THE ROLE OF MODIFIABLE RISK FACTORS IN THE PRESENCE AND DEVELOPMENT OF LOWER URINARY TRACT SYMPTOMS (LUTS) AND SEXUAL DYSFUNCTION IN AGEING MEN

A Thesis Submitted for Consideration for the Award of

DOCTOR OF PHILOSOPHY

By

Sean Aaron Martin, B. Sc. (Hons 1)

School of Medicine

University of Adelaide

*

July 2013

Table of Contents

Originality Certification

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The Author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed..... **Dated**.....

List of tables

List of figures

Abbreviations

AUA-SI: American Urology Association – Symptom Index

ALSH: Australian Longitudinal Study of Health and Relationships

BLSA: Baltimore Longitudinal Study on Aging

BDI: Beck Depression Inventory

BPH: Benign prostatic hyperplasia

BMI: Body mass index

BACH: Boston Area Community Health survey

BMSI: Brief Male Sexual Inventory

CVD: Cardiovascular disease

CNS: Central Nervous System

CI: Confidence Interval

CATI: Computer-Assisted Telephone Interviewing

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV

DA: Dopamine

DEXA: Dual energy x-ray absorptiometry

EWP: Electronic White Pages

ED: Erectile dysfunction

EAU: European Association of Urology

EMAS: European Male Ageing Study

EPIC: European Prospective Investigation into Cancer and Nutrition

FAMAS: Florey Adelaide Male Ageing Study

FFQ: Food Frequency Questionnaire

GVA: General Visceral Afferent

GIR: Global Impotence Rating

HbA1c: Haemoglobin A1c

HPFU: Health Professionals Follow-up study

HDL: High density lipoproteins

HSDD: Hypoactive sexual desire disorder

IGFBP-3: IGF-binding protein-3

IGF: Insulin-like growth factor

ICCSM: International Consultation Committee for Sexual Medicine

ICPCPD: International Consultation on New Developments in Prostate Cancer and Prostate Diseases

ICS: International Continence Society

IPSS: International Prostate Symptoms Scale

ISSM: International Society for Sexual Medicine

LTPA: Leisure-time physical activity

LC–MS/MS: Liquid chromatography–tandem mass spectrometry

LDL: Low density lipoproteins

LUTS: Lower urinary tract symptoms

LMHS: Lyell McEwin Health Service

MMAS: Massachusetts Male Aging Study

MAO: Monoamino-oxidase

MSAM-7: Multinational Survey of the Aging Male

NHANES: National Health and Nutrition Examination Survey

NHSLS: National Health and Social Life Survey

NHS: National Health Service

NATSAL: National Survey of Sexual Attitudes and Lifestyles

NO: Nitric oxide

OSA: Obstructive sleep apnoea

MrOS: Osteoporotic Fractures in Men Study

OAB: Overactive bladder

PCPT: Prostate Cancer Prevention Trial

PSA: Prostate specific antigen

SSRI: Selective serotonin reuptake inhibitor

SDI-2: Sexual Desire Inventory 2

SF-36: Short-form health survey 36

TQEH: The Queen Elizabeth Hospital

T3: Triiodothyronine

T4: Thyroxine

UI: Urinary incontinence

WHO: World Health Organisation

Acknowledgements

There's an old Sumerian saying which loosely translates into: "*Give me my own tools, and I will launch my (own) boat*". To that end, I owe a debt of gratitude to the experienced hands of my supervisory team: Dr. Evan Atlantis, Dr. Grant Buchannan, Dr. Peter O'Loughlin, Prof. Richard Ivell, and led by our long-term skipper – the inimitable Prof. Gary Wittert. I would also like to thanks the many other academics and staff of the Discipline of Medicine, both past and present, for their support during my candidature and time in the department.

I owe an equal debt of gratitude to the Freemasons Foundation, particularly Mr. Robert Clyne (Yes, Rob, it's finally finished), for their support of my candidature and their role in establishing our Freemason's Foundation Centre for Men's Health. Heartfelt thanks are also extended to Dr. Vanessa Glennon for her multiple avenues of assistance.

Whatever value this work has it is, by definition, a product of the generous time given by the wonderful participants of the Florey Adelaide Male Ageing Study (FAMAS) and their families – I thank them for that, and for their patience with our never-ending enquiries. I particularly want to thank all of our FAMAS staff over the many years, especially my long-time confrère Ms. Leanne Owen and the other establishing member of the FAMAS fraternity, Dr. Matt Haren. From our study's inception, we have received an enormous amount of support from the all the staff at the Population Research and Outcome Studies group (finally got the name right!) – my

thanks you all, but particularly A/Prof Anne Taylor and Ms. Janet Grant for your constant generosity over the many years.

I've been lucky in my life to count a veritable cavalcade of characters as family and friends. In your varying ways, you've all been an important crutch during this period of my life. Most are likely to never read a single word written herein, and I love you all the more for it. Finally, and most importantly, to my treasured travel mate in life, Lexi, who has had carried this with me more than most could or would – this one's dedicated to you.

Smooth waters. Strong winds. Full sails… Thanks to all!

Sean Martin

July 2013

SECTION I

LITERATURE REVIEW AND STUDY DESIGN

CHAPTER 1

Australia's Ageing Male Population

1.1 Australia's ageing population

Currently, around 9 per cent of our population (approximately 2 million people) is aged 70 years or older [1]. This is projected to rise to 13 per cent by 2021 and to 20 per cent (around 5.7 million people) in 2051. The proportion of oldest-old (those aged 80 years and over) currently make up around 4 per cent of the population and is expected to increase to 10 per cent by 2051 (Figure 1-1).

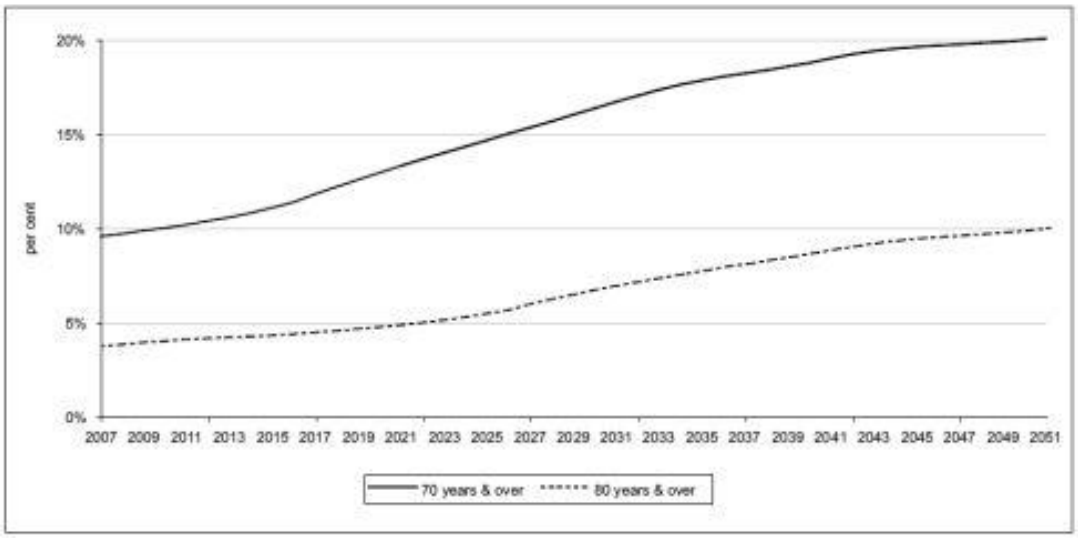


Figure 1-1. Australian population growth 2007-2051. 70+ and 80+ age groups as a percentage of the total population (*Source: ABS 3222.0 Population projections, Australia: 2006-2101).*

This increasing proportion of older Australians in the population has significant implications for Australia's health, social and economic welfare. As a consequence,

Australia's recent health policy settings have focussed on the identification of preventative measures, especially in those conditions most prevalent in the elderly, as an important strategic factor in the overall management of an ageing demographic [2].

1.2 The male health disadvantage

As a population group, men generally display poorer health outcomes when compared with women in most developed countries, including Australia [3], [4]. Men in Australia have a lower life expectancy than women (76.6 years compared with 82.0 years) with higher rates of mortality at all ages, a discrepancy that begins from birth [5]. There is a disproportionate level of chronic physical and psychological disease in Australian men, and higher rates of illness-related disability [6]. In addition, men display a higher prevalence of the major risk factors – notably smoking, lack of physical activity, poor nutrition and alcohol abuse – linked to the development of most major chronic diseases [7] [8]. Men are also less likely to adopt healthy lifestyle choices [9] and are more resistant to public health messages [10]. These factors have led to the identification of a 'male health disadvantage' [11], recognition of which has led to an increased attention to men's health issues from a variety of government and non-government organisations in both Australia and other countries [4] [12] [13] [14].

1.3 Prospective cohort studies of ageing men

An evidence-based approach to improving the health of males is critical to maximising the effectiveness of any policies and programs aimed at improving health outcomes in men. One of the most important research tools in understanding the biological,

physical, psychological and social-demographic determinants of male health is the use of the longitudinal (or cohort) study design [15].

Cohort studies are uniquely suited to the study of health-related conditions over time, including the effects of age and other factors that contribute to their development. Cohort studies offer numerous advantages over other epidemiological study designs. Firstly, cohort studies allow a uniform measurement of exposure history and other factors related to outcome. Second, cohort studies provide information about individual patterns of changes. Such data are required for the prediction of individual changes and for the causal interpretation of relationships between outcome and independent predictors. Finally, cohort studies can provide more accurate estimates of a covariates impact on an outcome, with the same number and patterns of measures as a cross-sectional study [16].

The use of cohort samples that are representative of their target population offer additional advantages such as allowing the estimation of distributions and prevalence rates of relevant conditions in the reference population (e.g. information on risk factors is used for the calculation of population attributable risks). A representative sample is also the ideal setting to examine additional hypotheses between any variables of interest [17].

Despite their methodological advantages in examining the effects of age and other related factors on health conditions in men, cohort studies carry high costs and logistical complexities such as selection bias, missing data, attrition, and temporal confounders [17]. Broadly speaking, a cohort study is of maximum value when it is: conducted prospectively; is representative of its target population; is sufficiently sized

for the condition(s) under examination; collects a wide variety of covariate data; have a high number of person-follow-up years; and links with existing data sources [16].

Table 1-1 summarises the existing prospective cohort studies that have focussed on the health and health-related behaviours of men. Most of these cohort studies have commenced with the resurgent interest in men's health issues that occurred circa 1990 (see [18] for summary).

Table 1-1. Male prospective cohort studies (*male participants only; active-published since 2002)*

Study	Location	Sample	Size/Age	Measures	Start date	Linkages
British Doctors Cohort Study	Multicentre, U.K.	Health professionals	40, 701 men, aged 25-75 years	Demographic; Chronic conditions (incl. family history); Medication; Surgeries; Nutrition, Smoking; Physical Activity; Mood disorders	1951	Family / partner hospital records
New Mexico Aging Process Study	New Mexico, USA	Patient registry	300 men, aged 18-85 years	Demographic; Chronic conditions (incl. family history); Medication; Surgeries; Nutrition, Smoking; Physical Activity; Mood disorders	1979	None
Massachusetts Male Aging Study (MMAS)	Boston, USA	General population	1709 men, aged 35-75 years	Demographic; Chronic conditions (incl. family history); ; BMI; Waist /hip; Blood pressure; Hormonal measurement; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Bone fractures; QoL; Mood disorders; Cognition; Sexual dysfunction; LUTS; Health Service Use	1987	None
Olmsted county study of urinary symptoms and health	Minnesota, USA	General population	2115 men, aged 40 - 79 years	Demographic; Chronic conditions (incl. family history); Body composition (incl. DEXA); Blood pressure; Hormonal measurement; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Bone fractures; QoL; Mood disorders; Cognition; Sexual dysfunction; LUTS; Health Service Use	1989	None
Bambuí Health and Ageing Study	Babui, Brazil	General population	1742 men, aged 65-99 years	Demographic; major health conditions; Blood pressure; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Mood disorders; Sexual dysfunction	1991	None
Health in Men Study (HIMS)	Perth, Australia	General population (aortic	12, 203 men, aged 65-79	Demographic; CV conditions; Blood pressure; Brachial pressure; Aortic diameter; Hormonal measurement; Medication; Surgeries; Nutrition,	1996	Western Australian Information

		aneurysms)	years	Smoking; Physical Activity; Mood disorders; Cognition; Sexual dysfunction		System
Health Professionals Follow-up Study	Boston, USA	Health professionals	51, 529 men, aged 20-65 years	Demographic; Chronic conditions (incl. family history); Medication; Surgeries; Nutrition, Smoking; Physical Activity; Bone fractures; QoL; Mood disorders; Cognition; Sexual dysfunction; LUTS; Dental	1996	None
Cologne Male Survey	Cologne, Germany	General population	4489 men, aged 30-80 years	Demographic; Chronic conditions; Surgeries; Nutrition, Smoking; Physical Activity; Sexual dysfunction; LUTS	2000	None
Osteoporotic Fracture in Men (Mr. OS) Study	Multicentre, USA	General population	5995 men, aged 65 – 92 years	Demographic; Chronic conditions; Bone measures and fracture history; Body composition (incl. DEXA); Blood pressure; Hormonal measurement; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Mood disorders; Sexual dysfunction; LUTS	2000	None
Florey Adelaide Male Ageing Study (FAMAS)	**Adelaide, Australia**	**General population**	**1195 men, aged 35-80 years**	**Demographic; Chronic conditions (incl. family history); Body composition (incl. DEXA); Blood pressure; Hormonal measurement; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Bone fractures; QoL; Mood disorders; Cognition; Sexual dysfunction; LUTS; Health Service Use**	**2002**	**Medicare; Pharm. Benefits Scheme; Cancer, Death registries**
Epidemiologia de la Disfuncion Erectil Masculina (EDEM) Study	Multicentre, Spain	Patient registry	2476 men, aged 25-70 years	Demographic; Chronic conditions (incl. family history); Body composition; Blood pressure; Hormonal measurement; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Sexual dysfunction; LUTS	2004	None

European Male Ageing Study (EMAS)	Multicentre, Europe	General population	4800 men, 35-75 years	Demographic; Chronic conditions; Body composition (incl. DEXA); Blood pressure; Hormonal measurement; Medication; Nutrition, Smoking; Physical Activity; QoL; Mood disorders; Cognition; Sexual dysfunction	2004	None
UrEPIK Study	Multinational	General population	4876 men, aged 40 – 80 years	Demographic; Chronic conditions; Medication; Surgeries; Nutrition, Smoking; Physical Activity; Mood disorders; Sexual dysfunction; LUTS	2004	None

CHAPTER 2

Lower urinary tract symptoms (LUTS) in men

2.1 Anatomy and function of the male lower urinary tract

The male urinary tract is broadly divided into two systems, the upper urinary tract and the lower urinary tract. The upper urinary tract is composed of the kidneys and ureters, and functions to filter the blood of water soluble waste and produces urine. The lower urinary tract is composed of the bladder, urethra and urethral sphincters, and functions to store and eliminate urine.

