Identifying the predictors of change in severity of untreated lower urinary tract symptoms (LUTS) in men: a systematic review

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Submitted: August 2018

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ABSTRACT

Background:

Lower urinary tract symptoms (LUTS) fluctuate in severity. Factors that influence the change in symptomatology are a key area of interest, and knowledge of these may provide the opportunity for both primary prevention of LUTS and secondary prevention of worsening LUTS.

Objective:

The objective of this systematic review was to synthesise the available evidence assessing the predictors of change in the severity of untreated LUTS in men in a non-hospital setting.

Method:

Studies that included human males aged > 18 years of age in a non-hospital setting with untreated LUTS were considered for this review. A comprehensive search strategy was designed to find both published and unpublished studies that examined individual exposures and their influence on LUTS severity. Databases searched included PubMed, Embase, Scopus, Web of Science, Grey Literature Report and DIVA Academic Archive Online.

Results:

Twelve studies were included in this systematic review. The total number of men with untreated LUTS examined was 16,105. The mean age of men ranged from 49.7 to 72.7 years. The duration of follow-up ranged from 3-17 years. Heterogeneity within the study methodology, patient groups and outcome measures prevented the conduct of a meta-analysis. Fourteen grouped modifiable exposures and three non-modifiable exposures were examined that indicated that psychological health, cardiovascular risk factors, hormone status and some medications may influence the natural history of LUTS.

Conclusion:

Lower urinary tract symptoms are influenced by factors outside the urological system. Systemic diseases, hormonal status and some medications appear to be associated with fluctuations in LUTS. A causative relationship is still hypothesised, rather than proven, as is the potential role of intervening on modifiable factors.

DECLARATION

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Dr. Simon John Douglas Harley

22/8/18

ACKNOWLEDGEMENTS

I would like to extend my deepest appreciation to the following individuals who provided me with their assistance, expertise and guidance.

This work would not have even started without the initial direction afforded to me by both Associate Professor Gary Wittert and Associate Professor Nick Brook. The experience, intellect and energy that both have contributed to the academic world of urology is highly commendable and I am privileged to have had both as clinical supervisors. It is clear that when disciplines work together, each contributing their own knowledge and expertise, great mysteries can be unravelled.

Associate Professor Craig Lockwood and Dr. Jared Campbell provided me with extensive professional and scientific guidance. For the vast majority of my candidature, I was living more than 2700km away from Adelaide, but although out of sight it appeared I was never out of mind and their understanding and flexibility surrounding my work schedule is greatly appreciated. What I now know of good scientific processes, analysis and interpretation is largely as a result of their teaching.

To Ms Siew Siang Tay who undertook professional copyediting of the thesis in accordance with the Australian Standards for Editing Practice (specifically sections D and E) in a timely manner, thank you.

My Mum and Dad have always served as wonderful examples of community minded, altruistic individuals. I am forever indebted to them in too many ways to list here. They know I'm thankful.

Finally, it would be remiss of me not to mention my wife, Kate, whose love and guidance are with me in whatever I do. She now knows more about old men who cannot pee, better than any paediatrician needs to.

This thesis would not have been possible without you. Thank you.

CHAPTER 1: INTRODUCTION

1.1 Focus of the thesis

Male lower urinary tract symptoms (LUTS) which include urinary urgency, frequency, nocturia, straining, hesitancy, post-micturition dribbling, incontinence and a feeling of incomplete bladder emptying can cause significant bother and morbidity.[1] Up to 31% of men 50 years and older suffer from moderate to severe LUTS.[1] In the United States, 70% of men aged 60-69 years have LUTS whilst 90% of men over 90 years are similarly affected.[2, 3] Previously believed to be symptoms suffered by the elderly, a recent, large population-based international survey found that 51% of men aged 39 and under also complained of at least one lower urinary tract symptom.[4] As a result of its high frequency, there is considerable cost associated with the management of LUTS worldwide.[3, 5]

The natural history of LUTS suggests that although they are common, symptoms fluctuate in their presence and severity. Parsons *et al.* found that 45% of untreated men with severe LUTS at baseline reported an improvement in their symptoms while 17% reported change consistent with progression.[6] Other studies have described similar fluctuating symptomatology in the natural history of LUTS over time.[7-9]

Factors that influence the change in symptomatology are a key area of interest, and knowledge of these would provide the opportunity for both primary prevention of LUTS, and secondary prevention of worsening LUTS. Several studies have examined the association between LUTS and other disease processes, lifestyle, socio-economic status and race[10-14] in cross-sectional analyses, and whilst useful in generating hypotheses on LUTS aetiology, they do not provide information on whether these factors play a role in LUTS fluctuating natural history. Large, population-based cohort studies provide a valuable method of analysing both the natural history of LUTS suffered by men and competing or associated co-morbidities. While some attempts have been made to examine individual risk factors such as weight loss,[15] to the best of my knowledge, a synthesis of all published cohorts of untreated men with LUTS has yet to performed and thus forms the focus of this review.

1.2 Anatomy of the urological system

The urological system is divided into both an upper urinary tract (kidneys and ureters) and a lower urinary tract (bladder, prostate and urethra) (see Figure 1).

1.2.1 The upper urological tract

The kidneys have four main functions and are essential for haematopoiesis, electrolyte and fluid balance, and the elimination of metabolic waste products. Urine is produced and excreted into the collecting system of the kidney by a complex substrate and solute exchange system called the nephron and transported to the bladder by the ureters.

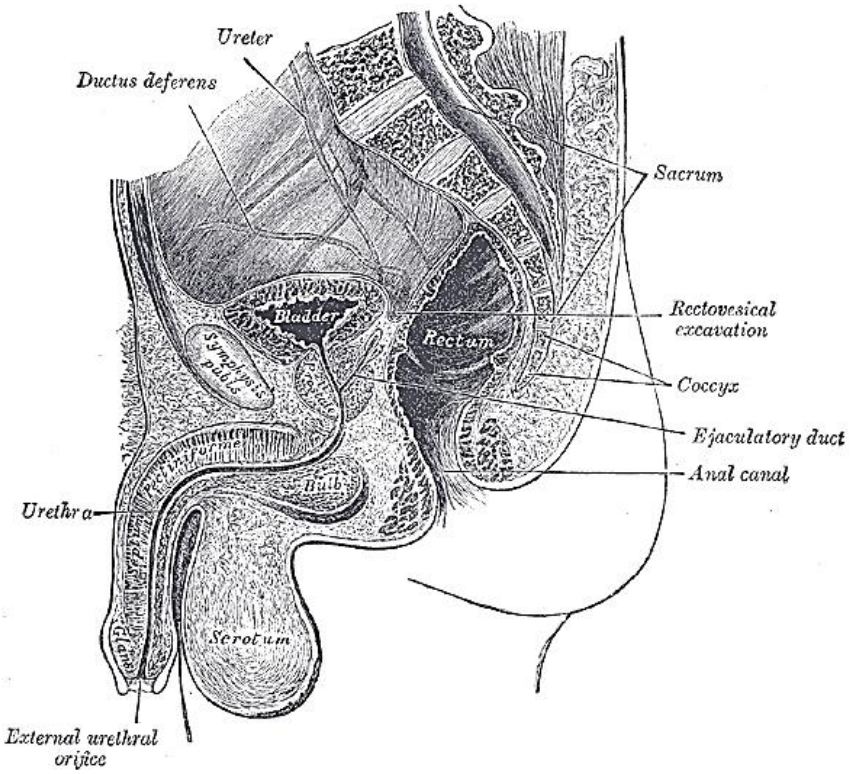

Figure 1: Male Pelvis, median sagittal view. Used with permission from Grant's Anatomy of Human Body.

1.2.2 The bladder

In a non-diseased, matured state, the bladder acts as a reservoir for urine to be stored until elimination. The bladder is a tetrahedral shaped structure in the collapsed state and ovoid when filled with an average capacity of 500ml.[16] The internal surface of the bladder is lined with transitional epithelium which is unique to the urological system. Transitional epithelium possesses tight junctions which prevent absorption of urine and exchange of most solutes through the bladder wall, whilst the cuboidal cell shape and multiple cellular layers equip it with the capacity to distend during the filling phase. Once thought to simply provide a mechanical barrier for the storage of urine, the urothelium is now understood to be an important mechanosensor for the bladder and it influences micturition via sensory nerve modulation and release of numerous neurotransmitters.[16] Beneath the transitional epithelium is a well-developed submucosa which sits on the detrusor muscle, the contractile muscular unit of the bladder. The detrusor is arranged as random, smooth muscle fibres with circular, spiral and longitudinal configurations. This feature provides the muscle with the capability of increasing its fibre length by more than 75% during the filling phase.[16] The random interdigitating layers form three much more discrete muscular layers (inner longitudinal, middle circular, outer longitudinal) at the bladder neck, known as the trigone. The middle circular layer is called the internal (involuntary) urethral sphincter and is only present in men. It contributes to continence at the level of the bladder neck and plays an important role during intercourse by preventing retrograde ejaculation.

1.2.3 The prostate

The prostate lies inferior to the bladder neck and is a fibromuscular and glandular organ containing collagen, smooth muscle and a complex exocrine network. The prostate's primary function is to contribute fluid during ejaculation important for liquefaction of semen. The trigone is also intimately related to the prostate and the two interplay as a functional unit during voiding.

1.2.4 The pelvic floor

A voluntarily controlled external urethral sphincter sits inferior to the apex of the prostate and provides the most important mechanism for urinary continence. Unlike the internal urethral sphincter which is composed of smooth muscle, the external urethral sphincter is composed of skeletal muscle and is part of the pelvic floor. The synchronous contraction of the detrusor muscle and relaxation of both urethral sphincters is required for normal voiding.

1.2.5 The urethra

The male urethra is 20cm long and is a continuation of the bladder neck. It is lined with transitional epithelium to the level of the meatus. The latter is lined with squamous epithelium, reflecting its embryological origin. The urethra contains both smooth and striated muscle, and through these components, acts as a tubular conduit for the passage of urine and semen.

1.3 Physiology of the bladder

1.3.1 Micturition

The two phases of bladder function are 'storage' (the bladder fills) and 'voiding' (the bladder empties). Normal bladder filling requires a compliant bladder wall free of involuntary bladder contractions, which permits low pressure expansion of the bladder. Normal voiding requires a sustained, coordinated detrusor contraction and an outflow tract (bladder neck/prostatic urethra) that is free of obstruction.

The neural control of micturition is a complex process controlled predominantly by both the autonomic and somatic nervous system. The parasympathetic nervous system (PNS) innervation to the bladder originates from spinal cord nerve roots S2-S4, travels via the inferior hypogastric plexus and innervates the bladder via release of acetyl choline (ACh) on Muscarinic-3 (M3) receptors. The sympathetic nervous system originates from spinal cord nerve roots T10-L2, travels via the superior and inferior hypogastric plexuses and innervates two separate anatomical components of the bladder. The release of noradrenaline on beta-3 adrenergic receptors within the bladder wall and alpha-1 receptors within the bladder neck leads to detrusor muscle relaxation and bladder neck contraction, respectively. The pudendal nerve carries the somatic innervation to the external urethral sphincter. Spinal nerve roots

arising from S2-S4 (Onuf's nucleus) release ACh on nicotinic cholinergic receptors, which leads to the contraction of the muscle and provides urinary continence.

Micturition in adults is mediated by the vesico-bulbo-vesical reflex. As the bladder fills, afferent signals are relayed via the pelvic nerve to the central nervous system. Neural pathways between the cerebral cortex and Barrington's nucleus, (also known as the Pontine Micturition Centre [PMC]) process the afferent stimuli and regulate the coordinated contractions of the detrusor and relaxation of the pelvic floor to achieve normal bladder function (see Figure 2).

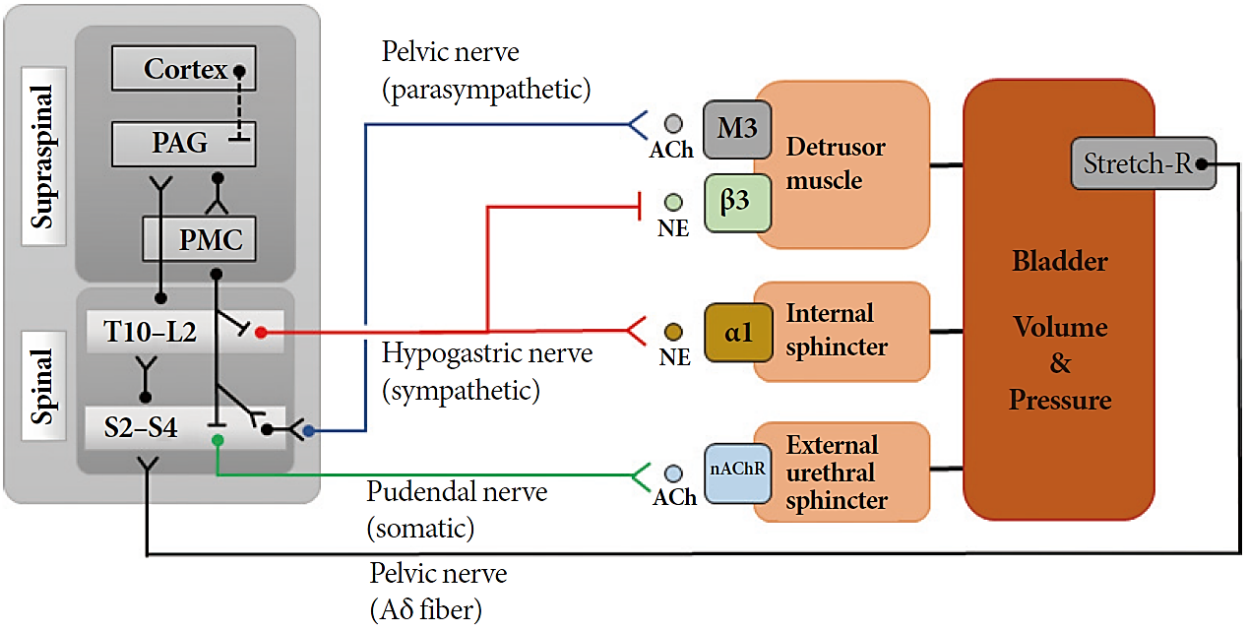

Figure 2: Functional block diagram of the bladder neural control.[17] Used with permission from the *International Neurourology Journal*.

1.3.2 Neurophysiology of the lower urinary tract

The lower urinary tract is a functional unit influenced by central and peripheral neural stimuli as well as paracrine and hormonal mediators. An intimate understanding of the cellular environment of the bladder becomes essential when hypothesising how systemic factors may influence the cellular components of the lower urinary tract and how pharmacological interventions may modulate pathological processes within the bladder.

Much of the research examining the neurophysiology of the lower urinary tract comes from animal studies and have been thus extrapolated to the human bladder. There does however appear to be differences amongst species in relation to the contributing factors to bladder contraction and relaxation, and this needs to be taken into consideration when extrapolating findings to the human bladder.[18]

1.3.2.1 Smooth muscle

The detrusor can be influenced by the same processes that influence smooth muscle found

in the gastro-intestinal tract, respiratory tract and penis. Smooth muscle responds to changes in systemic factors including autonomic nervous system tone, hormones, low grade inflammation, infectious aetiologies and psychological stress as well as local factors such as stretch, prolonged obstruction, temperature and local metabolites, including nitric oxide (NO).[16, 19, 20] Subsequently, diseases that affect smooth muscle outside of the lower urinary tract may well affect the bladder, prostate and urethra, and thus may explain the strong association between LUTS and erectile dysfunction[21] and functional disorders of the bowel.[20]

1.3.2.2 Central nervous system

Many neurotransmitters within the central nervous system are involved in the micturition reflex. Their clinical relevance is somewhat limited as supported by the limited number of effective centrally acting pharmaceutical agents to target micturition.[22]

Gamma-aminobutyric acid (GABA) is a central nervous system inhibitory neurotransmitter that modulates the micturition reflex. GABA functions by binding to $GABA_A$ and $GABA_c$ receptors, and stimulation leads to inhibition of the voiding reflex, whilst receptor blockade within the central nervous system (CNS) promotes micturition in animal models.[23]

Serotonergic (5-HT) mechanisms influence the micturition reflex via neural pathways within the CNS and PNS. 5-HT_{1A}, 5-HT_2 and 5-HT_7 receptors appear to play the greatest role in facilitating normal bladder function through inhibitory effects. Duloxetine, a combined serotonin and noradrenalin reuptake inhibitor (SNRI), increases bladder capacity and increases sphincteric tone in a cat model.[24] Clinically, Steers *et al.* demonstrated an improvement in voiding interval time and incontinence episodes in women with detrusor overactivity when treated with duloxetine compared with placebo.[25]

Opioid receptors are distributed throughout the CNS and activation of μ-opioid receptors can lead to increased bladder capacity and inhibit detrusor contractions. Administration of the opioid antagonist, naloxone, can stimulate the micturition reflex.[18]

Dopaminergic pathways modulate different pathways in the CNS and can have both inhibitory and stimulatory effects on the micturition reflex. Patients suffering from Parkinson's disease, a disorder of nigro-striatal dopaminergic depletion, most commonly display neurogenic detrusor overactivity, possibly from a lack of stimulation on inhibitory D1-like receptors. D2-like receptor stimulation, however, can facilitate the micturition reflex.[18]

1.3.2.3 Peripheral nervous system

There is an increasing understanding of the urothelium, suburothelium and detrusor muscle and the role they play in initiating and mediating the afferent nerves within the bladder wall. The urothelium is rich in cell surface nicotinic, muscarinic, tachykinin, bradykinin and transient receptor potential (TRP) receptors (e.g. vanilloid receptors) and releases the neurotransmitter adenosine triphosphate (ATP), nitric oxide (NO) and acetylcholine when

stimulated by stretch and changes in pH and osmolality.

The interstitial cells within the sub-urothelial layer and detrusor muscle appear to function as an organised sensory unit within the bladder wall[18] and are modulated by a rich sub-urothelial nerve plexus that resides predominantly within the trigone and bladder neck. Immunohistochemical staining of rat bladders has demonstrated that these afferent nerve axons predominate within the epithelium, blood vessels and detrusor muscle bundles.[26] The most important of these afferent nerves are the myelinated Aδ-fibres which convey afferent impulses secondary to distension and unmyelinated C-fibres that are triggered by chemicals and cold temperature. The understanding on the role of the neurotransmitters is still rudimentary, but they likely play a role in both direct neural signalling as well as modulation of neurotransmission. Whilst the cellular environment within the bladder wall is highly complex and poorly understood,[18] the following cell signalling pathways are important in both normal bladder function and the development of LUTS.

Cholinergic mechanisms

The predominant cellular receptors in the bladder wall are the muscarinic subtypes 1-3. M_2 receptors predominate, but the M_3 receptor appears to be most important in bladder contraction.[18] M_3-receptors are stimulated by acetylcholine which activates phospholipase C mediated hydrolysis of IP3, resulting in intracellular calcium release and detrusor contraction[16] (see Figure 3). Intra-cellular calcium levels are also influenced by transmembrane, nifedipine -sensitive L-type calcium channels and contribute to detrusor contraction.[18] Detrusor contraction can occur through a third pathway, the Rho-kinase pathway. It is postulated that activation of Rho-kinase may lead to enhanced calcium sensitisation of detrusor smooth muscle, resulting in smooth muscle contraction at reduced levels of intracellular calcium.[18] Increased activation of the Rho-kinase pathway is thought to lead to detrusor overactivity and increased prostatic smooth muscle tone[27] (see Figure 4). Inhibition of L-type calcium channels or the Rho-kinase pathways produces a much more profound inhibition of detrusor contractility in carbachol (a cholinergic agonist) induced detrusor muscle than blockade of IP3 or phospholipase C which demonstrates the importance of these pathways.

In pathological states such as bladder outlet obstruction and neurogenic bladder, muscarinic receptor function appears to change, and in diabetic mice it is enhanced.[18] This suggests that cellular changes within the bladder occur with local disorders of the lower urinary tract as well as systemic diseases.

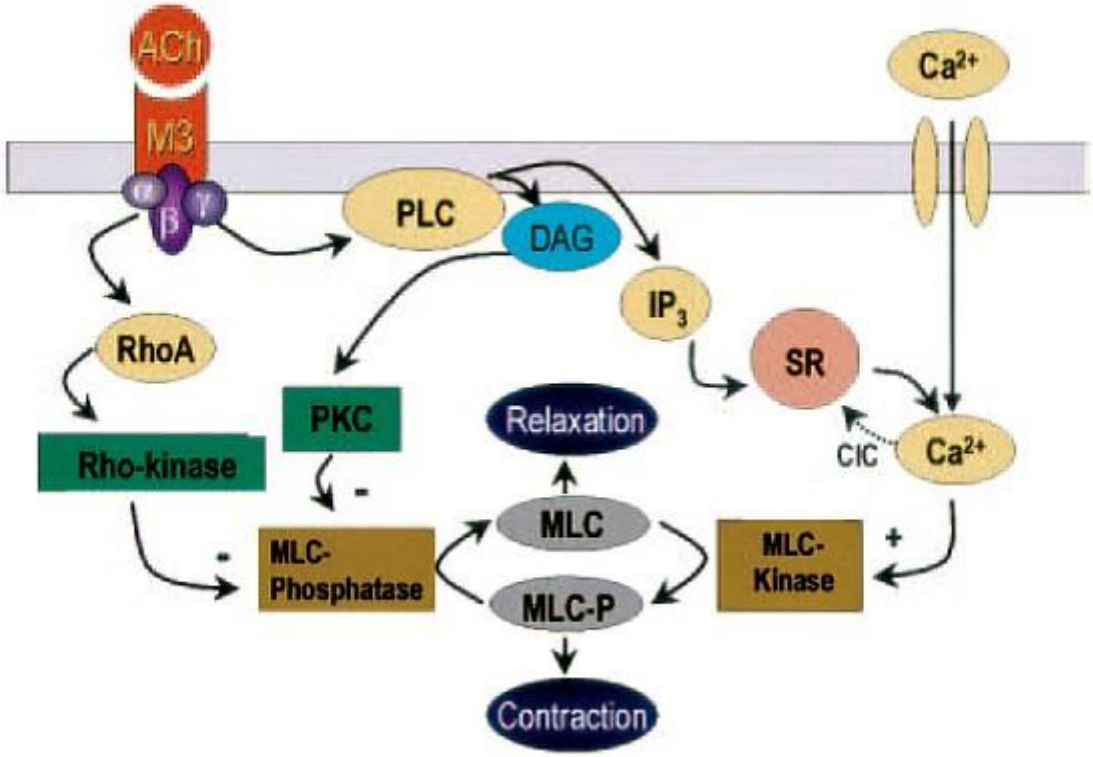

Figure 3: Transmitter signal pathways involved in the activation of detrusor contraction via muscarinic (M3) receptor. ACh, acetylcholine; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; MLC, myosin light chain; SR, sarcoplasmic reticulum; CIC, calcium induced calcium release.[18] Artwork used with permission from K.E Andersson.

