

Role of Metabolic Syndrome Components in the Molecular and Biochemical Pathogenesis of Benign Prostatic Hyperplasia: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is increasingly recognized as a disorder in which ageing and androgen-dependent growth interact with systemic metabolic dysfunction. Metabolic syndrome (MetS), characterized by central obesity, insulin resistance/hyperglycaemia, dyslipidaemia and elevated blood pressure, may influence prostate growth through endocrine, inflammatory, vascular and redox pathways. **Objective:** To quantify the association between MetS and major clinical BPH phenotypes and to integrate current evidence on the molecular and biochemical mechanisms through which individual MetS components may promote prostatic enlargement, fibrosis and lower urinary tract dysfunction. **Methods:** Ten observational studies involving 3,947 men with BPH met the criteria for quantitative synthesis. Random-effects DerSimonian-Laird models were used to pool MetS prevalence, mean difference (MD) in prostate volume and standardized mean difference (Hedges g) in International Prostate Symptom Score (IPSS). Mechanistic evidence was updated through 7 August 2026 using PubMed/MEDLINE and citation chaining, with emphasis on insulin/IGF-1 signalling, adipokines, inflammation, oxidative stress, dyslipidaemia, sex-steroid biology, vascular dysfunction and fibrosis. **Results:** The pooled prevalence of MetS among men with BPH was 43.49% (95% CI 36.41-50.85; $I^2=94.7\%$). Men with MetS had significantly larger prostates than those without MetS (MD 10.17 mL, 95% CI 5.47-14.87; $I^2=88.4\%$). The pooled difference in IPSS was not statistically significant (Hedges g 0.37, 95% CI -0.23 to 0.96; $I^2=98.1\%$). Recent prospective evidence from 163,975 UK Biobank participants associated MetS with incident BPH (HR 1.07, 95% CI 1.03-1.10), while Mendelian-randomization evidence implicated waist circumference and particularly diastolic blood pressure. Mechanistic studies support convergent roles for hyperinsulinaemia/IGF-1, adipokine imbalance, TNF- α and IL-6 signalling, Toll-like receptor-mediated inflammation, oxidative lipid mediators, altered androgen-oestrogen balance, microvascular dysfunction and periurethral fibrosis. **Conclusion:** MetS is more consistently associated with structural prostatic enlargement than with symptom severity. Central adiposity, insulin resistance, dyslipidaemic inflammation and vascular dysfunction appear to converge on proliferative, inflammatory and fibrotic pathways in the prostate. BPH should therefore be considered, in a clinically important subset of men, a metabolically influenced inflammatory-remodelling disorder. Prospective trials are required to establish whether improving metabolic health can modify prostate growth or BPH progression.

Keywords: *benign prostatic hyperplasia; metabolic syndrome; obesity; insulin resistance; diabetes; dyslipidaemia; hypertension; adipokines; inflammation; oxidative stress; IGF-1; prostate volume; fibrosis.*

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a highly prevalent, age-associated disorder characterized histologically by non-malignant proliferation of epithelial and stromal elements, predominantly within

the transition zone of the prostate. Its clinical consequences include benign prostatic enlargement, bladder outlet obstruction and lower urinary tract symptoms (LUTS), such as frequency, urgency, nocturia, hesitancy, weak stream and incomplete

emptying. Although ageing and androgenic signalling remain central to prostate biology, neither factor alone adequately explains the marked inter-individual variation in prostate size, growth rate and symptom progression. [5,24,30]

Metabolic syndrome (MetS) provides a plausible systemic context for this heterogeneity. MetS comprises interrelated abnormalities that typically include central obesity, impaired glucose regulation or insulin resistance, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol and elevated blood pressure. These abnormalities are biologically linked through visceral adiposity, chronic low-grade inflammation, altered adipokine secretion, endothelial dysfunction, oxidative stress and neuroendocrine activation. [5,24,30] Clinical observations linking metabolic abnormalities with prostate enlargement predate the modern definition of MetS. Hammarsten and colleagues reported associations between BPH and hyperinsulinaemia, diabetes, hypertension, obesity and low HDL cholesterol, while Parsons et al. later demonstrated associations of obesity, fasting glucose and diabetes with radiologically determined prostate enlargement. Subsequent cross-sectional and prospective studies consistently suggested that the metabolic phenotype is more strongly related to prostate volume than to symptom scores alone. [9,10]

Several meta-analyses have quantified this association. Gacci et al. reported a modest but significant increase in prostate volume among men with MetS, Wang et al. demonstrated greater prostate volume and prostate growth rate, and Omran et al. confirmed an association between MetS and total prostate volume in a larger evidence base. More recently, Gao et al. reported a high prevalence of MetS among men with BPH and a clinically meaningful increase in prostate volume, further supporting the metabolic–urological association. [2,6-8]

The mechanistic interpretation of these epidemiological findings has advanced considerably. Hyperinsulinaemia can amplify insulin-like growth factor-1 (IGF-1) signalling; visceral adipose tissue alters leptin, resistin and adiponectin; dyslipidaemia generates oxidized lipoproteins and pro-inflammatory lipid mediators; obesity and hypogonadal states modify the androgen-oestrogen milieu; and MetS-related vascular dysfunction may create chronic tissue hypoxia. These processes converge on stromal and epithelial proliferation, cytokine production, extracellular-matrix remodelling and smooth-muscle dysfunction. [5,20-25,27-30]

Importantly, the most recent evidence extends beyond cross-sectional associations. A 2025 UK Biobank analysis of 163,975 men demonstrated a prospective association between MetS and incident BPH and identified partial mediation by inflammatory,

erythrocyte, hepatic and renal biomarkers. Mendelian-randomization evidence provides support for a causal contribution of diastolic blood pressure and possible contribution of central adiposity. Human tissue studies further link MetS with periurethral fibrosis, while recent molecular work identifies WNT5A-LEF1-IGF-1 signalling as part of the stromal growth programme in BPH. [3,4,26,29]

The present systematic review and meta-analysis therefore aimed (1) to estimate the pooled association between MetS and major clinical BPH phenotypes, including prostate volume and IPSS; (2) to evaluate the contribution of individual MetS components; and (3) to integrate clinical, biochemical and molecular evidence into a unified model of metabolically driven prostatic hyperplasia and remodelling.