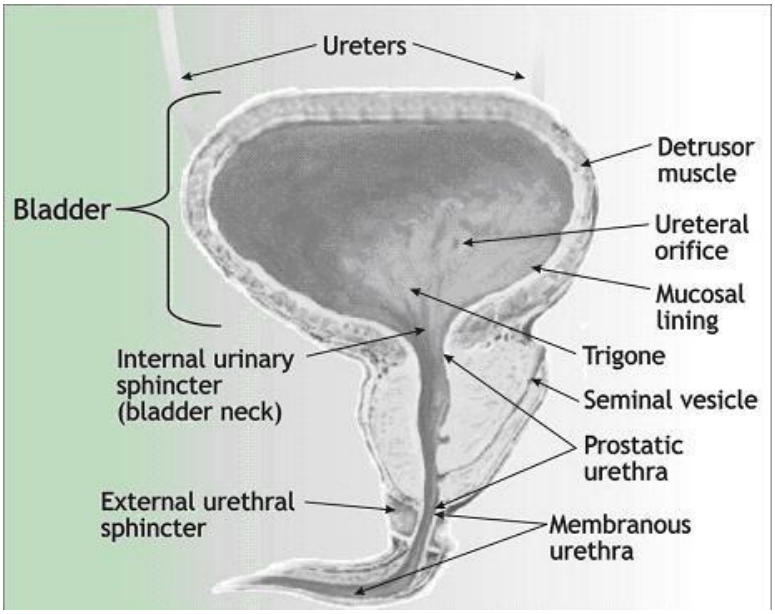


Figure 2-1. The male lower urinary tract (*Source: Endotext*)

The bladder is a musculo-membranous structure whose primary function is to act as a reservoir for urine following excretion by the kidneys. In males, the bladder lies between the rectum and the pubic symphysis, superior to the prostate (in females, bladder is positioned inferior to the uterus and anterior to the internal urethral orifice;

producing a lower maximum capacity than in males). The detrusor muscle of the bladder wall is made of smooth muscle fibres arranged in spiral, longitudinal, and circular bundle to maximise torsion [19]. The bladder is heavily innervated, receiving signals from both sympathetic and parasympathetic fibres. Sensation from the bladder is transmitted to the central nervous system (CNS) via general visceral afferent fibres (GVA). GVA fibres on the superior surface follow the course of the sympathetic efferent nerves back to the CNS, while GVA fibres on the inferior portion of the bladder follow the course of the parasympathetic efferents [20].

Normal bladder function consists of two phases: filling and emptying.

2.1.1 Filling phase

During the filling phase, the bladder accumulates increasing volumes of urine while maintaining lower pressure than the urethra to prevent leakage.

The filling of the urinary bladder depends on the intrinsic elastic properties of the bladder and the inhibition of the parasympathetic nerves. Thus, bladder filling primarily is a passive event. Sympathetic nerves also facilitate urine storage through inhibiting parasympathetic nerve-driven contraction of the urinary bladder; relaxation and expansion of the detrusor muscle; and closure of the bladder neck through the constriction of the internal urethral sphincter. This sympathetic input to the lower urinary tract is constantly active during bladder filling.

As the bladder fills, the pudendal nerve becomes excited. Stimulation of the pudendal nerve results in contraction of the external urethral sphincter. Contraction of the external sphincter, coupled with that of the internal sphincter, maintains urethral pressure (resistance) higher than normal bladder pressure.

As the bladder initially fills, a small rise in pressure occurs within the bladder (intravesical pressure). When the urethral sphincter is closed, the pressure inside the urethra (intraurethral pressure) is higher than the pressure within the bladder. While the intraurethral pressure is higher than the intravesical pressure, urinary continence is maintained [20].

2.1.2 Emptying phase

The storage phase of the urinary bladder can be switched to the voiding phase either involuntarily (reflexively) or voluntarily. When the bladder is filled to capacity, the stretch receptors within the bladder wall signal the sacral cord which, in turn, sends a message back to the bladder initiating micturition.

The pudendal nerve causes relaxation of the pelvic floor muscle and the opening of the external sphincter. In turn, sympathetic nerves activate the internal sphincter, causing it to relax and open and resulting in a lower urethral resistance. Simultaneously, the parasympathetic nerves trigger contraction of the detrusor. When the bladder contracts, the pressure generated by the bladder overcomes the urethral pressure, resulting in urinary flow. These coordinated series of events allow unimpeded, automatic emptying of the urine [20].

2.2 Urinary dysfunction in men

There are a variety of disorders of regular micturition in men. Table 2-1 summarises the major urinary conditions in men as identified by the International Continence Society (ICS).

Table 2-1. Major urinary conditions in men (*Source: Abrams et al. Neurol Urodyn, 2002;21: 167–78*)

Urinary Condition	ICS Definition
Increased daytime frequency	The complaint by the patient who considers that he/she voids too often by day
Nocturia	The complaint that the patient has to wake at night one or more times to void
Urgency	A sudden compelling desire to pass urine, which is difficult to defer
Urinary incontinence (UI)	Any involuntary leakage of urine. (Stress urinary incontinence (SUI) is the involuntary leakage on effort or exertion, or on sneezing or coughing. Urgency urinary incontinence (UUI) is the involuntary leakage accompanied by or immediately preceded by urgency
Nocturnal enuresis	Loss of urine occurring during sleep (Involuntary; *c.f.* Nocturia)
Weak stream	The perception of reduced urine flow, usually compared to previous performance or in comparison to others
Splitting or spraying	Description of the urine stream
Intermittent stream (Intermittency)	Urine flow, which stops and starts, on one or more occasions, during micturition
Straining	The muscular effort used to either initiate, maintain or improve the urinary stream
Terminal dribble	A prolonged final part of micturition, when the flow has slowed to a trickle/dribble
Incomplete emptying	A feeling experienced by the individual after passing urine
Post-micturition dribble	The involuntary loss of urine immediately after an individual has finished passing urine, usually after leaving the toilet in men
Painful bladder syndrome/ interstitial cystitis (PBS/IC)	Subrapubic pain associated with other urinary symptoms, usually increased frequency (but not urgency)

2.3 Definition

The term **lower urinary tract symptoms (LUTS)** was formally adopted in 2002 by the ICS following suggestions from both researchers and clinicians who sought to standardise the disparate terminology that existed for many urinary dysfunctions [21]. Previously, collections of urinary symptoms had generally been referred to on the basis of their presumed origin (e.g. prostatism [22]). This was problematic for several reasons. First, concerns were raised that terms such as ‘prostatism’ and ‘benign prostatic

hyperplasia syndrome (BPH-S)' gave a dubious diagnostic authority, leading to improper diagnoses [23]. Second, data from emerging prospective cohort studies were demonstrating that such symptoms were also common in younger men and women where no prostatic abnormalities existed [24]. Third, experimental data also demonstrated that attempts to correlate either individual symptoms or groups of symptoms with objective measurements of prostatic enlargement failed to show any significant associations [25]. Finally, the often poor outcome in patients following either surgical or medical intervention suggested other underlying mechanisms were not being addressed [23].

As a consequences, despite some older terminology still being in use, the term LUTS has now gained almost universal acceptance in describing major bothersome urinary symptoms for both men and women [26].

2.4 LUTS measurement

Reflecting its etymological diversity, there are a number of validated self-report instruments that are used in the measurement of LUTS. The most commonly used are summarised below:

2.4.1 International Prostate Symptoms Scale (IPSS)

The IPSS (formerly known as the American Urological Symptoms Score (AUA-S before being adapted by the World Health Organisation) is currently the most widespread measure for the assessment of bothersome urinary symptoms in men. It is an 8-item

measure that assesses the 7 most common urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia) and an eighth question assessing degree of overall bother was added in 1992 [27]. The IPSS has a high level of internal consistency (Cronbach's α=0.86), an excellent test-retest reliability (R=0.92), and a strong specificity (ROC area=0.85).

2.4.1 Other common instruments

- King's Health Questionnaire: Symptoms score specific to urinary incontinence and women [28]
- Bladder Control Self-Assessment Questionnaire (B-SAQ): Shows good correlation with the IPSS (Pearson's r= 0.81) however takes longer to administer [29]
- Incontinence Quality of Life Measure (I-QOL): Has only been validated in a clinical population [30]

2.5 LUTS sub-types

As a global term, LUTS encompasses all bothersome urinary symptoms. These symptoms can be classified further into storage and voiding symptoms. The most common storage symptoms include increased *frequency* of urination, *nocturia* (the need to wake at night one or more times to void), increased *urgency* to void and *urinary incontinence* (UI). UI can be further categorised into *stress UI* (SUI), *urinary urgency incontinence* (UUI) and *mixed UI* (MUI) (a combination of both SUI and UUI). Voiding symptoms include *weak* and/or *intermittent stream*, *straining* whilst voiding and *incomplete emptying* [21]. *Overactive bladder* (OAB) forms a subset of storage LUTS

that are defined by the International Continence Society (ICS) as urgency, with or without incontinence, and usually with frequency and nocturia [21].

This terminology follows suggestions that disorders of micturition would be better described as a ‘‘failure to store’’ or ‘‘failure to empty ’’ [31], reflecting recent attempts to avoid organo-centric nomenclature. It is however important to acknowledge that it has been known for at least four decades that symptoms do not relate to the underlying pathophysiology in many patients; indeed the phrase ‘‘the bladder is an unreliable witness’’ was coined to acknowledge this [32].

In this context, there is increasing contemporary recognition that the lower urinary tract acts as an “integrated functional unit” [26] susceptible to a wide range of both local and systemic factors. In more recent studies, this has been reflected by attempts to examine the rate and determinants of urinary symptoms according to LUTS type (particularly storage and voiding symptoms).

2.6 Prevalence

Studies conducted in different populations and geographic regions have demonstrated that LUTS occur commonly in most populations, but with marked differences observed across regions [33].

2.6.1 Global

Storage LUTS

Two landmark population-based prevalence surveys conducted using telephone interviews in Europe [33] and the United States [34] suggest that storage symptoms affects up to 17% of the population, with a striking age-related increase in both sexes, starting approximately at the age of 40 and beyond. In the case of the study by Irwin et al [33], this meant that an individual who reported the presence of any one of the storage symptoms (urgency, frequency, incontinence, or nocturia) was included in the OAB prevalence. The current ICS definition of OAB specifies that urgency must be present. Hence, these earlier studies show a higher prevalence of OAB than later research conducted using the current ICS definition.

Another recent international population-based survey, the European Prospective Investigation into Cancer and Nutrition (EPIC) study [35], was conducted in five countries using the 2002 ICS definitions for LUTS [21]. This survey assessed the prevalence of OAB, urinary incontinence, and LUTS in more than 19 000 men and women. The EPIC study confirmed the previous findings that overactive bladder (OAB) was common in men, and that its prevalence increased with age; the overall prevalence among men aged 18 years and over was 11.8%. EPIC additionally found that all LUTS were highly prevalent, occurring in both men and women to a similar extent, for example, storage (51.3% and 59.2%, respectively), voiding (25.7% and 19.5%), and post-micturition symptoms (16.9% and 14.2%). These data clearly demonstrate that storage symptoms are not sex specific and that the prostate is often not the underlying cause of voiding symptoms, because women have a similar prevalence. Of importance to note, the data also show that there is a higher prevalence of storage (51.3%) versus voiding symptoms (25.7%) in men. Yet, current medical treatment of male patients with LUTS focuses on prostate-

related voiding symptoms. It is likely that storage symptoms are predominantly age-related in terms of their prevalence, and that the traditional association of these symptoms with prostate disease, suggesting that the prostate does have a major causal role in storage symptoms, may be entirely fortuitous.