Adrenergic mechanisms

The role of adrenergic mechanisms in the normally functioning bladder is less pronounced than that of cholinergic mechanisms. Whilst both β_2 and β_3 receptors are found within the bladder, it is the β_3-receptor that modulates detrusor relaxation through activation of adenylate cyclase and conversion of ATP to cyclic-AMP, with subsequent reduction in intracellular calcium levels. Phosphodiesterase (PDE) catalyses the conversion of cyclic Adenosine Monophosphate (c-AMP) to 5'AMP and leads to an increase in smooth muscle tone through increased intra-cellular calcium levels. PDE inhibitors are utilised in erectile dysfunction by inducing smooth muscle relaxation. There is consequently interest in the role of PDE inhibitors in the potential treatment of bladder diseases, particularly when associated with erectile dysfunction.[28] There are 21 families of PDEs and whilst some tissues demonstrate several PDEs, other tissues such as the penis are receptive for or dominated by a single isoenzyme. PDEs 1-5 have been discovered within the human bladder, with PDE-5 predominantly found on the detrusor, vasculature and endothelium of the bladder;[29] it appears to modulate relaxation of smooth muscle at the bladder outlet.

Nitric Oxide/cyclic Guanosine Monophosphate signalling pathway

The nitric oxide/cyclic Guanosine Monophosphate (cGMP) signalling pathway plays a role in lower urinary tract function. Post-ganglionic nerves contain nitric oxide-synthase (NOS) which is released from both nerve endings (nNOS) and the bladder endothelium (eNOS).

NOS synthesises NO which acts primarily to reduce the tone of the urethral smooth muscle during micturition[16] however its direct action on the bladder is less clear.[28] A deficiency of NO could therefore play a role in the development of or fluctuation in LUTS.

Sex hormones

Estrogen receptors are found predominantly in the trigone and urethra of the lower urinary tract. Animal models have demonstrated variable findings regarding the role of estrogen in bladder function, but suggest a role in the relaxation of the detrusor through both a direct effect and modulation of the ANS.[18 30]

The effects of androgens on bladder function have not been well examined in humans. In animal models, androgen receptors are found in highest concentrations in the mucosa and are also found within the detrusor itself.[18] *Ex-vivo* studies show that testosterone may increase the density of muscarinic receptors in bladder tissue and inhibit detrusor contractions[18] which may explain LUTS amelioration with testosterone replacement in hypogonadal men.[31] The enzyme aromatase is present in the bladder and converts testosterone to estrogen. The consequent smooth muscle relaxation properties of estrogen are an additional mechanism by which testosterone may modulate bladder function.[30]

1.4 Lower urinary tract symptoms

1.4.1 Definition

Disease processes affecting any single anatomical component of the lower urinary tract can lead to voiding dysfunction and the symptoms are termed lower urinary tract symptoms (LUTS). Previously, a lack in standardised terminology used to describe LUTS resulted in ineffective comparison of results between research investigators and led to the International Continence Society's endeavour to standardise terminology, with separate categories for symptoms, signs, disease conditions and urodynamic findings.[32] The aim of each terminology is to be a descriptor of symptomatology without implying the underlying disease process. LUTS incorporates all urinary symptoms associated with storage (urgency, frequency, nocturia), voiding (hesitancy, intermittency, straining) and post-micturition (terminal dribbling, sensation of incomplete emptying). These are summarised in Appendix 1.

1.4.2 Historical errors in the use of LUTS terminology

LUTS are symptoms described by a patient or their caregiver but do not signify a definitive urological diagnosis. LUTS may be symptoms of disease processes from within and outside the urological system.[32] This contrasts to previous terminology used such as 'prostatism'[33] and 'benign prostatic hyperplasia (BPH)'[34] to describe a similar constellation of symptoms whilst incorrectly alluding to the prostate as the organ responsible. These terminologies were adopted historically and as such, symptoms of hesitancy, intermittency and nocturia were mostly associated with males. It also party arose from the adoption of the now most widely utilised LUTS scoring system, the International Prostate Symptom Score. Initially named the

American Urological Association Symptom Index, it was developed to distinguish between BPH patients and controls, and demonstrated excellent concordance when 'BPH patients' had prostatectomies and their LUTS improved. It unfortunately resulted in men with high American. Urological Association Symptom Index (AUA-SI) scores being diagnosed with 'prostatism' and LUTS being inappropriately synonymous with BPH.[35]

It is clear if females are similarly affected with LUTS and if application of these terms to females would be counter-intuitive, given the absence of the prostate. Similarly, the role of prostatic enlargement in the development of LUTS most likely represents only part of the pathological process.

Whilst an enlarged prostate has been shown to increase the risk of progression to clinically significant LUTS outcomes (surgery, medical therapy and acute urinary retention),[36, 37] a correlation between the severity of LUTS and prostate size is poor,[38] and young men are known to be affected by voiding symptoms[39] before benign prostatic hyperplasia occurs. Demonstrating this, Sarma *et al.* described worsening LUTS in diabetic men recruited to the Olmsted County Study, despite no change in prostate volume, prostate specific antigen (PSA) or urinary flow rates,[40] and Karazindiyanoglu *et al.* showed that clinically hypogonadal men treated with exogenous testosterone had improvement in the LUTS despite an increase in prostate size.[31]

Obstruction of the bladder undoubtedly contributes to many LUTS. In an attempt to achieve clarity in this domain, the European Association of Urology recommends the following terminology:

- Bladder outlet obstruction (BOO): a generic term for obstruction during voiding and is characterised by increasing detrusor pressures and reduced urine flow rates
- Benign prostatic obstruction (BPO): a form of BOO, characterised by benign prostatic enlargement
- Benign prostatic hyperplasia (BPH): a term used (and reserved) for the typical histological pattern which defines the disease

It is important for both treatment and research purposes to differentiate between symptoms and disease processes, as examining men with LUTS is not necessarily examining men with prostatic disease and *vice versa*.

Other commonly used terms relating to LUTS are provided in Appendix 1 and 2.

1.4.3 Symptom scores

Patients complaining of LUTS can find these difficult or embarrassing to describe so it was a major milestone in clinical urology when the AUA-SI was developed in 1992 and

demonstrated to have equal or better sensitivity and test-retest reliability than previous LUTS scoring systems despite having fewer assessed items.[41] This self-administered questionnaire aims to assess the severity of storage and voiding LUTS as well as the level of patient bother. Repeating the same tool after treatment implementation can help the patient and clinician assess the patient's response. The I-PSS (a revision of the AUA-SI which includes an extra question on the global impact of LUTS on the patient's quality of life) is an eight-part questionnaire (seven symptom questions, one quality of life question) which asks the patient to describe the frequency with which they suffer a symptom. These are graded on a 0 to 5 score, with a maximum total score of 35. Symptoms are classified as mild (0-7), moderate (8-19) and severe (20-35) (see Appendix 3). Other scoring systems such as the Danish Prostate Symptoms Score (DAN-PSS) and the International Consultation on Incontinence Questionnaire – Male Urinary Tract Symptoms (ICIQ-MLUTS) exist, and whilst some authors have advocated the DAN-PSS as a more sensitive modality for detecting changes in LUTS,[42] it is the I-PSS that has had more global adoption of its use.[43]

1.4.4 Pathology

When describing the aetiology of LUTS, the literature must be carefully reviewed to ensure the correct terminology is used and subsequent conclusions are drawn appropriately. Many studies use a validated symptom score as part of the study design to investigate the aetiology of surrogate markers of BPH such as LUTS, maximum urinary flow rate (Q_{max}), and prostatic volume (PV).[37, 44-46] As BPH is a pathological diagnosis requiring histological assessment of biopsied or surgically removed tissue, these surrogate markers have been used to better examine men with possible BPH. In fact, what these studies most reliably uncover are the etiological factors of LUTS, more than those of BPH.

A false paradigm previously existed that presumed that all LUTS in men were a result of prostatic disease whilst all women with LUTS had an overactive bladder. It is becoming increasingly accepted that the cause of LUTS is not necessarily gender- nor organ-specific, but rather the result of interrelated pathological, anatomical, functional, hormonal and cellular processes.[47]

1.4.4.1 Structural disorders of the lower urinary tract

Any process that leads to obstruction of urine flow from the bladder may contribute to LUTS. The most common structural disorders of the lower urinary tract that contribute to this process are benign prostatic enlargement or hyperplasia, urethral strictures and less commonly malignant tumours involving the bladder neck, and malignant infiltration of prostate cancer.[22] These processes obstruct the flow or urine from the bladder, leading to high detrusor pressures. Symptomatically, they are typically characterised by voiding symptoms, and in severe cases, acute urinary retention. In addition, either primary changes to the bladder (e.g. from malignancy) or secondary changes from prolonged urinary

obstruction, can lead to storage symptoms, pain and haematuria.

Benign prostatic hyperplasia (BPH) is a pathological process resulting in an increased prostatic volume. The underlying pathological process of BPH is still not fully understood but via a combination of increased cell production and impaired apoptosis,[16] an increased number of stromal and glandular cells within the prostate is found. BPH is a disease process of the transition zone of the prostate and can cause bladder outlet obstruction. LUTS caused by BPH is not simply caused by a narrowing calibre of the urethra because of an enlarging prostate size. Whilst the physical encroachment on the urethral lumen plays a 'static' role in bladder outlet obstruction, bladder outlet resistance is additionally caused by an increased smooth muscle tone within the prostatic stroma and bladder neck, and by impaired detrusor contractility. Being rich in alpha-1 adrenergic receptors and under the influence of the SNS, systemic factors (outside the prostate) that may increase sympathetic tone within the prostate may contribute to LUTS, separate to the BPH disease process. Similarly, systemic factors that may impair detrusor contractility and thus voiding, will result in a similar constellation of LUTS.

1.4.4.2 Systemic factors influencing the lower urinary tract

Cross-sectional population studies and placebo arms of randomised controlled trials make the largest contribution to the possible etiological factors of LUTS, but findings are inconsistent. Non-modifiable risk factors such as age, sex and race,[48, 49] modifiable risk factors such as BMI[49-51], level of physical activity[52, 53] and comorbidities,[54, 55] as well as social factors such as socio-economic status, mobility capabilities and living arrangements[56] have been assessed with conflicting conclusions. Biochemical states such as clinical hypogonadism and high oestradiol/sex hormone binding globulin (SHBG) levels show a mixed correlation but a trend has emerged of worse LUTS in hypogonadal or elderly men with low bio-available testosterone and improvement when testosterone is replaced[31, 57-59]

Recently, the role of metabolic syndrome (MetS) in the aetiology of LUTS has gained interest. A number of studies have examined an increase in prostate size and growth in men with components of the metabolic syndrome without exploring their correlation with symptom severity.[49, 60] Pashootan *et al.* observed 4666 French men aged 55-100 years and found on cross-sectional analysis that metabolic syndrome was positively correlated with the severity of LUTS ($p < 0.001$) and each component of the metabolic syndrome (except for high-density lipoprotein [HDL] levels) was an independent risk factor in LUTS treatment and high mean International Prostate Symptom Score (IPSS)on multivariate analysis.[61] Similar findings have been reported by other authors examining individual components of the metabolic syndrome. Parsons *et al.* observed a correlation between high serum low-density lipoprotein [LDL] levels and the risk of having BPH-related surgery or medical treatment for LUTS within the Rancho Bernardo Study which examined a cohort of white, middle to upper class adults in Southern California since 1992.[62] Rohrmann *et al.* examined data from the Third National

Health and Nutrition Examination Survey conducted in the USA between 1988 and 1994. As data was collected before the AUA-SI was introduced, LUTS cases were defined as at least three of these symptoms: nocturia, incomplete emptying, weak stream, and hesitancy. These LUTS were positively correlated with weight gain after 25 years of age, although this was not statistically significant (odds ratio [OR]: 1.90 confidence interval [CI]: 0.89-4.05). Interestingly, men who were obese at age 25 were less likely to develop LUTS than those who were of normal weight (OR: 0.49, 95% CI: 0.27, 0.91) which may suggest that weight gain rather than overall weight may contribute to LUTS.[50] Similarly, Sarma *et al.* examined the data from two large cohorts of men in the USA (Olmsted County Study and Flint Men's Health Study) and found diabetes to be significantly associated with storage but not voiding LUTS on multivariate analysis.[63] Prostate volume was once again not positively associated with diabetes which strengthens the statement that LUTS should not be automatically associated with BPH.

The underlying pathophysiological process by which systemic illness may influence the lower urinary tract have been keenly observed and, in addition to previously discussed mechanisms, have been hypothesised to be modulated by four main processes; a) autonomic nervous system imbalance, b) inflammation c) pelvic reduction in NOS, and d) atherosclerosis and ischemia of the lower urinary tract[27] (see Figure 4).

Inflammation

Chronic inflammatory processes are risk factors for systemic illnesses, including cardiovascular disease. With a strong correlation between cardiovascular disease and LUTS, chronic inflammation may be the shared aetiology. The source of the systemic inflammation is thought largely to arise from adipose tissue such that obesity may be the driving force in metabolic syndrome-induced inflammation and LUTS development.[64, 65] Fowke *et al.* examined the relationship between anthropometric measures of obesity, systemic markers of inflammation, prostatic tissue and LUTS in 191 men. They found that central obesity was associated with the severity of inflammatory tissue in the prostate and LUTS.[66] Other studies have shown associations between increased levels of pro-inflammatory cytokines IL-1, IL-6, TNF-α and the acute phase reactant, C-reactive protein (CRP), with histological prostatitis and BPH, overactive bladder symptomatology as well as LUTS scores.[65] Chronic inflammation is also associated with the development of insulin resistance. Insulin resistance is itself a pro-inflammatory state and this can lead to aberrant wound healing, tissue remodelling and fibrosis, and has been postulated as a mechanism for LUTS.[65]

Autonomic nervous system imbalance

An imbalance in the autonomic nervous system (ANS) contributes to LUTS and for decades this aetiology has formed the basis of the treatment of LUTS with alpha-receptor blockade. An increased sympathetic tone causes an increase in the prostatic and urethral smooth

muscle tone and exaggerates the dynamic component of BPH related LUTS, however, in the absence of BPH, this mechanism for LUTS development still exists.[27] No longitudinal studies have examined the relationship between overactive ANS parameters and LUTS, however three small cross sectional studies have examined men with LUTS and the correlation with autonomic function (based on tilt-table testing, heart rate measures, the Valsalva manoeuvre and the quantitative sudomotor axon reflex test), with mixed results,[67-69] however animal studies have demonstrated this response.[27]

Atherosclerosis of the lower urinary tract blood supply

Berger *et al.* performed Doppler ultrasound studies on men with peripheral arterial occlusive disease, diabetes, coronary artery disease and healthy controls; the men with vascular disease had significantly lower perfusion of the transition zone of the prostate, increased prostate volume and worse IPSS scores.[70] Whilst this radiological observation does not demonstrate a causal relationship, animal and *ex-vivo* models do demonstrate cellular and structure changes within the bladder and prostate when hypoxic injury ensues. Two mechanism that may contribute to LUTS are: 1) a dysfunction of eNOS signalling and subsequent smooth muscle dysfunction within the lower urinary tract, and 2) an overexpression of the hypoxia inducible factor pathway (HIF-α) which may lead to an upregulation of growth factors and reduced cellular apoptosis of prostatic stromal cells.[71] In animal models that have induced hypoxic injury to the lower urinary tract, the bladder has been observed to undergo fibrosis, smooth muscle atrophy,[72] neurodegeneration[73] and upregulation of muscarinic receptor activity,[74] and thus may play a contributing role to LUTS development in men with vascular disease and the elderly.

1.4.4.3 Medications

Pharmacological management of comorbidities is likely to affect bladder function. Certainly, in a cross-sectional analysis of 1865 subjects from the Boston Area Community Health study, monotherapy with thiazide diuretics was associated with voiding symptoms (OR: 2.9, 95% CI: 1.17, 7,19), and loop diuretics (with or without additional anti-hypertensive medication) was associated with nocturia (OR: 2.55, 95% CI: 1.25, 5.14) in men. For women under 55 years of age, there was an association with nocturia and voiding symptoms with calcium channel blocker use.[75] Wuerstle *et al.* examined men from the California Men's Health Study (CMHS) and concluded that antihistamines, bronchodilators, diuretics and antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants) contributed approximately 1%, 2%, 3% and 4% of LUTS, respectively, and subsequently these medications accounted for at least 10% of all LUTS in their cohort.[76] Additional medications that have been found to contribute to LUTS include narcotics and decongenstants[77] whilst men who take alpha-blockers, 5α-reductase inhibitors, antichoinergics[9] (the cornerstones of current pharmacological management of LUTS) and PDE5 inhibitors[27] may get a reduction in their symptoms.

Whilst cross-sectional analysis cannot demonstrate a cause-effect phenomenon, medications are hypothesised to modulate LUTS via alterations in detrusor muscle contraction (calcium channel blockers), increase in urine volume (diuretics), augmentation of the autonomic nervous system (sympathomimetics/bronchodilators) and alterations in central neural control (selective serotonin reuptake inhibitors/tricyclic antidepressants).

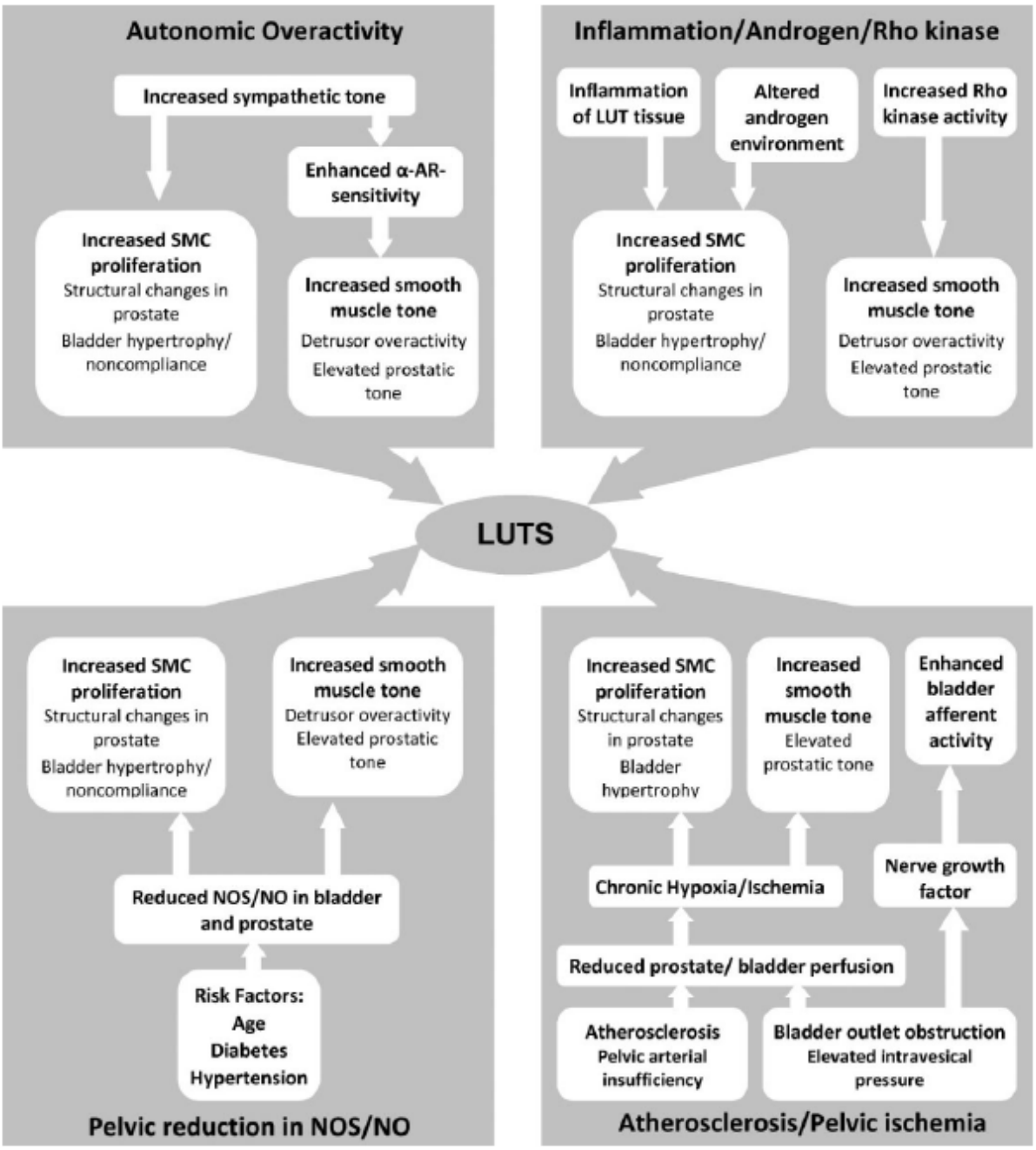

Figure 4: Potential pathways leading to LUTS in men.[27] Used with permission from K.E Andersson.