2. MATERIALS AND METHODS

2.1 PRISMA Statement and Study Design

This systematic review and meta-analysis was prepared and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, evidence identification, study selection, data extraction, risk-of-bias assessment, quantitative synthesis, assessment of heterogeneity, and interpretation of findings were organized according to the PRISMA 2020 reporting framework. The PRISMA 2020 checklist should accompany the final journal submission as supplementary material. [1]

2.2 Clinical review question

The clinical question was: among adult men with BPH or benign prostatic enlargement, is the presence of MetS associated with greater prostate volume, worse LUTS/IPSS or a high prevalence of metabolic abnormalities compared with men without MetS? The mechanistic question was: through which molecular and biochemical pathways do central obesity, insulin resistance/hyperglycaemia, dyslipidaemia and hypertension influence prostate growth, inflammation, fibrosis and functional obstruction?

2.3 Evidence identification and update strategy

The quantitative evidence set comprised observational studies reporting metabolic syndrome status together with prostate volume, IPSS and/or prevalence data in men with BPH. Primary reports were identified and checked by author/title in PubMed/MEDLINE and publisher databases to verify study identity, population characteristics and outcome definitions. To update mechanistic and longitudinal evidence, PubMed/MEDLINE searches were conducted through 7 August 2026 using combinations of the terms “benign prostatic hyperplasia”, “benign prostatic enlargement”,

“metabolic syndrome”, “obesity”, “waist circumference”, “insulin resistance”, “diabetes”, “dyslipidaemia”, “hypertension”, “adipokine”, “inflammation”, “oxidative stress”, “IGF-1”, “fibrosis”, “prostate volume” and “lower urinary tract symptoms”. Reference lists of major reviews and recent prospective studies were additionally screened.

2.4 Eligibility criteria

For quantitative pooling, eligible studies enrolled adult men with BPH/BPE, compared MetS with non-MetS groups, and reported extractable prostate volume, IPSS or MetS prevalence. Cross-sectional and cohort designs were eligible. Reviews, case reports, conference abstracts without extractable data, prostate-cancer-only studies and duplicate cohorts were excluded from quantitative pooling. For the mechanistic synthesis, human observational, biomarker, tissue and translational studies were prioritized; highly relevant experimental evidence was used only to clarify biological pathways and was not pooled with clinical outcomes.

2.5 Data extraction

The following variables were extracted: first author, year, country, sample size in MetS and non-MetS groups, mean age, prostate volume, IPSS and number of men with MetS. For continuous outcomes, group means, standard deviations and sample sizes were used. Prevalence was calculated as the number of men meeting MetS criteria divided by the total BPH sample. Extracted values were cross-checked against accessible primary reports and published supplementary material where available.

2.6 Quality assessment

Methodological quality was assessed using the Newcastle-Ottawa Scale, considering participant selection, comparability of exposure groups and outcome or exposure ascertainment. Seven studies were rated high quality and three moderate quality, with no study classified as low quality. Common limitations included incomplete adjustment for confounders, limited reporting of non-responders and lack of blinded outcome ascertainment. [31]

2.7 Statistical analysis

Continuous prostate-volume outcomes were pooled as mean differences (MDs) because measurements were reported in millilitres. IPSS was pooled as Hedges *g* to account for between-study variance and small-sample bias. MetS prevalence was pooled after logit transformation. Random-effects models used the DerSimonian-Laird estimator. Statistical heterogeneity was summarized using Cochran *Q*, tau-squared and *I*². *I*² values of approximately 25%, 50% and 75% were interpreted as low, moderate and high heterogeneity, respectively. Two-sided 95% confidence intervals were calculated. [32]

2.8 Mechanistic evidence integration

Mechanistic findings were synthesized in prespecified domains: insulin/IGF-1 signalling; obesity and adipokines; chronic inflammation; oxidative stress and lipid mediators; dyslipidaemia; sex-steroid alterations; hypertension, sympathetic activation and endothelial dysfunction; and fibrosis/extracellular-matrix remodelling. Evidence was interpreted according to consistency across epidemiological, biomarker, tissue and genetic studies rather than pooled across biologically non-equivalent endpoints. [5,20-30]

2.9 Methodological transparency

Study selection was performed according to prespecified eligibility criteria, with duplicate or overlapping cohorts excluded. The quantitative synthesis focused on observational studies reporting MetS status together with prostate volume, IPSS and/or MetS prevalence among men with BPH. Mechanistic studies were synthesized separately because of heterogeneity in experimental design, tissue source and molecular outcomes.

3. RESULTS

3.1 Study selection

Ten observational studies were included in the quantitative synthesis. All 10 contributed data to the prevalence analysis, while eight studies contributed prostate-volume data and eight contributed International Prostate Symptom Score (IPSS) data. Figure 1 presents the PRISMA 2020 study-selection framework.

