regression produced non-significant results suggesting that predictors (age, country, study rating, publication year) had no effect on heterogeneity. Our study found no association between MetS and IPSS or its subgroups, PSA, Qmax, and PVR. Several studies have demonstrated that MetS causes inflammation and prostatic hyperplasia in men with BPH/LUTS. The results of our meta-analysis are consistent with other literature. Zou *et al.*[88] conducted a meta-analysis on 16 studies (BPH patients,

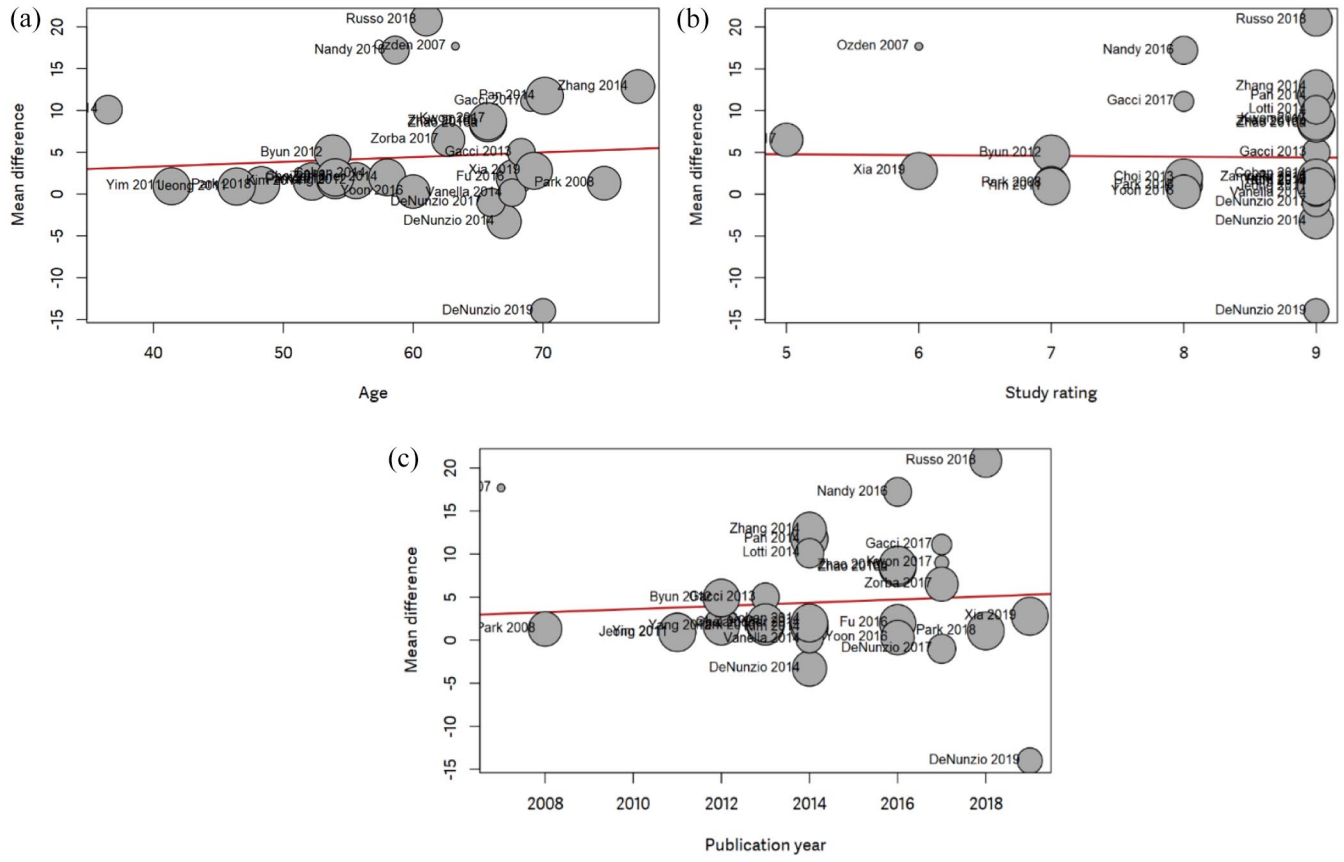

Figure 3. Meta-regression analysis for predictors: (a) age, (b) study rating, and (c) publication year. Results were not significant.