1.5 The natural history of LUTS

The severity of lower urinary tract symptoms tends to progress with age but can fluctuate over time[78, 79]. Whilst there is no standardised definition of LUTS progression or regression

based on current symptom scoring systems, the American Urological Association considers a three-point improvement in scores 'meaningful',[80] whilst studies including the Medical Therapy of Prostatic Symptoms (MTOPS) and Combination of Avodart and Tamsulosin (CombAT) studies have used a change in score of 4 or more to be clinically significant when assessing LUTS response to medical therapy.[6, 8, 81, 82] This value was extracted from research by Barry *et al.* who examined 1218 men and found that those who rated themselves slightly improved in their symptoms had a mean AUA-SI score decrease of 3.1 and those who had a global sense of worsening, a mean increase of 2.7 points. Men's baseline AUA-SI score strongly influenced one's bother about their symptom progression, with men with lower scores being able to tolerate a greater score progression (3.3 mean score progression) than those with higher baseline scores (1.2 mean score progression).[83] Other studies have used alternate values such as change in score of 5 points,[84] annual change in score (change in points/year)[44], progression or regression to a different symptom severity category,[85, 86] or progression to what is often defined as 'BPH related outcomes' such as LUTS requiring medication or surgical treatment, acute urinary retention, renal failure from bladder outlet obstruction or recurrent urinary tract infections.[82, 87]

Observations from the Osteoporotic Fractures in Men Study (MrOS) demonstrated that whilst 90% of untreated men aged 40-75 years with mild symptoms at baseline remained stable in their symptomatology, 49% with moderate baseline symptoms progressed and 17% showed remitting trajectories. Whilst only 28 men were reported to have severe symptoms at baseline, over 50% of these showed some improvement in their symptomatology trajectories.[88] Temml *et al.* examined the progression of untreated LUTS in Austrian men who attended voluntary health examinations in Vienna and found the mean IPSS increased from 4.6 to 5.5 ($p<0.0001$) over five years, however roughly 30% of men experienced an improvement in their symptoms.[89] Djavan *et al.* observed a more dramatic change in symptoms in men recruited from four European urological outpatient practices. Three hundred and ninety-seven men with a mean age of 67 years who presented with mild LUTS (IPSS <8) and who elected for watchful waiting (i.e. no medical or surgical treatment) were observed over two years. At the end of the study, 31% of men had progressed to experience moderate LUTS (IPSS 8-19) and a minimum of 3-point rise in their baseline IPSS.[90] This dynamic progression of LUTS is mirrored in the female population where presumably some overlap in the systemic etiological factors (non-prostate) contributing to LUTS in men will occur. In their systematic review, Irwin *et al.* identified seven longitudinal studies on overactive bladder and 14 longitudinal studies on urinary incontinence in women. They identified a significant lack in consistency of symptom definition which partly contributed to their inability to perform meta-analysis, but concluded that LUTS in women progressed dynamically over time.[91]

Identification of men who are likely to progress, regress or become stable in their

symptomatology is important in managing the expectations of the patient as well as implementing the correct treatment at the most opportune time. The MTOPS Research group has been the most successful in identifying clinical parameters that strongly predicted clinical progression of 'BPH'. A four-arm randomised clinical trial was performed with men either being allocated to a placebo, finasteride, doxazosin or combination of finasteride and doxazosin. They defined clinical progression as either a 4-point rise in baseline AUA-SI, acute urinary retention, incontinence, renal impairment and recurrent urinary tract infections. Men were included if they had moderate to severe LUTS and an enlarged prostate on digital rectal examination. Of the 737 men randomised to the placebo arm, the risk of progression was significantly higher in men with a baseline total prostate volume >31ml, PSA >1.6, Q_{max} <10.6ml/sec, baseline post-void residual >39ml and age greater than 62 years.[37] These however are clinical and investigation findings which are non-modifiable and do not offer the opportunity for primary or secondary prevention strategies. Secondly, the reported incidence rates for 'BPH related outcomes' (symptom progression, requirement for treatment and acute urinary retention) were significantly lower in the MTOPS population when compared to community dwelling men in the Olmsted County Study which raises concerns about the generalisability of the findings.[92] Thirdly, pooled data from registered RCTs on LUTS through the Food and Drugs Administration and the European Medicines Agency demonstrated a 9-34% decrease in symptom scores in placebo-treated patients which may suggest that this population of men may not represent the true natural history of LUTS.[93]

1.6 Justification of the need for evidence synthesis in this area

It is established that the natural history of LUTS is one of dynamic progression. The mediators of this fluctuating symptomatology are not fully understood at a macroscopic or microscopic level, but a more comprehensive understanding by examining these risk factors through a systematic review (SR) will benefit future researchers and clinicians.

Systematic reviews aim to synthesise a comprehensive and unbiased collection of published and unpublished studies with the goal to provide evidence to clinicians and policy makers. By adhering to a transparent method, there can be confidence that errors and biases are minimised and discussed. Meta-analysis is the statistical method of synthesising the retrieved data but requires homogeneity between studies.[94] A systematic review of randomised controlled trials (RCT) represents the highest level of evidence. It must be stressed however that not all SRs are recognised as Level I evidence. The National Health and Medical Research Council (NHMRC) in Australia recognises SRs of Levels III and IV as the same level of evidence as the primary research included in the review.[95] This acknowledges that a single well performed RCT provides less risk of bias than a systematic review of cohort studies by evenly distributing unmeasured confounders between the control and intervention group. However, some research endeavours, such as examination of etiological factors, are not conducive to examination via a RCT. Subsequently, reliant on

lower levels of evidence provide the most realistic source of information and the SR provides a validated and useful form of synthesis and critical appraisal.No SRs have been published which examine the natural history or risk factors for LUTS in men. As discussed, Irwin *et al.* performed a SR with the aim to assess whether overactive bladder (OAB) and urinary incontinence (UI) progressed dynamically over time and to assess which factors may be associated with symptom progression or regression. Gender and age effects were the most commonly associated factors linked with symptom fluctuation, and further analysis of comorbidities was not possible and included studies with a predominate female population.[96] This differs substantially from this SR which focuses on men with any type on LUTS (without the need for a clinical or pathological diagnosis such as OAB) and which has a wide as scope as possible to be able to investigate any possible risk factor for symptom fluctuation.

As discussed previously, a consensus definition on what constitutes a significant change in LUTS severity is not available. Barry *et al.* showed however that small variations in symptoms scores are not noticeable to the affected individual,[83] such that these values possess little clinical utility. In concordance with recently published, large RCT examining LUTS, examining a change in symptom score of 4 or more meant that this review would hopefully be clinically useful.

This review may be used for hypothesis generation and to assist researchers in designing appropriately designed trials that examine how new interventions may affect LUTS progression. Secondly, by identifying risk factors, clinicians and patients may be able to modulate symptom severity by encouraging exposures that promote regression of symptoms and treating or avoiding exposures that may encourage progression of symptoms. If this can be done without the prescription of additional medication or surgery, then this would be a significant advantage for the individual patient, and the cost of managing LUTS in this population could be reduced.

1.7 Statement of review question

The review question is: What baseline patient characteristics predict a change in severity of untreated lower urinary tract symptoms (LUTS) in men in a non-hospital setting?

CHAPTER 2: SYSTEMATIC REVIEW PROTOCOL

This systematic review was conducted according to the Joanna Briggs Institute (JBI) methodology for performing systematic reviews and meta-analysis.[94] The protocol reported in this chapter was critically appraised by two academic surgeons and subsequently underwent independent peer review and publication in the *JBI Database of Systematic Reviews and Implementations Reports*.[97]

2.1 Objective and statement of the review question

The objective of this systematic review was to synthesise the best available evidence regarding the predictors of change in severity of untreated lower urinary tract symptoms (LUTS) in men in a non-hospital setting.

The potential value of natural history or prognostic studies such as those included in this review is wide-ranging. From a pathophysiological perspective, they can improve the understanding of a disease process; clinically, they can help with patient counselling, risk stratification, predicted disease course and clinical decision making; and from an academic perspective they can aid in the generation of scientific hypotheses and improved design and analysis of future clinical trials.[98]

When critically examined, however, prognostic studies tend to be methodologically weak.[98] Importantly, a structured methodological framework must exist which includes a clearly defined and described sample of patients with sufficiently long follow-up. Outcomes and prognostic variables measured must be objective, fully defined and appropriate; and the appropriate analysis must be used with important confounders adjusted for.

Variations in methodology and characteristics between studies can make meta-analysis of published data difficult and in some cases inappropriate, however analysis by systematic review may result in a more reliable overall assessment.

There are no universal criteria for assessing the quality of prognostic studies[98, 99] which has resulted in variations in quality standards used by authors when performing systematic reviews of prognostic studies. A systematic review of systematic reviews of prognostic studies revealed significant deficiencies in: a) operationalisation of items to address potential opportunities for bias, b) assessment of bias, c) synthesis of the evidence, and d) reporting of results.[99] This is important to consider as the internal validity of a review is reduced when methodologically weak studies are included.

A meta-analysis and systematic review of prognostic studies examining LUTS is yet to be performed and offers the opportunity to synthesise the best available data whilst also identifying barriers and opportunities for future clinical trials.

The specific question that this review sought to answer was:

What baseline patient characteristics predict a change in severity of untreated lower urinary tract symptoms (LUTS) in men in a non-hospital setting?

2.2 Inclusion criteria

2.2.1 Types of studies

This review considered studies that identified independent predictors of change in the severity of LUTS. Studies needed to have duration of at least one year. A period shorter than one year may not represent substantial time for changes in LUTS severity to occur and be examined. The review considered research papers utilising the following study designs:

Cohort study

Case-control studies

These study designs are the most appropriate for studying the risk factors associated with diseases, where a large variety of subjects can be evaluated and observed over time to assess what baseline characteristics are associated with either progression, remission or stagnation of LUTS severity.

2.2.2 Population

Studies that included human males aged > 18 years of age in a non-hospital setting with untreated lower urinary tract symptoms were considered for this review.

The definition of ‘untreated’ LUTS was: subjects with LUTS who were yet to receive any pharmacological or surgical intervention directed to improve their LUTS.

2.2.3 Exclusion criteria

Studies that includes participants with a baseline history of prostate cancer, LUTS related surgery or medication use for LUTS were excluded.

2.3 Exposure of interest

Exposures were categorised into three distinct groups, including but not limited to:

Modifiable exposures

- Environmental (e.g. medications not taken for LUTS, smoking status, alcohol intake)
- Social (e.g. employment, marriage status, socio-economic status)
- Biological (e.g. co-morbidities)

Non-modifiable exposures

- Genetic (e.g. race)

Disease factors (e.g. type of LUTS, severity of LUTS at time of inclusion in study)

2.4 Outcomes

The primary outcome of interest was change in severity of LUTS over time in men with untreated LUTS. Progression and improvement of symptoms were defined by several methods, firstly, by a change in baseline score as measured with a validated LUTS tool. Whilst there is no standardised definition of LUTS progression or improvement, the protocol initially defined clinically relevant change in symptoms based on treatment guidelines and prior studies[8, 100] using the International Prostate Symptom Score, as below:

- Improvement – ≥ 4-point reduction in score from baseline
- Progression - ≥ 4-point increase in score from baseline
- Stable – not fitting into above criteria

Other validated symptoms scores were assessed individually based on the definitions used to assess progression and regression.

After reviewing studies that fulfilled the strict methodological requirements, it became apparent that only two studies utilised this definition of progression based on the IPSS.[46, 89] Upon discussion from the supervisory panel, it was agreed that the definition of progression based on symptom score be amended to ‘any change in symptom score’. Whilst this would increase the risk of heterogeneity across the included studies, it was felt that it could be justified to produce a more meaningful review.

Progression of symptoms was also defined as:

- Receiving new medications prescribed for LUTS
- Undergoing LUTS related surgery
- Requiring bladder catheterisation for acute urinary retention (AUR)

Medication prescribed for the treatment of LUTS included:

- Alpha-blockers
- Anticholinergics
- 5-alpha reductase inhibitors
- PDE-5 inhibitors
- Beta-3 agonists
- Desmopressin
- Intra-vesical botulinum toxin A injections

LUTS related surgery included but was not limited to:

- Trans-urethral resection of prostate (TURP) or similar procedure that establishes an opening within the prostatic fossa
- Sacral nerve modulator
- Percutaneous tibial nerve stimulation

Any validated LUTS severity tools was eligible for inclusion, including but not limited to the:

- American Urological Association Symptom Index (AUA-SI)
- International Prostate Symptoms Score (I-PSS) and
- The Danish Prostate Symptom Score (DAN-PSS)
- International Consultation on Incontinence Questionnaire - Male Lower Urinary Tract Symptoms (ICIQ-MLUTS)

2.5 Exclusion criteria

This study did not examine the predictive properties of investigational tools such as ultrasound, prostate volume, PSA level and urinary flow rates on disease course. These factors have been examined thoroughly in previous studies[101] and represent non-modifiable, objective clinical parameters rather than possible etiological contributors to LUTS.

2.6 Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised. An initial limited search of MEDLINE and CINAHL was undertaken, followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. A second search using all identified keywords and index terms was then modified to meet the indexing language of each individual database and undertaken across all included databases. Thirdly, the reference list of all identified reports and articles was searched for additional studies as was the PubMed ‘related articles’ feature. Only studies published in English were considered for this review. Only studies published between January 1991 to January 2017 were considered. Studies published prior to this date are unlikely to include symptomatology scores such as the DAN-PSS, developed in 1991, and the IPSS (1992).

The databased included in the search included PubMed, Embase, Scopus and Web of Science.

Grey literature was searched through Grey Literature Report and DIVA Academic Archive Online.

Initial keywords used were: lower urinary tract symptoms; men; hypertrophy (benign) of prostate and prognosis. disease progression; risk factors; epidemiology

The search strategy utilised for each database can be found at Appendix 4

2.7 Assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological quality prior to inclusion in the review using 'Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework of Potential Biases' published by Hayden *et al*.[99] Six potential biases are described by Hayden *et al.*: 1. study participation, 2. study attrition, 3. prognostic factor measurement, 4. outcome measurement, 5. confounding measurement and account, and 6. statistical analysis. Reviewers assessed each study to determine whether sufficient efforts were made to limit these biases. Studies were deemed acceptable quality and included in the synthesis if they at least 'partly' demonstrated efforts to limit the potential of each of the six biases. Discrimination between 'low' and 'moderate' overall risk of bias was not provided by this means of analysis but aimed to omit those studies that were deemed at high risk of any important bias. Items to be considered for assessment of potential opportunity for bias can be found in Appendix 5. These item responses guided the reviewers in their scientific judgement on the potential for bias. Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

2.8 Data extraction

Data was extracted from papers included in the review into Microsoft Excel by a single reviewer. The data extracted included specific details about the populations, study methods and outcomes of significance to the review question. Predictors and their accompanying odds ratios when reported as multivariate analysis were also extracted. Where details were missing or unclear, efforts were made to contact the corresponding authors for clarification.

2.9 Data synthesis

Quantitative data was to be pooled in statistical meta-analysis using RevMan (Copenhagen: The Nordic Cochrane Centre, Cochrane), however the studies were not sufficiently homogenous to combine or examine in subgroup analysis. Instead, a narrative summary of results is provided. Tables are used to aid in data presentation where appropriate.

2.10 Summary of amendments to the protocol

The definition of 'change in symptoms' based on a validated symptom score was amended from a four-point change in score (based on IPSS or AUA-SI) to 'any change in symptom score' in an attempt to produce a more meaningful review. The original definition provided in the published protocol[97] was utilised to find exposures that resulted in a clinically detectable change in LUTS severity,[83] with the hope that this SR could be relatable and translatable into clinical practice. It became apparent however that only two studies fulfilled all the inclusion

criteria outlined in the protocol.[46, 89] Other studies did utilise this definition of symptom change but were excluded based on contamination of the population by men with LUTS that had undergone treatment. As the 'untreated' status of men forms the unique and unstudied basis for this review, it was decided with consensus that the measure for symptom change must be amended.

2.11 Assumptions

Endeavours to contact authors were always made in cases of ambiguity or confusion, however in cases where no further information could be obtained, several assumptions were required and firmly adhered to, such as:

a) Even with standardised international terminology,[32] variations in the definitions of severity of LUTS in many cohorts of men were present between publications. Men with an IPSS 1-8 have mild symptoms, however, in the literature retrieved, this cohort were often described as being asymptomatic. Subsequently, men with incident or new onset LUTS were often described as men who reported moderate to severe LUTS (IPSS >8), while some studies grouped asymptomatic men and men with mild symptoms together. As this systematic review aimed to examine fluctuations in symptomatology, we required studies of men who were already symptomatic and could demonstrate improvement or worsening of their symptoms.

In studies where the percentage of symptomatic and asymptomatic men within the cohort was unknown or unclear, it was presumed that most would have at least one symptom and the study was included. This is based on the observation that LUTS are very common and 60% of men over 18 years of age report at least one LUTS.[4] The populations examined in this review were older and thus the incidence was even higher. If a study described asymptomatic men and these could not be separated from symptomatic men, the study was excluded.

Whilst this method had a high likelihood of including some asymptomatic men within the review, it was felt that this number would be small and where relevant these cohorts are described in greater detail in Chapter 3 and Chapter 4.

b) In many studies retrieved in the search phase of this review, the treatment status of some cohorts was unknown or unclear. This review aimed to assess men's LUTS without prior or current pharmacological or surgical intervention. The following methods were used to ensure that the men were untreated:

- The exclusion criteria explicitly stated that men who had been treated were excluded.
- Correspondence with authors confirmed that men were untreated at the time of enrolment.

Studies in which treatment status was not clear and could not be clarified with the authors

were excluded from the review.

CHAPTER 3: RESULTS

3.1 Search results

The search identified a total of 5948 studies. Following removal of duplicates (n = 257) and screening of study title and abstract (n = 5558), a total of 133 articles were retrieved for full text review and detailed examination. A total of 121 studies were excluded as they did not meet the inclusion criteria. An additional four studies were identified through examination of reference lists of identified studies. Sixteen studies underwent assessment of methodological quality and four were subsequently excluded (discussed in Chapter 3.2). A total of 12 studies were included in this systematic review (see Appendix 6). The search results are summarised in the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) flow diagram (see Figure 5). Reasons for exclusion after full text review are provided in Appendix 7.

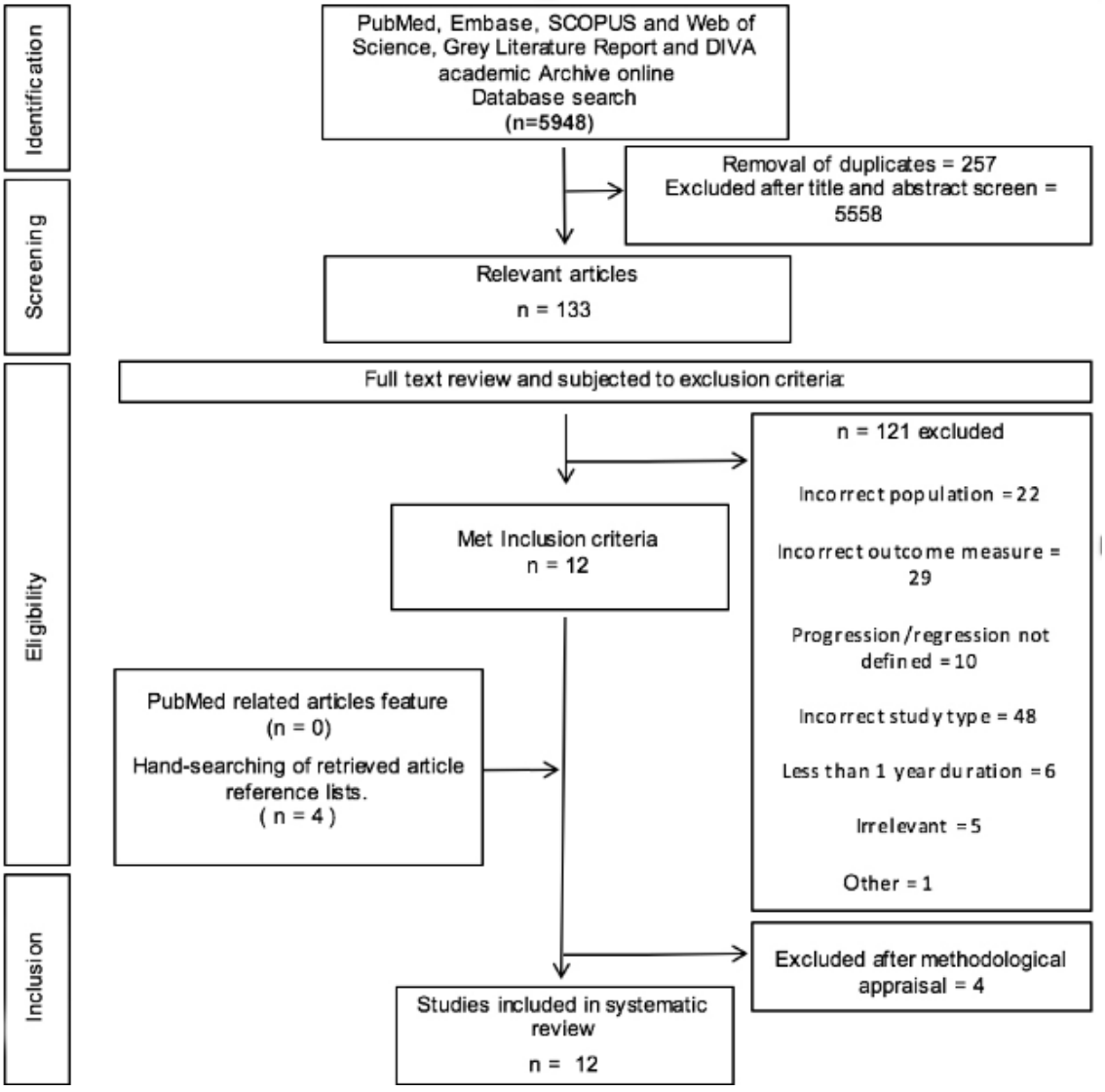

Figure 5: Flowchart of study selection and inclusion process

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

3.2 Assessment of methodological quality

Sixteen studies were assessed on six domains for potential biases as described by Hayden *et al.*:[99] 1) study participation, 2) study attrition, 3) prognostic measurement, 4) outcome measurement, 5) confounding measurement and account, and 6) analysis. A summary of the potential biases is provided in Appendix 5

Twelve studies satisfied the methodological quality assessment. Of the four studies that were excluded,[44, 102-105] exclusion was predominantly based on a high risk of selection or attrition bias and failing to account for significant confounding variables within the statistical analysis (Appendix 8).

3.2.1 Excluded studies

Detailed reasons for study exclusion are provided in Appendix 9.

3.2.2 Included studies

Methodological quality of the remaining articles was relatively similar with most demonstrating similar strengths and weaknesses. Most domains were felt to have 'partly' satisfied the requirements to sufficiently limit potential biases.

Study participation was generally well described, with most articles reporting the method of recruitment, inclusion and exclusion criteria as well as adequate participation of eligible individuals. Descriptions of the characteristics of the source population was generally poorly done, however given many of these studies were large population cohort studies, this point is of less significance as this information was provided within the study itself. All studies utilised the AUA-SI or IPSS. As described in Chapter 1, the IPSS is a modification of the AUA-SI; it is generally used interchangeably and thus will be considered the same measurement modality and referred to as the IPSS.

The risk of attrition bias is inherent to population-based cohort studies due to the logistical difficulties of following large numbers of individuals over a long period of time. All articles sourced their data from large cohort studies such as the Boston Area Community Health (BACH) study,[106] the Olmsted County Study (OCS)[45, 85, 107-109] or the Osteoporotic Fractures in Men Study (MrOS),[86, 88, 110] and have the potential to be affected by this bias. Included studies provided adequate explanations on attempts to collect data on participants that dropped out and provided descriptions of key characteristics of those lost to follow-up.

Predictor and risk factor measurement was generally performed well. Clear definitions were more frequently provided in smaller studies[46, 89, 111] in which clinicians at appointments or trained researchers were able to collect observed data such as blood pressure, weight or access medical records.[46, 89, 111] Those studies utilising large population cohorts partly relied on participant recall via the administration of questionnaires, thus increasing the risk of recall

and misclassification bias.[45, 85, 86, 88, 106-110, 112] Despite this, the method of data accrual within the larger studies was consistent between participants and utilised standardised and validated questionnaires, either administered by trained researchers, physicians or completed by the subjects.

