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: blood pressure ≥ 130/85mmHg, fasting blood glucose ≥ 5.6mmol/L, triglycerides concentration ≥ 1.7 mmol/L, waist circumference ≥ 102 cm (for men), and high-density lipoprotein cholesterol concentration < 1.03mmol/L (for men). MetS has been associated with worse lower urinary tract symptoms (LUTS) and higher International Prostate Symptom questionnaire scores.

Materials and Methods: Medical Literature Analysis and Retrieval System online (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 Hartung Knapp random effects model and predefined covariates.

Results: A total of 70 studies (n = 90206) were included in qualitive synthesis. From these, 60 studies focused on MetS and LUTS: 44 reported positive correlations; 5 reported negative correlations; 11 reported no association; 10 studies focused on MetS and total prostate volume (TPV). MetS positively correlated with moderate LUTS (OR 1.56, 95% CI 1.35–1.80), severe LUTS (OR 2.35, 95% CI 1.82–3.03), 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 = 22206) were included in meta-analysis; MetS was significantly associated with higher TPV (mean difference 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 metabolic syndrome, which commonly coexists with obesity and benign prostate enlargement.

ABBREVIATIONS

MetS, Metabolic Syndrome; LUTS, Lower Urinary Tract Symptoms; BOO, Bladder Outlet Obstruction; BPH, Benign Prostatic Hyperplasia; BPE, Benign Prostatic Enlargement; OAB, Overactive Bladder; DO, Detrusor Overactivity; UUI, Urgency Urinary Incontinence; SUI, Stress Urinary Incontinence; IC, Interstitial Cystitis; BPS, Bladder Pain Syndrome; IPSS, International Prostate Symptom Score; IPSS-T, International Prostate Symptom Score Total; IPSS-QOL, International Prostate Symptom Score Quality of Life; UVV, Uroflowmetry Voided Volume; Qmax, Uroflowmetry Qmax; PVR, Post-void Residual volume; PSA, Prostate-Specific Antigen; PV, Prostate Volume; TPV, Total Prostate Volume; TRUS, transrectal ultrasonography; DRE, digital rectal exam; BMR , Basal Metabolic Rate; BMI, Body Mass Index; WC, Waist circumference; HC, Hip Circumference; NC, Neck Circumference; WHR, Waist-to-hip Ratio; HDL-C, High Density Lipoprotein-Cholesterol; LDL-C, Low Density Lipoprotein-Cholesterol; FBG, Fasting Blood Glucose; FBS, Fasting Blood Sugar; TG, Triglycerides; HT, Hypertension; BP, Blood pressure; DM, Diabetes Mellitus; T2D, type II diabetes; IR, Insulin Resistance; HbA1c, Haemoglobin A1C; HOMA-I, Homeostatic model assessment Index; NCEP, The National Cholesterol Education Program; MEDLINE, Medical Literature Analysis and Retrieval System Online; CENTRAL, Cochrane Central Register of Controlled Trials; MeSH, Medical Subject Heading; NOS, Newcastle-Ottawa scale; NGF, Nerve Growth Factor; EjD, Ejaculatory Dysfunction; WHO, World Health Organisation; NHS, National Health Service; CDC, Centers for Disease Control and Prevention; HR, Hazard Ratio; OR, Odds Ratio; p, p-value; t, t-value; QUIPS, Quality in Prognosis Studies; MD, pooled weighted mean differences.

1. INTRODUCTION

Metabolic syndrome (MetS) is defined as the presence at least three of the following: blood pressure (BP) ≥130/85 mmHg, fasting blood glucose (FBG) ≥5.6mmol/L, triglycerides (TG) concentration ≥1.7, waist circumference (WC) ≥102 cm for men and ≥89cm for women, and high-density lipoprotein cholesterol (HDL-C) concentration <1.03mmol/L for men and <1.4mmol/L for women [1]. One of the major contributing factors to MetS is Obesity; the prevalence of those with obesity has almost since 1975 [2]. In England, it affects 28% of adults and it was directly associated with 1117 hospital admissions in 2018/19 [3,4].

Body Mass Index (BMI) ≥35 kg/m^2 has been positively correlated with moderate-severe lower urinary tract symptoms (LUTS) (OR 1.38, 95% CI 1.171.63) [5]; WC ≥42 inches (106.7cm) was also significant factor [6]. Additionally, low density lipoprotein-cholesterol (LDL-C) concentration >7.4mmol/L caused a fourfold increased risk of BPH (OR 4.00, 95% CI 1.27-12.63, p = 0.02) [7]. LUTS encompass a variety of bladder conditions: benign prostatic hyperplasia (BPH); urinary tract infection (UTI); overactive bladder (OAB); nocturia;

interstitial cystitis (IC); bladder pain syndrome (BPS). LUTS consists of storage symptoms (urinary incontinence, urgency, frequency, and nocturia), voiding symptoms (intermittency, slow stream, hesitancy, straining to void, terminal dribble, and splitting of stream), and post micturition symptoms (incomplete bladder emptying) [8], [9] Obesity and more specifically patients with a BMI ≥35 kg/m^2 have been positively correlated with moderate-severe LUTS (OR 1.38, 95% CI 1.171.63) [5],[7] LUTS leads to worsening quality of life, sleep, and mental health in men and women [9]. LUTS severity may be quantified by the International Prostate Symptom Score (IPSS) that looks mild, moderate, and severe symptoms [8].

This systematic review and meta-analysis aims to review all existing evidence on the association between MetS and in LUTS; more specifically, the effect of MetS on prostatic inflammation and subsequent hyperplasia in patients with LUTS and BPH. MetS is a growing problem worldwide, and its role in LUTS is unclear; LUTS aetiology is not entirely understood. Whilst studies point towards 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.

2. MATERIAL & 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.

2.1 Search Strategy

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

2.2 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 – firstly by title and abstract and then by full text. Studies were selected using specific 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, randomised clinical trials, cross-sectional studies (no limit on sample size, setting, follow-up period, or intervention); men and/or women aged 18 or above; any component of MetS; any LUTS condition (e.g. LUTS/BPH, OAB, DO, UI); and original articles. Exclusion criteria: studies including children, pregnant women, bladder or prostate cancers/other forms of cancers or animal models; editorials, letters, case reports, opinion pieces, commentaries, systematic reviews and metanalyses; and articles not in English.

2.3 Data extraction

Five reviewers extracted data using Covidence (Covidence (Veritas Health Innovation, Melbourne, Australia; http://www.covidence.org)) [15]. A second reviewer checked the data extracted. Finally, the data were exported to Microsoft excel from Covidence. Example of columns: reference; country; study design; start date; end date; method to classify LUTS; type of LUTS; sample size; gender; population description; MetS criteria; outcome measured; summary of association of Mets and LUTS; quality assessment. Meta-analysis and meta-regression were conducted from February 2021 to 26th April 2021.