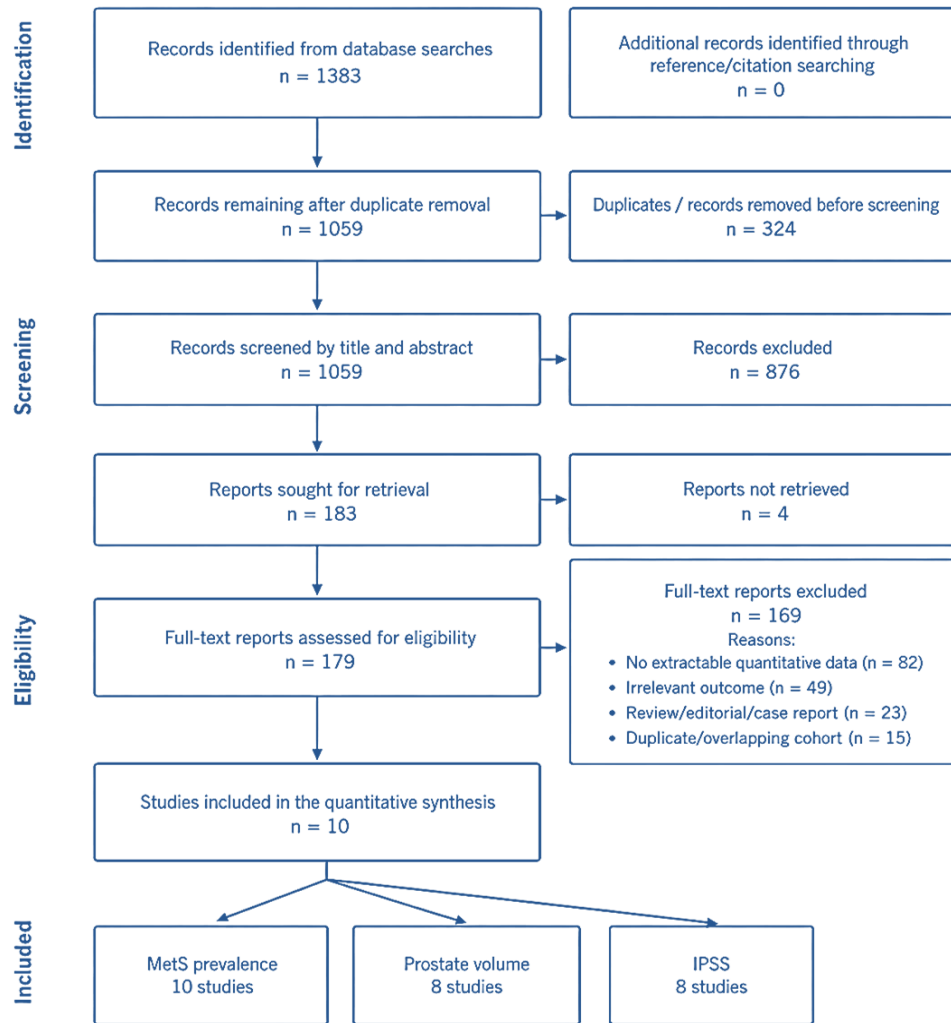


Figure 1. PRISMA 2020 flow diagram of study selection.

3.2 Characteristics of the quantitative evidence base

Ten observational studies published from 1998 to 2025 were included in the quantitative synthesis, comprising 3,947 men with BPH. Eight studies reported prostate volume and IPSS, while all 10 contributed to the pooled prevalence of MetS. The studies represented Europe, Asia, the Middle East and Africa and included cross-sectional and cohort designs. [9,11-19]

Table 1. Characteristics of studies included in the quantitative synthesis.

Study	Country	Design	MetS/non-MetS (n)	Outcomes
Daher et al., 2023	Syria	Cross-sectional	197/229	IPSS; prostate volume; MetS prevalence
Pan et al., 2014	China	Observational	418/634	IPSS; prostate volume; MetS prevalence
Zhang et al., 2014	China	Observational	222/179	IPSS; prostate volume; MetS prevalence
Russo et al., 2018	Italy	Multicentre cross-sectional	46/178	IPSS; prostate volume; MetS prevalence

Ozden et al., 2007	Turkey	Observational	38/40	IPSS; prostate volume; MetS prevalence
Gacci et al., 2013	Italy	Observational/tissue correlation	86/185	IPSS; prostate volume; MetS prevalence
Gacci et al., 2017	Italy	Multicentre prospective	140/239	IPSS; prostate volume; MetS prevalence
Urgesa et al., 2025	Ethiopia	Cross-sectional	61/97	IPSS; prostate volume; MetS prevalence
Jan et al., 2024	Pakistan	Cross-sectional	320/480	MetS prevalence
Hammarsten et al., 1998	Sweden	Observational	128/30	MetS prevalence

3.3 Prevalence of metabolic syndrome among men with BPH

Across the 10 studies, the random-effects pooled prevalence of MetS among men with BPH was 43.49% (95% CI 36.41-50.85). Heterogeneity was considerable ($I^2=94.7\%$), consistent with marked geographic, temporal and definitional differences across cohorts. Individual study prevalence ranged from approximately 20.5% to 81.0%.