Voiding LUTS

All LUTS, including voiding symptoms, in addition to histologic benign prostatic hyperplasia (BPH) increase in prevalence as men age. Studies of the prevalence of BPH report that half of men aged 51–60 yr have histologic BPH, with prevalence increasing to up to 90% in those older than 80 yr [36]. A comprehensive epidemiologic study [37] in a pan-European study has evaluated the correlation of different types of voiding symptoms in men in a general population setting. Of the more than 17 000 men aged 18 yr and over, 8% of all men reported at least one type of voiding symptom, with weak stream being the most prevalent type. Between 25% and 40% of men had sought the advice of a physician, and <5% had undergone surgery for their condition. Similarly, a smaller study in almost 3000 men from an urban Swedish population demonstrated that more than 10% of men between the ages of 30 and 49 yr reported at least one voiding symptom, with only 6% of these men having sought treatment for their condition [38].

A review of the literature demonstrates that voiding symptoms are less common in men than in women, and when it is present in men, it usually is related to previous prostatic surgery [39]. However, the importance of storage symptoms in the context of LUTS is clearly emphasised by the landmark studies from the ICS [40], which found that although voiding symptoms were most prevalent in male patients being referred to

secondary care centres for surgery, storage symptoms were the most bothersome [40]. Nevertheless, the age-related prevalence of LUTS in the male has been demonstrated by numerous studies, including the Triumph study [41].

2.6.2 Australian

Comparatively few Australian studies exist that examine the prevalence rate of LUTS, and none examine the prevalence of storage and voiding LUTS separately. In 1997, a group of 1200 men aged 18- 80 years from the north-western suburbs of Adelaide were examined by telephone survey, with 17% of all men examined reporting troublesome LUTS [42]. However, men who had prior lower urinary tract surgery were not excluded from this study. A study of 2000 Italian immigrants in Sydney found a much higher prevalence of total LUTS (32%), however this was conducted in men aged over 65 years [43]. In a recent nationwide phone survey of almost 6,000 Australian men the overall prevalence of total LUTS was 16.2% [44].

2.7 Incidence

2.7.1 Global

Although the knowledge of the prevalence of LUTS in men has increased substantially over the years, the natural history of LUTS is still poorly understood. A recent 6.5- year study in men participating in a health screening survey in Austria demonstrated that LUTS in men without urinary incontinence has a mean annual incidence of 5.3% , with

storage symptoms the most likely to improve [45]. In another prospective cohort study of African-American men, the natural history of LUTS in men was assessed over 5 years , with a much lower annual incidence of 1.3% reported [46].

2.7.2 Australian

To date there are no known studies of incident LUTS in Australian men.

2.8 Associations and risk factors

Most recent studies of male LUTS have focussed on identifying novel risk factors for male LUTS, in keeping with the view of the lower urinary tract as an integrated functional unit. This has reinforced the view that there is generally a poor correlation between LUTS (both storage and voiding) and the presumed underlying mechanisms (age, BPH, declining urine flow). There remain however few studies of a sufficiently robust design to examine the independent effects of many of these interrelated factors.

Summarised below are some of the most recent findings of associations of LUTS in men.

2.8.1 Obesity & metabolic disturbance

The rise in the proportion of obese men (and women) to epidemic levels has been well documented in Australia [5], and most other developed countries [47]. In terms of obesity and urinary dysfunction in men, there is a long-established link between BPH and obesity [48], however similar studies on storage symptoms are sparse. The EPIC study

found that, on average, 8% of men from five countries in Europe and the USA were affected by OAB however no anthropometric measures were included in the subsequent analysis [49]. In a recent study, a link between BMI and storage symptoms was demonstrated, however this involved men with pre-existing renal dysfunction [50]. For voiding symptoms, increased adiposity has been consistently associated with both increased ultrasound and MRI-determined prostate volume [51]. Increased body weight, BMI, and waist circumference have also been associated with increased prostate volume. In the Olmsted County Study of Urinary Symptoms and Health Status among Men (Olmsted Survey), each 1 kg/m^2 increase in BMI corresponded to a 0.41 ml increase in prostate volume [52]. It remains to be conclusively demonstrated which of the many obesity-related factors (e.g. dietary factors, lower physical activity, increased inflammation, alterations in endogenous sex steroids and glucose homeostasis) are responsible for this increased risk for LUTS in men.

2.8.2 Diet

An emerging area of interest is the role of macronutrient and micronutrient on LUTS, however data is scarce. To date, only one study has examined the role of macronutrient intake on storage symptoms, finding that increased sodium and polyunsaturated fat intake was associated with storage symptoms in a cross-sectional study of community-based men [53]. Two case-control studies of surgically treated cases of BPH showed inconsistent results regarding macronutrients [54]. One prospective study found a positive association between total fat and an inverse association between protein intake and BPH [55]. Yet a separate prospective study showed that the role of protein differed by outcome definition; a positive association was observed for BPH

surgery, but no association was found with high or moderate to severe LUTS [56]. Similarly, total energy and polyunsaturated fats were positively associated with BPH, as defined by BPH surgery or high symptom score, yet when the researchers separated these outcomes, they found that the associations held only for total LUTS [56]. To date, there remains no consensus on which dietary modifications may lead to a reduced risk of developing LUTS or the precise mechanisms by which these changes act. Recent studies in other cohort studies have demonstrated that greater total energy intake were positively associated with LUTS, whereas greater protein intake was inversely associated with LUTS [53 56].It remains to be conclusively demonstrated through which mechanisms these associations may occur. One common avenue suggested is that higher energy and protein intake may affect LUTS, independent of other effects on obesity or physical activity, by, respectively, increasing and decreasing sympathetic nervous system activity [57]. Higher protein intake has also been suggested to alter sex steroid concentrations [58], although no associations were found in a recent cohort study of ageing men [59].

2.8.3 Diabetes, hyperinsulinaemia, and insulin resistance

Disruptions in glucose homeostasis have been strongly and robustly associated with a higher likelihood of LUTS.

In the Baltimore Longitudinal Study on Aging (BLSA) cohort, investigators demonstrated increased fasting glucose and diabetes were associated with the presence of total LUTS [60]. In an analysis of the National Health and Nutrition Examination Survey (NHANES) III cohort, men with diabetes were 67% more likely to have LUTS compared with those

without [61]. Moreover, the odds of LUTS increased with increasing levels of haemoglobin A1c (HbA1c). These findings were also observed in the Flint Men's Health study, in which men with diabetes were 95% more likely to have LUTS [62].

Glucose regulatory mechanisms appear to regulate prostatic growth. Insulin-like growth factor (IGF) is involved with growth signalling pathways throughout the body [60]. Several cohort studies have demonstrated that higher serum IGF and insulin have been associated with increased prostatic volume and voiding symptoms [63], [64]. In the recent Olmsted Survey, men with elevated fasting glucose were three times more likely to have BPH than men with normal glucose levels [65].

Recently, further analysis of the NHANES III cohort examined IGF-1 and IGF-binding protein-3 (IGFBP-3) levels in men with and without LUTS, finding that increased levels of IGFBP-3 were inversely related to having LUTS [66]. Recently, a similar effect was observed when examining a case–control group of the placebo arm of the Prostate Cancer Prevention Trial (PCPT [67]). The investigators noted that a high IGF-1:IGFBP-3 ratio was associated with an increased risk of BPH in men with severe voiding symptoms.

2.8.4 Lifestyle factors

Physical activity

Several cross-sectional studies have demonstrated that increased levels of physical activity are associated with decreased risk of LUTS, which may be secondary to an underlying protective mechanism. In the Massachusetts Male Aging Study (MMAS), men with the highest level of physical activity had half the risk of total LUTS compared with the least active men [68]. In the Health Professionals cohort, men who walked 2–3 h

per week had a 25% lower risk of total LUTS compared with those who did not. Additionally, physical inactivity resulted in an increased risk for BPH, especially among those with the lowest level of physical activity [34]. Similar findings were also observed in the earlier Physicians Health study, in which men who engaged in exercise were found to have a decreased risk of overall LUTS [69]. Analysis of the NHANES III cohort demonstrated that moderate and vigorous physical activity was inversely related to the presence of LUTS, whereas men who were not physically active had greater odds of LUTS [70]. Orsini and colleagues [71] examined the temporal relationship between physical activity and the risk of developing LUTS in a cohort of 30,000 Swedish men. The authors examined the relationship to past physical activity levels at the age of 30 years and current activity levels. Those men with a history of current inactivity demonstrated a two-fold increase in risk of LUTS. Interestingly, the authors found that men who had high levels of activity at the age of 30 years were protected against developing LUTS, even whether current activity was lower.

These findings were confirmed in a recent meta-analysis of 11 studies involving 43,083 men [72]. After stratifying for levels of physical activity and adjusting for multiple confounders, the authors found that moderate-to-vigorous physical activity can reduce the risk of LUTS by as much as 25% compared with a sedentary lifestyle.

Alcohol

An inverse association of alcohol intake on LUTS has been consistently observed in several large studies. In the Health Professionals cohort moderate alcohol consumption was associated with a 41% decreased risk of total LUTS [73]. In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), of the urinary conditions

examined men who consumed moderate alcohol were 30% less likely to have clinical BPH, 40% less likely and 20% less likely to have nocturia [74]. Of the almost 20,000 participants enrolled in BPH and prostate cancer trials those who consumed alcohol had higher baseline urinary flow rates and less severe LUTS compared to those who did not [75]. Compared to non-drinkers, moderate alcohol drinkers in NHANES III were 40% less likely to have LUTS [70].

Smoking

Data regarding associations of smoking and LUTS are conflicting. Although several studies support the existence of an inverse, protective effect of smoking and LUTS, several others have reported either no or increased risk (see [76], [77]). Thus, no definitive conclusions may be drawn at this time.

2.8.5 Sexual function

There is currently a tremendous interest in the role male sexual dysfunction (particularly erectile dysfunction (ED)) relates to LUTS in men. Again, most of these studies focus on the relationship between ED and LUTS / BPH, with few studies examining the relationship between storage symptoms and sexual dysfunction. Recently, a study of 6,236 men participating in the on-line EpiLUTS survey, demonstrated that men with OAB were more likely to report erectile and ejaculatory dysfunction [78].

In the first report from the seminal Massachusetts Male Aging Study, 52% of men aged 42–70 years had some degree of ED, ranging from 39% in the men aged 40 years to

67% in those aged 70 years [79]. In a later study, 8% of men in their 40s report moderate or complete ED, rising to nearly 40% in men aged 60–69 years [80]. Several interrelated mechanisms may explain the observed relationship between LUTS and ED. One purported mechanism could be a low testosterone level, which has been shown to be associated with severe ED [81], possibly via a mechanism of diminished nitric oxide (NO) synthesis [82]. The role of testosterone in maintaining erectile function however remains contentious [83]. Another mechanism is peripheral arterial insufficiency due to an atherosclerotic disease. The presence of arterial vasculogenic ED is associated with ischemic heart disease (diagnosed using cardiac stress testing) in men >40 years old [84]. Furthermore, men with ED are almost twice as likely to have sustained a myocardial infarction compared with men without ED, and the risk becomes more pronounced with increasing age [85]. Increased α‑adrenergic activity is also a potential mechanism that could explain the link between LUTS and ED. Evidence supporting this mechanism has come from studies demonstrating that patients with non-organic ED had significantly higher sympathetic activity than those without (see [86]). This mechanism is also supported by clinical intervention studies, which have concluded that treatment with non-selective α1-receptor antagonists, such as doxazosin and alfuzosin, improves sexual function, including ED [87]. This link was confirmed by the Multinational Survey of the Aging Male (MSAM‑7), a study including more than 14,000 men, aged 50–80 years, representative of the population of six European countries and the USA [88]. A fourth mechanism explaining the link between LUTS and ED involves increased activation of the Rho/Rho-kinase pathway, acting downstream of norepinephrine and endothelin‑1 receptors. Increased activity in Rho/Rho-kinase results in the inhibition of smooth

muscle myosin regulatory light chain (MLC) phosphatase, which leads to an increase in MLC phosphorylation by MLC kinase and subsequent smooth muscle contraction [36].

2.8.6 Sex steroids

Many studies have tried to establish a relationship between sex steroids, LUTS and BPH, with most studies specifically analysing the relationship between circulating testosterone and LUTS symptoms. One study found that hypogonadism was seen in approximately 20% of elderly men with LUTS, but it had no impact on symptom status [81]. Another study found a relationship between symptoms of LUTS and plasma total and bioavailable testosterone, but this relationship disappeared after statistical adjustment for age [59]. No consistent correlations were found between total and calculated free testosterone and symptoms of LUTS in another NHANES analysis, however a relationship with androstanediol glucuronide (3 alpha-diol-G; a metabolite of dihydrotestosterone) and with estradiol [89].

Low T levels have been observed in clinical bladder outlet obstruction correlated negatively with detrusor pressure at maximum flow and at urethral closure while promoting detrusor overactivity[90].

Overall it has been difficult to relate plasma testosterone to either storage or voiding LUTS, but it is of note that, within certain limits of testosterone levels, the signs and symptoms of testosterone deficiency in men do not relate in a uniform pattern to testosterone concentrations [83]. Nevertheless, it must be concluded that so far no clear relationship between LUTS and testosterone could be demonstrated. It could well be

that the detrimental effects of testosterone deficiency and the benefits of testosterone treatment occur through indirect mechanisms.