Outcome measurements varied dramatically between the studies, and there was both clinical and methodological heterogeneity. This resulted in both a change to the systematic review protocol (described in Chapter 2) and the inability to perform a meta-analysis. Sixteen different LUTS endpoints were used to define a 'change' in disease course. These endpoints included discrete numerical changes in IPSS score (e.g. ≥3-point change), continuous numerical changes (e.g. rate of change), categorical change (e.g. from mild to moderate symptoms), trajectory models and clinical endpoints such as acute urinary retention, urinary incontinence, renal failure and recurrent urinary tract infections (Appendix 10).

Adjustment for confounding measurements was assessed to have been performed well in all the included studies. Examined exposures and covariate(s) adjusted for during statistical analysis can be found in Appendix 11. For prognostic studies that considered the impact of multiple potential prognostic factors on LUTS outcomes, confounders needed to be identified for each individual prognostic factor, however this was seldom performed. Confounders were rarely identified *a priori*.

Statistical analyses were assessed to have been performed well in most included studies. Two studies were criticised for the statistical methodology based on the reporting of numerous outcomes that were not defined *a priori* (and thus increasing the risk of Type 1 statistical errors)[85, 108] and one due to the lack in clarity of the confounders used within the analysis.[46]

3.3 Description of included studies

All 12 included studies were prospective cohort studies. Nine studies relied upon data extracted from three established population-based cohorts, the BACH[106] study, the OCS[45, 85, 107-109] and the MrOS[86, 88, 110]. All three of these cohorts were men from North American communities, and the remaining three included studies examined men in China,[46] Hong Kong[111] and Austria.[89] The total number of men with untreated LUTS examined in this review was 16,105. As some studies examined different risk factors from within the same cohort, it is probable that some men were included in more than one study. The mean age of men ranged from 49.7 to 72.7 years. Duration of follow-up ranged from 3 to 17 years.

3.3.1 Recruitment and follow-up

The recruitment strategy and data extraction utilised varied between included studies and is summarised in Appendix 6.

The BACH study employed a stratified, two-stage cluster sampling design to recruit both men and women (only data on males was extracted for this systematic review) aged 30-79 years between 2002 to 2006.[113] This randomly selected, community-based sample subsequently completed a validated questionnaire collecting information including, but not limited to, urologic symptoms, comorbidities, medications, quality of life and sociodemographic features. Follow-up, in-person interviews were carried out roughly five years later with a conditional response rate of 80.4%.[106]

The MrOS study employed a non-randomised method of recruitment which entailed a mailed invitation to all men ≥ 65 years who resided in nearby communities and were identified through vehicle registration, voter registration and healthcare enrolment, in addition to newspaper listings and community events.[114] Recruitment was performed between the years 2000 and 2002. A self-administered questionnaire, interviewer-led questionnaire and a clinical examination was performed at baseline, then updated every two years for each participant.

Temml *et al.* recruited men in a non-randomised convenience sampling method. Men who had previously attended a free, voluntary health examination provided at seven 'sites' and 'employees of large companies' across Vienna, Austria, in 1996 were invited for a repeat health examination if they met the inclusion criteria of the study.[89] Enrolled men underwent a detailed medical examination, including medication history, physical examination, sociodemographic questionnaire, urinalysis, blood tests and IPSS. Follow-up was performed after five years.

Wong *et al.* recruited men through a non-randomised, convenience sampling method by placing notices in housing estates and community centres, and assessed their health, sociodemographic features, physical activity and LUTS with the use of a questionnaire and interview.[111] Whilst the frequency of their assessment was not clear, they were followed up for four years.

Fu *et al.* conducted at a single institution study where a survey was carried out by trained researchers gathering information on LUTS, as well as recording anthropometric measurements, blood pressure and comorbidities with follow-up at three years.[46]

Five studies utilised data obtained from the OCS.[45, 85, 107-109] In the OCS, men aged 40-79 years were recruited using stratified random sampling from Olmsted County (MN, USA) in 1990. Of the 3874 eligible men, 2115 (55%) participated in in-home interviews which assessed family history, urologic disease, medication use and clinical urinary measurements and the AUA-SI. Subjects were re-assessed every two years for 16 years.

3.3.2 Baseline severity of LUTS

Five studies examined men with any severity of LUTS at baseline[46, 88, 89, 107, 108] whilst one

only examined men who could be defined as progressing (based on a ≥3-point increase in AUA-SI) and thus men with AUA-SI ≤33 were enrolled.[106] Holton *et al.* included men with mild to moderated LUTS (AUA-SI <20)[110] and five studies examined men with IPSS ≤ 7.[45, 85, 86, 109, 111] Whilst an IPSS ≤ 7 could potentially include men with IPSS = 0, (i.e. asymptomatic), only 2% of men enrolled in the MrOS study were asymptomatic at baseline and given the mean age of men enrolled in the other studies (Wong *et al.*: 71.3 years, OCS: 56.59 years), it is likely that only a small percentage of men across the included studies were completely asymptomatic.

3.3.3 Defining a change in severity of LUTS

All studies included a definition for a progression of LUTS. Only three studies examined risk factors for regression of LUTS[88, 107, 108] and one study examined men with a stable LUTS severity trajectory.[88] Definitions varied significantly between studies (see Appendix 10) and even within the same research group, three different definitions were utilised[86, 88, 110] which can partly be explained by the subgroup of men that were analysed within the studies but also perhaps due to advancements in statistical analyses.

3.3.4 Statistical analysis

All studies utilised either multivariate logistic regression models, stepwise logistic regression models or cox-regression analyses adjusted for age, and reported either odds ratios (OR), hazard ratios (HR), relative risk (RR) ratios, Spearman Coefficient or p-values for trends.

3.4 Exposures of interest

3.4.1 Modifiable predictors

Fourteen grouped modifiable predictors were assessed for a relationship with changes in LUTS severity.

Diabetes mellitus

Two studies examined diabetes as a risk factor for progression.[46, 88] Fu *et al.* found that diabetes mellitis (DM) was related to an increased risk of progression (HR 1.37, 95% CI 1.12-1.59, p = 0.025) after adjusting for other features of the Metabolic Syndrome and age. Marshall *et al.* however found no association between progressing symptomatology and a history of DM when compared to men with stable symptoms (OR 0.6, 95% CI 0.3-1.2, p = 0.12). Fu *et al.* assessed DM by the National Cholesterol Education Program-Adult Treatment Panel III criteria for Asian Americans by: 1) fasting BGL ≥5.6mmol/l, previous diagnosis of type 2 diabetes, or 2) use of anti-diabetic medication or insulin which contrasts to Marshall *et al.* who utilised a less precise patient reported 'physician diagnosed diabetes.' Both studies examined men with any severity of LUTS at baseline but defined progression differently. Neither study reliably described patients' type of diabetes, time since diagnosis

and diabetic control or treatment interventions, which may have confounded the results.

Mental health

Two studies examined depression and the risk of progressive symptoms and found similar outcomes.[88, 111] Wong *et al.* found that men with mild LUTS and a possible depressive disorder (15-item Geriatric Depression Score (GDS) ≥ 4) were twice as likely to develop moderate-severe LUTS after four years (OR 2.08, 95% CI 1.28-3.40). The 15-item GDS is used to identify depression in people 55 years and over; a score >4 indicates the possibility of a depressive disorder.[115] Marshall *et al.* examined the relationship between men with mild LUTS and mental health disorders using the Short Form -12 (SF-12) Mental Components Score. The SF-12 is a frequently used measure of self-rated mental and physical health in the community. A score of ≤50 has been suggested as a cut-off point to adequately discriminate between mentally healthy people and people with either an anxiety disorder or other common mental disorder; the lower the score, the more disabling the disease.[116] Men with a score < 50 were twice as likely to have progressing compared to stable LUTS (OR 1.9, 95% CI 1.1-3.4, p=0.03). This relationship strengthened when examining men with moderate symptoms at baseline (OR 2.5, 95%CI 1.3-4.9, p=0.005).

Cardiovascular disease

Three studies examined the relationship between blood pressure and LUTS changes[46, 88, 89] and two examined cardiovascular disease (CVD) and LUTS.[88, 111] Fu *et al.* found that hypertension was related to an increased risk of progression (HR 1.5, 95%CI 1.08-1.94, p=0.18)[46] and Temml *et al.* found a statistically significant but unlikely clinically significant association between baseline systolic blood pressure and progression (RR 1.05, 95%CI 1.0-1.1, p=0.024).[89] Both studies recruited men with any severity LUTS and defined progression similarly (IPSS ≥ 4 compared with IPSS ≥ 5). However, Marshall *et al.* found no association between men with mild symptoms (OR 1.5, 95%CI 1.0-2.4, p=0.06), or men with moderate symptoms who had progressing trajectories when compared to men with remitting symptom trajectories (OR 0.6, 95% CI 0.3-1.0, p=0.04) and their baseline blood pressure.[88]

A history of diagnosed angina had no effect on disease progression (OR 0.4, 95%CI 0.2-1.1, p=0.07),[88] however Wong *et al.* reported that having a history of coronary heart disease was associated with a 1.65 time risk of developing moderate to severe LUTS (OR 1.65, 95%CI 1.05-2.59).

Hyperlipidaemia

Only one study examined an association between symptom fluctuation and hyperlipidaemia and did not find a relationship (HR 0.91, 95%CI 0.65-1.26, p=0.37).[46]

Diet

Two studies examined dietary factors and their relationship to LUTS with relatively similar findings.[106, 110] The population in the study by Curto *et al.* included men who were treated at baseline with medical therapy for LUTS.[106] A sensitivity analysis was performed that excluded men using antispasmodics, anticholinergics, α-blockers and 5-α-reductase inhibitors, however results were unchanged from the main analysis so they are not presented. Communications with the authors revealed these sensitivity analysis results were no longer available. In the main analysis, however, men in the highest quartile of dietary baseline vitamin C intake (median 186mg/day) were less likely to have progressive daytime storage symptoms when compared to those in the lowest quartile (median 40mg/day) (OR 0.63, 95%CI 0.41-0.97). This however does not suggest that a low vitamin C diet increases the risk of progression, but rather a higher vitamin C diet is associated with a lower likelihood of progression, i.e. stabilisation of symptoms. When assessing total intake, however, (dietary and supplementary) there was no evidence that changes in total vitamin C intake altered the course of LUTS.[106] Similarly, Holton *et al.* did not observe any significant associations between dietary antioxidant intake (vitamin C, vitamin, β-carotene, α-carotene, β-cryptoxanthin, lycopene and lutein/zeaxanthin) and LUTS progression (p-value for trend all > 0.1).[110]

Weight

Five studies examined the influence that weight may have on disease progression.[45, 46, 86, 88, 89] Four studies did not find significant relationships between BMI, waist size or waist/hip ratio at baseline or changes in BMI with changes in LUTS. Parsons *et al.* however observed that LUTS was 41% more likely to progress in overweight and obese men (BMI ≥25.0) with mild LUTS than normal weight (BMI <25.0) individuals (OR 1.41, 95%CI 1.03-1.93, p=0.03). Three studies examined men with any severity at baseline and two examined only those with mild symptoms. All five studies defined progression differently and adjusted for different variables in their analysis.

Smoking

Only one study examined cigarette smoking and LUTS progression,[89] and no association was demonstrated (data not published). Data was requested from the authors but was not provided.

Alcohol

Two studies found a link between alcohol and changes in LUTS[88, 111] whilst one did not.[89] In the study by Marshall *et al.*, men with remitting trajectories were 60% less likely to have a history of problem drinking than men with progressive trajectories (OR 0.4 95%CI 0.2-0.9, p=0.03). Drinking ≥7 alcoholic drinks per week in the past year increased the risk of progression by 2.5 times in the study by Wong *et al.* (OR 2.51 95%CI 1.32-4.79). This

contrasted with Temml *et al.* who did not find any association (data not published). All three studies used different definitions to characterise progression.

Medications

Three classes of medications were found to protect men from worsening LUTS. Men with remitting trajectories were found to be 2.3 times more likely to use central nervous system medication than men with progressive trajectories (OR 2.3, 95%CI 1.1-4.9, p=0.03).[88] Nonsteroidal anti-inflammatory drug (NSAID) use was significantly inversely associated with overall symptom progression (HR 0.64, 95%CI 0.56-0.73) (including irritative, obstructive and nocturia symptoms) and need for treatment (HR 0.80, 95%CI 0.66-0.98), but not acute urinary retention (HR 0.93, 95%CI 0.62-1.32). These results did not appear to change when examining the duration of or type of NSAID taken.[85] Statin use was inversely associated with progression of symptoms (HR 0.39, 95%CI 0.31-0.49) and prolonged use was associated with an increased protection from progression (duration >0-33rd percentile: HR 0.55, 95%CI 0.39-0.78; duration >66th percentile: HR 0.32, 95%CI 0.22-0.48; p-value for trend: <0.001).[109]

Hormonal factors

One study examined the relationship between baseline and changes in oestradiol and testosterone levels with changes in LUTS. A higher baseline oestradiol and a rapid decline in oestradiol was associated with a greater increase in symptoms (R^2 0.20, p <0.001). Whilst lower testosterone levels were associated with more rapid increases in prostate volume, this did not alter the course of LUTS.[107]

Inflammation

One study examined the association between CRP, a surrogate marker for inflammation and LUTS. Men with baseline CRP levels >3.0mg/L did not show an overall increased annual rate of change in LUTS when compared to men with lower levels (OR 1.49, 95%CI 0.77-2.86). They did have a greater risk of developing more irritative LUTS (OR 2.00, 95%CI 1.04-3.82) but not obstructive LUTS (OR 1.25, 95%CI 0.64-2.41).[108]

Physical activity and mobility limitations

Two studies examined physical activity, mobility and LUTS.[86, 88] Parsons *et al.* observed a 20% reduction in LUTS progression in men who walked daily compared with men who did not (OR 0.8, 95%CI 0.65-0.98, p=0.03). Interestingly this observation was not reciprocated by the same research group assessing trajectory types in the same cohort of men but with different baseline LUTS severity (OR 1.4 95CI 0.9-2.2, p=0.1).[88] Marshall *et al.* also did not find that mobility limitation, back pain in the last 12 months or troubles with dizziness were any more likely in men with progressive trajectories compared with a stable trajectory after multivariate analysis.

Education

Studies by Temml *et al.* and Parsons *et al.* did not find a relationship between the level of education obtained and change in LUTS.[86, 89]

Relationships

Two studies examined whether relationship status was associated with the course of LUTS. There were no statistical differences in living arrangements between men with progressive and stable trajectories[88] and Temml *et al.* did not find that marital status influenced LUTS.[89]

3.4.2 Non-modifiable predictors

One study examined predictors that could be considered non-modifiable.[88]

Race

In a cohort of men with moderate baseline LUTS, Marshall *et al.* observed that being white (Caucasian) or non-white did not significantly alter risk of LUTS progression.[88]

Cancer

Marshall *et al.* found that men with progressive LUTS were more likely to have a history of non-prostate cancer than men with stable symptomatology, however this was not clinically relevant (OR 1.7, 95%CI 1.0-2.9, p=0.03)[88]

3.4.3 Disease factors

One study, *Temml et al.*, examined disease factors that might predict a change in LUTS.[89]

LUTS severity, type and quality of life

No studies included in this review examined the risk of progression or regression of symptoms based on the initial baseline severity or predominant type of LUTS, however in one study, the degree to which a man's LUTS affected their quality of life was statistically significant predictor of initiation of therapy (RR 5.2, 95%CI 1.6-17, p=0.007).[89]

CHAPTER 4: DISCUSSION

This systematic review represents the largest synthesis of data examining men with untreated LUTS and thus provides insight into factors that may contribute to the variable progression and regression of LUTS severity in these men.

The identification of suitable studies and the extraction of data proved difficult due to the variable reporting quality of primary data. Clinical and statistical heterogeneity meant that meta-analysis could not be performed, however within the data extracted for this review, there appears to be some correlation between systemic illnesses, lifestyle factors and medications with alterations in LUTS severity.

When examining an association between two observations, Hill designated nine factors that must be considered before interpreting the association as causation; strength of association, consistency of the observed association, specificity, temporality (a temporal relationship to the association), a biological gradient (a dose-response effect), plausibility, coherence (observed inference should not conflict with established understandings of the disease), experiment and analogy.[117] This review retrieved 12 studies examining 17 individual exposures that were observed to effect LUTS severity, however, only six exposures were assessed by more than one study. Of these six risk exposures, only one (mental health) demonstrated concordant results. Consequently, whilst these exposures demonstrate an association with LUTS and fulfil some of the factors described by Hill, a true causation relationship must be described with caution until these results are reproduced or demonstrated in controlled trials (with subject randomisation and researcher blinding, where possible).

4.1 Current practice

Investigating a male with LUTS includes taking a detailed history of severity and type with a validated symptom score in addition to physical examination and urinalysis. Other tests may include urine cytology, renal function analysis, PSA level, ultrasound of the kidney, ureter, bladder and prostate (including post-void residual volume), uroflowmetry and a bladder diary detailing the frequency and volume of voids.[118] Visualisation of the lower urinary tract with cystoscopy is indicated in the case of microscopic or macroscopic haematuria, suspicion of urethral stricture disease, concern or history of bladder cancer and a history of previous lower urinary tract surgery. These investigations are minimally invasive, however, cystoscopic procedures require insertion of a sterile fibre-optic camera into the bladder via the penis and has a roughly 2% risk of febrile urinary tract infection without prophylactic antibiotics.[119]

Treatment strategies for LUTS depends on the presumed aetiology. In any case, men who

present with symptoms that cause them minimal bother can be initially managed safely with watchful waiting strategies. Given the known fluctuating natural history of LUTS, this provides the opportunity for the severity to reduce without intervention. Approximately 65% of men will have stable symptomatology with watchful waiting after five years.[118] Lifestyle advice including fluid intake, moderation of alcohol and caffeine, pelvic floor exercises and bladder re-training can be offered in the first instance.[118] Brown *et al.* randomised 140 men with LUTS to a small self-help education program, or standard of care (defined as initial watchful waiting with escalation to pharmacological or surgical treatment as deemed necessary by the treating physician). It was observed that the self-help programs significantly reduced the severity of symptoms and progression to medical and surgical intervention[120] This Level 1 evidence highlights the possibility that lifestyle intervention may play a role in controlling and managing LUTS.

Medical treatment of LUTS can be an effective treatment strategy for men who have failed conservative management. Treatment is targeted at the underlying disease process, whether it be a primary bladder or prostate pathology and, in some cases, both. Patient compliance however can be an issue due to side effects.[118]

Alpha-receptor blockers such as Tamsulosin influence the dynamic component that BPH contributes to LUTS by reducing the smooth muscle tone within the prostate whilst 5α-reductase inhibitors (5-ARI) reduce the static component by reducing the overall size of the prostatic stroma.[118] The MTOPS and CombAT trials showed that a combination of alpha-blocker and 5-ARI prevents the progression to worse voiding symptoms (AUA score increase > 4), need for BPH surgery and acute urinary retention, with the greatest benefit seen in men with a PSA >1.5 and prostate volume > 40cc. These trials included men with moderate to severe LUTS with presumed BPH based on prostate volume and reduced flow rates. Side effects include dizziness, postural hypotension, decreased libido, erectile dysfunction and abnormal ejaculation which occurs in between 2-5% of treated individuals[121]

Medications that modulate detrusor contractility and compliance include anticholinergic agents, M_3 receptor antagonists, beta-3 receptor agonists and onabotulinum toxin A (Botox).

When medication is ineffective in treating LUTS or the side effects are not tolerated, then surgery is indicated. Strong indications for surgical intervention for LUTS secondary to bladder outlet obstruction include obstructive uropathy, recurrent UTIs, refractory acute urinary retention and bladder calculi. Transurethral resection of the prostate (TURP) is an effective means of treatment and for a long time has been the gold standard surgical intervention for LUTS secondary to bladder outlet obstruction from the prostate. Intra-operative and peri-operative complications are uncommon but include blood transfusion (2.9%) and hyponatraemia (<1%). Long term complications include retrograde ejaculation (65%), bladder neck stenosis (3.8%) and incontinence (2.2%).[118] Retrograde ejaculation is

almost an unavoidable ‘complication’ of TURP as the deliberately resected tissue is both responsible for the bladder outlet obstruction as well as normal ejaculatory function. Bladder neck stenosis and incontinence however can cause significant bother to the patient and may require secondary surgical interventions. The status of TURP as gold standard has now been challenged, with the results of other modes of tissue resection or ablation published with equivalent medium term results (Photo-selective Vapourisation of the Prostate [PVP][122] and Holmium Laser Enucleation of the Prostate [HoLEP[123]]). Other modes such as Aqua-ablation and Rezum™ have emerged and Urolift™ (not a volume-reduction procedure) has short-term published data.[124]

Percutaneous Tibial Nerve Stimulation and sacral neuromodulation can be used for LUTS due to overactive bladder, and in severe refractory cases, bladder augmentation is utilised.

In summary, current treatment for LUTS is generally well tolerated by patients and has a low associated morbidity. However, as discussed, LUTS may in fact be a manifestation and symptom of a systemic disorder and it is plausible to argue that local treatment on the lower urinary tract is being instigated for a systemic disease process. Whilst alleviating the frustration of LUTS, practitioners may be overlooking the severity of disease processes such as Metabolic Syndrome or depression and thus missing the opportunity to intervene. If the true natural history of LUTS was known and factors that influenced their severity could be modified, then it would provide the opportunity to intervene on the disease process at its source, rather than at the pathological end-point.

4.2 Overview of the findings

The results of this systematic review provide information to help better understand influencing factors on the natural history of LUTS in untreated men in the community. Significant heterogeneity prevented examination by meta-analysis, but the published results provide some insight into the influencing factors on LUTS. There has been a surge in research examining the role that comorbidities play on the function of the lower urinary tract and it is prudent to compare this against the findings of this review.

The metabolic profile and presence of cardiovascular risk factors in men appears to play an interesting role in the development and change in severity of LUTS. In this review, associations between LUTS and these risk factors were conflicting and tended to trend toward the null hypothesis; further discussion on possible explanations for the inconsistency of results are explored later in this chapter. Cross-sectional analyses examining cardiovascular and metabolic risk factors show a stronger association compared to this review. This may be explained by both the different study methodologies as well as less strict inclusion and exclusion criteria, however, a review of these is worth discussing.

