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 $\geq 130/85$ mmHg, fasting blood glucose $\geq 5.6$ mmol/l, triglycerides concentration $\geq 1.7$ mmol/l, waist circumference $\geq 102$ 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
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. One of the major contributing factors to MetS is obesity; the prevalence of those with obesity has almost since 1975. 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/m² 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/m² 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.5

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 (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. 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. 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. 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 $\chi^2$ 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. 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. 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
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 as presented in 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/m²); only FBG was significant at multivariate analysis (β = 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

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**Figure 1.** PRISMA flow diagram for studies assessed for eligibility from Moher et al.21
| Study                  | Country          | Study design | MetS criteria | Type of LUTS | Method to assess LUTS | Start date     | End date     | Sample size (n) | Sex   | Population description                                                                 |
|-----------------------|------------------|--------------|---------------|--------------|-----------------------|----------------|--------------|-----------------|-------|----------------------------------------------------------------------------------------|
| Akin et al.           | Turkey           | Cohort       | NCEP          | OAB          | OAB-V8                | August 2012    | December 2013| 204             | Female | Patients divided into two groups: patients with OAB and patients without OAB           |
| Aktas et al.          | 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                 |
| Barbosa et al.        | 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 |
| Baykam et al.         | Turkey           | Cohort       | NCEP-ATP III  | LUTS/BPH     | PRI                   | January 2013   | March 2014   | 120             | Male  | Men over 50years                                                                         |
| Bray et al.           | 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 |
| Byun et al.           | Korea            | Retrospective| NCEP-ATP III  | BPH          | TRUS, PSA             | January 2005   | December 2010| 521             | Male  | Men aged who underwent TRUS; mean age was 53.8 ± 6.9 years                             |
| Choi et al.           | 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   |
| Chung et al.          | Taiwan           | Cross-sectional | Ethnicity-specific for Chinese | OAB          | OABSS                 | May 2008       | November 2008| 1301            | Male  | Diabetic male patients with or without nocturia                                      |
| Coban et al.          | 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 |
| Dagdeviren and Cengiz | 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] |
| Demir et al.          | 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] |
| De Nunzio et al.      | Italy            | Cohort       | ATP III       | LUTS        | IPSS                  | January 2009   | Onward       | 431             | Male  | Patients >50 at urology outpatients with LUTS due to BPE                               |