$n = 1895$) on MetS and BPH in Chinese patients; TPV (MD = 10.15 ml; 95% CI = 7.37–12.93) and annual prostate growth rate (MD = 0.49 ml/year; 95% CI = 0.24–0.73) were significantly higher in BPH patients with MetS compared with patients without MetS. A meta-analysis by Gacci *et al.*[89] reported similar findings; TPV was significantly higher in BPH patients with MetS (+1.8 ml, 95% CI = 0.74–2.87, $p < 0.001$). In addition, no association was found between MetS and IPSS.[89] Wu *et al.*[90] also reported a significant association between MetS and TPV (OR = 2.34, 95% CI = 1.25–3.42) after performing a meta-analysis on six comparative studies ($n = 61{,}826$). Again, similar to our study, Wu *et al.* found no significant association between MetS and IPSS or PVR.[90] Wang *et al.*[91] ($k = 8$, $n = 3093$) reported that BPH patients with MetS had significantly higher prostate growth rates (MD = 0.67 ml/year, $p < 0.001$) and prostate volumes (MD = 6.8 ml, $p = 0.010$). No significant association between MetS and IPSS, and Qmax was found; however, there was an almost significant association with PSA (MD = 0.24 ng/ml, $p = 0.056$).[91] Li *et al.*[92] also significantly associated MetS with higher annual prostate growth rate and prostate volume; no association was found between MetS and IPSS/IPSS subgroups. In contrast to our study, Li *et al.*[92] significantly associated MetS with reduced Qmax (MD = –0.48, $p = 0.001$) and increased PVR (MD = 8.28, $p < 0.001$). Russo *et al.*[93] demonstrated that a significant association between MetS and prostate volume (MD = 2.18, $p = 0.03$) was found; no association was reported with IPSS. Differences in results may be due to the number and type of studies included in meta-analysis. Our meta-analysis included retrospective, cross-sectional studies and randomized controlled trials (RCTS; $k = 30$, $n = 22206$); not all studies used transrectal ultrasonography (TRUS) to measure TPV. Wu *et al.*[90] included retrospective studies and one prospective study ($k = 6$, $n = 61{,}826$); studies used TRUS; one study used suprapubic ultrasound. Wang *et al.*[91] included cohort or

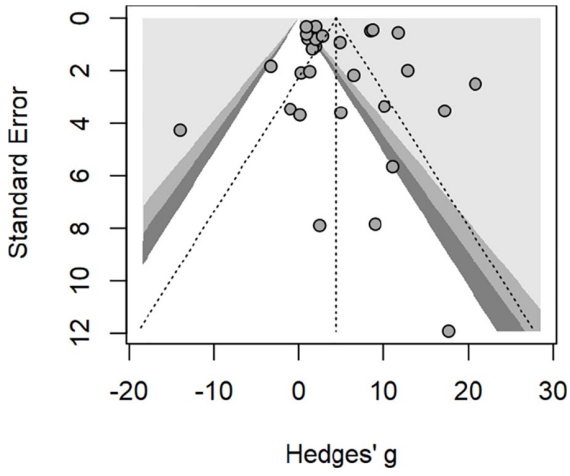

Figure 4. Publication bias assessment. Egger's test of the intercept: intercept 1.073; 95% CI = 1.71–3.86; $t = 0.754$; $p = 0.4570147$. Egger's test does not indicate the presence of funnel plot asymmetry.

case-control studies ($k = 8$, 3093), all of which used ultrasound or TRUS; heterogeneity (I^2) was also high (90.1%). Li *et al.*[92] included prospective and retrospective studies ($k = 21$, $n = 15{,}317$); 17 studies used TRUS to measure TPV. Forest plot results indicated a significantly lower heterogeneity of 49%, while our heterogeneity was 96%.[92] Russo *et al.*[93] ($k = 19$, $n = 18{,}476$) included six studies in the forest plot for prostate volume and heterogeneity was 85%; BPH definitions varied, and studies used TRUS and/or digital rectal examination (DRE) or IPSS alone.