2.4 Quality assessment

Each study was assessed for bias using the Newcastle-Ottawa scale (NOS). Studies were evaluated on eight factors, categorised into three groups: selection (including whether the cohort is representative of the population), comparability (assessed on grounds of study design and the analysis performed) and outcome (i.e., the assessment of outcome, follow-up rate, and adequacy of follow-up period). Stars were awarded per category, with a maximum of four, two and three stars possible for the ‘selection’, ‘comparability’ and ‘outcome’ categories respectively [16]. Five reviewers assessed the studies to be of poor (3 stars or less), fair (4-6 stars) or good (7-9 stars) quality (NOS). A risk of bias assessment using the Quality in Prognosis Studies (QUIPS) tool was also carried out for all 30 studies included in meta-analysis [17]. The QUIPS tool assessed study participation; study attrition;

prognostic factor measurement; outcome measurement; study confounding; statistical analysis reporting; overall risk of bias.

2.5 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 odds ratios (OR) were calculated with 95% confidence intervals (CI) from the extracted count data, whilst 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 x^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 visualise the results of meta-regression analysis. Odds ratios 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 posits higher odds of an outcome occurring as anan association with an intervention [14]. Any potential publication bias was assessed with Eggers' test of intercept and visual evaluation of the funnel plot.

3. Results

1741 studies were imported into Covidence, which removed 4 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. 70 studies were included in qualitative synthesis and 30 in meta-analysis (Fig. 1). Three studies used the same patient cohorts and were excluded [18–20]. General characteristics of the included studies are presented in Table 1, while the outcomes measured and a summary of the association between MetS and LUTS are detailed in Table 2. A forest plot for 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; publication year. The results of the Publication Bias assessment - Egger's test of the intercept – are presented in Figure 4. Figure 5 represents a QUIPS Risk of Bias Assessment for the 30 studies included in meta-analysis is presented as a graph (Fig. 5) and table (Table 4).

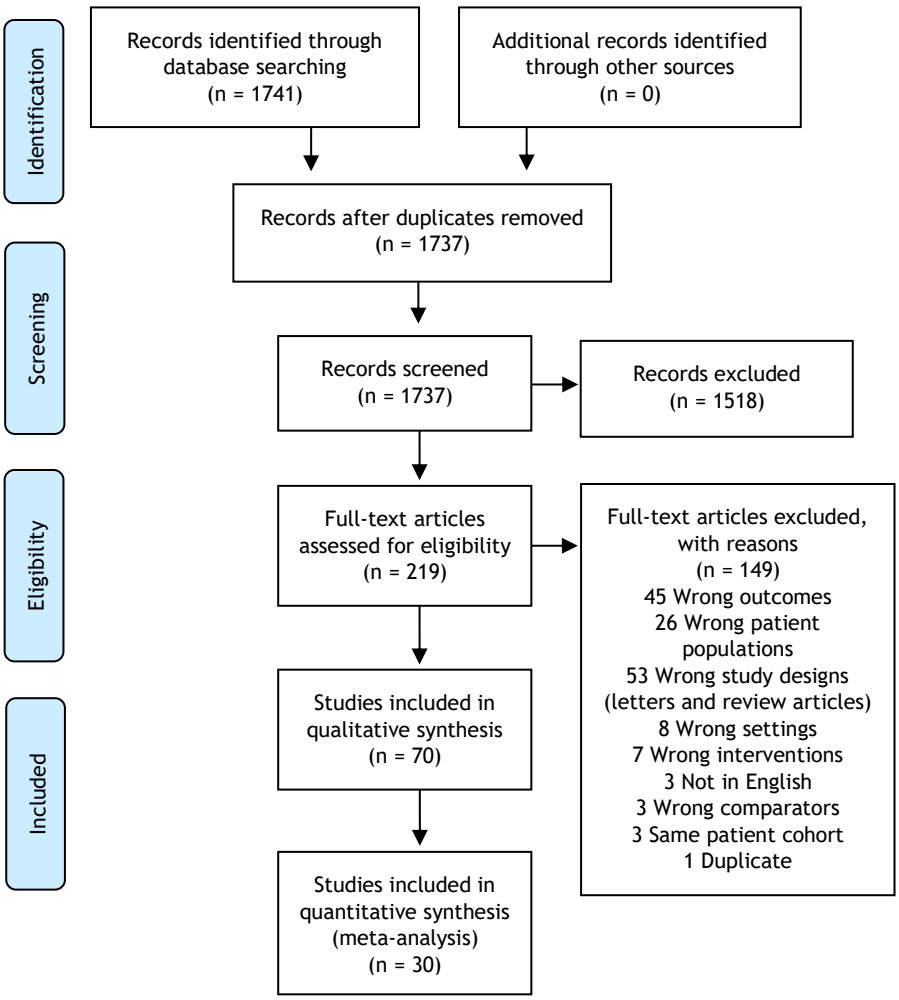

Fig. 1 PRISMA Flow-diagram for studies assessed for eligibility from Moher *et al.* (2009) [21]

239 **Table 1 (i)** General characteristics of studies included in systematic review