(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. | 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. | Italy | Cross-sectional | ATP III | LUTS, nocturia | IPSS | October 2009 | Onward | 492 | Male | Men with LUTS/BPE | 8 – Good |
| De Nunzio et al. | Italy | Prospective cross-sectional | ATP III | LUTS | IPPS | 2015 | Onward | 227 | Male | Patients with moderate-severe nocturia (voids per night), LUTS, and BPE undergoing monopolar TURP | 9 – Good |
| Doğan et al. | 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. | 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 | Turkey | Retrospective cohort | IDF | LUTS | IPSS | January 2016 | March 2018 | 356 | Male | Community-dwelling men with LUTS/BPH aged 45 to 78 within Beijing region; out of 1007 enrolled, 325 were carried forward | 9 – Good |
| Fu et al. | China | Prospective cohort | NCEP-ATP III for Asian Americans | UI, UTI, LUTS | IPSS | April 2013 | April 2016 | 1007 | Male | 742 males with BPH/LUTS, 356 included in final analysis | 9 – Good |
| Gacci et al. | 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. | 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. | 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. | 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. | Korea | Retrospective cross-sectional | NCEP | Voiding, storage | IPSS | January 2006 | September 2010 | 1506 | Male | Korean men between 30 and 60 years, excluded men with prostate, high PSA or abnormal DRE or TRUSG findings | 9 – Good |
| Karoli et al. | 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. | 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 |
| Study | Country | Study design | MetS criteria | Type of LUTS | Method to assess LUTS | Start date | End date | Sample size | Sex | Population description | NOS rating |
|-------|---------|--------------|---------------|--------------|----------------------|------------|---------|-------------|-----|------------------------|------------|
| Kupelian et al. | 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. | Korea | Retrospective cohort | Not defined | BPH | Omax, PVR | March 2012 | March 2016 | 151 | Male | Patients who underwent HoLEP for BPH; patients received BPH medication at least 6 months prior to surgery | 9 – Good |
| Lai et al. | The United States | Observational cohort | ATP III, IDF | LUTS | OAB-SI | June 2015 | January 2017 | 920 | Male, female | Patients >18 years who presented to a urologist or urologist for treatment of LUTS; 456 males and 444 females | 8 – Good |
| Lee et al. | Korea | Retrospective cohort | Not defined | LUTS | IPSS, QOL, Qmax, PVR | March 2012 | March 2016 | 151 | Male | Patients who underwent HoLEP for BPH; patients received BPH medication at least 6 months prior to surgery | 9 – Good |
| Lee et al. | The United States | Observational cohort | ATP III, OAB, UI | LUTS | Not defined | June 2010 | December 2014 | 1033 | Male | LUTS group patients with IPSS ≥ 8; Control group: patients with IPSS ≥ 7 | 8 – Good |
| Lotti et al. | Italy | Retrospective cohort | NCEP Infertility | LUTS | IPSS, NIHCPSI | January 2010 | December 2011 | 187 | Male | Male patients attending infertility clinic | 9 – Good |
| Martin et al. | Australia | Cohort | Not defined | LUTS | IPSS | Not defined | Not defined | Not defined | Male | Men aged 55 to 80 residing in the Northern Territory of Australia | 8 – Good |
| Mitsui et al. | Japan | Cohort | Not defined | LUTS | IPSS | Not defined | Not defined | Not defined | Male | Men aged ≥50 years with moderate, severe LUTS | 8 – Good |
| Mossa et al. | Canada | Cohort | Not defined | OAB | OABSS, ICIQ, IIQ-7 | Not defined | Not defined | Not defined | Female | Women aged 50 to 80 years with clinical diagnosis of OAB (with or without treatment) | 9 – Good |
| Nandy and Saha | India | Cross-sectional | IDF | LUTS | IPSS | January 2015 | June 2016 | 58 | Male | Male, aged ≥50 years, prostate biopsy in men with serum PSA >4 ng/ml | 8 – Good |
| Ohgaki et al. | Japan | Cross-sectional | Not defined | LUTS | Japanese IPSS | April 2008 | March 2009 | 1031 | Male | Japanese men who visited the hospital for metabolic screening | 8 – Good |
| Ohgaki et al. | Japan | Cross-sectional | NCEP-ATP III, 2005 IDF | LUTS | IPSS | April 2008 | March 2009 | 900 | Male | Japanese men who visited the hospital for metabolic screening | 8 – Good |
| 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. | Turkey    | Prospective cross-sectional | NCEP-ATP III, AHA, WHF, IAS, ASO, IDF | SU1          | 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.     | 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             | 9 – Good   |
| Pan et al.       | 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. | 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.      | 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.      | 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.      | South Korea | Cross-sectional | NCEP-ATP III                  | LUTS         | IPSS, IEF-5, PEDT, NIHCPSI, ADAM | March 2013  | September 2013 | 1910            | Male   | Healthy Korean men aged 40 to 59 years                                                                                               | 7 – Good   |
| Park et al.      | Korea     | Cohort            | NCEP-ATP III                  | LUTS         | IPSS, IEF, 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.      | 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   |
| Pashoootan et al. | 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.     | Columbia  | Retrospective cross-sectional | IDF, AHA NHLBI, IAS, WHF, ASO | LUTS         | IPSS, IEF            | 2010        | 2011            | 616             | Male   | All male patients aged >40 years who attended outpatient urology clinic from 2010 to 2011                                          | 9 – Good   |
| Russo et al.     | Italy     | Cross-sectional   | IDF                           | LUTS         | IIEF, IPSS           | January 2008 | January 2013  | 544             | Male   | Patients with BPH-related LUTS                                                                                                       | 9 – Good   |