Studies included in our meta-analysis used the same laboratory parameters and equipment for blood and urine analysis. Prostate volume (PV) was used as a reliable measurement of LUTS, and TRUS was considered more accurate than DRE.[94] Confounding factors were identified and adjusted for age, sex, smoking, alcohol consumption, sexual activity, UTIs or infections, constipation, exercise, drug intake, race, and menopause. Confounders were adjusted for using logistical regression analysis,[10,63,66,68] multivariate analysis,[24,25,34,46,51,52,77,82] and sensitivity analysis.[22] Restrictions in design were also performed for age and sex; patients were also stratified according to age,[22] menopause,[57] or smoking status. Akin *et al.*[22] used receiver operating characteristics (ROC) curve and calculated area under the curve (AUC) for OAB and WC (AUC = 0.72 cm^2, 95% CI = 0.65–0.79, $p < 0.001$); this produced highly sensitive and specific cutoff values to determine OAB presence (WC = 98.5 cm). MetS criteria often included gender-specific and race-specific BMI and WC cutoffs for obesity. The exclusion criteria included patients with neurological disorders, depression, antidepressant use, anticholinergic medication use, diuretics, bladder or prostate cancer, UTI, stress urinary incontinence (SUI), and urinary symptoms since childhood.[10,22,63,66,68]

The strengths of our study include a clear objective and inclusion/exclusion criteria, not limited by sample size, follow-up period, length of intervention, or setting. We performed an extensive search of MEDLINE, SCOPUS, CENTRAL, and ClinicalTrials.gov; reference lists of selected articles and other literature sources were also searched to ensure a comprehensive search of sources. Each study was screened by two independent reviewers; conflicts were resolved by a

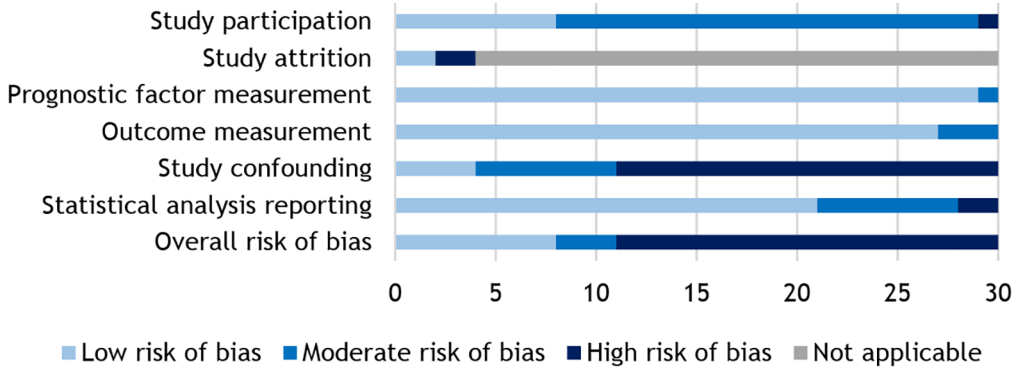

Figure 5. QUIPS risk of bias assessment graph for the 30 studies included in meta-analysis. Risk of bias for the following components: study participation, study attrition, prognostic factor measurement, outcome measurement, and study.

Table 4. QUIPS risk of bias assessment table for each study included in meta-analysis ($k = 30$).