Study	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (n)	Sex
Akin 2016 [22]	Turkey	Cohort	NCEP	OAB	OAB-V8	Aug-2012	Dec-2013	204	Fema
Aktas 2011 [23]	Turkey	Cohort	US NCEP-ATP III	LUTS	IPSS	Jan-2009	Oct-2009	106	Male
Barbosa 2013 [24]	Brazil	Cohort	IDF; AHA; NHLBI	LUTS	IPSS	2012	2012	907	Male
Baykam 2015 [25]	Turkey	Cohort	NCEP-ATP III	LUTS/ BPH	PRI	Jan-2013	Mar-2014	120	Male
Bray 2017 [26]	UK	Cohort	None given	OAB	ICIQ-FLUTS	Not defined		212	Fema
Byun 2012 [27]	Korea	Retrospective	NCEP-ATP III; AHA; NHLBI	BPH	TRUS, PSA	Jan-2005	Dec-2010	521	Male
Choi 2013 [28]	Korea	Retrospective	IDF 2009; NHLBI; WHF; IAS; IASO	BPH	TRUS, PSA	Jan-2007	July-2011	4111	Male
Chung 2014 [29]	Taiwan	Cross-sectional	Ethnicity-specific for Chinese	OAB	OABSS	May-2008	Nov-2008	1301	Male
Coban 2014 [30]	Turkey	Cohort	IDF 2005 criteria	LUTS	IPSS, QOL	May-2012	Apr-2013	107	Male
Dagdeviren 2018 [31]	Turkey	Cohort	IDF 2006	OAB	OAB-V8	Jan-2015	Sep-2015	90	Fema
Demir 2009 [10]	Turkey	Cross-sectional	NCEP-ATP III	LUTS	IPSS-QOL	Not defined		190	Male
de Nunzio 2014 [32]	Italy	Cohort	ATP III	LUTS	IPSS	Jan-2009	Onward	431	Male
de Nunzio 2017 [33]	Italy	Cohort	NCEP-ATP III	LUTS	IPSS, IIEF, MSHQ-EjD	Jan-2012	Mar-2016	220	Male
de Nunzio 2018 [34]	Italy	Cross-sectional	ATP III	LUTS, nocturia	IPSS	Oct-2009	Onward	492	Male
de Nunzio 2019 [35]	Italy	Prospective cross-sectional	ATP III		IPPS	2015	Onward	227	Male
Doğan 2015 [36]	Turkey	Cross-sectional	NCEP-ATP III	LUTS	IPPS	Not defined		78	Male
Eom 2011 [37]	South Korea	Cross-sectional	NCEP-ATP	LUTS, nocturia	IPSS	Oct-2003	Feb-2010	33841	Male
Eren 2019 [38]	Turkey	Retrospective cohort	IDF	LUTS	IPSS	Jan-2016	Mar-2018	356	Male
Fu 2016 [39]	China	Prospective cohort	NCEP-ATP III for Asian Americans	UI, UTI, LUTS	IPSS	Apr-2013	Apr-2016	1007	Male
Gacci 2013 [40]	Italy	Retrospective cohort	IDF; AHA; NHLBI	LUTS	IPSS, IS	Jan-2010	Sep-2011	271	Male
Gacci 2017 [41]	Italy	Prospective cohort	NCEP-ATP III	LUTS/ BPE	IPSS, PSA, PV	Jan-2012	Sep-2013	379	Male
Gao 2012 [13]	China	Cross-sectional	2005 NCEP-ATP III	LUTS	IPSS, QOL	Sep-2009	Dec-2009	3103	Male

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241 **Table 1 (ii)** General characteristics of studies included in systematic review continued

Reference	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (n)	Sex	Population description	NOS rating
Haghsheno 2015 [42]	Sweden	Cross-sectional	Not defined	LUTS, UI, BPE	IPSS, UI questionnaires	Not defined		976	Male	Random selection using national population registers. Swedish study population of 3014 men, aged 69–80 years, from three centres. Study on Gothenburg group	8-Good
Jeong 2011 [43]	Korea	Retrospective cross-sectional	NCEP	Voiding, Storage	IPSS	Jan-2006	Sep-2010	1506	Male	Korean men between 30 and 60 years, excluded men with prostatitis, high PSA or abnormal DRE or TRUSG findings	9-Good
Karoli 2014 [44]	India	Cross-sectional cohort	NCEP-ATP III	OAB	AUA-SI, IUSS, PVR	Jan-2012	Dec-2012	102	Female	Women with T2D at diabetic clinic of a medical college hospital with LUTS	9-Good
Kim 2014 [45]	South Korea	Retrospective cohort	NCEP-ATP III	LUTS	IPSS	2012	2014	4256	Male	Healthy native Korean men aged 40-65 years who voluntarily underwent a medical checkup	9-Good
Kupelian 2013 [46]	USA	Randomised control trial	ATP III	LUTS	AUASI	Apr-2002	Jun-2005	1899	Male	A random sample of men aged 30-79 years	8-Good
Kwon 2017 [47]	Korea	Retrospective cohort	Not defined	BPO	IPSS, QOL, Qmax, PVR	Mar-2012	Mar-2016	151	Male	Patients who underwent HoLEP for BPO. Patients received BPH medication at least 6 months prior to surgery.	9-Good
Lai 2019 [48]	USA	Observational cohort	ATP III, IDF	OAB, UI	LUTS Tool	Jun-2015	Jan-2017	920	Male, Female	Patients > 18 years who presented to a urologist or urogynaecologist for treatment of LUTS: 456 males and 464 females	8-Good
Lee 2012 [49]	USA	Retrospective cohort	Not defined	LUTS	IPSS, TRUS	Jan-2006	Jun-2008	409	Male	Men aged > 40 years with moderate-severe LUTS with no previous treatment; divided into three groups according to WC	9-Good
Lee 2015 [11]	South Korea	Prospective cohort	NCEP-ATP III	LUTS	IPSS	2004	Onward	1520	Male	Resident within the borders of the survey area ≥ 6 months. Study on 328 men (aged 50-89 years) randomly selected among 1520	8-Good
Lotti 2014 [50]	Italy	Retrospective cohort	NCEP	Infertility	IPSS, NIHCPSI	Jan 2010	Dec 2011	187	Male	Male patients attending infertility clinic mean age 36.5	9-Good
Martin 2011 [51]	Australia	Cohort	Not defined	LUTS	IPSS	Not defined		1103	Male	Males aged 35–80 residing in the northern and western suburbs of Adelaide	7-Good
Mitsui 2018 [52]	Japan	Cohort	Not defined	LUTS	24-hour bladder diary, IPSS, QOL	Not defined		58	Male	LUTS group: patients with IPSS ≥8 Control group: patients with IPSS ≥7	8-Good
Mossa 2020 [53]	Canada	Cohort	WHO criteria	OAB	24-h voiding diary, OABSS, ICIQ, IIQ-7	Not defined		40	Female	Women aged 50-80 years with clinical diagnosis of OAB (with/without treatment)	9-Good
Nandy 2016 [54]	India	Cross-sectional	IDF 2005	LUTS	IPSS, PV	Jan-2014	Jun-2015	94	Male	Male, 50-65 years of age, prostate biopsy in men with serum PSA > 4 ng/ml	8-Good
Ohgaki 2011 [55]	Japan	Cross-sectional	2005 JASSO, 2005 NCEP-ATP III, 2005 IDF	LUTS nocturia	Japanese IPSS	Apr-2008	Mar-2009	900	Male	Japanese men who had participated in a general health checkup from April 2008 to March 2009	8-Good
Ohgaki 2012 [56]	Japan	Cross-sectional	Same as above	OAB	OABSS	Apr-2009	Mar-2010	1031	Men	Japanese men who visited the hospital for metabolic screening	8-Good
Otuncte mur 2014 [57]	Turkey	Prospective cross-sectional	NCEP-ATP III, AHA, WHF, IAS, ASO, IDF	SUI	ICIQ, Cough stress test	Feb-2011	Jan-2013	400	Female	Women who visited Okmeydani Training and Research Hospital. Stratified by menopausal status	9-Good
Ozden 2007 [58]	Turkey	Prospective	NCEP ATP-III	LUTS/ BPH	IPSS	May-2004	Dec-2004	93	Male	BPH patients with LUTS ≥50 years who visited urology outpatient clinic. Median age: 60 years. Range: 50–83 years	6-Fair
Pan 2014 [59]	China	Retrospective cohort	NCEP-ATP III criteria for Asian Americans	LUTS/ BPH	IPSS, QOL	Jan-2005	Dec-2011	1052	Male	Inpatients diagnosed with BPH and underwent TURP	9-Good