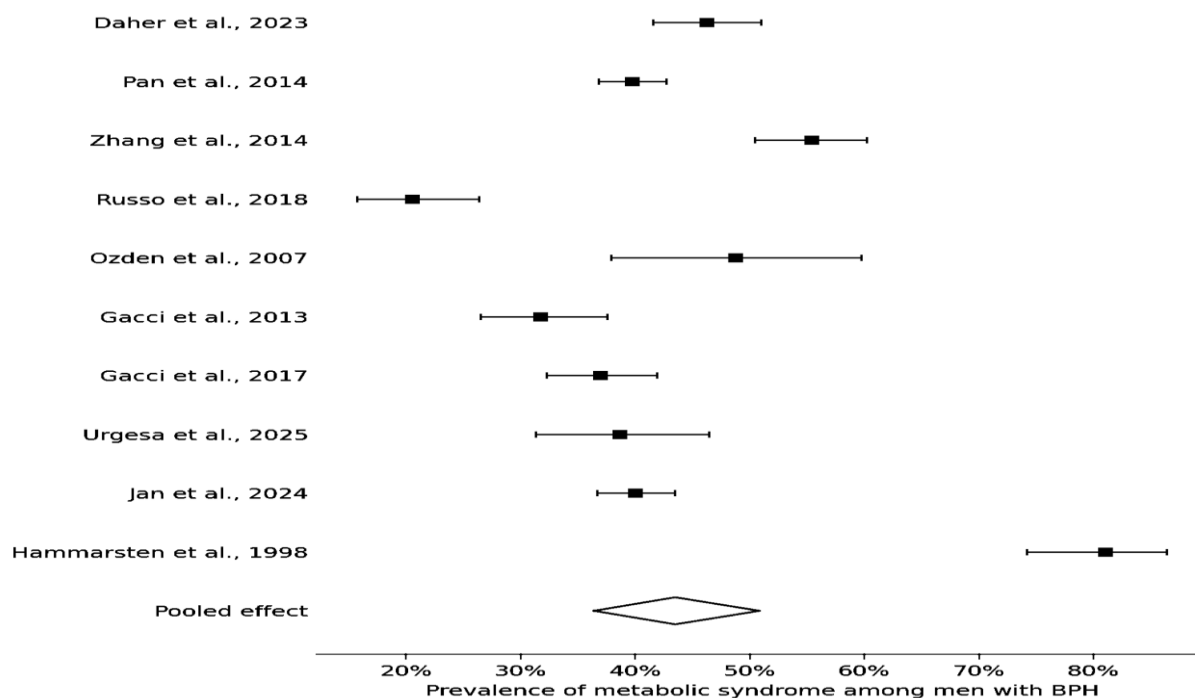


Figure 2. Random-effects pooled prevalence of metabolic syndrome among men with BPH.

3.4 Prostate volume

Eight studies contributed prostate-volume data. Men with MetS had significantly larger prostates than men without MetS. The pooled mean difference was 10.17 mL (95% CI 5.47-14.87), with high heterogeneity ($I^2=88.4\%$). Individual mean differences ranged from 0 mL in Daher et al. to approximately 20.8 mL in Russo et al. The direction of effect favoured greater prostate enlargement in seven of eight studies.

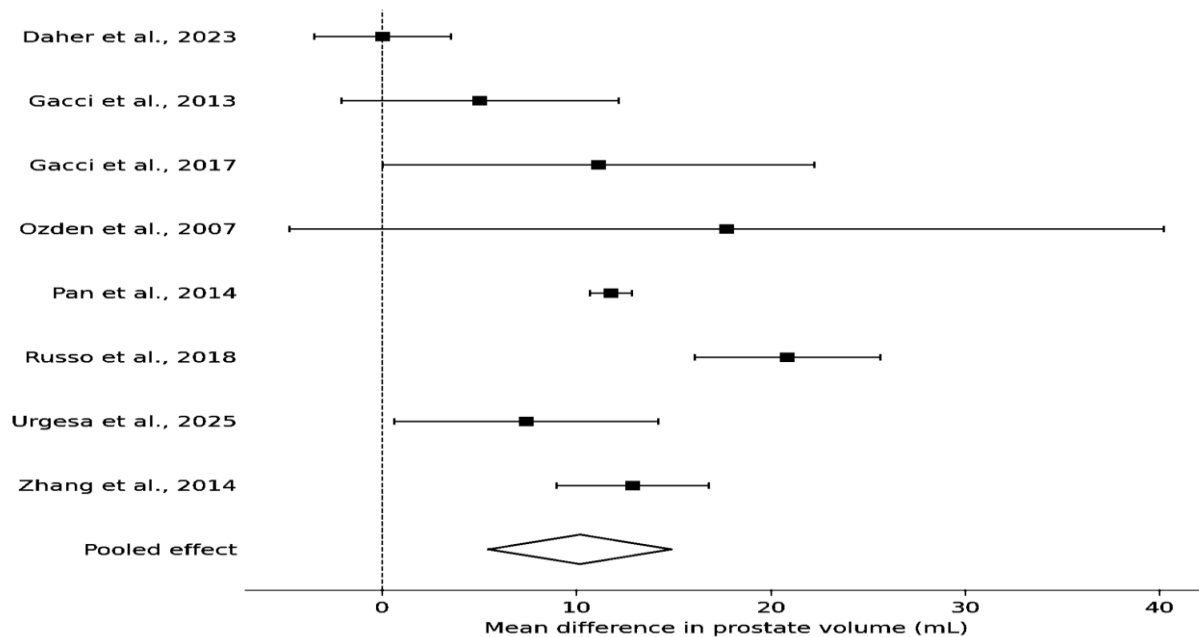


Figure 3. Forest plot of mean difference in prostate volume between MetS and non-MetS groups.