Study ID ($k = 30$)	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias
Coban *et al.*[30]	Low	NA	Low	Moderate	High	Moderate	High
De Nunzio *et al.*[32]	Moderate	NA	Low	Low	High	Low	High
De Nunzio *et al.*[33]	Moderate	Low	Low	Low	Moderate	Low	Low
De Nunzio *et al.*[35]	Moderate	NA	Low	Moderate	Moderate	Low	Moderate
Fu *et al.*[39]	Moderate	Low	Low	Low	High	Moderate	High
Gacci *et al.*[40]	Low	NA	Low	Low	Moderate	Low	Low
Gacci *et al.*[41]	Low	NA	Low	Low	Moderate	Low	Low
Kim *et al.*[45]	Moderate	NA	Low	Low	High	Low	High
Kwon *et al.*[47]	Moderate	NA	Low	Low	High	Low	High
Nandy and Saha[54]	High	NA	Low	Low	High	High	High
Pan *et al.*[59]	Moderate	NA	Low	Low	Low	Low	Low
Park *et al.*[62]	Moderate	NA	Low	Low	Moderate	Low	Low
Park *et al.*[64]	Moderate	NA	Moderate	Low	High	Low	High
Russo *et al.*[71]	Low	NA	Low	Low	High	Low	High
Vanella *et al.*[74]	Moderate	NA	Low	Moderate	High	Low	High
Yang *et al.*[76]	Moderate	NA	Low	Low	Moderate	Moderate	Moderate
Zamuner *et al.*[83]	Moderate	NA	Low	Low	High	Low	High
Zhang *et al.*[84]	Moderate	NA	Low	Low	High	Moderate	High
Zhao *et al.*[85]	Moderate	NA	Low	Low	Moderate	Low	Moderate
Zhao *et al.*[86]	Moderate	NA	Low	Low	High	Low	High
Byun *et al.*[27]	Moderate	NA	Low	Low	High	Moderate	High
Choi *et al.*[28]	Moderate	NA	Low	Low	Low	Low	Low
Yoon *et al.*[81]	Moderate	NA	Low	Low	Low	Low	Low
Ozden *et al.*[58]	Moderate	NA	Low	Low	High	High	High
Xia *et al.*[75]	Moderate	NA	Low	Low	Low	Moderate	Low
Zorba *et al.*[87]	Moderate	NA	Low	Low	High	Moderate	High
Park *et al.*[61]	Low	NA	Low	Low	High	Low	High
Yim *et al.*[80]	Low	NA	Low	Low	High	Low	High
Jeong *et al.*[43]	Low	High	Low	Low	High	Low	High
Lotti *et al.*[50]	Low	High	Low	Low	High	Low	High

QUIPS, Quality in Prognosis Studies.
Risk of bias for following components: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis reporting, and overall risk of bias.

third reviewer. Data extraction was reviewed by a second reviewer. We have included a PRISMA flowchart with reasons for exclusion of studies; the list of excluded studies (and conflicts) is available on Covidence. We included a table of eligible studies, detailed summaries, and characteristics. We performed a quality assessment (NOS) for each study included in our study (Table 1). Our current meta-analysis on TPV and MetS ($k = 30$, $n = 22{,}206$) indicated significant results, albeit heterogeneity was relatively high (Figure 3). Furthermore, a robust method with Sidik–Jonkman estimation and Hartung–Knapp adjustment was used to avoid type I error (false positives) in obtained results and to control for possible uncertainty due to heterogeneity. In addition, a meta-regression analysis was conducted to address the resultant high heterogeneity; there was no significance in predictors being associated with effect sizes (Figure 4(a)–(c); Tables 3 and 4). Furthermore, an Egger's test of the intercept indicated no funnel plot asymmetry (Figure 4(d)); publication bias was not present. We performed a risk of bias assessment using the QUIPS tool and generated a graph (Figure 5).