CHAPTER 3

Sexual Health and Function in Ageing Males

3.1 Background

Since antiquity, observations have been made on the decline of sexual function in men with advancing age [91]. More recently, the market opportunities arising from new medical treatments for erectile function (see [92] for historical perspective) and declining libidos (see [93] for historical perspective), in concert with greater attention to male health conditions, has resulted in a resurgence of studies investigating the mechanisms involved in maintaining sexual function in ageing men. As with LUTS, the most valuable evidence for these mechanisms has come from epidemiological and clinical studies of robust design (e.g. prospective cohort studies, randomised controlled trials).

3.2 Other male sexual dysfunctions

The following chapters will focus on the two most commonly reported male sexual functions: erectile dysfunction and low sexual desire [94]. However, there are a number of other male sexual dysfunctions, as summarised below:

Table 3-1. Major sexual dysfunctions in men (*Source: ICCSM Report, 2010*)

Sexual Condition	ICCSM Definition
Persistent genital arousal dysfunction (priapism)	Spontaneous, intrusive, and unwanted genital arousal (i.e., tingling, throbbing, pulsating) in the absence of sexual interest and desire
Premature ejaculation (Lifelong)	Ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy
Premature ejaculation (Acquired)	No consensus on evidence
Anorgasmia	The inability to achieve an orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm during any kind of sexual stimulation
Delayed ejaculation	The unwanted delay of ejaculation during sexual activities
Retrograde ejaculation	Occurs when semen enters the bladder instead of going out through the urethra during ejaculation
Dyspareunia	Persistent or recurrent pain during sexual activity

CHAPTER 4

Erectile Dysfunction (ED)

4.1 Mechanism of erection in men

Normal penile erections are maintained by two different mechanisms. The first one is the reflex erection, which is initiated by direct somatic activation of the penile shaft. The second is the psychogenic erection; the result of erotic or emotional stimuli. The former depends on the peripheral nervous system and the lower parts of the spinal cord, whereas the latter is mediated by the central nervous system (principally the limbic system) [95].

The penile erectile tissue, specifically the cavernous smooth musculature (e.g. corpora cavernosa) and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. In the flaccid state, these smooth muscles are contracted, allowing only a small amount of arterial flow for nutritional purposes. During sexual stimulation, neurotransmitters are released from nerve terminals resulting in relaxation of these smooth muscles and dilatation of the arterioles and arteries by increased blood flow and compression of the sub-tunical venular plexuses, reducing the venous outflow. This vasodilatation is activated through the cyclic GMP and cyclic AMP pathways, both of which are mediated principally through the release of nitric oxide (NO), but also involves other neurotransmitters (e.g. prostaglandins, endothelins) [95].

Following ejaculation, a series of local neuropeptide releases occurs (principally noradrenaline), leading to smooth muscle contraction, and consequent de-tumescence through the reversal of the veno-occlusive mechanism [96].

4.2 Definition

Erectile dysfunction (ED) is the major sexual arousal disorder in men. It is defined by the most recent report by the International Consultation Committee for Sexual Medicine (ICCSM) as "a consistent or recurrent inability of a man to obtain and/or maintain penile erection sufficient for sexual activity" [94].

4.3 Measurement

There are over 30 items that can be used in the assessment of ED (both self-report and administered). The most commonly used scales are summarised below:

4.3.1 International Index of Erectile Function (IIEF)

The IIEF is the most widespread tool for the assessment of ED in men. It was designed to be reliable and valid across cultures and can be used to monitor response to treatment. The full version of the IIEF (IIEF-15) [97] is a 15-item measure that can be used to assess overall sexual dysfunction, or can be specified to five separate domains of sexual function: erectile function (EF), sexual desire (SD), intercourse satisfaction (IS), overall satisfaction (OS), and orgasmic function (OF). A high degree of internal

consistency has been demonstrated for each of the five domains and for the total index (Chronbach's alpha values of 0.73 and higher, and 0.91, respectively). Each domain has a high degree of sensitivity and specificity to effects of treatment. Test-retest reliability correlation coefficients for the 5 domain scores were highly significant (EF = 0.84, SD = 0.71, IS = 0.81, OS = 0.77) [97].

- There is also a 5-item version of the IIEF (IIEF-5; or Sexual Health Inventory for Men (SHIM)) [98]. These 5 items focus on erectile function and intercourse satisfaction. This has been shown to be an excellent diagnostic test for erectile dysfunction.

4.3.2 Other common instruments:

Other major ED measures are listed below:

- Brief Male Sexual Function Inventory (BMSI): Popular measure, rapidly administered. Covers sexual drive, erection, ejaculation, perceptions of problems in each area, and overall satisfaction. Lower specificity that IIEF [99].
- Global Impotence Rating (GIR): Single-question item used to categorise participants as having no, mild, moderate or severe erectile dysfunction. This single question rating correlates well with the IIEF and the brief Male Sexual Function Inventory ($r = 0.71 – 0.78$, $P < 0.001$). Moreover, the prevalence of erectile dysfunction detected by the GIR is similar to that predicted by the IIEF and agreement was moderate (kappa = 0.56 – 0.58) [100].

- Sexual Functioning Questionnaire (SFQ): A standardised 62 items questionnaire which studies sexual dysfunction in both patient (14 items) and partner(both partners) [101].

- EDITS (Erectile Dysfunction Inventory of Treatment Satisfaction): A self-evaluation questionnaire on erectile dysfunction which is meant for male patients (13 items) and their partners (5 items). It explores achievements, perceived satisfaction, and treatment effectiveness [102].

4.4 Prevalence

Prevalence rates for ED are strongly supported by evidence-based literature, with over 100 studies from numerous regions now reporting some degree of ED in men.

4.4.1 Global

There is considerable variation in the prevalence rate reported in different regions of the world.

In Scandinavian studies, prevalence seemed to rise sharply after the age of 65 with rates of 20% or greater after this age and the rate doubling again when reaching the age of 70 years or older [103]. The prevalence of ED was generally quite low before the age of 61 years in the continental northern European studies (see [94]). Other European studies vary greatly, particularly for the age group 50–59 years of age. In general, rates of ED for elderly men (over 60 years) are comparatively high (20% to 40% of men examined). These rates increase dramatically for men in their 70s and 80s, ranging

from 50% to 75% in these decades. Below the age of 40 years, the prevalence rate is comparatively low, generally below 10%, although recent studies have demonstrated an increasing prevalence rates in these younger cohorts (20–30%), suggesting secular changes in health may be increasing the burden of ED in younger men [94].

In the seven available studies from North America, two studies (unstratified for age), reported the prevalence rate for ED of 16% and 22.5% [94]. The methods used for both of these studies were similar and involved 500 men from Canada in one report and 742 men in a report from the United States. For the other five U.S. studies that were stratified for age, prevalence rates for ED were between 13-19% for populations aged 18–59 [94]. However, the report from the Massachusetts Male Aging Study showed a prevalence rate of 23% for ED at age 40.

From Latin America there are 7 studies which have examined the population prevalence of ED, six of which came from Brazil. Of these, all reported prevalence rates for ED from 12–22% in younger men (below 40 years of age), and increasing to about 32–58% in older men (above 60 years of age) [94].

There are also several Asian studies that have investigated ED in community-based men (see [104] for review). As with studies from other regions though, Asian men similarly show an increased prevalence in ED in older age groups. In a recent Korean study, men aged 60–69 years were three times more likely to report ED than the youngest cohort age group, irrespective of whether ED was established through self-assessment or by IIEF-5 cut-off scores [105].

4.4.2 Australian

Overall, prevalence rates seen in Australian men was about 20%, ranging in age from 40–80 years [94]. For the studies that stratified for age, one study showed an increasing but still low rate of 13–19% for the decades 40–49 and 50–59 years. The two other studies stratifying for older ages showed marked increasing rates, starting at age 60, with increases across each of the three following decades [106]. The most recent report from Western Australia [107] utilized a wider age limit in their study (20-89 years) and reported an overall prevalence of 40%, an almost doubling of those seen in previous Australian studies.

In summary, the prevalence of ED on a worldwide basis shows a great deal of variability. This is for numerous reasons, including different age groups reported, differences in the definition of ED, population characteristics, sampling methods, duration and severity of ED, and geographic differences [94].

For younger men, the prevalence for ED is low at around 1–10%. In the immediately following decades (men in their 30's and 40's) there is a considerable range of prevalence's reported (from 2- 35%). Most of the world showed a rather high rate (between 20–40%) for elderly men (those aged in their 60's) and almost all of the reports showed a higher prevalence rate for those men in their 70s and 80s ranging from 50% to 100% prevalence of ED in these decades.

4.5 Incidence

4.5.1 Global

In comparison with the prevalence data available, there is a relative sparsity of incidence data on ED from prospective cohort studies. The crude incidence for ED is very similar in the American studies: 26 [108] and 28 [109] cases/1,000 man-years. A similar crude incidence of 28 cases/ 1,000 man-years was also presented in the study from the Netherlands [110], for clinically relevant ED at a mean follow-up of 2.1 years. The time of follow-up for the American studies were 8.8 years [108] and 2 years [109] respectively. However, in the study from the Netherlands [110], in the same group studied at a later period of time (almost doubling the follow-up time at 4.2 years), the crude incidence fell to 14 cases/1,000 man-years for clinically relevant ED. Age-specific incidence rates increased with aging for all of the studies. The crude incidence of ED from Finland [111], Brazil [112] and the UK [113] is higher with, respectively, 39, 54 and 66 cases/1,000 man-years.

4.5.2 Australian

To date there are no known studies of incident ED in Australian men.

4.6 Associations and risk factors

4.6.1 Age

Increasing age is the most consistent risk factor found in most epidemiological and clinical surveys of ED (see [114] for review). In ageing men, there is a degree of functional decline of endothelial repair mechanisms, vascular function and cavernosa integrity . Increasingly however it is recognised that many of the risk factors that accumulate with age can be modified to an extent where improvements in erectile function are discernible [95] [96].

4.6.2 Smoking

Data on the smoking behaviour as a risk factor for ED is equivocal. A cross-sectional study on the prevalence and risk factors for ED in the general population of Italian men found that current smokers had an odds ratio of ED of 1.7 (95% CI 1.2-2.3), while ex-smokers had an odds ratio of 1.6 (95% CI 1.2-2.3). The authors also found the association of smoking and ED risk to be present in men without a history of any cardiovascular disease [115]. Nicolosi *et al*. studied the epidemiology of ED in Brazil, Italy, Japan and Malaysia [116]. From each country, a random sample of around 600 men between the ages of 40 and 70 were interviewed. The authors found an odds ratio of ED of 2.12 (95% CI 1.26-3.56) in men who smoke >30 cigarettes/day compared to men who did not smoke [117, 118]. On the other hand, in a population-based survey of the 799 Belgium men aged 40 – 70 years, there was no correlation found between smoking and ED, either in current smokers or in ex-smokers [119]. Similarly, Morillo *et al.* reported on

the prevalence of ED in Columbia, Ecuador and Venezuela [120] in 1946 randomly selected men aged 49 and older. In their univariate analysis, the authors did not find any association of cigarette smoking with ED.

4.6.3 Alcohol

Alcohol has long been regarded as a risk factor for erectile dysfunction (ED), although the data from epidemiological surveys appears equivocal. Recent evidence suggests that alcohol may demonstrate a J-shaped (or inverse) relationship with ED, with moderate alcohol consumption conferring the lowest risk of ED. A recent meta-analysis of 11 cross-sectional studies found that consumption of 8 or more drinks/week significantly reduced the risk of ED (OR=0.85; 95% CI, 0.73–0.99), but consumption of less alcohol (1–7 drinks/week) was not significant (OR=0.73; 99% CI, 0.44, 1.20.) [121].

4.6.4 Diabetes

Erectile dysfunction has been reported to occur in at least 50% of men with diabetes mellitus, with the onset of ED occurring in an earlier age than those without diabetes mellitus [122]. In the Massachusetts Male Aging Study (MMAS) study, the age-adjusted probability of ED was three times higher in men who reported having treated diabetes mellitus than those without diabetes [77]. In the Health Professionals Follow-up Study (HPFU), men with diabetes had an age-adjusted relative risk of 1.32 (95% CI 1.3-1.4) for having ED compared to men without diabetes [73]. Men with type 2 diabetes had an increasingly greater risk of ED with increased duration since diagnosis, particularly for men diagnosed >20 years previously [73]. In a multicentre trial of 9,868 Italian men aged 20-69 years, subjects with insulin-dependent diabetes mellitus, diabetes present for

over ten years, with fair or poor control based on glycosylated haemoglobin, all showed a higher odds ratio for ED. A subset of 1,010 of these men without ED at baseline was followed prospectively for 2.8 years to determine the incidence of ED associated with diabetes [123]. The crude incidence rate was 68 cases per 1000 men years (95% CI 59-77). The incidence of ED increased with increasing age, duration of diabetes, and deteriorating metabolic control. The rate was higher for type 2 than in type 1.

4.6.5 Cardiovascular disease (CVD) and hypertension

Endothelial dysfunction is a condition present in many cases of erectile dysfunction, thus there is a shared pathway for other vascular disease states, such as cerebrovascular accidents, myocardial infarction, heart disease, hypertension, hyperlipidaemia, low serum levels of high density lipoproteins (HDL), arteriosclerosis, and peripheral vascular disease [106].