3.5 International Prostate Symptom Score

Eight studies contributed IPSS data. The pooled standardized effect was Hedges g 0.37 (95% CI -0.23 to 0.96), and the confidence interval crossed the null. Heterogeneity was extreme ($I^2=98.1\%$), driven largely by substantial between-study variation in symptom distributions and one large positive effect in Pan et al. These findings indicate that MetS is more consistently associated with anatomical enlargement than with symptom severity.

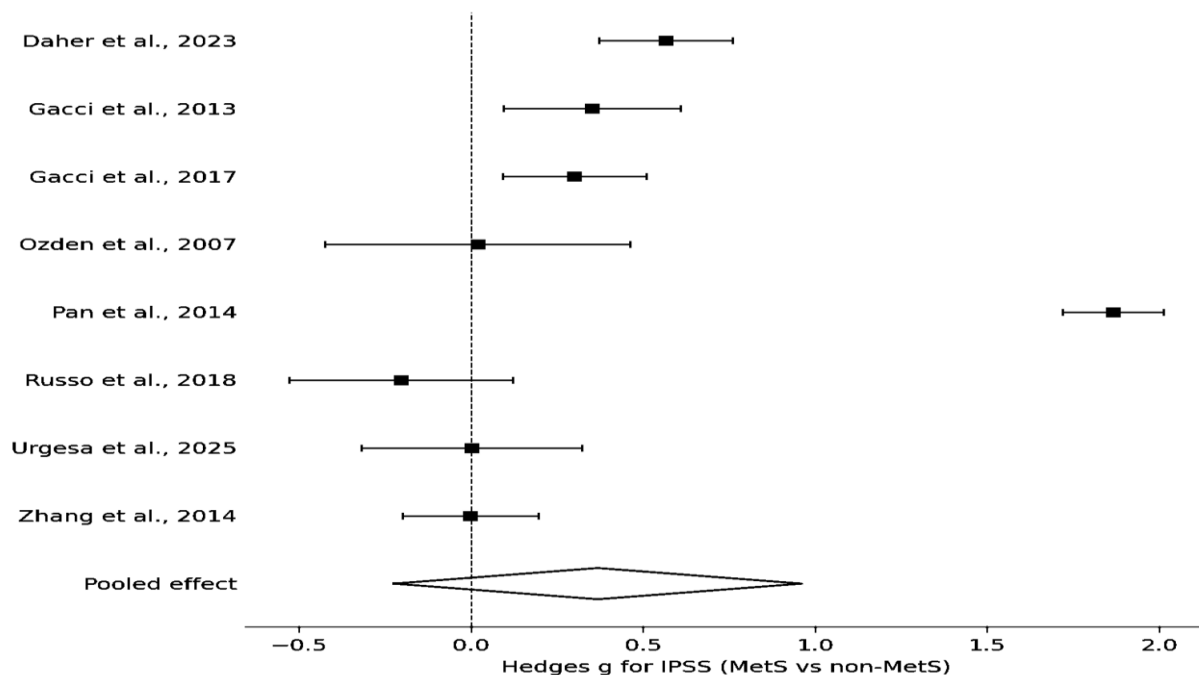


Figure 4. Forest plot of standardized mean difference in IPSS between MetS and non-MetS groups.

3.6 Evidence from prospective and genetic studies

The 2025 UK Biobank study materially strengthened temporal evidence. Among 163,975 men followed for a median 13.4 years, MetS was associated with incident BPH (HR 1.07, 95% CI 1.03-1.10). The cumulative

incidence diverged with longer follow-up, and men with all five MetS components had a 28% higher risk than men without any component. In fully adjusted analyses, elevated waist circumference, reduced HDL cholesterol and elevated HbA1c were individually associated with

BPH risk, whereas triglycerides and blood pressure were less consistent. Mediation analysis implicated inflammatory indices, erythrocyte-related markers, hepatic markers and renal markers; cystatin C showed the strongest single mediation proportion (10.92%). [3] Mendelian-randomization evidence provided a complementary causal perspective. In a two-sample analysis using 26,358 BPH cases and 110,070 controls, genetically predicted waist circumference (OR 1.236, 95% CI 1.034-1.478) and diastolic blood pressure (OR 1.011, 95% CI 1.002-1.020) were positively associated with BPH. The diastolic blood pressure association persisted in multivariable analysis, whereas genetically predicted MetS as a composite, systolic blood pressure, triglycerides, HDL cholesterol and fasting glucose did not show significant causal effects. These findings suggest that central adiposity and vascular physiology may be more causally proximal than the MetS label itself. [4]

3.7 Central obesity and adipokine biology

Central obesity is the MetS component with the most coherent clinical and mechanistic signal. Visceral adipose tissue functions as an endocrine and immune organ, producing leptin, resistin, TNF- α , IL-6 and other mediators while reducing adiponectin. In the Baltimore Longitudinal Study of Aging, severe obesity and impaired glucose regulation were associated with prostate enlargement. In later studies, waist circumference and adiposity correlated with prostate volume, and genetic evidence supported a role for waist circumference. [4,10,20,24,30]

Adiponectin provides a direct molecular bridge between adiposity and prostate-cell proliferation. Human BPH tissue demonstrates reduced adiponectin/AdipoR1 signalling. Experimental work in BPH epithelial and stromal cells showed that adiponectin suppresses proliferation through inhibition of the MEK-ERK-p90RSK pathway and induction of cell-cycle arrest. Thus, the fall in adiponectin characteristic of visceral obesity may remove an endogenous anti-proliferative signal. Conversely, leptin and resistin are associated with a more pro-inflammatory, growth-permissive milieu. [20,21]