Martin *et al.* examined 780 men aged of 35-80 years over a duration of five years. Some men

in this cohort were treated medically for LUTS and this was adjusted for in the analysis. Improvement in storage LUTS was associated with higher baseline high-density lipoprotein levels (HDLs) and lower serum triglycerides, whilst progression of voiding and storage LUTS were associated with greater abdominal fat and obstructive sleep apnoea. These are components of the metabolic syndrome and suggest a shared pathological process between LUTS and cardiovascular disease. The precise pathophysiological process is not fully understood but likely relates to vasculopathy, impaired insulin resistance, imbalanced oestradiol/testosterone levels, systemic inflammation and increased sympathetic nervous system tone.[46, 125]

Only one study in this review examined LUTS and smoking and did not find an association with changes in severity. On cross-sectional analysis, however, smokers and former smokers were at increased risk of moderate to severe LUTS when compared to never smokers (OR 2.51, (95%CI 1.54-4.10) and OR 2.17, (95%CI 1.37-3.42)) respectively.[126] Similar results have been found by other authors.[127] A three-year observational study demonstrated that smoking (>50-pack years history) resulted in a 5.1-fold probability in LUTS progression, with a particular effect on storage LUTS. Of note, treatment status of men enrolled in the study is unknown, therefore the effect could be considerably larger.[128] The pathological process of smoking contributing to LUTS may include smoking derived irritation of the bladder mucosa, nicotine induced sympathetic nervous system tone, increased systemic inflammation and atherosclerosis of the pelvic vasculature.[74, 126-128]

In a meta-analysis, daily consumption of alcohol was associated with a small decreased likelihood of BPH but with a trend towards an increased risk of LUTS overall.[129] Integral to this analysis was that 12 studies used ‘BPH’ as the primary outcome whilst four used ‘LUTS’. This most likely suggest that alcohol affects LUTS via alteration in the bladder physiology but does not increase the size of the prostate. They may also simply differ because of the populations examined and the definitions used. In this systematic review, two studies suggested a link between high levels of alcohol intake and progressive LUTS. Alcohol has several effects that can conceivably worsen and improve LUTS. Increased urine volume via a diuretic effect, mucosal irritation and changes to insulin sensitivity may worsen LUTS,[50, 128] whilst, in the same way that moderate alcohol intake can improve cardiovascular health, these positive effects may reduce ischemia and fibrosis of the urinary tract.

Meta-analysis examining the association between physical exercise and LUTS included eight studies based on cross-sectional analysis. Six studies examined BPH as an outcome, two examined LUTS, and pooled analysis found moderate to vigorous exercise may reduce the risk of BPH or LUTS by 25% compared to a sedentary lifestyle.[130] Physical exercise is a recognised protective factor against CVD and it is plausible to hypothesise that by preventing CVD, the previously described sequalae on the lower urinary tract may not develop.

In this review, one study found an association between obesity and progressive LUTS whilst four did not. Results from other studies are conflicting, however large, longitudinal studies have demonstrated a positive association. Men in the Health Professionals Follow-up Study (HPFS) were more likely to develop LUTS or experience progressive LUTS if they had higher total and abdominal adiposity or gained weight (50 lbs versus stable weight (HR=1.35; 95% CI 1.14-1.60, p-trend < 0.0001).[87] The men were not assessed to have taken LUTS related medication until six years into the study and this resulted in exclusion of this study from this review. Kristal *et al.* examined men in the placebo-arm of the Prostate Cancer Prevention Trial and observed a 10% increase in the need for BPH-related surgery or two consecutive IPSS scores >14 with each 0.05 increase in hip-to-waist ratio.[131] Martin *et al.* observed an association between progression of storage LUTS and greater abdominal fat mass at baseline.[9] Seitter *et al.* however did not find an association between obesity and risk of BPH-related surgery over 12 years when adjusted for age, however, importantly, the baseline severity of symptoms of included men were not known.[132]

One study included in this review examined the association between hyperlipidaemia and LUTS and did not find an association when adjusting for other components of the metabolic syndrome.[46] Paick *et al.* examined 75 men with impotence and LUTS by cross sectional analysis; it was observed that symptom scores did not correlate with cholesterol levels when examined as a continuous parameter, however when categorised, men with HDL levels <40mg/dL and LDL > 150mg/dL were more likely to have worse symptoms (19.4 ± 2.6 for HDL-cholesterol < 40 mg/dL vs. 14.4 ± 1.0 for HDL-cholesterol ≥ 40 mg/dL, P = 0.042) and (19.4 ± 2.4 vs. 14.3 ± 1.1, P = 0.033 for LDL levels).[133] Martin *et al.* observed that lower triglyceride levels and higher HDL levels at baseline were associated with improvement in storage LUTS over 5 five years and low HDL levels were associated with progressive voiding LUTS.[134]

Further examination on the role that lipid metabolism may play on LUTS was observed in one included study in this review that found that statin medication may be associated with a 6.5-7 year delay in development of moderate-to-severe LUTS after adjusting for age, BMI, diabetes, hypertension, CAD, smoking, alcohol use, physical activity and NSAID use.[109] This association was not seen by Mondul *et al.* when examining men in the HPFS.[135] The HPFS participants were of a higher SES and a less socio-demographically diverse population than those in the Olmsted County Study, and the men in the HPFS who were not taking statins might have been healthier, with greater access to health care, therefore the effect that statins had on LUTS might have been confounded.

Additional medications that were examined in this review included NSAIDs[85] and central nervous system (CNS) medication[88] which demonstrated a protective effect on LUTS progression. CNS medications examined in the study by Marshall *et al.* included anti-epileptics, benzodiazepines, antidepressants, opioids and sedatives. As described in

Chapter 1, opioids and anti-depressants affect the lower urinary tract function via interactions with μ-receptors and 5-HT-receptors, respectively, and sertraline, a serotonin and norepinephrine re-uptake inhibitor, can be used to manage stress urinary incontinence.[136] Other studies examining the association between NSAID use and LUTS demonstrated different results from those found by St Sauver *et al.,* however they were criticised for the small number of men using NSAIDs and patient reported outcome measures.[137, 138] The mechanism by which NSAIDs may prevent the onset of LUTS is largely unknown but it has been hypothesised to be mediated through reduced prostaglandin synthesis, inhibition of androgen receptor expression and reduced inflammation.[85]

Two studies in this review demonstrated an association between poor mental health and LUTS progression.[88, 111] Data from cross-sectional and longitudinal studies have demonstrated a positive association between LUTS and depression. A cross-sectional study of 547 male patients from a urology clinic found that men with depressive symptoms were three times more likely to present with severe LUTS,[139] and in a Korean population, depressed men had higher IPSSs when compared to euthymic men ($p = 0.03$) and were 5.81-fold more likely to have moderate to severe LUTS.[12] Martin *et al.* found that depression was an independent risk factor for storage LUTS progression and demonstrated temporality as depressive symptoms or anti-depressant use preceded progression of men's storage and voiding LUTS.[134] These findings are congruent with the findings of this review and demonstrate strength of association, consistency and temporality. Systemic inflammation has been hypothesised as an underlying aetiology of depression[140] as well as LUTS. In this review, St Sauver *et al.* observed an association between a rapid rise in irritative (storage) LUTS and CRP levels ≥ 3.0. Using the same CRP categories, there was no association with prostate volume growth or urinary flow rates, which suggests the disease process affects urinary storage rather than voiding; this helps strengthen the biological plausibility of a possible shared aetiology between LUTS and depression.

St Sauver *et al.* observed an association between higher baseline oestradiol levels and progressive symptoms[107] which is similar to Martin *et al.* who observed that higher oestradiol levels were protective of storage LUTS but associated with progressive voiding LUTS.[9] Testosterone levels did not alter the course of LUTS in the study by St. Sauver *et al.,* which is supported by a systematic review by Karthrins *et al.* who did not find any high quality prospective trials that demonstrated an association between testosterone replacement in hypogonadal men and changes in LUTS. Notably, the authors described similar challenges in summarising the retrieved results as experienced with this review.[141]

Social factors including education and relationship status were retrieved as a part of this review and in these three studies[86, 89 88] none demonstrated a relationship with the LUTS disease course. Martin *et al.* observed being widowed was associated with a higher likelihood in improvement of storage and voiding symptoms in Australian men,[134] whilst

Fowke *et al.* did not demonstrate an association with marital status or education levels in African American and white men in the USA.[56] Low socio-economic status on the other hand was associated with worse LUTS on cross-sectional analysis and higher risk of progression[13, 56]

Examining the association between race/ethnicity and LUTS yielded mixed results. Three large, population based longitudinal studies including the HPFS,[51] the Third National Health and Nutrition Examination Survey (NHANES III)[142] and the Boston Area Community Health Study[143] did not find race/ethnicity to be associated with increased risk of LUTS progression, whilst the control arm of the Prostate Cancer Prevention Trial[49] and a combined analysis of the Flint Men's Health Study and OCS[144] did find greater severity of LUTS in African American men compared to non-African American men when confounding for some socio-economic status factors. In their analysis of the Southern Community Cohort Study (SCCS), Fowke *et al.* found little difference between African American and white men and concluded that those studies that found a positive association had most likely not adjusted for other important socio-economic confounders associated with race/ethnicity differences.[13]

4.3 Strengths of the study

The data included in this review was predominantly from large population cohort studies with prospectively collected data available on large samples of men.

Conventional pharmacological treatment has been shown to affect the natural history of LUTS as demonstrated in the MTOPS and CombAT trials. Both studies showed that a combination of α-blocker and 5-ARI prevented the progression to acute urinary retention, the need for BPH surgery and progressive worsening of voiding symptoms (AUA score increase >4).[81, 82] By excluding men who had had or were having conventional treatments, this review obviated a potential treatment effect and assisted in generating a hypothesis regarding comorbidities, medications and social factors, and their possible interaction with the naive urological tract.

By excluding placebo-controlled arms from randomised controlled studies, we eliminated the potential for results to be confounded by the placebo effect. The placebo effect in LUTS has been shown to be considerable with a potential reduction in symptom score of 9-34%.[93] Additionally, the frequency of assessments in RCTs such as the CombAT trial was every three months compared to roughly two-yearly in most of the cohort studies. Being observed frequently and the consequent awareness of being studied can potentiate the Hawthorne effect, by which one's usual behaviour is altered as a result of being observed.[145]

The benefit of utilising a cohort study design is that it can measure a multitude of variables and confounding factors and thus minimise the risk of bias. Multiple outcomes (progressing, regressing and stable symptoms) can all be assessed from multiple exposures and relative

risks can be calculated to hypothesise the aetiology and influencing factors of a disease. Whilst they do not represent the highest level of evidence, many research questions cannot be answered with RCTs and cohort studies provide a useful method of doing so. Of note however is that reporting of a large number of endpoints which have not been established *a priori* can increase the chance of a type 1 statistical error (i.e. false-positive results) and was a concern for a few papers in this review[85, 109]

In retrospective cohort studies, data is collected after the outcome of interest has occurred and there is a potential of bias when collecting and examining the historical data on individuals, especially if the outcome is known.[146] Investigators in the included studies were able to collect information by standardised, validated questionnaires and in some cases took a full medical history and collected anthropometric measurements without being aware of the patient's outcome. Data was prospectively collected and whilst not free of contaminating biases, this was a more accurate method of data accrual.

4.4 Limitations of the study

There are significant limitations to this study which must be considered. There were methodological limitations within the design of the protocol, as well as the included studies that may have affected the results of this review.

The search strategy utilised in this review was comprehensive and covered four biomedical literature archives. Prognostic studies are prone to publication bias and it is likely that those demonstrating a statistically significant association are more likely to be published.[98] A search of two grey literature data-bases however did not reveal any studies that met the inclusion criteria. Suitable studies may have been missed however, as our search was limited to studies published in the English language and we did not include published abstracts from scientific conferences which may have been presented but never successfully published.

As discussed, determining the treatment status of men within studies was often difficult. Assumptions were made based on the criteria provided in Section 2.2.13, however this often relied on successful communication with the authors.

There is no standardised process for assessing the methodological quality of prognostic studies[98] and historically systematic reviews of prognostic studies have been suboptimal.[147] This review used guidelines published by Hayden *et al.*[99] which were developed following a systematic review of 163 systematic reviews examining prognostic studies. These guidelines have been cited more than 800 times but remain unvalidated. In this review, the potential bias was assessed within six domains of the studies' methodology and items to be considered were discussed between the reviewers prior to methodological assessment. However, the reviewers' academic qualifications are within the clinical practice of medicine

and science rather than research, and they are not trained data extractors or reviewers.

The reviewers thoughtfully considered the methodological issues of each study and instead of attributing a level of 'risk of bias' to the individual studies, it was ascribed to each individual domain within the study. Studies were included in this review if none of the six domains were deemed to have a high risk of bias. The advantage of this is that the reader can determine how well bias was limited to each component of the methodology but the review did not grade or categorise the entire study as a low, medium or high risk of bias as other reviews have. As seen in Appendix 8, most domains 'partly' satisfied the reviewers. As most domains were assessed to be at risk of some degree of bias, the overall quality of the papers included should be considered suboptimal with probable biases and unmeasured confounders. Of particular note was that none of the included studies adjusted for Obstructive Sleep Apnoea (OSA). There is emerging, well performed research suggesting a strong relationship between both OSA and storage LUTS[9, 148] and failing to adjust for this weakens the reliability of these studies.

Within the included studies, several limitations should be noted.

4.4.1 Study design

Cohort studies have inherent biases in the design and these must be discussed to assess the generalisability of results.

Selection bias can be introduced into a cohort through the sampling scheme, inclusion and exclusion criteria, subject participation and attrition as well as from subjects lost to follow-up. The BACH study and Olmsted County Study[149] were the only two cohort studies included in this review that recruited subjects based on random selection (see Appendix 6). MrOS recruited predominantly healthy, white, well-educated volunteers[114] which reduces the external validity with respect to other ethnicities. Results from studies that relied on voluntary recruitment through the means of free health checks,[89] recruitment notices[111] and hospital clinics[46] may have been influenced by non-participation of populations of men who were not enrolled (participation bias) and who may have represented risk factors of differing prevalence to those men who were studied. Lack of randomisation increases the risk of unaccounted variables affecting the overall results and reduces the external validity of the studies.

Large prospective cohorts are prone to loss of subjects over time either through voluntary withdrawal or loss to follow-up. Failing to address the significant differences between included subjects and those lost to follow-up can introduce attrition bias. Generally, an analysis of subjects lost to follow-up was poorly described in the included studies.

Baseline questionnaires were utilised in all but one study.[89] Data that relied on participants' memory may result in inaccuracies in recollection and may contaminate the results with

recall bias.

4.4.2 Population

As is demonstrated in Appendix 10, the baseline severity of symptoms experienced by men enrolled into the studies differed substantially. A total of four different baseline symptom severity categories were provided. For a reliable prognostic study, men should all be in the same stage of their disease[98] (i.e. the same severity), however, given this review focused on fluctuations in symptoms rather than just progressing symptoms, we required men of all stages to be included. Importantly though, progression and regression rates differ considerably based on the level of severity at baseline[150] and men who have predominantly storage LUTS appear to demonstrate a disease course different to those whose symptoms are predominantly associated with voiding.[134] Most studies did not adjust for the severity of symptoms at baseline and poorly described the type of LUTS, and this could thus have produced erroneous results. Whilst examining men with 'any' symptom severity provided information on the effect of risk factors' on men at different stages of their disease, it contributed to clinical heterogeneity and was one reason why meta-analysis was not possible.

The three major cohort studies included in this review were conducted over differing periods and may individually have been contaminated to a varying degree by 'treated' individuals. The MrOS began recruiting men in 2000-02, BACH conducted their baseline interviews in 2002-2005, whilst the OCS began enrolment in 1990. The use of 5-α-receptor antagonists and α_1-receptor blockers became more widely adopted in the early 1990s and whilst medication had been collected since enrolment, specific questioning of these medications was not undertaken until the late 1990s such that treated individuals may contaminate the results.

The inclusion criteria for this review required men to be untreated both from a surgical and pharmacological perspective. Exclusion criteria stated in the included studies often excluded men with previous prostatic surgery, however, medical treatment status was often less clear. In such cases, exclusions on the likelihood of treatment were based on specific wording, baseline characteristics tables, whether treatment was adjusted for in the analysis, and where possible through direct contact with the authors. Unless treatment status could be assessed with a high degree of certainty, the study was excluded.

4.4.3 Exposure of interest

Included studies examined the exposures of interest by different means as detailed in Chapter 3. Influenced primarily on the method of data accruement, there were varying levels of detail provided on the exposure of interest. Studies with objective measurements of exposures of interest[46, 89, 107, 108, 111] provide a more robust classification of risk factors when compared to participant recall.[85, 86, 88, 106, 109, 110] Collection of objective measurements from all

participants in a cohort study can understandably be logistically and financially challenging, however it remains an optimal means of measurement. Determination of a biological gradient cannot be made without further knowledge on the time of exposure and degree of control over the exposure (e.g. treated hypertension versus non-treated hypertension or well controlled diabetes versus poorly controlled diabetes).

4.4.4 Outcome

The definitions of LUTS progression, regression and stability showed considerable heterogeneity between the studies. Whilst the protocol aimed to include only studies that demonstrated clinically significant changes in LUTS (change in IPSS ≥ 4, surgical or medical treatment), an amendment was required to ensure a meaningful review could be undertaken. Subsequently, studies were included if they measured 'any' change in LUTS severity. In some cases, risk factors were analysed with the IPSS being measured as a continuous variable (i.e. annual change in IPSS), whilst in other studies it was dichotomised (IPSS change ≥ 4, yes or no), meaning that studies that require a greater change in symptom severity would be less likely to reject the null hypothesis. The third most commonly used definition was based on a change in the three severity categories (see Appendix 10). Misclassification bias may be introduced with this definition as whilst two men whose symptoms have progressed from 1 to 8 and from 6 to 8 on the IPSS are demonstrating the same change from mild to moderate symptom severity, they are clearly not demonstrating the same disease course. As discussed, annual progression rates vary between 1-2 points annually[89, 90] in untreated men and thus studies requiring an IPSS category shift or with shorter observation periods are also less likely to reject the null hypothesis.

An increase in LUTS severity, AUR, medication use and surgical intervention for LUTS are examples of composite end-points (CE) for LUTS progression. When designing a trial, several end-points may be considered of equal importance and it may be problematic to decide on the most appropriate one. A CE is the unification of multiple end-points and provides a means by which studies can assess treatment effect (or impact of a risk factor) and can provide a better explanation of the disease process and understanding of the clinical spectrum of important disease outcomes.[151] A disadvantage of using a CE lies in the event that the end-point with the least clinical significance demonstrates the greatest effect by a treatment or the strongest relationship with a causative agent in the case of a prognostic study. In this case, results may demonstrate a significant relationship, whilst realistically this has been over-exaggerated by the strong relationship with a soft end-point.

This review aimed to assess risk factors associated with either progression or regression of LUTS. As all men were untreated at enrolment, regression could only be defined as a reduction in the IPSS. Progression, on the contrary, could be defined as an increase in IPSS, AUR, new pharmacological treatment or surgical intervention. As discussed in Chapter 1, LUTS is a constellation of symptoms, rather than a specific disease process and whilst there

are strong indications for pharmacological and surgical intervention, most treatment is initiated based on the impact of a patient's symptoms on their quality of life (QOL). The importance of this is emphasised by the fact that a QOL question is incorporated into the IPSS. The implication of this on the studies included in this review is that the decision for treatment may be initiated by the patient based not on symptom progression but on QOL, and QOL is influenced by a whole myriad of factors other than LUTS. For instance, a man with LUTS with predominant nocturia and a night-time frequency of four urinations per night may not be bothered if he lives alone. However, upon starting a relationship, he may feel embarrassed or his partner may be frustrated by interrupted sleep and this may trigger his seeking treatment. In this example, his disease has not progressed but within the studies, he would be defined as doing so.

4.4.5 Timeline

Temporality is an important factor to consider when examining a causative relationship between two observations. As shown in Appendix 6, the mean length of follow-up ranged from three to 17 years. Importantly, a time-to-event analysis was not provided by any studies. Measured risk factors were those collected at enrolment, however further description of the length of time subjects had been exposed to that risk factor was not clear such that a proper time to event analysis was not possible. The protocol stipulated a minimal follow-up of one year as reported annual progression rates vary between 1-2 points annually[89, 90] and change in symptomatology over shorter periods would be difficult to measure; the protocol however did not stipulate a maximum length of follow-up. A longer duration of follow-up requires very stringent and regular assessment of new risk factors that subjects may be exposed to over the period of examination to ensure that unmeasured new exposures do not confound the strength of association.

4.4.6 Statistical analysis

Statistical analysis was generally assessed to have been performed in a manner that sufficiently limited the risk of potential biases, however a few points are of note. Whilst this review only included studies that demonstrated risk assessment by multivariate analysis, variations existed between adjusted confounders. Subsequently, there may have been factors relating to LUTS change in some studies not accounted for in the studies' analyses.

In a number of the included studies, multiple end-points and sub-categories of patients were examined without being defined *a priori*. This method of analysis is suboptimal as it essentially examines groups until a statistically significant finding is discovered and increases the risk of type-1 statistical errors.

4.5 Conclusions

4.5.1 Implications for practice

Current guidelines for the investigation of LUTS have been described in Chapter 4.1. The use and availability of these investigations depend partly on whether a man is visiting a general practitioner or a specialist urologist, but in both cases, the findings of this review provides both practitioners with some useful information. In addition to the investigative prognostic indicators of progression that include PSA, prostate volume, post-void residual and age, this review suggests that those with a mental health disorder are more likely to progress than men without a mental health condition. This provides an opportunity to identify at-risk groups and possibly intervene earlier from a urological perspective, or perhaps consider deferring urological intervention until the man's mental health is improved before subsequently reviewing their LUTS and need for treatment.

General practitioners treating men with LUTS should screen for cardiovascular risk factors, diabetes mellitus, problematic drinking and level of exercise, as well as review medications that may contribute to LUTS progression. Current lifestyle modifications recommended for LUTS include avoidance of caffeinated and alcoholic beverages, reduced fluid intake prior to bed and bladder training. Whilst this review did not demonstrate that intervening on comorbidities improved LUTS, men should be encouraged to manage known cardiovascular risk factors in addition to other already recommended lifestyle modifications, as existence of these diseases may be associated with LUTS progression.

4.5.2 Implications for research

The findings of this review and the challenges that were faced in conducting a meta-analysis strengthen the argument for the establishment of research methodology guidelines specific to examining prognostic factors for LUTS. There has been a paradigm shift away from the historical view that all men with LUTS have BPH, therefore it is prudent to ensure that modern research methodologies reflect this.