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243 **Table 1 (iii)** General characteristics of studies included in systematic review continued

Reference	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (n)	Sex	Population description	NOS rating
Papaefstathiou 2019 [60]	Greece	Cross-sectional case-control	Not defined	LUTS	IPSS	Dec-2016	Mar-2017	137	Male, Female	20-79 years with DM type I, type II, subclinical and gestational who visited outpatient clinics and people from general population	8-Good
Park 2008 *[61]*	Korea	Prospective cohort study	NCEP ATP-III; AHA; NHLBI	Voiding symptoms QOL, PV	IPSS, TRUS, PSA	Sep-2005	Sep-2006	348	Male	Men aged > 65 years. Exclusion criteria: use of medications for BPH, history of urologic surgery, pyuria	7-Good
Park 2013 [62]	South Korea	Cross sectional	NCEP-ATP III	LUTS	Korean version of the IPSS	Aug-2011	Dec-2011	1224	Male	Male police officers aged 50-59 in Korea	9-Good
Park 2015 [63]	South Korea	Cross sectional	NCEP-ATP III	LUTS	IPSS, IIEF5 PEDT, NIHCPSI, ADAM	Mar-2013	Sep-2013	1910	Male	Healthy Korean men aged 40-59 years	7-Good
Park 2018 [64]	Korea	Cohort	NCEP-ATP III	LUTS	IPSS, IIEF, AMS	Mar-2015	Nov-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 2019 [65]	South Korea	Retrospective cohort	Not defined	BPH/ LUTS	IPSS	Apr-2006	May-2016	4880	Male	Men post TURP with average age 54.1±8.6 years	9-Good
Pashootan 2015 [66]	France	Cohort	NCEP/ATP III	LUTS	IPSS	Nov-2009	Nov-2009	4666	Male	379 GPs randomly selected in France who included all male patients aged 55–100 years seen in consultation (2-week study)	9-Good
Plata 2017 [67]	Columbia	Retrospective cross-sectional	IDF, AHA NHLBI, IAS, WHF, ASO	LUTS	IPSS, IIEF	2010	2011	616	Male	All male patients aged ≥ 40 years who attended outpatient urology clinic from 2010 to 2011	9-Good
Russo 2014 [68]	Italy	Cross-sectional	IDF	LUTS	IIEF, IPSS	Jan-2008	Jan-2013	544	Male	Patients with BPH-related LUTS	9-Good
Russo 2015 [69]	Italy	Cross-sectional	IDF	LUTS/ BPH	IPSS	Jan-2009	Jan-2013	448	Men	Men with LUTS	8-Good
Russo 2016 [70]	Italy	Prospective cohort	IDF	LUTS/ BPH, BOO	Not specified	Jan-2012	Jun-2014	264	Male	13.8% (32/232) patients affected by MetS, 13.8% (32/232) affected by NAFLD, 42.7% (99/232) affected by MetS and NAFLD	8-Good
Russo 2018 [71]	Italy	Cross-sectional	IDF	BPE	DRE, IPSS	Jan-2015	Jan-2017	224	Male	224 patients (46 MetS, 178 non-MetS)	9-Good
Saratlija Novakovic 2017 [72]	Croatia	Case-control	AHA	OAB	OAB-V8	Mar-2016	May-2016	114	Male, Female	57 MetS (27 men and 30 women) 57 Controls (28 men and 29 women)	8-Good
Telli 2015 [12]	Turkey	Retrospective cohort	SEMT Criteria	LUTS	IPSS	Feb-2009	Apr-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 2012 [73]	Turkey	Cross sectional	2006 IDF	OAB, UUi, frequency nocturia	OAB-V8	May-2009	Sep-2010	313	Female	30-70 years, female patients who applied to the policlinics with OAB symptoms or other urologic complaints	9-Good
Vanella 2014 [74]	Italy	Cohort	IDF	LUTS/ BPH, BOO	IPSS	Jan-2012	Jun-2019	132	Male	Patients affected by moderate-severe LUTS due to BOO, secondary to clinical BPH, and who underwent TURP	9-Good
Xia 2019 [75]	China	Cross-sectional	IDF	PSA	IPSS	Oct-2014	Aug-2015	506	Male	Men > 45 years who underwent routine physical examinations were recruited consecutively	6 -Fair
Yang 2012 [76]	Taiwan	Prospective cohort	NCEP-ATP III	LUTS	IPSS, QOL, Qmax	Jan-2010	Dec-2010	708	Male	Men ≥ 45 years (mean, 55.6±9.72 years) who voluntarily underwent a self-paid medical checkup at the Health Management Center of the National Taiwan University Hospital	9-Good
Yang 2016 [77]	Taiwan	Cohort	NCEP-ATP III	LUTS	PV, Chinese version of IPSS	Not defined		616	Male	Males ≥ 40 years recruited from a self-paid medical check-up at the Health Management Center in National Taiwan University Hospital	9-Good

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246 **Table 1 (iv)** General characteristics of studies included in systematic review continued

Reference	Country	Study design	MetS criteria	Type of LUTS	Method to assess LUTS	Start date	End date	Sample size (n)	Sex	Population description	NOS rating
Lee 2019 [78]	Hong Kong, China	Cross-sectional	Not defined	LUTS	IPSS	Jan-2013	Sep-2015	1176	Male	Male subjects ≥ 18 years, referred to a tertiary centre urology clinic for LUTS, elevated PSA or haematuria. 966/1176 included	8-Good
Yeh 2012 [79]	Taiwan	Cross-sectional Cohort	NCEP-ATP III	LUTS	IPSS, QOL	Mar-2008	Aug-2009	764	Male	Males who lived in Kaohsiung city and aged > 40 years	9-Good
Yim 2011 [80]	Korea	Retrospective cohort study	NCEP ATP-III; AHA; NHLBI	PV	TRUS, PSA, DRE	Mar-2009	Jun-2010	968	Male	Men aged 30-49 years who underwent TRUS of prostate for a routine health check-up.	7-Good
Yoon 2016 [81]	Korea	Prospective	NCEP-ATP III	LUTS	IPSS, PVR, KHQ, OAB questionnaire	Not defined		92	Male, Female	Prospective multicentre clinical trial including patients aged 20-75 years. Patients who successfully completed trial: aged 35-75 yrs (median 61, mean 60.0 ± 9.0)	8- Good
Zacche 2017 [82]	UK	Prospective cohort	NCEP-ATP III IDF, MHLW	OAB, DO, SUI, rUTI, bladder pain	KHQ, PPIUS	Oct-2012	Jan-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 2014 [83]	Brazil	Cross-sectional	2001 NCEP-ATP III	LUTS	IPSS	Not defined		490	Male	Unselected and consecutive 490 male adults (mean age 58±9 years) from urologic clinics at community hospital	9-Good
Zhang 2014 [84]	China	Cross sectional	NCEP-ATP III	BPH	IPSS	Feb-2009	Mar-2012	401	Male	BPH patients older than 60 years	9-Good
Zhao 2016a [85]	China	Cross-sectional	NCEP-ATP III criteria for Asian Americans	LUTS	Chinese IPSS	Oct-2014	Dec-2014	530	Male	Elderly male residents who had IPSS> 7	9-Good
Zhao 2016b [86]	China	Cohort	Modified NCEP-ATP III	LUTS	TRUS, IPSS, Qmax	Oct-2014	Aug-2015	551	Male	Aged ≥ 45 years with moderate-severe LUTS due to BPE recruited by consecutive routine physical examination programs	9-Good
Zorba 2017 [87]	Turkey	Retrospective cross-sectional	NCEP-ATP III; IDF; IDF-AHA	LUTS	IPSS	Not defined		807	Male	Men aged 46-89 with LUTS due to BPE (PV>30 mL and IPSS >7)	5-Fair