Earlier reports demonstrated that 64% of men, aged 31 to 86, hospitalized for acute myocardial infarction had current ED or were impotent [124]. More recently Swedish researchers demonstrated an 18% prevalence of ED in 49 men before experiencing a myocardial infarction compared to a prevalence of 45% after the event, and a 43% new onset or increase in ED in this group of men [125].

Physician-diagnosed heart disease and hypertension, and low serum levels of HDLs were significantly correlated with ED in the first ED study of the MMAS [79]. This group found that HDL vales of more than 90 mg/dL were associated with no probability of complete ED and conversely when the level of HDL dropped to 30 mg/dL the probability of complete ED was 16%. Clinical ED was present in 15% of men with treated hypertension and this incidence was associated with the duration and severity

of the hypertension [79]. In an analysis of the first two MMAS waves, it was shown that ED and coronary heart disease share some modifiable determinants in men who are free of manifest ED or predisposing illness at baseline [80]. Data from the placebo arm of the Prostate Cancer Prevention Trial examined the association between ED and subsequent CVD [113]. Of the 4247 men aged over 55 years without erectile dysfunction at study entry, 2420 men (57%) reported incident erectile dysfunction after 5 years. In multi-adjusted analyses, this equated to a hazard ratio of 1.45 (95% CI, 1.25-1.69) for a subsequent CV event, an equivalent to being either a current smoker or having a family history of myocardial infarction [113]. A detailed study from a registry of West Australian men with ED linked to hospital and death records also examined the association between ED and subsequent CV events [126]. By comparing the incidence of atherosclerotic CV episodes following the occurrence of ED in a cohort of 1660 men aged over 20 years, the authors were again able to demonstrate a predictive capability of ED for manifest CVD, most notably when ED appeared in younger men [126].

4.6.6 Lower urinary tract symptoms (LUTS)

See Section 2.8.5 (*Sexual function as risk factor for LUTS*)

4.6.7 Depression

It is well established that psychological disorders may lead to ED [127]. Using the Hospital Anxiety and Depression Scale (HAD), Dunn *et al.* found that depression, but not anxiety, significantly predicted ED onset [128]. Independent of antidepressant usage, Araujo *et al.* found that depression was associated with a doubling on the rate of ED [129].

4.6.8 Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) occurs when there are repeated episodes of complete (apnea) or partial (hypopnoea) blockage of the upper airway during sleep. These episodes lower the level of oxygen in the blood and frequently produce sleep disruption. Symptomatic OSA syndrome (OSAS) describes the combination of OSA together with significant daytime sleepiness [130]. In general, OSA is seldom considered in the clinical evaluation of ED [131]. An earlier review of 100 OSAS patients followed and treated with tracheostomy for their syndrome indicated that 48 had erection problems; 12 of them were individuals younger than 45 years and had absence of any other health problems, including depression. Tracheostomy led to complete resolution of ED in 47 of them, despite occurrence of depression post-treatment in some [132]. Despite these early reports, little advance has occurred in the understanding of ED and its association with OSA. There are many physiological mechanisms associated with obstructive sleep apnea (OSA) to support a theoretical relationship between OSA and ED, such as increased sympathetic tone, endothelial dysfunction, intermittent hypoxia, but these factors have not been studied together to better suggest the underlying mechanisms responsible for this association.

4.6.9 Medications

ED due to prescription medications is sometimes difficult to prove and is probably often under-reported. In the MMAS, a statistically significant correlation between ED and vasodilators, anti-hypertensives, cardiac and hypoglycemic agents was observed. However, after adjustments for co-morbidities and health behaviours only non-thiazide

diuretics and benzodiazepines remained statistically significant [132]. Other major classes of prescription drugs commonly reported to be associated with ED are histamine-2 receptor antagonists, hormones, anticholinergics, psychotropics and certain cytotoxic medications [133].

CHAPTER 5

Sexual desire in ageing males

5.1 Regulation of sexual desire

The regulation of sexual desire in men is an understudied area of scientific research. Researchers and sexologists have tended to use two main theoretical frameworks in understanding male sexual desire. The first and most common depict sexual desire as an innate motivational driving force (commonly referred to as *sexual motivation*). The second framework emphasises the relational aspects of sexual desire, conceptualizing desire as one factor in a broader psychosocial context (generally referred to as *sexual arousability*) [134]. There is still intense debate about the relative contributions of each [135], with the sexual desire responses in men generally appearing to be situational.

5.1.1 Mechanisms of Sexual Excitation

Brain pathways for sexual excitation involve the activation of incertohypothalamic and mesolimbic dopamine transmission in the medial preoptic area (mPOA) and nucleus accumbens (NAcc) (Figure 5-1) that focuses attention on incentive sexual stimuli and engages motor patterns of approach and consummation [134]. Collectively, the behavioural patterns stimulated by those systems and the subjective feelings that accompany them constitute sexual drive or, when mixed with genital and sympathetic

arousal, "libido" [134]. The tuberoinfundibular dopamine system controls hormone release from the anterior pituitary gland [134].

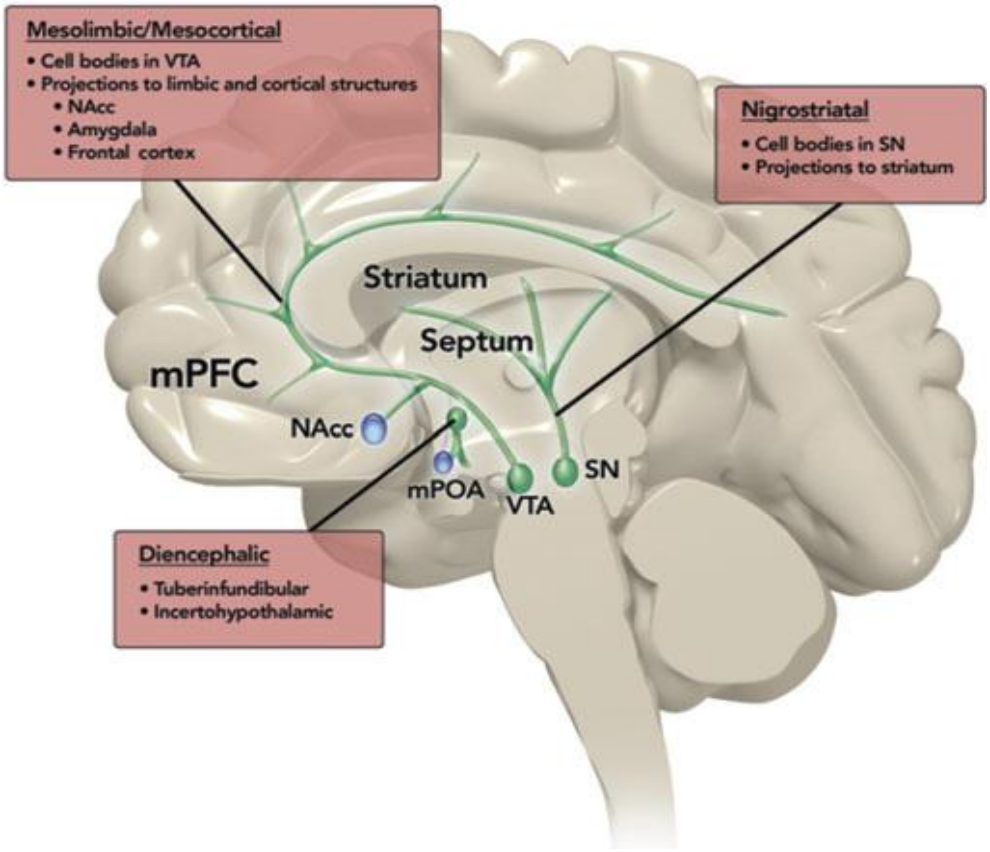


Figure 5-1. Major brain centres controlling sexual arousal and drive. Dopamine (DA) systems include the diencephalic incertohypothalamic DA system, with terminals in the anterior hypothalamus, the mesolimbic and mesocortical DA system, with terminals in the NAcc (and other limbic regions) and mPFC, respectively, and the nigrostriatal system, with terminals in the striatum (caudate and putamen). (*Source: Pfaus et al., 2009*)

5.1.2 Mechanisms of Sexual Inhibition

Relative to sexual excitation, far less is understood about mechanisms of sexual inhibition. Brain pathways for sexual inhibition involve the activation of inhibitory opioid, endocannabinoid, and serotonergic systems to various levels of the excitatory pathway [134]. Collectively, the behavioural patterns stimulated by those actions, include sexual reward, satiety, refractoriness, and exhaustion [134]. The excitatory pathway is stimulated hormonally and conditioned by the expectancy of sexual rewards. The

inhibitory pathway is activated by sexual stimulation that reaches critical thresholds for sexual reward, sedation, and satiety [136]. As a general rule, inhibition appears to be more "powerful" than direct excitation in the nervous system [134]. Bancroft and Janssen [137] argued that a normal amount of sexual inhibition keeps individuals from engaging in risky or inappropriate sexual behaviours, which a lack of inhibition would promote (as occurs in individuals with dementia, or brain damage sustained after head trauma). Conversely, too much central inhibition was viewed as increasing the risk of sexual dysfunction, including inhibited arousal, desire, and/or a diminished capacity to achieve sexual gratification [137]. Excessive inhibition may thus lead to reduction in intimacy and disruption of bonding between partners, to the point that sexual activity, if it is engaged in at all, becomes a routine of "going through the motions" rather than an enriching and rewarding experience.

5.2 Definition

There is no universally accepted definition of male (or indeed, female) sexual desire. The Diagnostic and Statistical Manual of Mental Disorders -Edition IV-Text Revision (DSM-IV-TR) from the American Psychiatric Association requires the following criteria for a diagnosis of hypoactive sexual desire disorder(HSDD): 1) persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity; and 2) the disturbance causes marked distress or interpersonal difficulty [138].

The latest report from the ICCSM similarly defines sexual interest/desire dysfunction in men as: '*diminished or absent feeling of sexual interest or desire, absent sexual*

thoughts or fantasies, and a lack of responsive desire; motivations (reason-incentives*) for attempting to become sexually aroused are scarce or absent'* [94].

Neither definition has seen widespread uptake in studies investigating low sexual desire in men, with most using a variety of measures to assess perceived symptoms of low sexual desire.

5.3 Measurement

A number of validated self-report instruments are now in use to assess the sexual desire in men. There is no one measure regarded as a "gold standard", however, the most commonly used are summarised below:

5.3.1 Sexual Desire Inventory 2 (SDI-2)

The SDI-2 is a well-validated self-report questionnaire that specifically evaluates sexual desire in the absence of consummatory behaviour [139]. Furthermore, the SDI-2 measures two aspects of sexual desire: dyadic, meaning an interest in or wish to engage in sexual activity with another person, or a desire for intimacy and sharing with another; and solitary sexual desire, meaning an interest in engaging in sexual behaviour with oneself and may involve a wish to refrain from intimacy and sharing with others. Internal consistency of the inventory is high with Chronbach's alpha values of 0.86 for dyadic and 0.96 for solitary sexual desire [139].

5.3.2 Sexual Desire domain of the IIEF (IIEF-SD)

See Section 4.3.1

5.3.3 Brief Sexual Function Inventory

See Section 4.3.2

5.3.4 Sexual Excitation / Inhibition Scales (SES; SIS 1)

Developed to measure the self-assessment of the two theorised mechanisms of sexual desire [140].

5.3.5 Sexual Arousability Inventory

A 28-item questionnaire that psychometrically evaluates the level of arousability produced by sexual experiences. Meant for men and women regardless their psychosexual orientation [141].

5.4 Prevalence

For men, dysfunction of sexual desire is generally much less prevalent than a loss of interest in all sexual activity. The population level of sexual interest appears quite stable from adolescence into older age (around 60 years of age), after which it decreases markedly [142].