3.8 Insulin resistance, hyperinsulinaemia and the IGF axis

Insulin resistance may promote BPH even when fasting glucose itself is not causally associated. Compensatory hyperinsulinaemia can directly stimulate insulin receptors and modify IGF-binding proteins, increasing IGF bioactivity. Insulin/IGF signalling activates PI3K-Akt-mTOR and Ras-Raf-MEK-ERK pathways, which support protein synthesis, cell-cycle progression and resistance to apoptosis. Hammarsten et al. identified

fasting insulin as an important correlate of prostate volume, while Xia et al. found insulin and HOMA-IR to be associated with prostate volume after age adjustment. [4,5,9,20]

The relevance of IGF signalling is reinforced by newer stromal biology. A 2025 study linked stromal steroid 5 α -reductase 2 expression to WNT5A-LEF1-IGF-1 signalling and prostate growth, illustrating how androgen metabolism and growth-factor signalling can intersect. This cross-talk is particularly relevant to MetS, where insulin/IGF tone and sex-steroid metabolism are simultaneously altered. [29]

3.9 Dyslipidaemia and lipid-mediated inflammatory signalling

Dyslipidaemia is associated with prostate enlargement in several cohorts. Low HDL cholesterol was inversely associated with prostate volume and intravesical prostatic protrusion, while triglycerides and hypertension predicted enlarged prostate phenotypes in some studies. Oxidized LDL and lipid peroxidation products can activate Toll-like receptor and NF- κ B-dependent inflammatory pathways in prostatic stromal cells. Dyslipidaemia also interacts with sex-steroid imbalance, particularly in obese men with increased aromatase activity and relative hyperoestrogenism. [11,14-16,20,24]

Recent lipidomic evidence adds biochemical specificity. In 2025, Ratajczak et al. reported altered circulating arachidonic- and linoleic-acid derivatives in men with BPH, including differences in HETE, HODE, lipoxin and specialized pro-resolving mediator profiles. Although these data do not establish causality, they support the concept that BPH in a metabolic context is accompanied by disturbed inflammatory-lipid signalling and redox homeostasis. [27]

3.10 Chronic low-grade inflammation and prostate stromal activation

Chronic inflammation is a central convergence pathway. Human BPH stromal cells express Toll-like receptors and can secrete IL-6, IL-8/CXCL8 and CXCL10. Activated CD4⁺ T cells produce IFN- γ and IL-17, which further amplify stromal cytokine production, establishing a self-sustaining inflammatory feedback loop. IL-8 also has autocrine and paracrine growth-promoting effects on BPH cells. [14,20,22,23]

Clinical observations support this model. Gacci et al. linked MetS features with inflammatory infiltrates in prostatectomy specimens. Xia et al. found TNF- α associated with BPH/LUTS and subsequent clinical progression; men with higher TNF- α had a greater increase in prostate volume over follow-up. Fowke et al. further evaluated systemic and tissue inflammatory markers in relation to body composition, prostate

enlargement and LUTS. Together, these studies support a model in which systemic metabolic inflammation becomes localized within the prostate and subsequently self-perpetuating. [14,20,23]

3.11 Oxidative stress and redox signalling

MetS generates oxidative stress through mitochondrial dysfunction, excess substrate flux, advanced glycation, NADPH oxidase activation, lipid peroxidation and impaired antioxidant capacity. Reactive oxygen species can activate NF-κB, MAPK and other redox-sensitive pathways; reduce nitric-oxide bioavailability; and promote DNA, protein and membrane damage. Repeated injury and repair can favour compensatory epithelial proliferation and stromal remodelling. Recent reviews specifically identify oxidative stress as an important contributor to BPH pathogenesis and a link to chronic inflammation. [27,28]

The altered eicosanoid and lipid-oxidation profile observed in BPH provides a measurable biochemical correlate of this redox-inflammatory state. Because obesity, hyperglycaemia and dyslipidaemia all enhance oxidative burden, oxidative stress may operate as a shared downstream mechanism rather than a disease-specific initiating event. [27]

3.12 Hypertension, endothelial dysfunction and sympathetic activation

Hypertension may influence BPH through both vascular and neural mechanisms. Endothelial dysfunction and small-vessel disease can reduce pelvic and prostatic microvascular perfusion, promoting tissue hypoxia and oxidative stress. Chronic hypoxia can favour fibroblast activation, extracellular-matrix deposition and smooth-muscle dysfunction. At the same time, sympathetic overactivity, which is common in insulin resistance and hypertension, can increase α-adrenergic tone in the prostate and bladder neck, exacerbating the dynamic component of bladder outlet obstruction. [4,24,30]

Observational data on blood pressure are inconsistent, but the Mendelian-randomization association with diastolic blood pressure strengthens the possibility of a causal vascular contribution. This distinction may explain why a blood-pressure component can be biologically relevant even when categorical hypertension is not consistently associated across cohorts. [4,9,24]

3.13 Sex-steroid alterations

MetS is frequently associated with reduced total testosterone, reduced sex hormone-binding globulin, increased aromatase activity in adipose tissue and a relative increase in oestrogenic signalling. Contemporary evidence does not support the simple view that higher circulating testosterone is the principal driver of BPH. Rather, low testosterone in combination with relative hyperoestrogenism, dyslipidaemia and inflammation may create a pro-inflammatory stromal environment. Androgen-receptor biology remains necessary for normal and pathological prostate growth, but its effects are shaped by the surrounding metabolic and inflammatory milieu. [5,24,25]