247

248 **Abbreviations:** MetS, Metabolic Syndrome; OAB, Overactive Bladder; LUTS, Lower Urinary Tract Symptoms; BPH, Benign Prostatic Hyperplasia;
249 UUI, Urinary Urgency Incontinence; SUI; Stress Urinary Incontinence; BOO, Bladder Outlet Obstruction; BPO, Benign Prostatic Obstruction; TURP,
250 Transurethral Resection Of The Prostate; DO, Detrusor Overactivity; rUTI, recurrent Urinary Tract Infection; BPS, Bladder Pain Syndrome; OAB-
251 V8, Overactive Bladder-Validated 8-Question awareness tool; IPSS, International Prostate Symptom Score; IPSS-QOL, International Prostate
252 Symptom Score Quality of Life; PRI, Prostatic Resistive Index; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire-Female Lower
253 Urinary Tract Symptoms; OABSS, Overactive Bladder Symptom Score; IIEF, International Index of Erectile Function; IIEF5, Internal Index Of Erectile
254 Function-5; IIEF, International Index of Erectile Function; MSHQ-EjD, Male Sexual Health Questionnaire ejaculatory dysfunction; IS, Inflammatory
255 Score; PSA, Prostate-Specific Antigen; PV, Prostate Volume; AUA-SI, American Urological Association Symptoms Index; IUSS, Indevus Urgency
256 Severity Scale; PVR, Post-Void Residual Volume; Qmax, Peak urinary flow; TRUS, Transrectal Ultrasound; HoLEP, Holmium Laser Enucleation of
257 the Prostate; ICIQ, International Consultation on Incontinence Questionnaire; IIQ-7, Incontinence Impact Questionnaire; NIHCPSI, National
258 Institutes of Health Chronic Prostatitis Symptom Index; ADAM, Androgen Deficiency In Aging Males; PEDT, Premature Ejaculation Diagnostic Tool;
259 AMS, Aging Male Symptom scale; DRE, Digital Rectal Examination; PPIUS, Patient Perception of Intensity of Urgency Scale; KHQ, King's Health
260 Questionnaire; NOS, Newcastle-Ottawa scale; T2D, Type II diabetes. NCEP, The National Cholesterol Education Program; ATP III, Adult Treatment
261 Panel III; IDF, International Diabetes Federation; AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; WHO, World
262 Health Organization; JASSO, Japan Society for the Study of Obesity; WHF, World Heart Federation; IAS, International Atherosclerosis Society;
263 IASO, International Association for the Study of Obesity; SEMT, Society of Turkish Endocrinology and Metabolism; MHLW, Japan's Ministry of Health
264 Labour and Welfare.

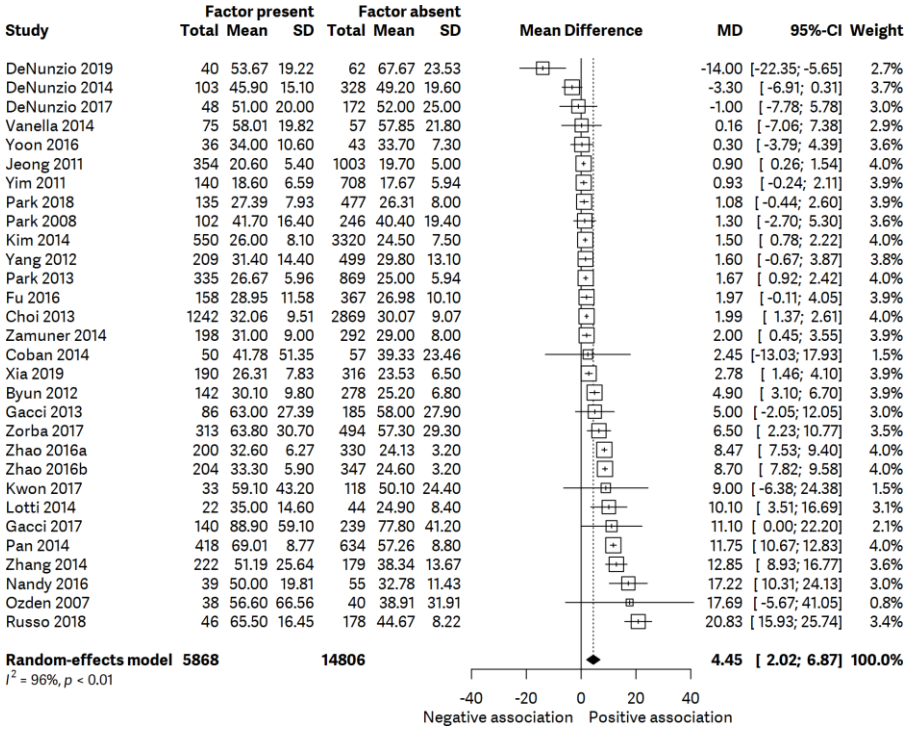

Fig. 2 Forest plot for TPV and MetS. Number of studies combined: k = 30 (n= 22206). MD = 4.4450; 95% CI [2.0177; 6.8723]; t 3.75; p = 0.0008. Quantifying heterogeneity: tau^2 = 37.0851 [18.9614; 71.7320]; tau = 6.0898 [4.3545; 8.4695]. I^2 = 96.3% [95.4%; 96.9%]; H = 5.17 [4.67; 5.72]. Test of heterogeneity: Q 774.09; degrees of freedom, d.f. 29; p < 0p < 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.