5.4.1 Global

The National Health and Social Life Survey (NHSLS) involved face-to-face interviews with 1,419 American men aged 18–59 years who were asked questions about the prevalence of seven different sexual symptoms [143]. The prevalence of low desire ranged from 14% (for 18–29 year olds) to 17% (for 50–59 year olds). Men in the eldest

cohort (age 50–59 years) were three times more likely than men in the youngest cohort to experience low desire. In the National Survey of Sexual Attitudes and Lifestyles (NATSAL), in which 11,161 British men participated in a computer-assisted self-interview, lack of interest in sex was the most prevalent problem in men, reported by 17.1% of those who had at least one heterosexual partner in the past year [144]. However, persistent lack of interest in sex (i.e. lasting at least 6 months in the previous year) was reported by only 1.8% of the male sample. In a nationally-representative Swedish survey of 1,475 men aged 18–74 years, sexual desire was assessed by asking participants, in face-to-face interviews, the frequency of decreased "interest in sex." Any respondent who answered that the symptom had occurred in the last 12 months "quite often/nearly all the time/all the time" was categorized as having a sexual "disability." Similar to the reported rates from the NHSLS and NATSAL, low sexual interest in men was the most frequent sexual complaint (16% of men). Moreover, although the prevalence was significantly lower for men in the youngest age group (6% in those aged 18–24 years), 41% of men aged 66–74 years reported decreased interest in sex—a rate that was comparable to that for women in the same cohort [145]. In another Scandinavian study, 10,458 Danish, randomly-selected men aged 16–67 years took part in interviews during which sexual desire was assessed with two questions [146] ("How often do you have sexual desire?", and "If you compare your sexual desire with your sexual desire five years ago, is it higher or lower now?"). Sexual desire decreased with age, such that 72% of men aged 16–24 years "often" had sexual desire, whereas only 14% of men aged 67 years or older reported this. With increasing age, men were also more likely to report a change in sexual desire over the last 5 years, although there was no change in the age group 45–66 years reflecting back on the past 5 years. In

computer-assisted telephone interviews with 742 American men aged 40–80 years, frequent lack of sexual interest was reported by 3.3% of men and periodic lack of desire by 4.8% of men [147]. This represented the third most common sexual complaint in men, after premature ejaculation and ED. Focusing specifically on middle-aged and older men internationally, the Global Study of Sexual Attitudes and Behaviours studied 11,205 men who had had intercourse at least once in the past year, with the prevalence of frequent lack of sexual interest ranged from 1.3% in Southern Europe to 3.1% in the Middle East [148]. Researchers from the MMAS examined within-person changes in sexual function among 1,156 men who participated at baseline (in 1987–1989) as well as at follow-up (in 1995–1997). Sexual desire was assessed by asking: "How frequently do you feel sexual desire?" [149]. Men reported feeling desire slightly more than once per week. Changes from baseline were associated with age; men aged 40–49 years had the smallest decline in desire as well as all other sexuality variables (e.g., erectile function, ejaculation frequency, sexual satisfaction).

5.4.2 Australian

Of the Australian studies, there are two large-scale studies that have specifically investigated low sexual desire in men. Using a random cross-sectional design and computer-assisted telephone interviews with 876 Australian men aged 18–59 years, the prevalence of lack of interest in sex lasting "several months or more" ranged from 19% (youngest cohort aged 18–29 years) to 16% (aged 50–59 years) [150]. After premature ejaculation (PE), low sexual interest comprised the second most common sexual problem reported by men. In the Australian Longitudinal Study of Health and relationships (ALSH), 3,240 men were asked about their sexual desire, with 16% of

respondents reporting low levels of sexual desire (and an equivalent amount also reporting dissatisfaction with their sexual frequency) [151].

5.5 Incidence

To date there is no known data on incidence of low sexual desire in men from Australia or elsewhere.

5.6 Associations and risk factors

5.6.1 Age

Increasing age has long been thought of as the most important determinant of sexual desire. In their landmark reports of human sexuality, Kinsey *et al.* found that of the eleven factors examined in relation to desire, none seemed more important than age [152]. Sexual behaviour in men overall declines steadily from adolescence into older age, however the decline in desire in men is thought to be less dramatic and variable [153]. Recent studies suggest that older adults continue to be interested in sex as long as poor health does not affect their sexual desire [153]. In the MMAS, researchers reported that sexual desire and frequency of sexual thoughts and dreams decreased with age [149]. In a group of 894 UK healthy men in stable sexual relationships, sexual desire decreased as age increased [154]. Others have also found that sexual interest declines in ageing men (see [135] for review).

5.6.2 Sex steroids

The effect of androgens on desire/interest and sexual behaviour is well established but few reports show direct end organ-dependency on androgens. In an extensive study of 1,647 men attending an outpatient clinic for sexual dysfunction, Corona *et al.* found an association between HSDD and low testosterone was significant only in the youngest quartile of men (ages 17–42 years), whereas in the intermediate age group (43–62 years), there was no link between testosterone and any sexual parameters [81]. Treatments which increase testosterone have variable effects on men's sexual desire. In one double-blind, randomized, controlled trial of 207 elderly men with baseline low-normal testosterone (all men were below the 50th percentile of testosterone values) receiving oral testosterone for 6 months, there were no significant improvements in sexual fantasies, desire for sex, or frequency of sexual behaviour [155]. A review of testosterone efficacy in hypogonadal men suggests that, overall, treatment does result in a significant increase in sexual desire, although effects on partnered sexual activity are less consistent given that the latter is influenced by partner-related factors [137]. Measures of sexual arousal, including penile rigidity and the nocturnal penile tumescence response, are also restored when hypogonadal men receive testosterone [137].

5.6.3 Psychological factors

Psychological factors are major determinants of the intensity of sexual desire. In a sample of male outpatients seeking treatment for sexual dysfunction, psychological symptoms were more predictive of low desire than hormonal/physical markers [81]. This

strong association between mood and sexual desire was also found in an earlier study that compared 22 men with a DSM-III diagnosis of inhibited sexual desire vs. a control group of 19 men without low desire [156]. The relationship between mood and sexual desire in men is complex and not necessarily linear. For example, in the Zurich Cohort Study, a longitudinal study of 591 men and women aged 20–35 years, depression was significantly associated with low libido, however this was more pronounced among women than men [157]. Roughly equal proportions of men responded to depressed mood with increased and decreased sexual desire. In the proposed upcoming diagnosis of hypersexual disorder in men, using sexual activity to regulate a depressed or anxious mood has also been recognized as one important function of this condition [158].

5.6.4 Cardiovascular disease

Cardiovascular diseases, such as myocardial infarction, hypertension, and peripheral vascular insufficiency (atherosclerosis), are commonly associated with low sexual desire in men [146]. Many studies have reported a loss of sexual drive in as few as 10% to as many as 70% of patients after myocardial infarction [159]. Studies on sexual behaviour after a stroke report decreased levels in sexual desire [160], [161]. There are, however, methodological issues to be considered in evaluating the results of these studies, including the lack of consideration of age effects and the level of sexual function and desire prior to infarction. Further, all of the cited research involved treated patients, confounding the effects of disease and treatment. Hypertension is prevalent among older adults, and it is also associated with peripheral vascular disease, myocardial infarction, and stroke. Although there are numerous studies on the sexual

consequences of anti-hypertension treatment (see [162] for review), there are few on sexual functioning in persons with these illnesses who are not receiving treatment.

5.6.5 Diabetes

Diabetes mellitus is one of the most frequent systemic disorders associated with sexual disorders in ageing adults. While the type of diabetes (e.g. type 1 diabetes mellitus vs. type 2 diabetes mellitus) appear to operate through different mechanisms in the development of ED [163], the type of the diabetes appears less important to the development of ED than the duration of diabetes [164]. Unfortunately, there are few controlled studies of the psychology of sexual dysfunction (e.g. arousal, desire) in those with diabetes [165].

5.6.6 Prostate disease

Prostate disease occurs frequently in ageing men. Prostate cancer is the most common cancer in Australian men, present in almost 90% of men aged 80 and older, and is the second most common cause of cancer deaths in men [4]. Sexual dysfunction is a common complication of this disease and its treatment. Recent advances in prostate surgical techniques have allowed for a greater degree in nerve-sparing during prostatectomy, leading to better outcomes for the sexual functioning of patients [166], however a full recovery also depends on the age of the patient. Moreover, conclusions are limited by insufficient information about sexual response and functioning prior to surgery, other diseases, and medications [167].

5.6.7 Medications

Numerous prescription drugs have adverse effects on sexual desire including antidepressant and anti-hypertension medications [168]. Moreover, adverse drug effects have been reported much more frequently in the ageing population than in the general population [137]. Medications may influence sexual desire by nonspecific effects on general well-being, energy level, and mood [169]. Drugs for the treatment of high blood pressure represent the single largest medication group responsible for sexual side effects. These drugs include alpha-blockers, diuretics, and calcium - channel blockers [170]. Previous studies have shown that the incidence of drug-induced sexual dysfunction increases as men take increasing dosages of anti-hypertensive drug treatments [169]. Drugs used to treat psychiatric disorders can also cause sexual side effects. Antipsychotic medications, tricyclic antidepressants, monoamino-oxidase (MAO) inhibitors, and sedative drugs may contribute to decreasing levels of sexual desire [171]. However, among drugs used to treat psychiatric illnesses, the selective serotonin reuptake inhibitors (SSRIs) are the major medications that have been implicated in diminished sexual desire. The effects of SSRIs on sexual functioning seem strongly dose-related and are also connected to the tendency for SSRIs to accumulate over time [171].

5.6.8 Socio-demographic factors

The presence or absence of a sexual partner is an extremely important factor in understanding differing levels of sexual desire and activity among ageing men. Many people consider sexual intimacy to be only or most appropriate in marriage [137]. Many

older persons are not married or no longer live with a spouse. Thus, the death of a spouse usually leads to the cessation of sexual behaviour [172]. For those who do have a sexual partner, monotony in sexual relationships, such as predictability of sexual activities and over-familiarity with the partner, may also contribute to a loss in sexual desire [173]. As the length of the marital relationship increases, habituation to sex with one's partner increases and frequency of sexual activities declines [173]. However, data from the Consumers Union Survey on Sex and Ageing involving 4,246 men over the age of 50 and their partners, the majority of happily married men rated sex as important in marriage, while 54 per cent of their partners rated sex as being "of little importance" [174]. These results suggest that satisfaction with the relationship may be an important influence on desire. Other contrary results may reflect marital unhappiness rather than loss of desire. Sex is important for many unmarried older adults, too. Some such men fulfil their desire for sexual intimacy within a long-term committed relationship [173], however little information is known about the sexual activity of older persons who live alone.

Household income is potentially an important social factor. An individual or couple with a higher income has access to health care and activities that may maintain general physical and mental health. Better health, in turn, is likely to be associated with sexual desire [134]. The problem of decreased to almost non-existent sexual desire is significantly more common in men of lower social class [175].

Employment has also been shown to be a particularly strong determinant of sexual desire in men (see [176] for review). This is purported to be confounded by concomitant changes in mood, marital status, income and access to health care [135]. However, as yet

no study has been able to examine changes to employment status on any of these factors and their related outcomes.

CHAPTER 6

The Florey Adelaide Male Ageing Study (FAMAS)

6.1 Study design and participant recruitment

The FAMAS is a population-based cohort study that commenced in 2002 involving 1195 men aged 35-80 years recruited from the north-west regions of Adelaide [177]. As a result of funding availability men were enrolled in two phases: from August 2002 until July 2003, inclusive (Phase 1, 568 participants) and June 2004 to May 2005 (Phase 2, 627 participants). Participants are asked to complete annual follow-up questionnaires, and full follow-up clinic evaluations occur at five-yearly intervals.

6.2 Sampling

Participants in the study were required to be male, aged between 35 and 80 years at the time of recruitment, living in the defined catchment area of north and west Adelaide with a connected telephone and number listed in the Electronic White Pages (EWP), be willing and able to comply with the protocol, and give written, informed consent. Exclusion criteria were limited to living outside the catchment area and telephone numbers that belonged to non-residential properties (i.e. businesses, institutions and residential-care facilities) in accordance with the desire to accurately reflect the male population of the sample. Highly trained recruitment staff were also

instructed to exclude respondents if they were: a) of insufficient mental or physical ability to understand the requirements of participation or adequately participate; b) to ill or otherwise incapacitated to attend clinics; c) currently residing in an institution (e.g. aged care facility); or d) had severely limited English.

The sample was stratified into the two health regions directly under investigation: Western Adelaide and Northern Adelaide. The northern and western areas of Adelaide comprise approximately half of the city's population and over a third of the state's population, and broadly reflect the demographic profile of the state's population. Residential households were selected at random, with the male person aged between 35 and 80 years to last have his birthday invited for interview and study participation. This method of randomly selecting within the household avoids a selection bias towards the unemployed, retired or homemakers [178].

6.3 Recruitment & CATI survey

In accordance with established mailing protocols [179], a letter introducing the study, along with an information brochure, was sent to selected households approximately 2 weeks prior to attempting to contact the residence. The letter and brochure informed potential participants of the purpose of the study and indicated that they could expect to be contacted by telephone. Contact details were also supplied for willing participants who for logistical reasons, could not be contacted during regular recruitment period hours. A number of initiatives were undertaken to increase general awareness of the study in the target community. These included local media events (television, print and radio) and a study launch held at a national sporting complex and

opened by the State's health minister, with various political, sporting and business identities and members of the general public attending.

The telephone recruitment was conducted by an external agency with qualified staff utilizing a Computer-Assisted Telephone Interviewing (CATI) system. This method utilises the Electronic White Pages (EWP) as the sampling frame, using six digits of the standard eight digit telephone number in addition to prefixes and exchanges provided by the directory's administrator (Telstra) within geographically defined areas. This technique yields a final sampling frame that is more than adequate to cover all households within the catchment areas and has been demonstrated to be as effective as other survey methods [180].

The CATI transcript included a series of questions relating to the interviewees demographics (age group, residential location, predominant occupation, number of adults/children in household), history of health conditions/events (physician nominated diabetes, asthma, bronchitis, emphysema, heart attack, stroke, angina or none) and nominated risk factors (smoking, weight/height self-estimates, hypercholesterolemia, hypertension). The transcript also allowed the coding of all reasons for non-participation (i.e. poor to no English skills, too busy, lack of perceived benefit, too old, don't want to, too sick, none given or other).

Following removal of all non-residential telephone numbers from the drawn sample, calls were made on alternate evenings and weekends to maximize chance of contact. Calls were also made on other occasions if specifically requested. In general, no more than ten attempts were made to the same phone number. Upon contacting the household, the interviewer firstly identified themselves and the purpose of the study.