Whilst findings of this review did not demonstrate a strong association between LUTS changes and baseline characteristics, cross-sectional studies and other longitudinal studies that adjusted for LUTS treatment suggest that an evolving understanding of the etiological factors contributing to LUTS is in play and further research needs to be conducted.

Difficulties encountered in this review stemmed largely from studies that attributed all male LUTS to BPH and thus used the terms interchangeably. Significant attempts have been made within this review to reinforce the importance of distinguishing the difference between the constellation of symptoms (LUTS) and the histological diagnosis of BPH, both for clinical and research purposes. The lower urinary tract however is clearly affected by many disease processes and attempts should still be made to investigate the etiological factors contributing

to individual pathological processes. When this is done, however, careful use of definitions needs to be ensured to avoid misclassification of patients and misinterpretation of data by clinicians.

A greater emphasis must be made on reporting standards for primary research. A clearer description of the population of interest, method of recruitment (preferably randomised), follow-up strategies, key characteristics and reasons for loss-to-follow up needs to be undertaken. Cost effectiveness studies based on the benefit of primary and secondary prevention of developing or worsening LUTS is also necessary.

Baseline information does not necessarily reflect the subsequent alteration in this risk factor. For example, changes in diet over the course of the study by Holton[110] were not assessed and may have introduced bias. Serial measurements throughout the studies were rarely done. Length of exposure (e.g. the duration that patients were obese or smoked) prior to enrolment was rarely known. St Sauver's study on statin use and LUTS[109] examined the length of statin use and its relationship with LUTS, however this was on the assumption that once a man reported taking a statin, he continued to take it. Understanding the temporal and gradient relationship of an exposure and LUTS severity strengthens the argument of a causation relationship.

It is beyond the scope of this review to examine individual definitions of progression and regression of symptoms and their suitability for use in LUTS, however, it is prudent to reinforce that significant heterogeneity exists within the literature and that statistical significance can be markedly different from clinical significance. An attempt was made to investigate symptoms that only affected LUTS in a clinically significant way, however insufficient studies met the criteria for a meaningful review. Defining change in symptoms based on a change in severity category (mild, moderate or severe) should be avoided however, as it can require between a 1-11 change in the IPSS score to move its category which introduces misclassification bias. Whilst the composite end-points used in many of the included studies (and in this review) enable the examination of multiple end-points of LUTS, a distinction between progression of symptoms and the need for treatment should be made as treatment need is based on many factors other than just symptom severity.

Few studies examined factors that improved LUTS and from a clinical perspective and to be able to counsel patients, demonstration of factors that improve symptoms rather than just those that worsen symptoms will be useful.

No studies in this review examined the impact of intervention or management of comorbidities and the impact this had on LUTS. No studies described whether comorbidities were well controlled and this both has the potential to confound results and represents a missed opportunity to describe or predict a biological gradient. Further endeavours should be made to explore these aspects of competing comorbidities and their effect on the lower

urinary tract.

Finally, measurement of known factors that influence the lower urinary tract should be collected and adjusted for by multivariate analysis; these include but are not limited to: CVD risk factors, the Metabolic Syndrome, mental health, alcohol, medications (NSAIDS, calcium channel blockers, ACE-inhibitors, beta-blockers, alpha-blockers, 5-alpha-reductase inhibitors, PDE-1 inhibitors and statins), race, age, severity of symptoms and type of symptom (storage or voiding).

4.5.3 Future directions

The management of LUTS was significantly changed in the latter years of the 20th century with the adoption of alpha-blockers and 5-α reductase inhibitors, and the introduction of anti-cholinergic and anti-muscarinic medication into clinical urological practice. Surgical procedures to relieve refractory voiding symptoms in men secondary to bladder outlet obstruction continue to evolve with new technology such as PVP, HoLEP and Urolift^{Tm} becoming frequently performed operations in place of TURP. All these surgeries come with significant costs and are performed on men based on medical reasons or men who can no longer tolerate their symptoms. These interventions however tend to be reserved for men well into the pathological course of their disease. There remains an evidence-based void in our understanding of what interventions can be provided to men as primary and secondary prevention measures and the non-pharmacological, non-surgical measures for preventing progression, or at least, of slowing the progression of symptoms.

LUTS must be considered the end of a pathophysiological pathway which is influenced by biological, psychological and social factors rather than just anatomical ones. This thesis demonstrates the evolving understanding of the influence that systemic disorders have on the urological system but strong evidence that supports intervening on these as a form of treatment of LUTS is still lacking.

The future of LUTS research must involve examining the effect of treating systemic diseases on men with LUTS.

4.5.2 Recommendations

The recommendations from this review can be used by clinicians and researchers alike.

Firstly, there appears to be enough evidence to suggest an association between LUTS and systemic illness including metabolic syndrome, cardiovascular disease, mental health disorders, socio-economic factors including education and wealth, and some medications. Whether a causation relationship exists is still largely unknown, but some theories link these processes through systemic inflammation, growth factors, autonomic nervous system and hormonal imbalances. In any case, this review should prompt clinicians to explore the presence of these factors in all men presenting to them with LUTS. Whilst intervening on

these disorders may not improve their LUTS, it provides the opportunity to screen and treat this population of men and improve their overall health in a holistic manner.

Secondly, this review has highlighted several deficiencies in LUTS research methodology. A standardised, reproducible, clinically significant definition of LUTS progression and regression must be agreed upon by international urological and incontinence societies so that studies can be compared and examined by meta-analysis. Future studies need to ensure that treatment status of all men is known and well described in the published work and that important confounders, such as those described in this review, are examined and adjusted for in their analysis.

These recommendations provide a simple guideline to ensure future LUTS research is robust and methodologically strong in order to help guide clinicians provide the best care for men with LUTS.

4.8.3 Final statement

Lower urinary tract symptoms are a burden to the individual and to society. Some systemic illnesses, medication and social determinants have been shown to be associated in cross sectional and longitudinal analysis. A causation relationship is still hypothesised, rather than proven, as is the potential role of intervening on modifiable factors. Research in this area must mimic the natural history of LUTS and become ‘dynamic and progressive.’

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APPENDICES

Appendix 1: International Continence Society LUTS terminology[1]

Group	Symptoms	Description
Storage	Daytime frequency	Complaint by the patient who considers that he/she voids too often by day
Storage	Nocturia	Complaint that the individual must wake at night one or more times to void
Storage	Urgency	Complaint of a sudden compelling desire to pass urine which is difficult to defer
Storage	Urinary incontinence	Complaint of any involuntary leakage of urine
Voiding	Slow stream	Reported by the individual as his or her perception of reduced urine flow, usually compared to previous performance or in comparison to others
Voiding	Splitting or spraying	Splitting or spraying of the stream
Voiding	Intermittency	When the individual describes urine flow which stops and starts, on one or more occasions during micturition
Voiding	Hesitancy	When the individual describes difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine
Voiding	Straining	Muscular effort used to either initiate, maintain or improve the urinary stream
Post micturition	Feeling of incomplete emptying	Self-explanatory term for a feeling experienced by the individual after passing urine
Post micturition	Post-micturition dribble	Involuntary loss of urine immediately after he or she has finished passing urine

Appendix 2: Terminology for voiding abnormalities[2] – comparison of International Continence Society Terms and previously used terminology

Diagnosis based on	International Continence Society term	Previous term	Description
Symptom	Stress urinary Incontinence (SUI)	Stress urinary incontinence	Involuntary leakage of urine on effort, exertion, sneezing or coughing
Symptom	Overactive Bladder	Overactive Bladder	Urgency usually accompanied with frequency and nocturia in the absence of UTI or other obvious pathology
Symptom	Urge Urinary Incontinence (UUI)	Urge Urinary Incontinence	Involuntary leakage of urine associated with urgency
Symptom	Mixed Urinary Incontinence	Mixed Urinary Incontinence	A combination of SUI and UUI
Symptom	Nocturnal enuresis	Nocturnal Enuresis	Involuntary leakage of urine that occurs during sleep
Symptom	Continuous Urinary Incontinence	Continuous Urinary Incontinence	Continuous leakage of urine
UD	Detrusor Overactivity (DO)	Uninhibited bladder contractions	Involuntary detrusor contractions during filling phase
	Idiopathic DO	Detrusor Instability	DO when cause is not known
	Neurogenic DO	Detrusor hyperreflexia	DO in the presence of a neurological condition
UD	Acontractile Detrusor	Atonic Bladder	Absent detrusor contraction when the cause is not known
UD	Neurogenic acontractile Detrusor	Detrusor areflexia	Absent detrusor contraction in presence of a neurological condition
UD	Detrusor Sphincter Dyssynergia	Detrusor Sphincter Dyssynergia	Involuntary contraction of the urethral sphincter during a detrusor contraction
UD	Incompetent Urethral Closure Mechanism	Intrinsic Sphincter Deficiency	Leaking of urine during an increase in abdominal pressure, but in the absence of detrusor contraction

UD	Urodynamic SUI	Genuine SUI	SUI in the absence of detrusor contraction

Definitions: UD – Urodynamic Studies

Appendix 3: International Prostate Symptom Score

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Appendix 4: Search Strategy

PubMed:

(risk factors[mh] OR risk factor*[tiab] OR disease progression[mh] OR worsening[tiab] OR improvement[tiab] OR improving[tiab] OR predictor*[tiab] OR decline[tiab] OR outcome*[tiab] OR prognostic marker*[tiab] OR prognostic characteristic*[mh])

AND

(disease management[mh] OR natural history[mh] OR untreated[tiab] or not treated[tiab])

AND

(Lower urinary tract symptoms[mh] OR prostatic hyperplasia[mh] OR lower urinary tract symptom*[tiab] OR LUTS[tiab] OR urination[tiab] OR prostatism[tiab] OR overactive bladder[tiab] OR overactive urinary bladder[tiab] OR BPH[tiab] or urination disorders[mh])

AND

(Epidemiology[mh] OR longitudinal study[mh] OR observational study[mh] OR cohort studies[mh] OR epidemiolog*[tiab] OR longitudinal[tiab] OR observation*[tiab] OR cohort stud*[tiab] OR longitudinal analys*[all] OR longitudinal design*[all] OR longitudinal evaluation*[all] OR longitudinal research[all] OR longitudinal studies[tw] OR longitudinal study[tw] OR longitudinal survey*[all] OR follow up evaluation*[all] OR followup evaluation*[all] OR followup stud*[all] OR follow up stud*[all] OR followup survey*[all] OR follow up survey* [all] OR prospective analys*[all] OR prospective evaluation*[all] OR prospective studies[tw] OR prospective study[tw] OR prospective survey*[all]) OR (cohort studies[mh] OR cohort analys*[tw] OR cohort design*[all] OR cohort evaluation*[tw] OR cohort research[all] OR cohort stud*[tw] OR cohort survey*[tw] OR concurrent stud*[tw] OR concurrent survey*[tw] OR incidence analys*[tw] OR incidence research*[all] OR incidence stud*[tw] OR incidence survey*[tw] OR longitudinal analys*[tw] OR longitudinal design*[all] OR longitudinal evaluation*[tw] OR longitudinal research[all] OR longitudinal studies[tw] OR longitudinal study[tw] OR longitudinal survey*[tw] OR follow up evaluation*[tw] OR followup evaluation*[tw] OR followup stud*[tw] OR follow up stud*[tw] OR followup survey*[tw] OR follow up survey*[tw] OR prospective analys*[tw] OR prospective design*[all] OR prospective evaluation*[tw] OR prospective studies[tw] OR prospective study[tw] OR prospective survey*[tw] OR retrospective analys*[tw] OR retrospective design*[all] OR retrospective evaluation*[tw] OR retrospective research[all] OR retrospective stud*[tw] OR retrospective survey*[tw])

Embase

'disease association'/exp OR 'risk factor'/syn OR 'general condition improvement'/exp OR 'general condition deterioration'/syn OR ‘disease severity’/syn

AND

‘Clinical course’/exp OR ‘disease evolution’/exp OR ‘watchful waiting’/exp

AND

'lower urinary tract symptom'/syn OR 'overactive bladder'/syn OR ‘prostate hypertrophy’/syn OR ‘prostatism’/syn

AND

(longitudinal NEXT/5 (analys* OR evaluation* OR research OR stud* OR survey*)) OR ((cohort OR concurrent OR incidence OR longitudinal OR followup OR ‘follow up’ OR prospective OR retrospective) NEXT/1 (analys* OR design* OR evaluation* OR research OR stud* OR survey* OR trial*) OR ‘prospective method’ OR ‘retrospective study’/syn)

Web of SCIENCE

“risk factors” OR “risk factor*” OR “disease progression” OR worsening OR improvement OR improving OR predictor* OR decline OR outcome* OR “prognostic marker*” OR “prognostic characteristic*”

AND

“disease management” OR “natural history” OR untreated OR “not treated”

AND

“Lower urinary tract symptoms” OR “prostatic hyperplasia” OR “lower urinary tract symptom*” OR LUTS OR urination OR prostatism OR “overactive bladder” OR “overactive urinary bladder” OR” BPH” OR “urination disorders”

AND

“Epidemiology” OR “longitudinal study” OR “observational study” OR “cohort studies” OR epidemiolog* OR “longitudinal” OR observation* OR “cohort stud*” OR “longitudinal studies” OR “longitudinal analys*” OR “longitudinal design*” OR “longitudinal evaluation*” OR “longitudinal research” OR “longitudinal studies” OR “longitudinal study” OR “longitudinal survey*” OR “follow up evaluation*” OR “followup evaluation*” OR “followup stud*” OR “follow up stud*” OR “followup survey*” OR “follow up survey*” OR “prospective analys*” OR “prospective evaluation*” OR “prospective studies” OR “prospective study” OR “prospective survey*” OR “cohort studies” OR “cohort analys*” OR “cohort design*” OR “cohort evaluation*” OR “cohort research” OR “cohort stud*” OR “cohort survey*” OR “concurrent stud*” OR “concurrent survey*” OR “incidence analys*” OR “incidence research*” OR “incidence stud*” OR “incidence survey*” OR “longitudinal analys*” OR “longitudinal design*” OR “longitudinal evaluation*” OR “longitudinal research” OR “longitudinal studies” OR “longitudinal study” OR “longitudinal survey*” OR “follow up evaluation*” OR “followup evaluation*” OR “followup stud*” OR “follow up stud*” OR “followup survey*” OR “follow up survey*” OR “prospective analys*” OR “prospective design*” OR “prospective evaluation*” OR “prospective studies” OR “prospective study” OR “prospective survey*” OR “retrospective analys*” OR “retrospective design*” OR “retrospective evaluation*” OR “retrospective research” OR “retrospective stud*” OR “retrospective survey*”

Scopus: (advanced search. ABS-TITLE-KEY […])

“risk factors” OR “risk factor*” OR “disease progression” OR worsening OR improvement OR improving OR predictor* OR decline OR outcome* OR “prognostic marker*” OR “prognostic characteristic*”

AND

“disease management” OR “natural history” OR untreated OR “not treated”

AND

“Lower urinary tract symptoms” OR “prostatic hyperplasia” OR “lower urinary tract symptom*” OR LUTS OR urination OR prostatism OR “overactive bladder” OR “overactive urinary bladder” OR” BPH” OR “urination disorders”

AND

“Epidemiology” OR “longitudinal study” OR “observational study” OR “cohort studies” OR “epidemiolog*” OR “longitudinal” OR “observation*” OR “cohort stud*” OR “longitudinal studies” OR “longitudinal analys*” OR “longitudinal design*” OR “longitudinal evaluation*” OR “longitudinal research” OR “longitudinal studies” OR “longitudinal study” OR “longitudinal survey*” OR “follow up evaluation*” OR “followup evaluation*” OR “followup stud*” OR “followup stud*” OR “followup survey*” OR “follow up survey*” OR “prospective analys*” OR “prospective evaluation*” OR “prospective studies” OR “prospective study” OR “prospective survey*” OR “cohort studies” OR “cohort analys*” OR “cohort design*” OR “cohort evaluation*” OR “cohort research” OR “cohort stud*” OR “cohort survey*” OR “concurrent stud*” OR “concurrent survey*” OR “incidence analys*” OR “incidence research*” OR “incidence stud*” OR “incidence survey*” OR “longitudinal analys*” OR “longitudinal design*” OR “longitudinal

evaluation*” OR “longitudinal research” OR “longitudinal studies” OR “longitudinal study” OR “longitudinal survey*” OR “follow up evaluation*” OR “followup evaluation*” OR “followup stud*” OR “follow up stud*” OR “followup survey*” OR “follow up survey*” OR “prospective analys*” OR “prospective design*” OR “prospective evaluation*” OR “prospective studies” OR “prospective study” OR “prospective survey*” OR “retrospective analys*” OR “retrospective design*” OR “retrospective evaluation*” OR “retrospective research” OR “retrospective stud*” OR “retrospective survey*”

Appendix 5: Extract from Guidelines for Assessing Quality in Prognostic Studies on the Basis of a Framework of Potential Biases

Potential Bias	Items to be considered for assessment of potential opportunity for bias
Study Participation The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results	- The source population or population of interest is adequately described for key characteristics. -The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g., referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location). - Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description). - There is adequate participation in the study by eligible individuals. - The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.
Study Attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias.	- Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate. - Attempts to collect information on participants who dropped out of the study are described. - Reasons for loss to follow-up are provided. - Participants lost to follow-up are adequately described for key characteristics. - There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic Factor Measurement The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias.	- A clear definition or description of the prognostic factor measured is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement). - Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). - Adequate proportion of the study sample has complete data for prognostic factors. - The method and setting of measurement are the same for all study participants. - Appropriate methods are used if imputation is used for missing prognostic factor data.
Outcome Measurement The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.	- A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct. - The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test). - The method and setting of measurement are the same for all study participants.

Confounding Measurement and Response Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	- All important confounders, including treatments (key variables in conceptual model), are measured. - Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposure). - Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). - The method and setting of confounding measurement are the same for all study participants. - Appropriate methods are used if imputation is used for missing confounder data. Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups). - Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Analysis The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results.	- There is sufficient presentation of data to assess the adequacy of the analysis. - The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model. - The selected model is adequate for the design of the study. - There is no selective reporting of results.

Appendix 6: Characteristics of included studies

Study (author, year)	Description	Study type	Age	Number of participants	Country	Population source	Follow-up duration, year (mean)	Method of data collection
Burke *et al.*, 2006[3]	Examines the association between anthropometric measures with presence and progression of benign prostatic hyperplasia	Prospective Cohort	40-79	2064	USA	Age stratified, random sample of Caucasian males in Olmsted County, USA	12	OCS
Curto *et al.*, 2014[4]	Examines the association between long-term dietary vitamin C intake and recent use of vitamin C supplements with the progression and severity of LUTS	Prospective Cohort	30-79	1100*	USA	Random stratified cluster sample design from Boston, USA	5	BACH Survey
Fu *et al.*, 2016[5]	Investigates whether metabolic syndrome may be associated with the clinical progression of BPH	Prospective Cohort	45-78	525	China	Single institution	3	Baseline questionnaire with annual repeat assessment
Holton *et al.*, 2016[6]	Examines the association of high dietary anti-oxidants and probability of LUTS progression	Prospective Cohort	65-100	1670	USA	Non-randomised volunteers	6.9	MrOS
Marshall *et al.*, 2014[7]	Examines lifestyle and health factors associated with progressing and remitting trajectories of untreated LUTS among elderly men	Prospective Cohort	65-100	1740	USA	Non-randomised volunteers	6.9	MrOS
Parsons *et al.*, 2011[8]	Examines the association between adiposity and physical activity with LUTS incidence*	Prospective Cohort	65-100	1695	USA	Non-randomised volunteers	4.6 years	MrOS
St Sauver	Examined whether statin use is	population-	40-79	2447	USA	Age stratified,	13.8 years[+]	OCS

et al., 2011[9]	associated with a decreased risk of developing LUTS	based cohort study				random sample of Caucasian males in Olmsted County, USA		
St Sauver *et al.*, 2011[10]	Examines whether rates of change in serum hormones were associated with rates of change in urological outcomes	population-based cohort study	40-79	648	USA	Age stratified, random sample of Caucasian males in Olmsted County, USA	17	OCS
St Sauver *et al.*, 2009[11]	Examines whether men with elevated CRP levels were more likely to experiences rapid increases in LUTS	population-based cohort study	40-79	442	USA	Age stratified, random sample of Caucasian males in Olmsted County, USA	9.67	OCS
St Sauver *et al.*, 2006[12]	Examines whether NSAID users were at lower risk than non-NSAID users in developing BPH/LUTS.	population-based cohort study	40-79	2447	USA	Age stratified, random sample of Caucasian males in Olmsted County, USA	12	OCS
Temml *et al.*, 2003[13]	Assesses the natural history of LUTS in a cohort of previously untreated men	Prospective Cohort	40-84	456	Austria	Men attending voluntary health examination	5 years	N/A
Wong *et al.*, 2010[14]	Evaluates the dietary, lifestyle and medical risk factors of LUTS	Prospective Cohort	>65 years	871	Hong Kong	Non-randomised, volunteers	4 years	N/A

BACH Survey = Boston Area Community Health Survey: baseline interview with follow-up in-person interview roughly 5 years later. MrOS = Osteoporotic Fractures in Men Study: baseline clinic visit with follow-up mailed questionnaire every 2 years. OCS = in-home interview with verbal questions with examinations and questionnaire repeated biennially.
*Number represents total number of men included in this study. The study included men who had been/were treated with LUTS related medication, however a subset analysis was performed on men who had never been treated and subsequently the subject number will be smaller. Results were similar and were subsequently not published. The data on untreated men was no longer available when requested from the authors.
[+]median length of follow-up

Appendix 7: Excluded articles after full text review

Albertsen PC. Socioeconomic factors, urological epidemiology and practice patterns. Journal of Urology. 2005;173(5):1706-7.[15]

Exclusion reason: incorrect study type (editorial commentary)

Al-Hayek S, Thomas A, Abrams P. Natural history of detrusor contractility: Minimum ten-year urodynamic follow-up in Men with Bladder outlet obstruction and those with detrusor underactivity. Scandinavian Journal of Urology and Nephrology. 2004;38(215):101-8.[16]

Exclusion reason: progression/regression not well defined

Arrighi HM, Metter EJ, Guess HA, Fozzard JL. Natural history of benign prostatichyperplasia and risk of prostatectomy. The Baltimore Longitudinal Study of Aging. Urology. 1991;38(1 SUPPL.):4-8[17]

Exclusion reason: incorrect study population (unclear treatment status of enrolled men)

Barry MJ, Cockett ATK, Holtgrewe HL, McConnell JD, Sihelnik SA, Winfield HN. Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. Journal of Urology. 1993 Aug;150(2):351-8.[18]

Exclusion reason: not relevant (assessed physiological findings/investigations)