Fig.3(a)

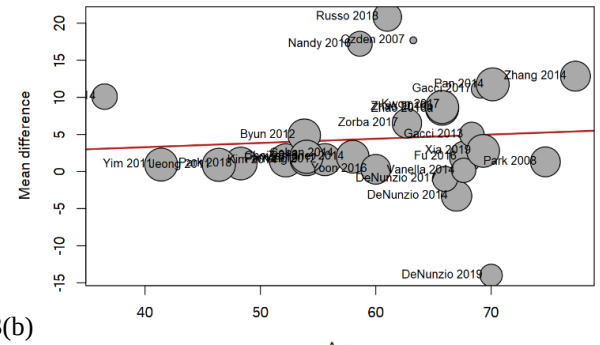

Fig.3(b)

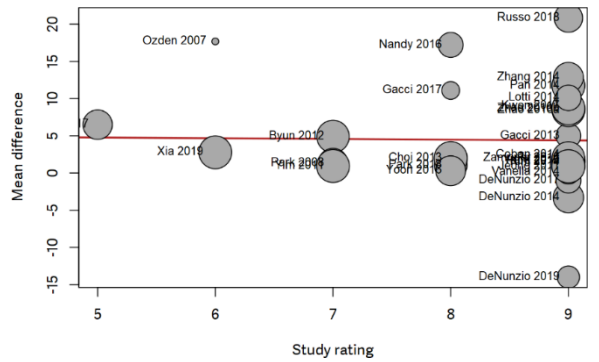

Fig.3(c)

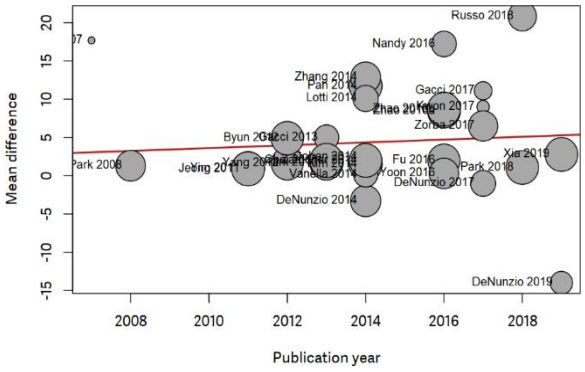

Fig. 3 Meta-regression analysis for predictors: (a) age; (b) study rating; (c) publication year. Results were not significant.

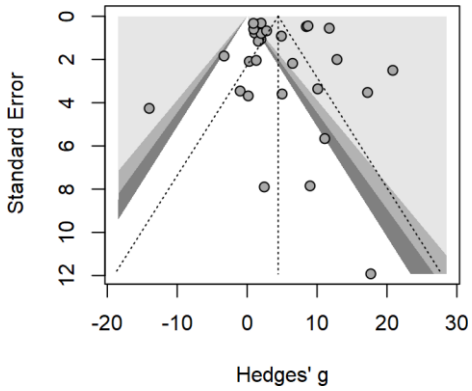

Fig. 4 Publication Bias assessment. Egger's test of the intercept: intercept 1.073; 95% CI -1.71 - 3.86; t = 0.754; p = 0.4570147. Egger's test does not indicate the presence of funnel plot asymmetry.

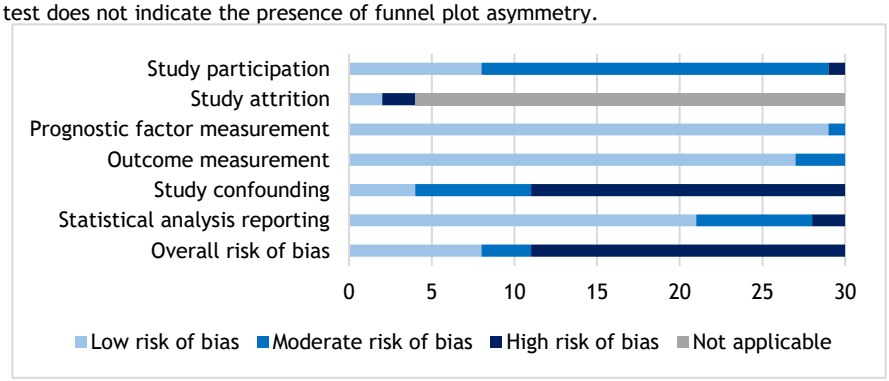

Fig. 5 QUIPS Risk of Bias Assessment graph for the 30 studies included in meta-analysis. Risk of bias for the following components: study participation; study attrition; prognostic factor measurement; outcome measurement; study

Study ID (k = 30)	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias
Coban 2014 *[30]*	Low	NA	Low	Moderate	High	Moderate	High
de Nunzio 2014 *[32]*	Moderate	NA	Low	Low	High	Low	High
de Nunzio 2017 *[33]*	Moderate	Low	Low	Low	Moderate	Low	Low
de Nunzio 2019 *[35]*	Moderate	NA	Low	Moderate	Moderate	Low	Moderate
Fu 2016 *[39]*	Moderate	Low	Low	Low	High	Moderate	High
Gacci 2013 *[40]*	Low	NA	Low	Low	Moderate	Low	Low
Gacci 2017 *[41]*	Low	NA	Low	Low	Moderate	Low	Low
Kim 2014 *[45]*	Moderate	NA	Low	Low	High	Low	High
Kwon 2017 *[47]*	Moderate	NA	Low	Low	High	Low	High
Nandy 2016 *[54]*	High	NA	Low	Low	High	High	High
Pan 2014 *[59]*	Moderate	NA	Low	Low	Low	Low	Low
Park 2013 *[62]*	Moderate	NA	Low	Low	Moderate	Low	Low
Park 2018 *[64]*	Moderate	NA	Moderate	Low	High	Low	High
Russo 2018 *[71]*	Low	NA	Low	Low	High	Low	High
Vanella 2014 *[74]*	Moderate	NA	Low	Moderate	High	Low	High
Yang 2012 *[76]*	Moderate	NA	Low	Low	Moderate	Moderate	Moderate
Zamuner 2014 *[83]*	Moderate	NA	Low	Low	High	Low	High
Zhang 2014 *[84]*	Moderate	NA	Low	Low	High	Moderate	High
Zhao 2016a *[85]*	Moderate	NA	Low	Low	Moderate	Low	Moderate
Zhao 2016b *[86]*	Moderate	NA	Low	Low	High	Low	High
Byun 2012 *[27]*	Moderate	NA	Low	Low	High	Moderate	High
Choi 2013 *[28]*	Moderate	NA	Low	Low	Low	Low	Low
Yoon 2016 *[81]*	Moderate	NA	Low	Low	Low	Low	Low
Ozden 2007 *[58]*	Moderate	NA	Low	Low	High	High	High
Xia 2019 *[75]*	Moderate	NA	Low	Low	Low	Moderate	Low
Zorba 2017 *[87]*	Moderate	NA	Low	Low	High	Moderate	High
Park 2008 *[61]*	Low	NA	Low	Low	High	Low	High
Yim 2011 *[80]*	Low	NA	Low	Low	High	Low	High
Jeong 2011 *[43]*	Low	High	Low	Low	High	Low	High
Lotti 2014 *[50]*	Low	High	Low	Low	High	Low	High

Table 4 QUIPS Risk of Bias Assessment table for each study included in meta-analysis (k=30). Risk of bias for following components: study participation; study attrition; prognostic factor measurement; outcome measurement; study confounding; statistical analysis reporting; overall risk of bias.