The interviews were conducted in English however every attempt was made to be as inclusive as possible for all interviewees. When required for poor-English speaking interviewees, a friend or family member of the interviewee was arranged to join the telephone interview as an interpreter (and attend the subsequent clinic session).To further facilitate recruitment, the interview was restricted to approximately 15 minutes duration. Participants were subsequently given reminder calls on the eve of their clinic visit. The period between screening call and clinic was generally within a fortnight and no more than two months

6.4 Ethics approval

All protocols above were approved by the Royal Adelaide Hospital Research Ethics committee (REC # 020305) and, where appropriate, the Aboriginal Health Research Ethics Committee of South Australia.

Participants were provided with feedback upon completion of all study procedures. Following clinics, a copy of all relevant results (laboratory, clinical) accompanied with an explanatory cover letter was sent to participants' and, where permission was given, to their nominated physician. In the case of a clinically significant result, participants were advised to immediately contact their treating physician for further examination.

6.5 Response rates

After adjusting for those not contactable or ineligible in accordance with the methods of Slattery *et al.*[181], the response rate for the study (percentage of sample eligible for recruitment) was 67.8%, the overall participation rate (percentage of eligible sample

who agreed to be interviewed) was 70.7% and the final response rate of the eligible sample that ultimately attended the clinic was 45.1%. Of the 3115 men sampled, 57 had “low English” or equivalent recorded.

6.6 Non- responders

Non-responders were those men that refused participation in the study but had completed some or all of a series of supplementary demographic questions.

There was no age difference observed between participants and non-responders. Similarly, there was no difference between groups for area of residence, estimated body mass index (BMI: calculated from self-reports of weight & height), or number of children in a household. Additionally, no obvious difference existed in the type of work men had done for most of their lives.

In terms of health status, non-responders were no different in prevalence of physician-diagnosed incidences of hypertension, asthma, bronchitis, emphysema, heart attacks, episodes of angina or mental health conditions (anxiety, depression, stress or other). However, there was an increased prevalence of diabetes and stroke in those that chose not to participate. There was no recorded difference between groups for participants reporting an absence of existing health conditions. Non-responders were, however, more likely to live alone and be current smokers (although there was no difference between groups on whether they had previously smoked regularly). Non-responders were also less likely to report elevated cholesterol levels (both previously and at time of interview).

6.7 Representativeness

The representativeness of the cohort against selected demographic data (age, region, marital status, educational data, income & work status) from the 2001 Census figures [182] for the target (northern & western Adelaide) and Australian population is shown below.

6.7.1 Age

The mean age of the study participants was 55.0 ± 11.6 (min. 35 – max 80 at clinic). Residual analysis from a goodness-of-fit test demonstrated that young males (<45) were under represented and 55-64 years old were over represented in comparison to Census data.

6.7.2 Marital status

Eighty-two per cent (N = 974) of men were married or living with a partner. In comparison to Census data, there was an under representation of men who had never married.

6.7.3 Region of birth

Sixty-seven per cent (N = 795) of participants were born in Australia, slightly higher proportions than observed in both Census figures. The most frequent countries of birth outside of Australia were the United Kingdom (including North Ireland, Scotland and Wales) & Ireland with 218 participants (18.2%). Such participants appeared to be overrepresented in the study sample as compared to the broader population. Of the

men born outside Australia, the average amount of time spent in Australia was 36.5 ± 11.9 years.

6.7.4 Employment status

Fifty per cent (N = 597) of participants were in full-time employment; 9% (N = 111) part-time and 4% (N = 42) self-employed, whilst 3% (N = 32) were unemployed at time of survey. Thirty-four precent (N = 405) had no active involvement with the work force, the majority of whom were retired (N = 351). In general, there was good agreement between study and Census figures of employment.

6.7.5 Education level

Seventy-one per cent (N = 848) of men had obtained some form of qualification since leaving school. Sixty-seven per cent (N = 392) had obtained a trade qualification or equivalent, 24% (N = 142) had a bachelor degree or higher whilst 8% (N = 48) reported having some other qualification (Table 4).The average age that participants left school was 16.0 ± 2.0 years old. When compared to Census figures, which include all males over the age of 15 years, the FAMAS cohort appears to display a higher proportion of study participants with some form of post-school qualification; specifically, a higher proportion of trade & tertiary qualifications were observed in the cohort when compared to North West Adelaide and Australian males, respectively.

6.7.6 Gross annual household income

For an approximate comparison, Census income data (Average Weekly Earnings) were extrapolated into annual figures. Of the 98% of study participants who disclosed their

gross annual household income, 7% (N = 80) of men had gross household incomes in the lowest bracket (up to $12,000 p.a.) which appeared to be a higher proportion than that observed in the target population. The remaining income brackets in the cohort were consistent with the distribution observed in the broader populations, with the noted exception of an absence of the high-income spike observed in the Australian data.

6.8 Measures

6.8.1 Clinic visits

Clinic visits took place at the Queen Elizabeth Hospital (TQEH) and Lyell McEwin Health Service (LMHS) depending on a participants residence. In general, clinics were held from Monday to Saturday (between 0700 and 1130) on alternating weeks at the respective locations. Participants arrived following an overnight fast of approximately 12 hours for a blood draw. If a subject's medication regimen prevented a fasting visit, this was duly recorded in the clinic notes.

Prior to participation, subjects were sent a clinic pack containing all study documentation (information & consent forms, personal, secondary & physician contact detail forms) as well as the self-administered FAMAS Questionnaire A. This was compiled as a general health and wellbeing questionnaire with well-validated measures extensively used in population research. Questionnaire A included standard demographic questions based on those in the Australian Census 2001 [182] regarding ethnicity, income, education and work status, and health information regarding medical conditions, prior surgery, medication use and cigarette smoking from other

statutory sources . Also included in this questionnaire was the 36-item short-form health survey 36 (SF-36) [183], the Beck Depression Inventory (BDI) [184], physical activity measure (1999 National Physical Activity Survey) [185], the International Prostate Symptom Scale (IPSS) [27] and items assessing symptoms of obstructive sleep apnoea (OSA) [186]. Clinic packs also included the Australian Cancer Council of Victoria's (ACCV) self-administered, optically scanned Food Frequency Questionnaire (FFQ), used to assess the composition of participants' diets [187].

During clinic visits, a separate questionnaire assessing sexual desire and erectile function (Questionnaire B) was completed in private. This included the SDI-2 [139], the IIEF [97] and the GIR [100]. Participants were also required to complete a brief survey recording their levels of engagement with a variety of health care providers and satisfaction with available services (Health Service Utilization Questionnaire). Anthropometry (height, weight, waist and hip measurements as per Norton & Olds [188]), blood pressure measurements, a brief neuropsychological assessment (Fuld Object Memory Evaluation, Trail Making Test and finger tapping & handgrip strength [189]), and uroflowometry tests were also completed during the approximate 45-minute clinic visit. In addition, clinic staff had the capacity to record any other observations on participants deemed to be of clinical relevance.

6.8.2 Blood sample

A fasting blood sample (approximately 25 ml) was taken upon arrival at clinic by venepuncture in the antecubital fussa and immediately refrigerated and transported to a NATA certified laboratory for analysis. Surplus serum was stored at -70°C for future analysis. An additional 5ml of whole blood was collected for DNA analysis.

6.8.3 Uroflowometry

A portable uroflowometry analyser (UROCAP-II, Laborie Medical Technologies, Ontario, Canada) was used to measure multiple characteristics of a participant's urine flow (peak & mean flow; voiding & flow time; time to peak flow; voided volume). Following completion of testing, a small sample (approximately 5 ml) was collected and stored for later analysis.

6.8.4 DEXA scans

Participants had whole body and lumbar spine bone mineral density (BMD) and whole body and regional body fat and lean mass measured by dual energy x-ray absorptiometry (DEXA) at their earliest convenience using the LUNAR DPX+ pencil beam densitometer (GE Lunar Corporation) [190]. Participants were informed of radiation exposure levels (~0.18 µSv per scan) and given the opportunity to discuss the procedure with an experienced administrator. Ultimately, 89.5% of participants agreed to a DEXA scan, with work commitments being the major reason cited for non-attendance.

6.8.5 Data linkage

Following specific consent from participants, data were obtained from Medicare Australia on participants' usage of the Medicare & Pharmaceutical Benefits Schemes and linked with self-reports of health conditions, health service and medication usage. These data are anticipated to be collected at every clinic wave.

SECTION II

PREVALENCE AND RISK FACTORS FOR LOWER URINARY TRACT SYMPTOMS & SEXUAL DYSFUNCTION IN MEN

CHAPTER 7

Prevalence and factors associated with uncomplicated Storage and Voiding Lower Urinary Tract Symptoms in community-dwelling Australian men

Sean A. Martin[1], Matthew T. Haren[2], Villis R. Marshall[1,3], Kylie Lange[4], Gary A. Wittert[1] and Members of the Florey Adelaide Male Ageing Study[1]

[1] Freemasons Foundation Centre for Men's Health, School of Medicine, The University of Adelaide, Adelaide, South Australia

[2] SANSOM Institute, Division of Health Sciences, University of South Australia, Adelaide, South Australia

[3] Surgery and Surgical Specialties, Royal Adelaide Hospital, Adelaide, South Australia [4] Centre of Clinical Research Excellence in Nutritional Physiology, Interventions and Outcomes, Discipline of Medicine, The University of Adelaide, Adelaide, South Australia

Published: World Journal of Urology (April 2011 Volume 29(2), pp 179-84)

Statement of Authorship

Sean A. Martin (Candidate)

Roles: Corresponding Author; Conception and Design; Acquisition of Data; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Matthew T. Haren

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Villis R. Marshall

Roles: Sought and Obtained Funding; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Kylie Lange

Roles: Design; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Gary A. Wittert

Roles: Principal Investigator; Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

7.1 Abstract

Purpose: To determine the prevalence of, and associated risk factors for, voiding and storage lower urinary tract symptoms (LUTS) in a population-based sample of Australian men.

Methods: Data were collected from 1,103 men randomly selected, community-dwelling men, as part of the Florey Adelaide Male Ageing Study, after exclusion of men with prostate or bladder cancer or prior surgery to either organ. The presence of LUTS was assessed using the International Prostate Symptom Score. Urine flow was measured via flow meter. Demographic, clinical, and bio-psychosocial data were collected by questionnaire.

Results: The prevalence of total, storage, and voiding LUTS was 18.1, 28.0 and 12.6%, respectively. The most common storage symptoms were frequency (12.3%), nocturia (9.9%) and urgency (8.1%), and voiding symptoms were weak stream (8.5%), intermittency (5.4%), incomplete emptying (5.1%) and straining (2.4%). There were linear associations between storage LUTS and increased abdominal fat mass, plasma glucose and low HDL cholesterol (components of the metabolic syndrome), obstructive sleep apnoea (OSA) risk, and retirement. Voiding symptoms were associated with a previous diagnosis of benign prostatic enlargement (BPH), mean peak urine flow, total energy intake, elevated risk of OSA, erectile dysfunction, physician-diagnosed thyroid dysfunction and higher household income.

Conclusions: The close association of storage LUTS with the metabolic syndrome, and of both storage and voiding LUTS with OSA, suggest that these conditions should be considered in men presenting with LUTS.

7.2 Introduction

Lower urinary tract symptoms (LUTS) are frequent in men and not necessarily the result of prostate abnormalities. While the prevalence and severity of LUTS increases with age, there is considerable geographic variation for this age effect. Bothersome urinary symptoms may also occur in younger men in the absence of abnormalities of the prostate, and there is growing recognition that LUTS may be a reflection of other systemic disease processes. Recent studies have reported independent associations between LUTS and excess body mass [48], smoking and alcohol consumption [70], physical activity [71], sexual dysfunction [191], cardiovascular, metabolic and endocrine factors [72]. In many of these studies a limited amount of these potentially interacting confounders are controlled for. Some studies also exclude younger males [192], include men with clinical BPH only [193], or use internet-based sampling without clinical assessment [194].There is also evidence that storage and voiding symptoms may be susceptible to different risk factors, yet the majority of studies examine potential associations with total LUTS only. In this study we report the relationships between voiding and storage LUTS and a range of clinical, urologic, behavioural and other health-related factors in a randomly selected cohort of community-dwelling Australian men, aged 35-80 years who attended clinics for assessment.

7.3 Methods

7.3.1 Study Subjects

Data were obtained from the Florey Adelaide Male Ageing Study (FAMAS), a randomly-selected population-based study of males, aged 35-80 years at recruitment and residing in the northern and western suburbs of Adelaide, Australia. Details of the FAMAS design, procedures and participants have been published elsewhere [195]. All protocols were approved by the Royal Adelaide Hospital Research Ethics Committee. Participants provided written, informed consent.

7.3.2 Lower Urinary Tract Symptoms (LUTS)

The seven-item International Prostate Symptom Score (IPSS) was used to evaluate the presence of LUTS. Initially, men were classified as having storage symptoms if the sum of their score on IPSS items 2, 4 and 7 was ≥ 4 and their score on item 4 (i.e. urgency) was ≥ 1. Subjects were classified as having voiding symptoms if the sum of their score on IPSS items 1, 3, 5 and 6 was ≥ 5. A portable analyser (UROCAP-II, Laborie Technologies, Ontario, Canada) was used to evaluate participants urine flow. Only men with a voided volume of > 150 ml were included for this study, with the peak recorded flow, adjusted by peak volume (Qmax (vol)).