Most previous studies did not record and adjust for all confounders. Not all studies excluded covariates, for example, neuropathy.[44,60] In diabetic patients, hyperglycemia can result in small nerve fiber damage, known as neuropathy. This disorder can lead to an array of urological conditions, including urgency, incontinence, incomplete emptying, UTIs, and ED. Diabetes can also cause uropathy, which is when there is an obstruction in the urinary tract; this results in bladder disorders, recurrent UTIs, and sexual dysfunction.[95] Oxidative damage can also cause a loss of bladder sensation.[96] Patients with neuropathy would be more likely to report worse LUTS symptoms and quality-of-life scores. In women, diabetic neuropathy was significantly associated with LUTS.[97] In men, prostatic growth is stimulated by elevated activity of the sympathetic nerve, which is caused by elevated insulin levels.[98] Studies did not always collect data on comorbidities such as cardiovascular disease or T2D.[35] Patients with diabetes have been shown to have higher incidences of DO and patients also tend to be older, which is another factor that increases the likelihood of developing LUTS.[99,100] In addition, the following confounding factors could also lead to a variation in results. At binary logistic regression, OAB significantly correlated ($p < 0.001$) with duration of menopausal >5 years (OR = 25.7, 95% CI = 5.82 = 113.72), parity more than twice (OR = 27.94, 95% CI = 8.25–94.6), and previous gynecological surgery (OR = 33.04, 95% CI = 8.78–124.38).[101] Moderate-to-severe LUTS incidence was increased twofold in men aged 70 to 79 years (OR = 2.11, 95% CI = 1.32–3.38) compared with other age groups.[102] OAB was linearly associated with asthma ($p = 0.001$), bladder or prostate cancer ($p = 0.001$), and neurological conditions (stroke, Parkinson's disease, multiple sclerosis; $p < 0.001$).[103] Major adverse cardiac events (MACE), such as acute myocardial infarction, were positively associated with moderate–severe LUTS (OR = 2.38, 95% CI = 2.56–3.07, $p < 0.001$).[104] Alcohol consumption >72 g/day caused close to a threefold increased risk of moderate–severe LUTS (OR = 2.96, 95% CI = 1.61–5.44). History of STIs was also a risk factor (OR = 1.50, 95% CI = 1.08–2.07). Vigorous physical activity negatively correlated with incidence of moderate–severe LUTS (OR = 0.61, 95% CI = 0.44–0.85).[102] Zhu *et al.*[105] negatively correlated OAB with employment status (OR = 0.64, 95% CI = 0.46–0.90). However, a meta-analysis by Zhu *et al.*[105] also found no significant association between OAB and the following: menopause, sex, vaginal delivery, educational level, parity, race, marital status, smoking, and alcohol consumption.

Moreover, multiple studies were cross-sectional, which cannot account for temporal relationships between MetS and LUTS. Retrospective studies rely on data previously collected; assessment of MetS and LUTS could not be controlled (Table 1). Furthermore, nocturia is self-reported; data rely on patients accurately recording their symptoms.[35] IPSS also relies on self-reporting of symptoms, an assessment which, although validated, can be subjective; the LUTS group may have been able to recall and report their symptoms better compared with control subjects (memory bias). IPSS also has high variability;[106] BPH/LUTS symptoms are not constant. Most studies selected patients from a single institution, and samples were relatively small.

Selecting patients from a specialist urology clinic can result in more severe presentations of LUTS. This is clearly at variance compared with the general population prevalence of severe LUTS. This was likely due to a referral bias as patients included

in this meta-analysis were referred to a specialist urology clinic from wider region; cases with milder symptoms were probably managed more locally (referral bias). Patients attending these clinics were older, which is a risk factor for LUTS and MetS. Aging increases the risk of developing obesity, T2D, hypertension, insulin resistance, and dyslipidemia. Participants were mostly men. In addition, asymptomatic control groups were not always included, and many studies did not include follow-up data. LUTS and MetS criteria were also highly heterogeneous; this made it difficult to compare studies. According to World Health Organization (WHO), American Heart Association (AHA); National Heart, Lung, and Blood Institute (NHLBI); and International Diabetes Federation (IDF), the WC cutoffs for MetS for Caucasian men and women are ⩾102 and ⩾88 cm, respectively. WHO and IDF have lower cutoffs for Asian men and women: ⩾90 and ⩾80 cm, respectively. The Japanese Obesity Society has an even lower cutoff for Asian men (⩾85 cm) and a slightly higher cutoff for Asian women (⩾90 cm).[1]