3.2 Summary of qualitative data

A total of 70 studies were included in qualitive synthesis. From these, 60 studies focused on MetS and LUTS: 44 reported positive correlations; 5 reported negative correlations; 11 reported no association; 10 studies focused on MetS and total prostate volume (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.* (2009) reported positive correlations between MetS and LUTS (OR 2.4, 95% CI 1.24–4.59, p = 0.009) [10]; however, significance was lost at multiple logistic regression analysis. Baykam *et al.* (2015) found no association between LUTS and BMI (kg/m^2); only FBG was significant at multivariate analysis (β = 0.001, t = 3.491, p = 0.001) [25]. Gao *et al.* (2012) found that MetS was not associated with the severity of LUTS (multivariate: OR 0.97; 95% CI 0.67-1.39) [13].

3.3 Summary of meta-analysis

Initially, data from 70 studies was extracted and a meta-analysis on MetS and LUTS, which included 33 studies, was conducted; this generated 16 forest plots. the following outcomes vs. MetS were evaluated: IPSS-T; IPSS voiding; IPSS storage; IPSS-QOL; TPV (ml); Prostate-Specific Antigen (PSA) (ng/ml); uroflowmetry Qmax (ml/s); Post-void residual volume (PVR) (ml). Furthermore, forest plots for IPSS severity and each MetS component were generated; results were not significant; however, heterogeneity was relatively low in some plots. Given that TPV proved significant, we explored this further and systematically searched for studies on TPV and MetS (10 additional studies were identified). We generated another forest plot for TPV and MetS (total of 30 studies), which proved highly significant, albeit heterogeneity was high: I^2 96.3% [95.4%; 96.9%]. Results are presented in Fig. 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; publication year; results were not significant ($p > 0.05$) therefore, predictors had no effect on heterogeneity (Fig. 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: -1.71-3.86; t = 0.754; p = 0.4570147) (Fig. 4). A Risk of Bias assessment was also performed, as shown in Fig. 5 and Table 4, with an overall high risk of bias in most studies.

4. 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 order to highlight any significant findings to date. Our meta-analysis (k = 30, n = 22206) on TPV and MetS indicated significant results confirmed a significant association (MD = 4.4450, 95% CI [2.0177; 6.8723], t = 3.75; p = 0.0008). However, heterogeneity was high (tau^2 = 37.0851 [18.9614; 71.7320], I^2 = 96.3% [95.4%; 96.9%], H = 5.17 [4.67; 5.72]). Meta-regression produced non-significant results suggesting that predictors (age; country; study rating; publication year) had no effect on heterogeneity. Our study found no association between MetS and IPSS or its subgroups, PSA, Qmax, and PVR. Several studies have demonstrated that MetS causes inflammation and prostatic hyperplasia in men with BPH/LUTS. The results of our meta-analysis are consistent with other literature. Zou *et al*. (2016) conducted a meta-analysis on 16 studies (BPH patients, n = 1895) on MetS and BPH in Chinese patients; total prostate volume (MD = 10.15 ml; 95% CI 7.37-12.93) and annual prostate growth rate (MD = 0.49 ml/year; 95% CI 0.24-0.73) were significantly higher in BPH patients with MetS compared to patients without MetS [88]. A meta-analysis by Gacci *et al*. (2015) reported similar findings; total prostate volume was significantly higher in BPH patients with MetS (+1.8 mL, 95% CI 0.74-2.87, p < 0.001). Additionally, no association was found between MetS and IPSS [89]. Wu *et al*. (2019) also reported a significant between MetS and total prostate volume (OR 2.34, 95% CI 1.25–3.42) after performing a meta-analysis on 6 comparative studies (n = 61826). Again, similar to our study, Wu *et al*. found no significant association was found between MetS and IPSS or PVR [90]. Wang *et al*. (2016) (k = 8, n = 3093) reported that BPH patients with MetS had significantly higher prostate growth rates (MD = 0.67 mL/y, p < 0.001) and prostate volumes (MD = 6.8 mL, p = 0.010). No significant association between MetS and IPSS, and Qmax; however, there was an almost significant association with PSA (MD = 0.24 ng/mL, p = 0.056) [91]. Li *et al*. (2020) also significantly associated MetS with higher annual prostate growth rate and prostate volume; no association between MetS and IPSS/IPSS subgroups. In contrast to our study, Li *et al*. significantly associated MetS with reduced Qmax (MD = -0.48, p = 0.001) and increased PVR (MD = 8.28; p < 0.001) [92]. Russo *et al*. (2015) demonstrated that a significant association between MetS and prostate volume (MD = 2.18; p = 0.03); no association with IPSS [93]. 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 randomised control trials (k = 30, n = 22206); not all studies used TRUS to measure total prostate volume. Wu *et al*. (2019) included retrospective studies and one prospective study (k = 6, n = 61826); studies used TRUS; one study used suprapubic

ultrasound [90]. Wang *et al*. (2016) included cohort or case-control studies (k = 8, 3093), all of which used ultrasound or TRUS; heterogenity (I^2) was also high (90.1%) [91]. Li *et al*. (2020) included prospective and retrospective studies (k = 21, n = 15317); 17 studies used TRUS to measure total prostate volume. Forest plot results indicated a significantly lower heterogenity of 49%, whilst our heterogenity was 96% [92]. Russo *et al*. *(*2015) (k = 19, n = 18476) included 6 studies in the forest plot for prostate volume and heterogenity was 85%; BPH definitions varied, and studies used TRUS and/or DRE or IPSS alone [93].