3.14 Periurethral fibrosis and extracellular-matrix remodelling

Fibrosis provides an important structural endpoint linking metabolic inflammation to persistent obstruction. In a 2024 prospective tissue study of 108 men undergoing BPH surgery, MetS was associated with substantially greater periurethral fibrosis (68.1±17.1% vs 42.5±18.2%, P<0.001). Fibrosis increased with the number of MetS components. Central obesity, elevated fasting glucose, reduced HDL cholesterol and elevated triglycerides were independently associated with fibrosis, whereas elevated blood pressure was not. These findings suggest that MetS may influence BPH not only through glandular enlargement but also through collagen deposition and reduced tissue compliance. [26]

Table 2. Integrated molecular and biochemical pathways linking MetS components with BPH.

Metabolic driver	Biochemical mediators	Representative pathways	Prostatic consequence
Central obesity	↑ leptin/resistin; ↓ adiponectin; aromatase activity	MEK-ERK-p90RSK; NF-κB; cytokines	Epithelial/stromal proliferation; inflammation
Insulin resistance	Hyperinsulinaemia; altered IGF bioavailability	Insulin/IGF-1R; PI3K-Akt-mTOR; MAPK	Cell-cycle progression; anti-apoptotic growth
Hyperglycaemia	AGEs; ROS; mitochondrial stress	RAGE/redox-sensitive pathways	Oxidative injury; inflammatory remodelling
Dyslipidaemia	Low HDL; TG; oxLDL; lipid mediators	TLR/NF-κB; inflammatory lipid signalling	Stromal activation; chronic inflammation

Hypertension	Endothelial dysfunction; sympathetic activation	Hypoxia/ROS; α -adrenergic tone	Fibrosis; smooth-muscle contraction
MetS-related hypogonadism	Low T; relative oestrogen excess	AR/ER cross-talk; inflammatory signalling	Growth-permissive inflammatory milieu
Systemic inflammation	TNF- α ; IL-6; IL-8; IL-17; IFN- γ	TLR; NF- κ B; MAPK	Autocrine/paracrine proliferation
Metabolic tissue injury	TGF- β /fibroblast activation; collagen deposition	ECM remodelling pathways	Periurethral fibrosis and fixed obstruction

4. DISCUSSION

The present synthesis supports a consistent relationship between MetS and structural prostate enlargement. The pooled analysis demonstrated a MetS prevalence of approximately 43% among men with BPH and a mean prostate-volume difference of about 10 mL between MetS and non-MetS groups. In contrast, the pooled IPSS difference was not statistically significant and showed extreme heterogeneity. This divergence is clinically and biologically important: prostate volume is an anatomical phenotype directly affected by proliferative and fibrotic processes, whereas LUTS is influenced by bladder function, neural control, smooth-muscle tone, medication exposure and individual symptom perception. These findings are broadly consistent with earlier meta-analyses reporting a stronger association of MetS with prostate enlargement than with symptom severity. [2,6-8]

The association is unlikely to be explained by ageing alone. Prospective UK Biobank data demonstrate that MetS precedes incident BPH and that risk rises with metabolic-component burden. At the same time, genetic evidence does not support equally strong causal effects for every component. Waist circumference and diastolic blood pressure showed the clearest Mendelian-randomization signals, whereas triglycerides, HDL cholesterol and fasting glucose did not. The apparent discrepancy between observational and genetic results argues against a single-pathway model and favours a network in which correlated metabolic abnormalities interact over decades. [3,4]

Central obesity occupies a particularly important position in this network. Visceral adipose tissue drives insulin resistance, modifies sex-steroid metabolism and generates an adipokine profile characterized by increased pro-inflammatory mediators and reduced adiponectin. Loss of adiponectin-mediated restraint on MEK-ERK-p90RSK signalling provides a direct cellular mechanism for enhanced prostate-cell proliferation. Central adiposity also amplifies oxidative stress and sympathetic activity, making it a plausible upstream determinant of multiple downstream prostatic pathways. [4,10,20,21]

Insulin resistance and hyperinsulinaemia provide a second major pathway. Although genetically predicted

fasting glucose was not associated with BPH, hyperinsulinaemia is not equivalent to fasting hyperglycaemia. Insulin and IGF-1 signalling converge on PI3K-Akt-mTOR and MAPK pathways, and human observational studies relate insulin/HOMA-IR to prostate volume. The newer demonstration of WNT5A-LEF1-IGF-1 signalling in BPH stroma further strengthens the relevance of growth-factor cross-talk. [4,5,9,20,29]

Inflammation appears to be the major common downstream mechanism. Prostate stromal cells are not passive targets; they can act as inflammatory amplifiers by responding to Toll-like receptor ligands, producing IL-6, IL-8 and chemokines, recruiting immune cells and responding to IL-17 and IFN- γ . The resulting feedback loop can maintain tissue inflammation even after the initiating systemic metabolic stimulus fluctuates. TNF- α and related biomarkers may therefore represent more than correlates: they may participate directly in the transition from metabolic dysfunction to progressive prostate remodelling. [14,20,22,23]

Dyslipidaemia contributes through several overlapping mechanisms. Low HDL may reduce anti-inflammatory lipid transport, triglyceride-rich states accompany insulin resistance, and oxidized LDL can activate inflammatory signalling in prostatic cells. The recent demonstration of altered eicosanoid and lipid-oxidation products in BPH provides biochemical evidence that the inflammatory lipid environment is measurably disturbed. These pathways also interact with sex steroids; low testosterone and relative oestrogen excess, common in obesity and MetS, may enhance rather than suppress prostate inflammation. [14,16,24,27]