Results rely on the population included in a study; the prevalence of MetS, obesity, and LUTS in a sample; and the smoking status of individuals. In RCTs, the effect of MetS components on LUTS is unclear because taking a random sample of men and women in the community does mean disorders of the uropoietic system will be present in the sample.[13,42,46] Furthermore, all RCTs are hypothetically designed for sample following a power calculation with 95% CI ($p = 0.05$). Even if results are significant, there is a 5% chance they are due to chance. Even though PV is associated with LUTS, some studies did not collect data concerning PV.[66,67,83] Most studies defined general obesity as BMI ⩾30 kg/m^2, while some studies included overweight participants (BMI = 25–29 kg/m^2). According to WHO (1999), BMI ⩾25 kg/m^2 indicates overweight and BMI ⩾30 kg/m^2 indicates obesity.[107] This classification was intended for international use; however, the classification was revised given that high rates of T2D and cardiovascular risk factors were reported in Asian populations with an average BMI below 25 kg/m^2, below the WHO cutoff for 'overweight'.[108] BMI does not take into account muscle mass, and percentage body fat and BMI can differ according to age, sex, and ethnicity. In addition to using IPSS to measure symptoms of LUTS and BPH, TRUS should be used to accurately measure TPV. MetS should be carefully managed when treating larger TPVs in individuals with LUTS and BPH. More studies are required to determine the role of MetS in prostate inflammation and enlargement. Improved study designs and homogenized samples led by hypothesis-driven ideas are required. Future research should focus on the development of multicenter, multinational controlled trials with accurate definitions of MetS and LUTS. Recruiting from specialist centers and clinics is a better option than RCTs as it ensures that the sample contains individuals with LUTS and MetS. Specialists will also diagnose LUTS and MetS more accurately. Specialist urologists should administer questionnaires to reduce error. In addition, all MetS components should be investigated, and asymptomatic groups should be included. A more patient-specific method of measuring LUTS severity is also needed. Combining measurements of LUTS, QOL, and overall health status may increase specificity and sensitivity.[109] TRUS should be used to measure TPV and LUTS. CIs above 95% would be ideal. More research into other uropoietic disorders especially on a genetic and molecular level is needed. More data on the inflammatory markers involved are essential in confirming the role of MetS on inflammatory uropoietic disorders.

Conclusion

The present meta-analysis indicated no significant association between MetS, or its components, and LUTS. This is likely due to significant heterogeneity of methods used to evaluate LUTS symptoms in the studies we included. Regarding TPV and MetS, a significant association was noted in our study and is consistent with other studies in this field. Obesity, large WC, hypertension, hyperinsulinemia, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia have been associated with worse symptoms of uropoietic disorders at multivariate analysis. Interventions aimed at weight loss including behavioral modification, obesity pharmacotherapy, and obesity surgery are recommended and should be at the forefront of management of patients with MetS and disorders of the uropoietic system.

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access to Covidence systematic review software. The data that support the findings of this manuscript are available by the corresponding author upon reasonable request.

Author contributions

A.O. involved in data curation, formal analysis, methodology, project administration, writing-original draft, and writing-review and editing. B.M.L. involved in data curation, formal analysis, methodology, and project administration. E.O. involved in data curation, formal analysis, investigation, methodology, project administration, resources, software, and validation. N.G. involved in data curation, methodology, project administration, and software. A.S.D.S. involved in data curation, methodology, project administration, and software. Z.M.Z. involved in data curation, methodology, project administration, software, and validation. A.D.M. helped in software and writing-review and editing. C.W.l.R. and R.P.V. contributed to resources, software, supervision, and writing-review and editing. L.C. contributed to resources, software, supervision, validation, and writing-review and editing. G.K.D. involved in conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, writing-original draft, and writing-review and editing.

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