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 transrectal ultrasonography (TRUS) was considered more accurate than digital rectal examination (DRE) [94]. Confounding factors were identified and adjusted for: age; sex; smoking; alcohol consumption; sexual activity; UTI's or infections; constipation; exercise; drug intake; race; 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*. (2016) used Receiver Operating Curves (ROC) and calculated area under curve (AUC) for OAB and WC (AUC 0.72 cm^2, 95% CI 0.65-0.79, $p < 0.001$) [22]; this produced highly sensitive and specific cut-off values to determine OAB presence (WC 98.5cm). MetS criteria often included gender-specific and race-specific BMI and WC cut-offs for obesity. The exclusion criteria included patients with neurological disorders; depression; antidepressant use; anticholinergic medication use; diuretics; bladder or prostate cancer; UTI; SUI; urinary symptoms since childhood [22]. [10,63,66,68]

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 third reviewer. Data extraction was reviewed by a second reviewer. We have included a PRISMA flow-chart 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 = 22206) indicated significant results, albeit heterogeneity was relatively high (Fig. 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. Additionally, a meta-regression analysis was conducted to address the resultant high heterogeneity; there was no significance in predictors being associated with effect sizes (Fig. 4 A-C; Table 3-7). Furthermore, an Egger's test of the intercept indicated no funnel plot asymmetry (Fig. 4 D); publication bias was not present. We performed a risk of bias assessment using the QUIPS tool and generated a graph (Fig. 5; Table 8).

Most previous studies did not record and adjust for all confounders. Not all studies excluded covariates, e.g., neuropathy [44,60]. In diabetic patients, hyperglycaemia 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, UTI's, and ED. Diabetes can also cause uropathy, which is when there is an obstruction in the urinary tract; this results in bladder disorders, recurrent UTI's, and sexual dysfunction [95]. Oxidative damage can also cause a loss of bladder sensation [96]. Patients with neuropathy would be more likely to report worse LUTS symptoms and quality of life scores. In women, diabetic neuropathy was significantly associated with LUTS [97]. In men, prostatic growth is stimulated by elevated activity of the sympathic nerve, which is caused by elevated insulin levels [98]. Studies did not always collect data on comorbidities such as cardiovascular disease or T2D [35]. Patients with diabetes have been shown to have higher incidences of DO and patients also tend to be older, which is another factor that increases the likelihood of developing LUTS [99,100]. Additionally, 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); previous gynaecological surgery (OR 33.04; 95% CI 8.78-124.38) [101]. Moderate to severe LUTS incidence was increased two-fold in men aged 70-79 (OR 2.11, 95% CI 1.32-3.38) compared to other age groups [102]. OAB was linearly associated with asthma ($p = 0.001$), bladder or prostate cancer ($p = 0.001$), and neurological conditions (stroke; Parkinson's disease; multiple sclerosis) ($p<0.001$) [103]. Major adverse cardiac events (MACE), such as acute myocardial infarction, were positively associated with moderate-severe LUTS (OR 2.38; 95% CI 2.56-3.07; $p<0.001$) [104]. Alcohol consumption >72 g/day caused close to a third-fold increased risk of moderate-severe LUTS (OR 2.96, 95% CI 1.61-5.44). History of STIs was also a risk factor (OR 1.50, 95% CI 1.08-2.07). Vigorous physical activity negatively correlated with incidence of moderate-severe LUTS (OR 0.61, 95% CI 0.44-0.85) [102]. Zhu et al. (2019) negatively correlated OAB with employment status

(OR 0.64, 95% CI 0.46–0.90). However, a meta-analysis by Zhu et al. (2019) also found no significant association between OAB and the following: menopause, sex, vaginal delivery, educational level, parity, race, marital status, smoking, and alcohol consumption [105].

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

Selecting patients from a specialist urology clinic can result in more severe presentations of LUTS. This is clearly at variance compared with the general population prevalence of severe LUTS. This was likely due to a referral bias as patients included in this meta-analysis were referred to a specialist urology clinic from wider region; cases with milder symptoms were probably managed more locally (referral bias). Patients attending these clinics were older, which is a risk factor for LUTS and MetS. Ageing increases the risk of developing obesity, T2D, hypertension, insulin resistance, and dyslipidaemia. Participants were mostly men. Additionally, asymptomatic control groups were not always included, and many studies did not include follow-up data. LUTS and MetS criteria were also highly heterogenous; this made it difficult to compare studies. According to WHO, American Heart Association (AHA), National Heart, Lung, and Blood Institute (NHLBI), and International Diabetes Federation (IDF), the waist circumference cut-offs for MetS for Caucasian men and women are ≥102 cm and ≥88 cm respectively. WHO and IDF have lower cut-offs for Asian men and women: ≥90 cm and ≥80 cm respectively. The Japanese Obesity Society has an even lower cut-off for Asian men (≥85 cm) and a slightly higher cut-off for Asian women (≥90 cm) [1].

Results rely on the population included in a study, the prevalence of MetS, obesity, and LUTS in a sample, and the smoking status of individuals. In randomised control trials (RCTs), the effect of MetS components on LUTS is unclear because taking a random sample of men and women in the community does mean disorders of the uropoietic system will be present in the sample [13,42,46]. Furthermore, all RCTs are hypothetically designed for sample following a power calculation with 95% CI ($p = 0.05$). Even if results are significant, there is a 5% chance they are due to chance. Even though PV is associated with LUTS, some studies did not collect data concerning PV [66,67,83]. Most studies defined general obesity as BMI

≥30 kg/m^2, whilst some studies included overweight participants (BMI 25-29 kg/m^2). According to WHO (1999), BMI ≥25 kg/m^2 indicates overweight and BMI ≥30 kg/m^2 indicates obesity [107]. This classification was intended for international use; however, the classification was revised given that high rates of T2D and cardiovascular risk factors were reported in Asian populations with an average BMI below 25kg/m^2, below the WHO cut-off 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 total prostate volume. Metabolic syndrome should be carefully managed when treating larger total prostate volumes in individuals with LUTS and BPH. More studies are required to determine the role of metabolic syndrome in prostate inflammation and enlargement. Improved study designs and homogenised samples led by hypothesis driven ideas are required. Future research should focus on the development of multicentre, multinational controlled trials with accurate definitions of MetS and LUTS. Recruiting from specialist centres and clinics is a better option than randomised control trials 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. Additionally, 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. Confidence intervals above 95% would be ideal. More research into other uropoietic disorders especially on a genetic and molecular level. More data on the inflammatory markers involved is essential in confirming the role of MetS on inflammatory uropoietic disorders.

5. CONCLUSION

The present meta-analysis indicated no significant association between metabolic syndrome, or its components, and lower urinary tract symptoms. This is likely due to significant heterogeneity of methods used to evaluate LUTS symptoms in the studies we included. Regarding total prostate volume and metabolic syndrome, a significant association was noted in our study and is consistent with other studies in this field. Obesity, large waist circumference, hypertension, hyperinsulinaemia, dyslipidaemia, hypercholesterolaemia, and hypertriglyceridemia have been associated with worse symptoms of uropoietic disorders at multivariate analysis. Interventions aimed at weight loss including behavioural 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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7. CONFLICT OF INTEREST

The authors of this work declare no conflicting interests.

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