Blanker MH, Driessen LFC, Ruud Bosch JLH, Bohnen AM, Thomas S, Prins A, et al. Health status and its correlates among Dutch community-dwelling older men with and without lower urogenital tract dysfunction. European Urology. 2002;41(6):602-7.[19]

Exclusion reason: incorrect study type (cross sectional study design)

Bogner HR, O'Donnell AJ, de Vries HF, Northington GM, Joo JH. The temporal relationship between anxiety disorders and urinary incontinence among community-dwelling adults. Journal of Anxiety Disorders. 2011;25(2):203-8[20]

Exclusion reason: incorrect outcome measure (presence of urinary incontinence only and development of anxiety disoder)

Burke JP, Jacobson DJ, McGree ME, Nehra A, Roberts RO, Girman CJ, et al. Diabetes and Sexual Dysfunction: Results From the Olmsted County Study of Urinary Symptoms and Health Status Among Men. Journal of Urology. 2007;177(4):1438-42.[21]

Exclusion reason: Incorrect outcome measure (relationship between diabetes and sexual dysfunction, not LUTS)

Burke JP, Jacobson DJ, McGree ME, Roberts RO, Girman CJ, Lieber MM, et al. Diabetes and benign prostatic hyperplasia progression in Olmsted County, Minnesota. Urology. 2006;67(1):22-5.[22]

Exclusion reason: incorrect outcome measure (data was age stratified but did not undergo multivariate analysis)

Choo MS, Han JH, Shin TY, Ko K, Lee WK, Cho ST, et al. Alcohol, smoking, physical activity, protein, and lower urinary tract symptoms: Prospective longitudinal cohort. International Neurourology Journal. 2015;19(3):197-206.[23]

Exclusion reason: incorrect study population (treatment status of men not clear)

Chou PS, Chang WC, Chou WP, Liu ME, Lai CL, Liu CK, et al. Increased risk of benign prostate hyperplasia in sleep apnea patients: A nationwide population-based study. PLoS ONE. 2014;9(3).[24]

Exclusion reason: incorrect study duration (12-week duration)

Chung RY, Leung JCS, Chan DCC, Woo J, Wong CKM, Wong SYS. Lower Urinary Tract Symptoms (LUTS) as a Risk Factor for Depressive Symptoms in Elderly Men: Results from a Large Prospective Study in Southern Chinese Men. PLoS ONE. 2013;8(9).[25]

Exclusion reason: incorrect outcome measure (measuring LUTS affect on depression)

Chung WS, Nehra A, Jacobson DJ, Roberts RO, Rhodes T, Girman CJ, et al. Lower urinary tract symptoms and sexual dysfunction in community-dwelling men. Mayo Clinic Proceedings. 2004;79(6):745-9.[26]

Exclusion reason: incorrect study design (cross sectional study design)

Chyou PH, Nomura AM, Stemmermann GN, Hankin JH. A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. Prostate. 1993;22(3):253-64.[27]

Exclusion reason: incorrect outcome measure (no validate LUTS tool at baseline)

Cinar A, Hall SA, Link CL, Kaplan SA, Kopp ZS, Roehrborn CG, et al.. Cluster analysis and lower urinary tract symptoms in men: findings from the Boston Area Comunity Health Survey. BJU Int. 2008 May;101(10):1247-56.[28]

Exclusion reason: progression/regression not well defined (cluster analysis of risk factors)

Clemens JQ, Brown SO, Kozloff L, Calhoun EA. Predictors of symptom severity in patients with chronic prostatitis and interstitial cystitis. Journal of Urology. 2006;175(3):963-7[29]

Exclusion reason: incorrect study design (cross-sectional study design)

Crawford ED. Management of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: The central role of the patient risk profile. BJU International, Supplement. 2005;95(4):1-5.[30]

Exclusion reason: incorrect study design (review article)

Crawford ED, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, et al. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. Journal of Urology. 2006;175(4):1422-6.[31]

Exclusion reason: incorrect outcome measure (PV, Q_{max}, PVR in placebo arm of RCT)

Dal Maso L, Zucchetto A, Tavani A, Montella M, Ramazzotti V, Polesel J, et al. Lifetime occupational and recreational physical activity and risk of benign prostatic hyperplasia. International Journal of Cancer. 2006;118(10):2632-5.[32]

Exclusion reason: progression/regression not well defined (no symptom score at baseline)

Debruyne FMJ, Behre HM, Roehrborn CG, Maggi M, Wu FCW, Schröder FH, et al. Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men. BJU International. [Article]. 2017;119(2):216-24.[33]

Exclusion reason: incorrect study population (treatment status of men not clear)

de Nunzio C, Franco G, Rocchegiani A, Iori F, Leonardo C, Laurenti C. The evolution of detrusor overactivity after watchful waiting, medical therapy and surgery in patients with bladder outlet obstruction. Journal of Urology. 2003 Feb;169(2):535-9.[34]

Exclusion reason: incorrect outcome measure (urodynamic studies)

Djavan B, Fong YK, Harik M, Milani S, Reissigl A, Chaudry A, et al. Longitudinal study of men with mild symptoms of bladder outlet obstruction treated with watchful waiting for four years. Urology. 2004 Dec;64(6):1144-8[35]

Exclusion reason: incorrect outcome measure (investigative parameters)

Djavan B, Waldert M, Ghawidel C, Marberger M. Benign prostatic hyperplasia progression and its impact on treatment. Current Opinion in Urology. 2004 Jan;14(1):45-50.[36]

Exclusion reason: incorrect study design (review article)

Emberton M. The Hallmarks of BPH Progression and Risk Factors. European Urology, Supplement. 2003;2(8):2-7.[37]

Exclusion reason: incorrect study design (review article)

Fong YK, Milani S, Djavan B. Natural history and clinical predictors of clinical progression in benign prostatic hyperplasia. Current Opinion in Urology. 2005 Jan;15(1):35-8.[38]

Exclusion reason: incorrect study design (review article)

Fowke JH, Murff HJ, Signorello LB, Lund L, Blot WJ. Race and Socioeconomic Status are Independently Associated With Benign Prostatic Hyperplasia. Journal of Urology. 2008;180(5):2091-6[39]

Exclusion reason: incorrect study design (cross sectional study design)

Fowke JH, Phillips S, Koyama T, Byerly S, Concepcion R, Motley SS, et al. Association between physical activity, lower urinary tract symptoms (LUTS) and prostate volume. BJU International. 2013;111(1):122-8.[40]

Exclusion reason: incorrect study population (unclear LUTS severity at baseline)

Franco G, De Nunzio C, Minardi V, Rocchegiani A, Iori F, Leonardo C, et al. Patients with bladder outlet obstruction who refuse treatment show no clinical and urodynamic change after long-term follow-up. Archivio Italiano di Urologia e Andrologia. 2004;76(1):6-10[41]

Exclusion reason: not published in English

Fukuta F, Masumori N, Mori M, Tsukamoto T. Incidence and risk of treatment for benign prostatic hyperplasia in Japanese men: A 15-year longitudinal community-based study. International Journal of Urology. 2013;20(1):100-6.[42]

Exclusion reason: incorrect outcome measure (investigative parameters only)

Gann PH, Hennekens CH, Longcope C, Verhoek-Oftedahl W, Grodstein F, Stampfer MJ. A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia. Prostate. 1995 Jan;26(1):40-9[43]

Exclusion reason: progression/regression not well defined (unclear if men had LUTS at

baseline)

Ganpule AP, Desai MR, Desai MM, Wani KD, Bapat SD. Natural history of lower urinary tract symptoms: Preliminary report from a community-based Indian study. BJU International. 2004;94(3):332-4.[44]

Exclusion reason: incorrect study type (cross sectional study design)

Garraway WM, Armstrong C, Auld S, King D, Simpson RJ. Follow-up of a cohort of men with untreated benign prostatic hyperplasia. European Urology. 1993;24(3):313-8.[45]

Exclusion reason: progression/regression not well defined (treatment based on bothersome symptoms)

Girman CJ, Jacobsen SJ, Guess HA, Oesterling JE, Chute CG, Panser LA, et al. Natural History of Prostatism: Relationship Among Symptoms, Prostate Volume and Peak Urinary Flow Rate. The Journal of Urology. 1995;153(5):1510-5.[46]

Exclusion reason: incorrect outcome measure (investigative parameters)

Hakkinen J, Koskimaki J, Huhtala H, Tammela TLJ, Hakama M, Auvinen A. Changes in prevalence of urinary symptoms in Finnish men - A population-based 5-year follow-up study. Scandinavian Journal of Urology and Nephrology. 2004 Nov;38(5):378-84.[47]

Exclusion reason: incorrect study population (unclear treatment status of men recruited)

Hall SA, Chiu GR, Kaufman DW, Wittert GA, Link CL, McKinlay JB. Commonly used antihypertensives and lower urinary tract symptoms: results from the Boston Area Community Health (BACH) Survey. BJU Int. 2012 Jun;109(11):1676-84[48]

Exclusion reason: incorrect study design (cross-sectional study design)

Hirayama A, Torimoto K, Mastusita C, Okamoto N, Morikawa M, Tanaka N, et al. Evaluation of factors influencing the natural history of nocturia in elderly subjects: Results of the Fujiwara-kyo study. Journal of Urology. 2013;189(3):980-6[49]

Exclusion reason: incorrect Study population (men were likely treated)

Hoke G, Baker W, Barnswell C, Bennett J, Davis R, Mason T, et al. Racial differences in pathogenetic mechanisms, prevalence, and progression of benign prostatic hyperplasia. Urology. 2006;68(5):924-30.[50]

Exclusion reason: incorrect study design (review article)

Howard DL, Taylor YJ, Louie ER. Differences in lower urinary tract symptoms, treatment and mortality among african-american and white elderly men. Journal of the National Medical Association. 2008;100(10):1146-52[51]

Exclusion reason: incorrect population (exclusion criteria not explicitly state)

Hunter DJW, McKee M, Black NA, Sanderson CFB. Health status and quality of life of british men with lower urinary tract symptoms: results from the sf-36. Urology. 1995;45(6):962-71.[52]

Exclusion reason: incorrect population (likely previous treatment)

Irwin DE, Milsom I, Chancellor MB, Kopp Z, Guan Z. Dynamic progression of overactive bladder and urinary incontinence symptoms: A systematic review. European Urology. 2010;58(4):532-43[53]

Exclusion reason: incorrect study design (systematic review)

Jacobsen SJ, Girman CJ, Guess HA, Panser LA, Chute CG, Oesterling JE, et al. Natural history of prostatism: Factors associated with discordance between frequency and bother of urinary symptoms. Urology. 1993;42(6):663-71[54]

Exclusion reason: incorrect study design (cross-sectional study design)

Jacobsen SJ, Jacobson DJ, Girman CJ, Roberts RO, Rhodes T, Guess HA, et al. Natural history of prostatism: Risk factors for acute urinary retention. Journal of Urology. 1997;158(2):481-7[55]

Exclusion reason: incorrect outcome measures (investigative parameters)

Johnson TV, Abbasi A, Ehrlich SS, Kleris RS, Chirumamilla SL, Schoenberg ED, et al. Major depression drives severity of American urological association symptom index. Urology. 2010;76(6):1317-20.[56]

Exclusion reason: incorrect study design (cross-sectional study design)

Jung JH, Jae SU, Kam SC, Hyun JS. Correlation between Lower Urinary Tract Symptoms (LUTS) and sexual function in benign prostatic hyperplasia: impact of treatment of LUTS on sexual function. J Sex Med. 2009 Aug;6(8):2299-304[57]

Exclusion reason: incorrect study duration (three months)

Kaplan SA. Serum sex hormones and the 20-year risk of lower urinary tract symptoms in community-dwelling older men. Journal of Urology. 2011;185(1):225-6[58]

Exclusion reason: progression/regression not well defined (no symptom score at baseline)

Kim S, Jeong JY, Choi YJ, Kim DH, Lee WK, Lee SH, et al. Association between lower urinary tract symptoms and vascular risk factors in aging men: The Hallym Aging Study. Korean Journal of Urology. 2010;51(7):477-82[59]

Exclusion reason: incorrect study design (cross sectional study design)

Kim JH, Shim SR, Lee WJ, Kim HJ, Kwon SS, Bae JH. Sociodemographic and lifestyle factors affecting the self-perception period of lower urinary tract symptoms of international prostate symptom score items. International Journal of Clinical Practice. 2012;66(12):1216-23[60]

Exclusion reason: incorrect study design (cross-sectional study design)

Kok ET, Bohnen AM, Groeneveld F, Busschbach JJV, Blanker MH, Bosch J. Changes in disease specific and generic quality of life related to changes in lower urinary tract symptoms: The Krimpen Study. Journal of Urology. 2005 Sep;174(3):1055-8[61]

Exclusion reason: not relevent (LUTS impact on quality of life)

Kosilov KV, Loparev SA, Ivanovskaya MA, Kosilova LV. Decrease of risk of developing symptoms of OAB in elderly men and women treated with loop diuretic for hypertensive disease using solifenacin. Current Aging Science. 2014;7(3):229-34.[62]

Exclusion reason: incorrect study duration (less than one year)

Kozminski MA, Wei JT, Nelson J, Kent DM. Baseline characteristics predict risk of progression and response to combined medical therapy for benign prostatic hyperplasia (BPH). BJU International. 2015;115(2):308-16[63]

Exclusion reason: incorrect study type (placebo arm of RCT)

Krambeck AE, Jacobson DJ, McGree ME, Lightner DJ, Lieber MM, Jacobsen SJ, et al. Effectiveness of medical and surgical therapies for lower urinary tract symptoms in the community setting. BJU Int. 2012 Nov;110(9):1332-7[64]

Exclusion reason: incorrect study design (intervention study)

Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Weiss N, Goodman P, et al. Race/Ethnicity, Obesity, Health Related Behaviors and the Risk of Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial. Journal of Urology. 2007;177(4):1395-400[65]

Exclusion reason: incorrect study design (placebo arm of RCT)

Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Goodman P, Penson DF, et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: Results from the Prostate Cancer Prevention Trial. American Journal of Epidemiology. 2008;167(8):925-34[66]

Exclusion reason: incorrect study (placebo arm of RCT)

Kwon H, Kang HC, Lee JH. Relationship between predictors of the risk of clinical progression of benign prostatic hyperplasia and metabolic syndrome in men with moderate to severe lower urinary tract symptoms. Urology. 2013;81(6):1325-9[67]

Exclusion reason: incorrect outcome measure (investigative parameters)

Lee AJ, Russell E, Garraway WM, Prescott RJ. Three-year follow-up of a community-based cohort of men with untreated benign prostatic hyperplasia. European Urology. 1996;30(1):11-7[68]

Exclusion reason: not relevant (impact of LUTS on bother)

Li MK, Garcia L, Patron N, Moh LC, Sundram M, Leungwattanakij S, et al. An Asian multinational prospective observational registry of patients with benign prostatic hyperplasia, with a focus on comorbidities, lower urinary tract symptoms and sexual function. BJU International. 2008;101(2):197-202.[69]

Exclusion reason: incorrect study duration (three to six months)

Loh AHP, Kok KN, Foo CN. Presentation and progression of benign prostatic hyperplasia: A Singapore experience profiling ethnic differences in a multiracial study cohort. Annals of the Academy of Medicine Singapore. 2009;38(5):451-6[70]

Exclusion reason: incorrect study population (included treated men)

Kathrins M, Doersch K, Nimeh T, Canto A, Niederberger C, Seftel A. The Relationship Between Testosterone-Replacement Therapy and Lower Urinary Tract Symptoms: A Systematic Review. Urology. 2016 Feb;88:22-32[71]

Exclusion reason: incorrect study design (systematic review)

Malmsten UGH, Molander U, Peeker R, Irwin DE, Milsom I. Urinary Incontinence, Overactive Bladder, and Other Lower Urinary Tract Symptoms: A Longitudinal Population-Based Survey in Men Aged 45-103 Years. Eur Urol. 2010;58(1):149-56.[72]

Exclusion reason: incorrect study design (longterm prevelence study)

Martin S, Lange K, Haren MT, Taylor AW, Wittert G. Risk factors for progression or

improvement of lower urinary tract symptoms in a prospective cohort of men. J Urol. 2014;191(1):130-7.[73]

Exclusion reason: incorrect study population (included treated men)

Martin S, Vincent A, Adams R, Taylor A, O'Louglin P, Wittert G. Are luts an independent indicator of cardiovascular disease (CVD) development? a cross-sectional and longitudinal analysis in middleaged to elderly men. Neurourology and Urodynamics. 2016;35:S72-S3[74]

Exclusion reason: not relevent (risk of developing cardiovascular disease with a history of LUTS)

Maserejian NN, Chen S, Chiu GR, Araujo AB, Kupelian V, Hall SA, et al. Treatment status and progression or regression of lower urinary tract symptoms in a general adult population sample. Journal of Urology. 2014;191(1):107-13.[75]

Exclusion reason: incorrect outcome measure (examined progression rates, rather than risk factors associated with it)

Masumori N, Tsukamoto T, Rhodes T, Girman CJ. Natural history of lower urinary tract symptoms in men - Result of a longitudinal community-based study in Japan. Urology. 2003;61(5):956-60.[76]

Exclusion reason: incorrect outcome measure (investigative parameters)

Meigs JB, Barry MJ, Giovannucci E, Rimm EB, Stampfer MJ, Kawachi I. Incidence rates and risk factors for acute urinary retention: The health professionals followup study. Journal of Urology. 1999;162(2):376-82.[77]

Exclusion reason: incorrect study population (treatment status of men was unclear)

Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. Journal of Clinical Epidemiology. 2001;54(9):935-44[78]

Exclusion reason: progression/regression not well defined (patient reported diagnosis of BPH)

Mondul AM, Rimm EB, Giovannucci E, Glasser DB, Platz EA. A Prospective Study of Lower Urinary Tract Symptoms and Erectile Dysfunction. Journal of Urology. 2008;179(6):2321-6[79]

Exclusion reason: incorrect outcome measure (examined LUTS and new erectile dysfunction)

Mondul AM, Giovannucci E, Platz EA. A prospective study of statin drug use and lower urinary tract symptoms in older men. American Journal of Epidemiology. 2013;178(5):797-803.[80]

Exclusion reason: incorrect study population (men may have been treated – medication was not assessed until six years into follow-up)

Mondul AM, Giovannucci E, Platz EA. A prospective study of obesity, and the incidence and progression of lower urinary tract symptoms. Journal of Urology. 2014;191(3):715-21.[81]

Exclusion reason: incorrect study population (men may have been treated – medication was not assessed until six years into follow-up)

Nasir AR, Zehri AA, Abbas F, Ather MH. The correlation between international prostate symptoms score and sexual health inventory in men with lower urinary tract symptoms. International Urology and Nephrology. 2011;43(3):625-9[82]

Exclusion reason: incorrect study design (cross sectional design study)

Ng CF, Wong A, Li ML, Chan SY, Mak SK, Wong WS. The prevalence of cardiovascular risk factors in male patients who have lower urinary tract symptoms. Hong Kong Medical Journal. 2007;13(6):421-6.[83]

Exclusion reason: incorrect study type (retrospective review)

Nuotio M, Luukkaala T, Tammela TLJ, Jylhä M. Six-year follow-up and predictors of urgency-associated urinary incontinence and bowel symptoms among the oldest old: A population-based study. Archives of Gerontology and Geriatrics. 2009;49(2):e85-e90.[84]

Exclusion reason: incorrect population (institutionalised men)

Oh DG, Cho DS, Yun IS, Lee KB, Choi JB, Lee JH. The difference of lower urinary tract symptoms between sympathetic hyperactive and hypoactive men. International Neurourology Journal. 2013;17(1):30-3[85]

Exclusion reason: incorrect study design (cross-sectional study design)

Paick JS, Yang JH, Kim SW, Ku JH. Are age, anthropometry and components of metabolic syndrome-risk factors interrelated with lower urinary tract symptoms in patients with erectile dysfunction? A prospective study. Asian Journal of Andrology. 2007;9(2):213-20[86]

Exclusion reason: incorrect study design (cross-sectional study design)

Park YW, Kim SB, Kwon H, Kang HC, Cho K, Lee KI, et al. The relationship between lower urinary tract symptoms/benign prostatic hyperplasia and the number of components of metabolic syndrome. Urology. 2013;82(3):674-9.[87]

Exclusion reason: incorrect study design (cross-sectional study design)

Park HK, Paick SH, Kim HG, Lho YS, Byun SS, Lee SB, et al. Effect of Depression on the Risk and Severity of Lower Urinary Tract Symptoms in Community-Dwelling Elderly Korean Men. LUTS: Lower Urinary Tract Symptoms. 2012;4(2):63-7[88]

Exclusion reason: incorrect study design (cross-sectional study design)

Parsons JK, Wilt TJ, Wang PY, Barrett-Connor E, Bauer DC, Marshall LM. Progression of lower urinary tract symptoms in older men: a community based study. J Urol. 2010 May;183(5):1915-20.[89]

Exclusion reason: incorrect outcome measure (examined progression rates but not risk factors associated with it)

Pinto F, Racioppi M, Sacco E, Totaro A, Brescia A, Volpe A, et al. Progression risk factors and subsequent medical management of symptomatic benign prostatic hyperplasia. Archivio Italiano di Urologia e Andrologia. 2009;81(1):1-8[90]

Exclusion reason: incorrect study design (review article)

Platz EA, Joshu CE, Mondul AM, Peskoe SB, Willett WC, Giovannucci E. Incidence and progression of lower urinary tract symptoms in a large prospective cohort of United States men. Journal of Urology. 2012;188(2):496-501.[91]

Exclusion reason: incorrect study design (asymptomatic men included)

Platz EA, Kawachi I, Rimm EB, Willett WC, Giovannucci E. Race, ethnicity and benign prostatic

hyperplasia in the health professionals follow-up study. Journal of Urology. 2000;163(2):490-5.[92]

Exclusion reason: incorrect study population (treatment status of men recruited was unclear)

Platz EA, Rimm EB, Kawachi I, Colditz GA, Stampfer MJ, Willett WC, et al. Alcohol consumption, cigarette smoking, and risk of benign prostatic hyperplasia. American Journal of Epidemiology. 1999;149(2):106-15.[93]

Exclusion reason: incorrect outcome measure (measured incident LUTS, not progression)

Ponholzer A, Temml C, Wehrberger C, Marszalek M, Madersbacher S. The Association Between Vascular Risk Factors and Lower Urinary Tract Symptoms in Both Sexes. European Urology. 2006;50(3):581-6.[94]

Exclusion reason: incorrect study design (cross-sectional study design)

Ponholzer A, Temml C, Obermayr RP, Rauchenwald M, Madersbacher S. The association between lower urinary tract symptoms and renal function in men: A cross-sectional and 5-year longitudinal analysis. Journal of Urology. 2006;175(4):1398-402[95]