(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.  | Italy          | Cross-sectional  | IDF           | LUTS/BPH     | IPSS                  | January 2009 | January 2013 | 448 Male        | Men with LUTS |                                                                                                                                  | 8 – Good   |
| Russo et al.  | Italy          | Prospective cohort | IDF           | LUTS/BPH, BOO | Not specified         | January 2012 | June 2014    | 244 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.  | Italy          | Cross-sectional  | IDF           | BPE          | DRE, IPSS             | January 2015 | January 2017 | 224 Male        | 224 patients [46 MetS, 178 non-MetS] |                                                                                                                                  | 9 – Good   |
| Saratlija et al.| 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   |
| Telili et al. | 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| 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 policlincs with OAB symptoms or other urologic complaints | 9 – Good   |
| Vanella et al.| 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.    | 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.   | Taiwan         | Prospective cohort | NCEP-ATP III  | LUTS          | IPSS, QOL, Qmax       | January 2010 | December 2010 | 708 Male        | Men >5 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.   | 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 et al.    | 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.    | 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   |
| 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.    | Korea              | Retrospective   | 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.   | 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. | The United Kingdom | Prospective     | 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. | 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   |
| Zhao et al.   | China              | Cross-sectional | NCEP-ATP III criteria for Asian Americans  | BPH          | IPSS                  | February 2009 | March 2012 | 401             | Male   | BPH patients older than 60 years                                                                                               | 9 – Good   |
| Zhao et al.   | China              | Cross-sectional | NCEP-ATP III                               | LUTS         | Chinese IPSS          | October 2014 | December 2014 | 530           | Male   | Elderly male residents who had IPSS >7                                                                                         | 9 – Good   |
| Zhao et al.   | 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.  | Turkey             | Retrospective   | 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; B00, 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; IASGO, 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; IUS, 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; NIHCPISI, 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; PRR, Prostatic Resitive 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, transperineal 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.        | 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.       | 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 ($p = 0.032$). |
| Baykam et al.      | LUTS and MetS and androgenetic alopecia in Latin American population | MetS were associated with moderate/severe LUTS and storage symptoms (and low testosterone): WHR $\geq 1$ [LUTS, $p < 0.001$; storage, $p < 0.001$; voiding, $p = 0.093$], cardiovascular event [LUTS/storage/voiding, $p < 0.001$]. |
| Bray et al.        | KODAMA and PAM clustering                              | Associations between metabolites and LUTS as per metabolome studies.                                      |
| Byun et al.        | 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 $\geq 90$ 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.        | 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.       | 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.       | 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 | 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 ± 111.8; group 3 (healthy), 292.9 ± 84.4. |
| Demir et al.       | 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.   | BPS, LUTS, MetS                                       | MetS associated with an increased risk of storage symptoms in patients with BPE.                        |
| De Nunzio et al.   | MetS and EjD in patients of LUTS and BPE              | MetS not associated with EjD evaluated with the MSHQ-EjD-SF.                                             |
| De Nunzio et al.   | 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. |
Table 2. (Continued)

| Reference            | Outcome measured                                   | Summary of association of Mets and LUTS                                                                 |
|----------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| De Nunzio et al.     | 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.         | 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.           | 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 Horsanal     | 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.            | 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.         | 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.         | 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.           | 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 $\geq 60$ years had a twofold increased likelihood of moderate–severe LUTS.|
| Haghsheno et al.     | 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.         | 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.        | 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.           | 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.       | 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.           | 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.            | 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 = 1.29/10 cm increase, \( p = 0.003 \)] in females, but not males. Dyslipidemia with nocturia >2 [OR = 1.46, \( p = 0.035 \)].                                                     |
| Lee et al.            | 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.            | 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.          | 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.         | 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.         | 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.          | 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        | LUTS including PV, MetS                                                         | Positive association between PV with MetS and its four components: BP, FBG, T0, 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.         | 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.         | 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.                                             |
Table 2. (Continued)

| Reference            | Outcome measured                                                                 | Summary of association of Mets and LUTS                                                                                                                                                                                                 |
|----------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Otunctemur et al.    | 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 $\left( p = 0.001 \text{ and } p < 0.001 \right)$. DM is an independent risk factor for UI.                                                                 |
| Ozden et al.         | 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.           | 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.                                                                                     |
| Papael-stathiou et al.| 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.          | 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.          | 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.          | 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.          | 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.          | 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.     | 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.         | 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.         | 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)
| 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 $\geq 40$ 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/m²) | 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 Zorba73           | 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 ($6.85 \pm 6.52$ versus $7.89 \pm 6.63$; $p = 0.05$), and reduced severity of weak urinary stream during voiding ($0.95$ versus $1.24$ and $1.60$; $p = 0.021$), 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 $p < 0.05$). 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.\(^8^0\) | 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.\(^8^1\) | 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.\(^8^2\) | 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.\(^8^3\) | 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.\(^8^4\) | 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.\(^8^5\)  | 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 \(\geq 1\) 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.\(^8^6\)  | 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.\(^8^7\) | 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; HA1c, 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-5, 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; T2V, 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 volume.
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