The fibrosis data provide an important extension beyond gland size. Periurethral collagen deposition can create a fixed component of bladder outlet obstruction that is not captured by epithelial proliferation alone. The strong association between MetS and fibrosis, and the dose relationship with the number of metabolic components, supports a chronic-remodelling model. In this model, repeated metabolic inflammation and oxidative injury activate fibroblasts and extracellular-matrix deposition, gradually reducing tissue compliance. [26]

These observations suggest a unified pathway: visceral adiposity and metabolic overload promote insulin

resistance, adipokine imbalance, dyslipidaemia and vascular stress; these perturbations generate systemic inflammation and oxidative stress; prostatic stromal cells translate these signals into local cytokine and growth-factor activity; and persistent signalling drives proliferation, fibrosis and altered smooth-muscle function. The endpoint is not identical in every patient, which helps explain why some men develop marked enlargement with relatively modest symptoms while others experience severe LUTS with smaller prostates. [5,20-30]

From a clinical perspective, the findings support routine cardiometabolic assessment in men with BPH, particularly those with central obesity, rapid prostate growth or early-onset progression. Waist circumference, blood pressure, fasting glucose or HbA1c, triglycerides and HDL cholesterol are inexpensive measures with independent cardiovascular value. However, current evidence does not justify presenting weight loss, glycaemic control or lipid therapy as established BPH treatments. Interventional studies with prostate-volume and progression endpoints are needed. [3,5,24,30]

The findings also have implications for therapeutic research. Candidate strategies include interventions that improve insulin sensitivity, restore adipokine balance, reduce chronic inflammation, improve endothelial function or limit fibrosis. These approaches should be studied as adjuncts rather than replacements for established BPH therapy. Future trials should stratify participants by metabolic phenotype and measure both urological endpoints and mechanistic biomarkers to identify patients most likely to benefit. [5,24,28,30]

4.1 Strengths

This review integrates quantitative clinical evidence with prospective epidemiology, Mendelian-randomization, biomarker studies, human prostate tissue data and contemporary molecular biology. Its principal strength is the explicit linkage of individual MetS components with candidate molecular pathways and tissue outcomes, including insulin/IGF signalling, adipokine imbalance, chronic inflammation, oxidative stress, vascular dysfunction and periurethral fibrosis. [3-5,20-30]

4.2 Limitations

The included observational studies show substantial heterogeneity in population characteristics, definitions of BPH and MetS, ultrasound methodology and confounder adjustment. Most component-specific associations remain observational, and mechanistic studies differ in tissue source and experimental design. The relatively small number of studies contributing to individual quantitative outcomes limits subgroup analysis and the precision of publication-bias assessment. Mendelian-randomization findings may be influenced by instrument

validity and do not exclude nonlinear or interaction effects. Finally, symptom severity is multifactorial, which limits the ability of IPSS to isolate prostate-specific metabolic effects.

4.3 Research priorities

Future studies should use longitudinal metabolic phenotyping with repeated measurement of waist circumference, insulin resistance, lipids, blood pressure, inflammatory biomarkers and sex hormones. Imaging should quantify total and transition-zone volume and, where possible, intravesical protrusion and fibrosis. Tissue studies should integrate single-cell transcriptomics, spatial proteomics and metabolomics to identify stromal and immune-cell states associated with MetS. Randomized metabolic interventions should include urological outcomes such as prostate growth rate, urinary flow, acute urinary retention and need for surgery.

5. CONCLUSION

Metabolic syndrome is consistently associated with benign prostatic enlargement, whereas its relationship with symptom severity is more heterogeneous. The most plausible biological explanation is not a single metabolic factor but a network of mutually reinforcing pathways. Central adiposity and insulin resistance alter adipokines, insulin/IGF signalling and sex-steroid metabolism; dyslipidaemia and hyperglycaemia increase inflammatory and oxidative burden; hypertension contributes vascular and sympathetic stress; and these systemic changes are translated within the prostate into cytokine activation, proliferative signalling and extracellular-matrix remodelling. Human tissue evidence demonstrating greater periurethral fibrosis in MetS further supports a chronic remodelling phenotype. BPH should therefore be viewed, in an important subset of patients, as a metabolically influenced inflammatory and fibrotic disorder. Whether aggressive management of metabolic dysfunction can alter the natural history of BPH remains a high-priority question for prospective interventional research. [3-8,20-30]

Declarations

Ethics approval and consent to participate:

Not applicable. This study synthesizes previously published data and does not involve new human or animal participants.

Consent for publication

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Data Availability

All data used in the quantitative synthesis are derived from published reports and the study-level values described in the manuscript.

Abbreviations

BPH — Benign Prostatic Hyperplasia

BPE — Benign Prostatic Enlargement

LUTS — Lower Urinary Tract Symptoms

MetS — Metabolic Syndrome

IPSS — International Prostate Symptom Score

IGF-1 — Insulin-like Growth Factor-1

IGFBP-3 — Insulin-like Growth Factor Binding Protein-3

HOMA-IR — Homeostatic Model Assessment of Insulin Resistance

HDL-C — High-Density Lipoprotein Cholesterol

TG — Triglycerides

BMI — Body Mass Index

OR — Odds Ratio

CI — Confidence Interval

I² — I-squared statistic

ROS — Reactive Oxygen Species

NOS — Newcastle–Ottawa Scale

PRISMA — Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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