Exclusion reason: not relevent (assessed LUTS impact on renal function)

Prajsner A, Chudek J, Szybalska A, Piotrowicz K, Zejda J, Więcek A. Socioeconomic profile of elderly Polish men treated for benign prostate hyperplasia: Results of the population-based PolSenior study. European Geriatric Medicine. 2015;6(1):53-7.[96]

Exclusion reason: Incorrect study design (cross-sectional study design)

Prezioso D, Catuogno C, Galassi P, D'Andrea G, Castelloe G, Pirritano D. Life-style in patients with LUTS suggestive of BPH. European Urology. 2001;40(SUPPL. 1):9-12[97]

Exclusion reason: incorrect study design (cross-sectional study design)

Rhodes T, Jacobson DJ, McGree ME, St Sauver JL, Girman CJ, Lieber MM, et al. Longitudinal Changes of Benign Prostate-specific Antigen and -2 Proprostate-specific Antigen in Seven Years in a Community-based Sample of Men. Urology. 2012 Mar;79(3):655-61[98]

Exclusion reason: incorrect outcome measure (PSA)

Rhodes T, Jacobson DJ, McGree ME, Sauver JLS, Sarma AV, Girman CJ, et al. Benign Prostate Specific Antigen Distribution and Associations With Urological Outcomes in Community Dwelling Black and White Men. Journal of Urology. 2012 Jan;187(1):87-91[99]

Exclusion reason: incorrect outcome measure (PSA)

Roberts RO, Jacobsen SJ, Jacobson DJ, Rhodes T, Girman CJ, Guess HA, et al. Natural history of prostatism in a community based cohort of men: Longitudinal decline in peak urinary flow rates is greater than expected. Journal of Urology. 1998 May;159(5):111[100]

Exclusion reason: incorrect outcome measure (investigative parameters)

Roberts RO, Jacobsen SJ, Rhodes T, Girman CJ, Guess HA, Lieber MM. Natural history of prostatism: Impaired health states in men with lower urinary tract symptoms. Journal of Urology. 1997;157(5):1711-7[101]

Exclusion reason: incorrect study design (cross-sectional study design)

Roberts RO, Jacobsen SJ, Jacobson DJ, Rhodes T, Girman CJ, Lieber MM. Longitudinal

changes in peak urinary flow rates in a community based cohort. Journal of Urology. 2000;163(1):107-13[102]

Exclusion reason: incorrect outcome measure (investigative parameters)

Roehrborn CG. BPH progression: Concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. BJU International, Supplement. 2008;101(SUPPL. 3):17-21.[103]

Exclusion reason: incorrect study design (review article)

Roehrborn CG, Bruskewitz R, Nickel GC, Glickman S, Cox C, Anderson R, et al. Urinary retention in patients with BPH treated with finasteride or placebo over 4 years - Characterization of patients and ultimate outcomes. European Urology. 2000 May;37(5):528-36[104]

Exclusion reason: incorrect study type (RCT)

Roehrborn CG, Dolte KS, Ross KS, Girman CJ. Incidence and risk reduction of long-term outcomes: A comparison of benign prostatic hyperplasia with several other disease areas. Urology. 2000;56(1):9-18.[105]

Exclusion reason: incorrect study design (review article)

Roehrborn CG, Kaminetsky JC, Auerbach SM, Montelongo RM, Elion-Mboussa A, Viktrup L. Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU International. 2010;105(4):502-7[106]

Exclusion reason: incorrect study duration (six weeks)

Roehrborn CG, McConnell JD, Saltzman B, Bergner D, Gray T, Narayan P, et al. Storage (irritative) and voiding (obstructive) symptoms as predictors of benign prostatic hyperplasia progression and related outcomes. European Urology. 2002;42(1):1-6.[107]

Exclusion reason: incorrect study type (placebo arm of RCT)

Roehrborn CG, Malice M, Cook TJ, Girman CJ. Clinical predictors of spontaneous acute urinary retention in men with LUTS and clinical BPH: a comprehensive analysis of the pooled placebo groups of several large clinical trials. Urology. 2001 Aug;58(2):210-6.[108]

Exclusion reason: incorrect study design (placebo arms from multiple RCTs)

Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. Urology. 1999;53(3):581-9[109]

Exclusion reason: incorrect outcome measure (assessed PSA)

Roehrborn CG, Oesterling JE, Auerbach S, Kaplan SA, Lloyd LK, Milam DE, et al. The Hytrin Community Assessment Trial study: a one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator Group. Urology. 1996 Feb;47(2):159-68.[110]

Exclusion reason: incorrect study type (placebo arm of RCT)

Rohrmann S, Giovannucci E, Willett WC, Platz EA. Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in US men. The American journal of clinical nutrition. 2007 Feb;85(2):523-9[111]

Exclusion reason: incorrect study population (men may have been treated – medications not assessed until 6 years into follow up)

Rosen RC, Yang M, Hall SA, Roehrborn CG. Progression and remission of urologic symptoms in the community: Results of a longitudinal cluster analysis approach. Urology. 2014;83(5):1041-50.[112]

Exclusion reason: incorrect study population (unclear treatment status)

Sarma AV, Jacobson DJ, Sauver JLS, Lieber MM, Girman CJ, Nehra A, et al. Smoking and Acute Urinary Retention: The Olmsted County Study of Urinary Symptoms and Health Status Among Men. Prostate. 2009 May;69(7):699-705.[113]

Exclusion reason: incorrect study population (unclear treatment status)

Sarma AV, McLaughlin JC, Jacobsen SJ, Logie J, Dolin P, Dunn RL, et al. Longitudinal changes in lower urinary tract symptoms among a cohort of black American men: The Flint Men's Health Study. Urology. 2004;64(5):959-65.[114]

Exclusion reason: incorrect outcome measure (investigatve paramters)

Sarma AV, St Sauver JL, Hollingsworth JM, Jacobson DJ, McGree ME, Dunn RL, et al. Diabetes treatment and progression of benign prostatic hyperplasia in community-dwelling black and white men. Urology. 2012 Jan;79(1):102-8.[115]

Exclusion reason: incorrect study type (data has not undergone multivariate analysis)

Moreno Sierra J, Fernandez Prez C, Cano Escudero S, Fuentes Ferrer M, Tolosa LB, Silmi Moyano Á. Progression of null or mild lower urinary tract symptoms indicative of benign prostatic hyperplasia after 2 years of follow-up in non-treated men aged 40 years or older. Urology. 2011;77(3):693-8.[116]

Exclusion reason: incorrect study population (>50% of patients were asymptomatic at recruitment)

Seitter WR, Barrett-Connor E. Cigarette smoking, obesity, and benign prostatic hypertrophy: a prospective population-based study. Am J Epidemiol. 1992 Mar 1;135(5):500-3[117]

Exclusion reason: progression/regression not well define (baseline symptoms not known)

Speakman M, Batista J, Berges R, Chartier-Kastler E, Conti G, Desgrandchamps F, et al. Integrating risk profiles for disease progression in the treatment choice for patients with lower urinary tract symptoms/benign prostatic hyperplasia: A combined analysis of external evidence and clinical expertise. Prostate Cancer and Prostatic Diseases. 2005;8(4):369-74.[118]

Exclusion reason: incorrect study design (expert opinion)

Stewart WF, Minassian VA, Hirsch AG, Kolodner K, Fitzgerald M, Burgio K, et al. Predictors of variability in urinary incontinence and overactive bladder symptoms. Neurourology and Urodynamics. 2010;29(3):328-35.[119]

Exclusion reason: incorrect study population (unclear treatment status)

St. Sauver JL, Sarma AV, Hollingsworth JM, Jacobson DJ, McGree ME, Dunn RL, et al. Associations between modest weight changes and onset and progression of lower urinary tract symptoms in two population-based cohorts. Urology. 2011;78(2):437-41.[120]

Exclusion reason: incorrect study population (men were not excluded based on treatment

status – as per correspondence with authors)

Suh B, Shin DW, Hwang SS, Choi HC, Kwon H, Cho B, et al. Alcohol is longitudinally associated with lower urinary tract symptoms partially via high-density lipoprotein. Alcoholism: Clinical and Experimental Research. 2014;38(11):2878-83.[121]

Exclusion reason: incorrect outcome measure (did not assess risk factors for progression/regression)

Sung HP, Meehan A, Lee M, Penson DF, Wessells H. The relationship among lower urinary tract symptoms, prostate specific antigen and erectile dysfunction in men with benign prostatic hyperplasia: Results from the proscar long-term efficacy and safety study. Journal of Urology. 2005;173(3):903-7.[122]

Exclusion reason: incorrect study type (placebo arm of RCT)

Sutcliffe S, Grubb Iii RL, Platz EA, Ragard LR, Riley TL, Kazin SS, et al. Non-steroidal anti-inflammatory drug use and the risk of benign prostatic hyperplasia-related outcomes and nocturia in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. BJU International. 2012;110(7):1050-9.[123]

Exclusion reason: incorrect study population (treatment status not confidently known)

Thomas AW, Cannon A, Bartleh E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: Minimum 10-year urodynamic follow-up of untreated detrusor underactivity. BJU International. 2005;96(9):1295-300[124]

Exclusion reason: incorrect outcome measure (urodynamic studies)

Tsukamoto T, Masumori N, Rahman M, Crane MM. Change in International Prostate Symptom Score, prostrate-specific antigen and prostate volume in patients with benign prostatic hyperplasia followed longitudinally. International Journal of Urology. 2007;14(4):321-4[125]

Exclusion reason: incorrect outcome measure (changes in PSA/prostae volume)

Tubaro A, La Vecchia C. The relation of lower urinary tract symptoms with life-style factors and objective measures of benign prostatic enlargement and obstruction: An italian survey. European Urology. 2004;45(6):767-72[126]

Exclusion reason: incorrect study type (cross-sectional study design)

Um YH, Koh JS, Ko HJ, Cho KJ, Kim JC, Lee SJ, et al. The predictor analysis of response to routine treatment in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Neuroendocrinology Letters. 2014;35(2):116-22[127]

Exclusion reason: incorrect study duration (12 weeks)

Van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JLHR. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: The Krimpen study. Journal of Urology. 2011;186(5):1956-61.[128]

Exclusion reason: incorrect outcome measure (did not assess risk factors associated with change in symptoms)

Van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JLHR. Prevalence, incidence, and resolution of nocturnal polyuria in a longitudinal community-based study in older men: The Krimpen study. European Urology. 2013;63(3):542-7.[129]

Exclusion reason: incorrect outcome measure (nocturia only)

Vaughan CP, Johnson Ii TM, Haukka J, Cartwright R, Howard ME, Jones KM, et al. The fluctuation of nocturia in men with lower urinary tract symptoms allocated to placebo during a 12-month randomized, controlled trial. Journal of Urology. 2014;191(4):1040-4.[130]

Exclusion reason: incorrect study type (placebo arm of RCT)

Wallner LP, Slezak JM, Loo RK, Quinn VP, Van Den Eeden SK, Jacobsen SJ. Progression and treatment of incident lower urinary tract symptoms (LUTS) among men in the California Men's Health Study. BJU International. 2014;115(1):127-33.[131]

Exclusion reason: incorrect outcome measure (did not assess risk factors associated with change in symptoms)

Wolin KY, Grubb RL, III, Pakpahan R, Ragard L, Mabie J, Andriole GL, et al. Physical activity and benign prostatic hyperplasia-related outcomes and nocturia. Medicine and Science in Sports and Exercise. 2014;47(3):581-92.[132]

Exclusion reason: progression/regression not well defined (no validated LUTS tool at baseline)

Yeh HC, Liu CC, Lee YC, Wu WJ, Li WM, Li CC, et al. Associations of the lower urinary tract symptoms with the lifestyle, prostate volume, and metabolic syndrome in the elderly males. Aging Male. 2012;15(3):166-72[133]

Exclusion reason: incorrect study design (cross-sectional study design)

Yoshimura K, Terada N, Matsui Y, Terai A, Kinukawa N, Arai Y. Prevalence of and risk factors for nocturia: Analysis of a health screening program. International Journal of Urology. 2004;11(5):282-7.[134]

Exclusion reason: incorrect study design (cross-sectional study design)

Zucchetto A, Tavani A, Dal Maso L, Gallus S, Negri E, Talamini R, et al. History of weight and obesity through life and risk of benign prostatic hyperplasia. International Journal of Obesity. 2005;29(7):798-803[135]

Exclusion reason: incorrect study popuation (hospital based)

Appendix 8:Methodological quality analysis of eligible studies

Study (author, year)	Study participation	Study attrition	Prognostic factor measurement	Other measurements	Confounding measurement and account	Analysis	Accept for systematic review?
Barry *et al.*, 1997[136]	No	Partly	Partly	Partly	No	No	Exclude
Burke *et al.*, 2006[3]	Partly	Partly	Partly	Yes	Partly	Yes	Accept
Burke et al., 2006[22]	Partly	Unsure	Partly	Partly	No	Partly	Exclude
Curto *et al.*, 2014[4]	Yes	Partly	Partly	Yes	Yes	Yes	Accept
Fu *et al.*, 2016[5]	Partly	Unsure	Yes	Yes	Partly	Partly	Accept
Holton *et al.*, 2016[6]	Partly	Partly	Yes	Yes	Partly	Yes	Accept
Marshall *et al.*, 2014[7]	Partly	Partly	Partly	Partly	Yes	Yes	Accept
Parsons *et al.*, 2011[8]	Partly	Partly	Partly	Partly	Yes	Yes	Accept
St Sauver *et al.*, 2011[9]	Partly	Unsure	Yes	Yes	Partly	Yes	Accept
St Sauver *et al.*, 2011[10]	Partly	Partly	Partly	Yes	Partly	Yes	Accept
St Sauver *et al.*, 2009[11]	Partly	Unsure	Partly	Partly	Partly	Partly	Accept
St Sauver *et al.*, 2006[12]	Partly	Unsure	Partly	Partly	Partly	Partly	Accept
Temml *et al.*, 2003[13]	Partly	Partly	Partly	Yes	Partly	Yes	Accept
Wallner *et al.*, 2013[137]	No	No	Partly	Yes	Partly	No	Exclude
Wong *et al.*, 2010[14]	Partly	Partly	Partly	Partly	Partly	Yes	Accept

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	

Luke *et al.*[138#]	No	No	No	Yes	Yes	No	Yes	Yes	Exclude

[#]JBI Critical Appraisal checklist for descriptive/case series

Appendix 9:– Detailed reasoning for excluded articles

Barry *et al.*[136] examined the risk of men with LUTS progressing to more severe LUTS or requiring treatment (either medical or surgical). The study recruited men in a non-randomised method from North American urology clinics who were felt to have 'clinical BPH' and were deemed appropriate for surgery but had elected an initial observation period. A definition of BPH was not provided (i.e. a clinical diagnosis of BPH was made), however the Maine Medical Assessment Program score was utilised on initial review and subsequently the IPSS was performed to assess the severity of men's LUTS. Men were excluded if there was a 'suspicion' of prostate cancer, previous surgery, could not speak English or had a strong indication for BPH surgery. It was also not clear how many men were medically treated upon recruitment. However, the authors argued that pharmacological management was scarcely utilised during this era and was unlikely to have confounded the results. Data presented in the analysis did not undergo multivariate analysis. A decision to exclude the study was made based on the recruitment methodology, the use of two different LUTS assessment tools and lack of adjustment for confounders in the statistical analysis. There was significant concern that selection bias could confound the results and whilst the data published may be applied to men presenting to a urologist, the generalisability of the results to all men within the community with LUTS was not possible.

Burke *et al.*[22] examined the association between diabetes and the progression of 'benign prostatic hyperplasia' based on changes in the AUA-SI, PSA, prostate volume and Q_{max}. Men were randomly recruited as a part of the Olmsted County Study of Urinary Symptoms and Health Status among Men (OCS). A decision to exclude this study was made because the data did not undergo multivariate analysis. It was deemed that the statistical analyses of this study were not performed in a manner which would sufficiently limit the potential biases introduced by competing comorbidities, and the relationship between diabetes and LUTS progression could therefore be confounded.

Luke *et al.*[138] conducted a prospective cohort study on both men and women undergoing bariatric surgery to assess the change in LUTS that occurred postoperatively in association with their weight loss. Whilst the study's exclusion criteria fulfilled this systematic review's requirement, the recruitment of participants was thought to introduce a high risk of bias. Recruitment was performed in a non-randomized manner based on involvement in other studies, the subjects' 'likely reliability', and patients' perceived willingness to participate, as such selection bias might have influenced the results. Additionally, those who withdrew or were lost to follow-up were poorly described and not included in the analysis, which might have introduced attrition bias. The data underwent multivariate analysis, however it incorporated both men and women. Correspondence with the authors requesting data excluding the female cohort was unsuccessful. For these reasons, the paper was not included.

Wallner *et al.*[137] examined the relationship between fasting serum glucose, insulin concentration, insulin resistance and measures of BPH (including LUTS) in a population based cohort of African American men as a part of the Flint Men's Health Study (FMHS). Initially 730 of 943 eligible African American men completed an interview and of these, 369 underwent a comprehensive urologic examination. Four years later, 186 (50%) of these men had a follow-up assessment resulting in a total follow-up close to just 20%. Those lost to follow-up were more likely to be younger, yet had greater symptoms, and whilst a definite 'follow-up percentage' was not required amongst included studies for this systematic review, it was decided that these factors could confound the results. Finally, progression rates did not take into account any significant confounding variables during the analysis and consequently this article was not included in the systematic review

Appendix 10: Symptoms scores and definitions utilised in included studies

Study (author, year)	Symptom score utilized	Symptom severity at recruitment	Symptom progression - definition	Symptoms stable - definition	Symptom regression - definition
Burke *et al.*, 2006[3]	AUA-SI	AUA-SI ≤ 7	AUA score > 7, AUR	N/A	N/A
Curto *et al.*, 2014[4]	AUA-SI	AUA-SI < 33	Increase of total AUA ≥ 3, increase in voiding symptoms ≥2 , increase in storage symptoms ≥2	N/A	N/A
Fu *et al.*, 2016[5]	IPSS	Any	≥ 4-point increase in IPSS, AUR, renal insufficiency, recurrent UTI, urinary incontinence	N/A	N/A
Holton *et al.*, 2016[6]	AUA-SI	AUA-SI < 20	LUTS trajectories: mild -> moderate, moderate -> severe, low moderate -> high moderate	N/A	N/A
Marshall *et al.*, 2014[7]	AUA-SI	Any	Grouped based trajectory modelling	Grouped based trajectory modelling	Grouped based trajectory modelling
Parsons *et al.*, 2011[8]	AUA-SI	AUA-SI ≤ 7	AUA-SI ≥ 8, received treatment (medical/surgical)	N/A	N/A
St Sauver *et al.*, 2011[9]	AUA-SI	AUA-SI ≤ 7	AUA-SI >7	N/A	N/A
St Sauver *et al.*, 2011[10]	AUA-SI	Any	Annual change – (points/year)	N/A	Annual change – (points/year)
St Sauver *et al.*, 2009[11]	AUA-SI	Any	Annual change (points/year)	N/A	Annual change – (points/year)

St Sauver *et al.*, 2006[12]	AUA-SI	AUA-SI ≤ 7	AUA-SI > 7, Received treatment (medical/surgical), AUR	N/A	N/A
Temml *et al.*, 2003[13]	IPSS	Any	Any increase in IPSS, IPSS increase of ≥ 5, received treatment (medical/surgical)	N/A	N/A
Wong *et al.*, 2010[14]	IPSS	AUA-SI ≤ 7	IPSS ≥ 8	N/A	N/A

Appendix 11:– Examined exposures and confounders

Study (Author, year)	Examined exposure	Co-variate(s) adjusted for as part of multivariate analysis
Burke *et al.*, 2006[3]	BMI, Waist (cm), waist/hip ratio	Age
Curto *et al.*, 2014[4]	Vitamin C intake	Age, total energy intake (kcal/day), race ethnicity, cardiac disease, antispasmodics/anticholinergics, diuretics, tricyclic antidepressants
Fu *et al.*, 2016[5]	Diabetes Mellitis, Hypertension, Hyperlipidaemia, Obesity	Age, Diabetes Mellitis, Hypertension, Hyperlipidaemia, Obesity
Holton *et al.*, 2016[6]	Dietary antioxidants	For 'mild baseline symptoms': energy intake (kcal quartiles), SF-12 mental component score, history of non-prostate cancer and mobility limitations. For 'moderate baseline symptoms': energy intake, SF-12 mental component score, hypertension, problem drinking, angina and education level.
Marshall *et al.*, 2014[7]	Mental Components Score, non-prostate cancer, mobility limitations, overweight, dizziness, daily walking for exercise, HTN, back pain, diabetes, CNS medications, problem drinking, hypertension, angina	Mental Components Score, non-prostate cancer, mobility limitations, weight, dizziness, daily walking for exercise, HTN, back pain, diabetes, CNS medications, problem drinking, hypertension and angina
Parsons *et al.*, 2011[8]	education, chronic medical conditions BMI, Physical Activity for the Elderly Score, Walking	Study site, education, chronic medical conditions BMI, Physical Activity for the Elderly Score and Walking
St Sauver *et al.*, 2011[9]	Statin medications use	Age, diabetes mellitis, coronary heart disease, hypertension, NSAID use, baseline BMI, smoking history, baseline alcohol usage and baseline activity
St Sauver *et al.*, 2011[10]	Baseline age, BMI, alcohol use, smoking status	Estradiol, change in estradiol, testosterone, change in testosterone, bioavailable testosterone, change in bioavailable testosterone.
St Sauver *et al.*, 2009[11]	CRP	Age, BMI, hypertension, smoking history
St Sauver *et al.*, 2006[12]	NSAID use	Age, baseline number of physician visits, diabetes, hypertension, coronary heart disease
Temml *et al.*, 2003[13]	Age, IPSS, individual IPSS score, IPSS-Q1, sociodemographic parameters (education, BMI, blood	Age, IPSS, individual IPSS score, IPSS-Q1, sociodemographic parameters (education, BMI, blood pressure, smoking status, marital status, alcohol intake).

	pressure, smoking status, marital status, alcohol intake).	
Wong *et al.*, 2010[14]	CHD, alcohol consumption, Depression	Coronary heart disease, ≥ 7 ETOH drinks/week in last 12 months, GDS score ≥ 4

BMI, Body Mass Index; cm, centimeters; kcal, kilocalories; HTN, hypertension; CNS, Central Nervous System; NSAID, non-steroidal anti-inflammatory drug; CVD, cardiovascular disease; CRP, C-reactive protein; CHD, coronary heart disease; IPSS, International Prostate Symptom Score; CHD, coronary heart disease; ETOH, alcohol; GDS, Geriatric Depression Score