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**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.
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 \((\text{MD} = 4.4450, \, 95\% \, \text{CI} = 2.0177–6.8723, \, t = 3.75; \, p < 0.0001)\). However, heterogeneity was high \((\text{tau}^2 = 37.0851 \, [18.9614; \, 71.7320], \, F = 96.3\% \, [95.4\%; \, 96.9\%], \, H^2 = 5.17 \, [4.67; \, 5.72])\). 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.\(^8\) conducted a meta-analysis on 16 studies (BPH patients,
A meta-analysis by Gacci et al. 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 3. Meta-regression analysis for predictors: (a) age, (b) study rating, and (c) publication year. Results were not significant.
case-control studies \((k=8, 3093)\), all of which used ultrasound or TRUS; heterogeneity \((I^2)\) was also high \((90.1\%)\). Li et al.\(^9\) 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 96.9.\(^2\) Russo et al.\(^9\) \((k=19, n=18,476)\) 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.\(^9\) 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 \((\text{AUC}=0.72\ \text{cm}^2, 95\% \text{CI}=0.65–0.79, \ p<0.001)\); this produced highly sensitive and specific cutoff values to determine OAB presence \((\text{WC}=98.5\ \text{cm})\). 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
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                           | High               | Moderate          | Moderate                      | High                 |
| Gacci et al.40   | Low                 | NA              | Low                           | Low                 | Moderate          | Low                           | Low                  |
| Gacci et al.41   | Low                 | NA              | Low                           | Moderate            | Low               | Low                           | Low                  |
| Kim et al.45     | Moderate            | NA              | Low                           | Low                 | High              | Low                           | High                 |
| Kwon et al.47    | Moderate            | NA              | Low                           | Moderate            | Low               | Low                           | High                 |
| Nandy and Saha54 | High                | NA              | Low                           | Low                 | High              | High                          | High                 |
| Pan et al.59     | Moderate            | NA              | Low                           | Low                 | Low               | Low                           | Low                  |
| Park et al.52    | Moderate            | NA              | Low                           | Moderate            | Low               | Low                           | Low                  |
| Park et al.54    | Moderate            | NA              | Moderate                      | Low                 | Moderate          | Low                           | Low                  |
| Russo et al.71   | Low                 | NA              | Low                           | High               | Low               | High                          | High                 |
| Vanella et al.74 | Moderate            | NA              | Low                           | Moderate            | High              | Low                           | High                 |
| Yang et al.76    | Moderate            | NA              | Low                           | Moderate            | Moderate          | Moderate                      | Moderate             |
| Zamuner et al.83 | Moderate            | NA              | Low                           | High               | Low               | Low                           | High                 |
| Zhang et al.84   | Moderate            | NA              | Low                           | Low                 | High              | Moderate                      | High                 |
| Zhao et al.85    | Moderate            | NA              | Low                           | Moderate            | Low               | Moderate                      | Moderate             |
| Zhao et al.86    | Moderate            | NA              | Low                           | High               | Low               | Low                           | High                 |
| Byun et al.27    | Moderate            | NA              | Low                           | High               | Moderate          | High                          | 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                           | High               | High              | High                          | High                 |
| Xia et al.75     | Moderate            | NA              | Low                           | Low                 | Moderate          | Low                           | Moderate             |
| Zorba et al.87   | Moderate            | NA              | Low                           | High               | Moderate          | High                          | High                 |
| Park et al.61    | Low                 | NA              | Low                           | High               | Low               | Low                           | High                 |
| Yim et al.80     | Low                 | NA              | Low                           | High               | Low               | High                          | High                 |
| Jeong et al.43   | Low                 | NA              | Low                           | High               | Low               | High                          | High                 |
| Lotti et al.50   | Low                 | NA              | Low                           | Low                 | Moderate          | High                          | 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. 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. Oxidative damage can also cause a loss of bladder sensation. 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. In men, prostatic growth is stimulated by elevated activity of the sympathetic nerve, which is caused by elevated insulin levels. Studies did not always collect data on comorbidities such as cardiovascular disease or T2D. 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. 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). 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. 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; $p<0.001$). 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, $p<0.001$). 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). Zhu et al. negatively correlated OAB with employment status (OR = 0.64, 95% CI = 0.46–0.90). However, a meta-analysis by Zhu et al. 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. 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. 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 $\geq 102$ and $\geq 88$ cm, respectively. WHO and IDF have lower cutoffs for Asian men and women: $\geq 90$ and $\geq 80$ cm, respectively. The Japanese Obesity Society has an even lower cutoff for Asian men ($\geq 85$ cm) and a slightly higher cutoff for Asian women ($\geq 90$ 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 $\geq 30$ kg/m$^2$, while some studies included overweight participants (BMI $= 25–29$ kg/m$^2$). According to WHO (1999), BMI $\geq 25$ kg/m$^2$ indicates overweight and BMI $\geq 30$ 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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Author contributions
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