7.3.3 Other co-variates

In addition to urological assessment, a number of other assessments took place during clinic visits. Details of these have been published previously [195]. These measures included assessments of age, education, marital, occupational and smoking status,

diagnosed and family history of major illness, medication usage (by self-report and through data linkage with the national pharmaceutical registry), depression, obstructive sleep apnoea, sexual desire and erectile function, macronutrient intake, physical activity, anthropometry (height, weight, waist and hip, body composition by DEXA), blood pressure, and handgrip dynamometry. Finally, a fasting blood sample was taken upon arrival at clinic by venepuncture for hormonal measurement (including lipid, glucose, PSA and sex steroids) by a NATA certified laboratory[195].

7.3.4 Statistical modelling

For the present study, men with a history of bladder (n=8) or prostate cancer (n=35) or surgery (n=41) and those with a self-reported urinary tract infection (n=7), together with men who regularly took alpha-blockers (n=16) or anti-androgens (n=2) for purposes other than BPH, were excluded from analysis. In addition, men who voided less than 150ml (n=17) were also removed from this analysis. In total, 92 men were excluded from this study having met one or more of these criteria. For the final regression model, independents were selected on the basis of demonstrated or suspected associations with outcome. Interactions between each final independent and selected or related covariates (age, BMI) were tested for their effects on the outcome measure. No significant interaction between independents was detected. All data were weighted according to the inverse of their probability of selection from the target population and analysed using SPSS (V. 15.0) with an α of $\leq .05$ for all tests.

7.4 Results

Table 7-1. Prevalence of total, storage and voiding LUTS in cohort of Australian men

Age Group	Total LUTS *		Storage LUTS *		Voiding LUTS *	
	%	*n*	%	*n*	%	*n*
35 – 39	13.4	(15)	24.1	(27)	7.1	(8)
40 – 49	13.3	(42)	23.4	(74)	8.9	(28)
50 – 59	12.8	(43)	23.4	(79)	8.6	(29)
60 – 69	28.5	(61)	33.6	(72)	20.1	(43)
70 – 80	31.5	(39)	46.0	(57)	25.0	(31)
All ages	**18.2**	**(200)**	**28.0**	**(309)**	**12.6**	**(139)**

***** *Presence of symptomatic LUTS defined by IPSS: Total ≥8, Stor ≥4, Void ≥5; (n = 1103)*

Overall 18.2% of the men reported some degree of bothersome LUTS (16.0% moderate; 2.2% severe). There was a marked effect of age, with 31.5% of men aged 70-80 years reported some degree of bothersome LUTS as compared to 13.4% of the youngest aged men in the cohort. Troublesome storage symptoms were reported by 28% of the men overall. The prevalence was relatively constant in the 35-59 year old age group, but increased thereafter , with 33.6% and 46.0% of men aged 60-69 and 70-80 years, respectively, reporting troublesome storage symptoms. The prevalence of voiding LUTS was approximately half that of storage LUTS at all ages; 12.6% overall of men indicating troublesome voiding LUTS. As with storage LUTS the prevalence of voiding symptoms increased sharply over the age of 60 years affecting 20.1% and 25.0% of men aged 60-69 and 70-80 years, respectively (Table 7-1).

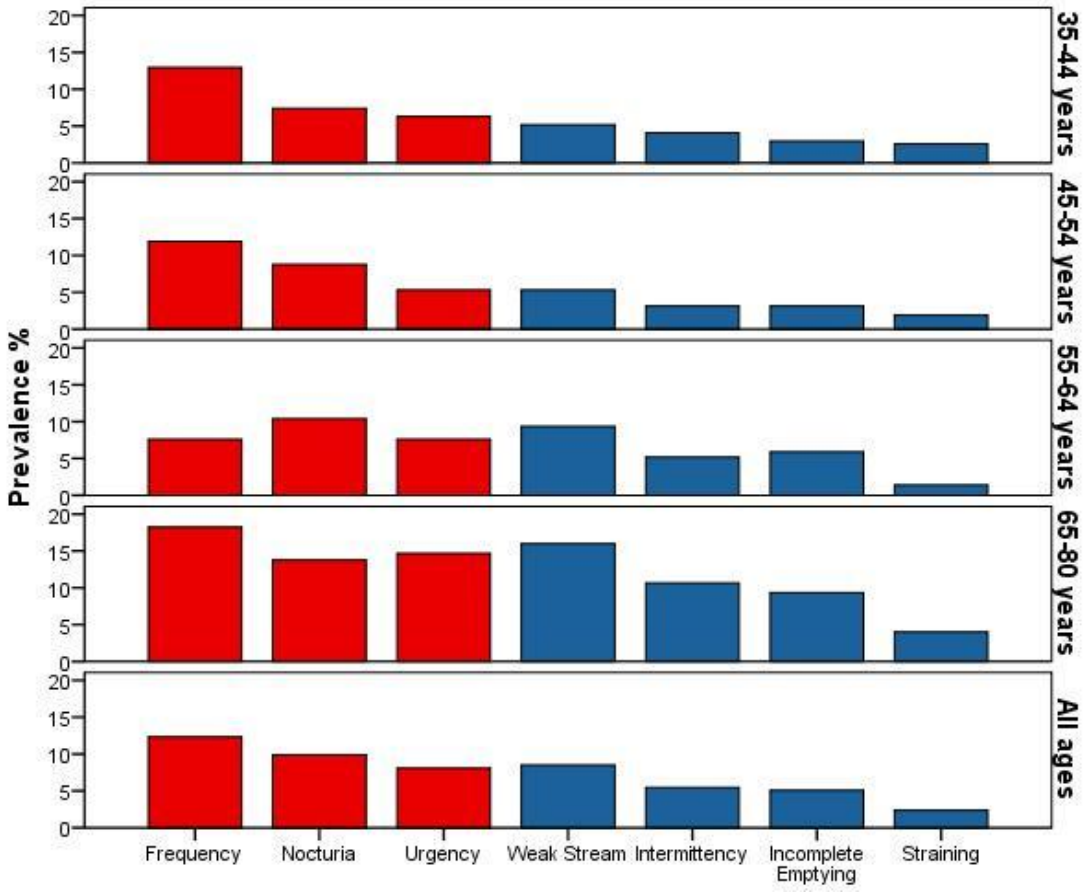


Figure 7-1. Prevalence of individual lower urinary tract domains amongst Australian men aged 35–80 *(Red = Storage symptoms; Blue = Voiding symptoms)*

Figure 7-1 illustrates the individual lower urinary symptoms within the cohort. Among those with storage LUTS, the most commonly reported symptoms were frequency and nocturia (12.3% and 9.9% of men, respectively). Significant urgency was present in 8.1% of respondents. Amongst the storage symptoms, men aged 50-59 years were found to have a slightly lower rate of increased frequency of urination in comparison to other age groups. Men aged over 60 years were found to have higher levels of urgency, with no significant difference between the age groups for nocturia. Of the voiding symptoms, a weak stream was most common (8.5% of men). Intermittent stream and a sensation of incomplete emptying had similar prevalence's overall (5.4% and 5.1% of

men, respectively), with straining during urination reported in 2.4% of men. Men aged over 60 years were more likely to report having a regular weak stream and incomplete emptying, whilst only men aged over 70 years reported an intermittent stream. There was significant age effect detected for straining.

Table 7-2. Linear regression model of storage and voiding IPSS scores.
Adjusted for physical, urological, lifestyle and socio-demographic covariates.

	Storage LUTS		**Voiding LUTS**	
Covariate	*β*	*p*	*β*	*p*
Age	-0.031	0.641	-0.034	0.601
BMI	0.072	0.495	-0.009	0.929
Abdominal total fat % (DEXA)	**0.368**	**0.046**	0.089	0.216
Glucose	**0.227**	**0.050**	-0.093	0.090
HbA1c	0.003	0.961	0.018	0.737
LDL cholesterol	0.012	0.755	0.045	0.222
HDL cholesterol	**-0.179**	**0.050**	0.033	0.433
Systolic BP	0.013	0.812	-0.016	0.765
Diastolic BP	-0.015	0.754	-0.044	0.353
PSA	-0.005	0.885	-0.009	0.178
Testosterone	-0.048	0.260	-0.017	0.685
SHBG	0.062	0.147	0.061	0.144
Energy (FFQ Quest. *1)	0.271	0.118	**0.375**	**0.002**
Saturated Fat (FFQ Quest. *1)	-0.146	0.086	0.233	0.137
Fibre (FFQ Quest. *1)	-0.035	0.554	-0.121	0.078
Alcohol (FFQ Quest. *1)	-0.053	0.267	-0.069	0.141
Marital status - Married	0.167	0.655	0.233	0.520
- Separated/Divorced	0.161	0.583	0.196	0.491
- Widowed	0.118	0.438	0.074	0.619
- Never	0.081	0.717	0.094	0.663
Current Smoker - Yes	0.010	0.794	-0.010	0.801
- No	0.036	0.300	0.027	0.431
Exercise (MET-hr*2: hr/wk)	-0.009	0.808	-0.021	0.541
Peak urine flow (vol. adj)	-0.060	0.103	**-0.115**	**0.001**
Hand Grip (dominant)	-0.101	0.119	**-0.019**	**0.024**
Obstr. Sleep Apnoea (estimated*3)	**0.183**	**0.050**	**0.138**	**0.003**
Erectile Dysfunction	-0.036	0.450	**0.116**	**0.012**

Sexual Desire	0.017	0.673	-0.024	0.055
Work Status - PT/Casual	0.001	0.980	0.072	0.545
- Unemployed	**0.292**	**0.041**	-0.026	0.486
- Retired	0.045	0.245	0.054	0.369
- Other	0.068	0.276	-0.003	0.929
Income - Low	-0.376	0.148	-0.222	0.228
- Middle	-0.312	0.112	-0.211	0.266
- High	-0.328	0.203	**0.222**	**0.048**
Angina	0.046	0.114	-0.015	0.691
Anxiety	-0.023	0.555	0.034	0.392
Asthma	-0.028	0.483	0.013	0.698
Depression	-0.028	0.415	0.045	0.253
Diabetes	0.100	0.093	0.051	0.297
BPH	0.144	0.113	**0.192**	**0.000**
Hypercholesterolemia	0.045	0.269	0.017	0.635
Hypertension	0.045	0.252	0.045	0.252
Insomnia	0.009	0.810	0.009	0.810
Osteoarthritis	0.036	0.303	0.036	0.303
Rheumatoid arthritis	-0.005	0.894	-0.005	0.894
Thyroid dysfunction	0.113	0.184	**0.119**	**0.006**
Other Cancer	0.026	0.460	0.026	0.460
Genitourinary medication [*4]	0.025	0.180	0.025	0.180

Bold data are given as standardized regression coefficients with P-values (P · 0.05)
a Energy intake (excluding alcohol consumption) and macronutrient intake as assessed by food frequency questionnaire; b Metabolic equivalent hours based on leisure time physical activity; c Calculated obstructive sleep apnoea risk based on screening survey; d As classified by WHO's anatomical therapeutic chemical (ATC) classification system (G04: Urologicals)

The clinical, behavioural, lifestyle and socio-demographic factors associating with storage and voiding LUTS are shown in Table 7-2. Despite the strong influence of age on prevalence of LUTS, no singular age effect was detected in multivariable regression models of either storage or voiding LUTS. There was a strong positive effect of abdominal fat mass percentage on storage LUTS (β=0.368; p=.046), but there was no effect of BMI. An elevated fasting plasma glucose was a predictor of storage LUTS (β=0.227; p=.050), but there was no significant relationship detected with physician-diagnosed diabetes per se and storage LUTS. There was also an association between

lowered plasma HDL cholesterol and storage symptoms (β=-0.179; p=.050). An increased risk of obstructive sleep apnoea was associated with a higher storage LUTS score (β=0.183; p=.050). Finally, retirement from the workforce was also found to be relate to a higher storage LUTS score (β=0.292; p=.041).

In the linear regression model of voiding LUTS, there was a significant association with a diagnosed thyroid condition (β=0.113; p=.004), higher energy intake (β=0.375; p=.002) and trends towards elevated saturated fat (β=0.233; p=.137) and reduced fibre intake (β=-0.121; p=.078). Other factors associated with an increase in voiding LUTS include a higher assessed risk of OSA (β=0.138; p=.003) and highest household income category (β=0.222; p=.048). There was a strong association between increased severity of voiding LUTS and reduced peak uroflow (β=-0.115; p=.001) and also with physician – diagnosed BPH (β=0.192; p=.000).

7.5 Comment

In this sample of middle-aged to elderly Australian men, almost one in five men (18.2%) reported significant LUTS. A higher proportion experienced storage (28.0%) than voiding symptoms (12.6%). The prevalence of total LUTS observed in this study is lower than that of an earlier, similarly-sized study of men from the same north west region of Adelaide (26%) [42]. Men who had prior lower urinary tract surgery were not excluded in either of these studies. A recent nationwide phone survey of almost 6000 Australian men reported a slightly lower prevalence of total LUTS (16.2%) than the current study, although telephone surveys generally report lower rates of disease than clinic-based studies [196].

The relative frequency of storage and voiding symptoms in the current study is consistent with clinic-based studies in the USA [197] and a multinational Asian study [198] where the prevalence of storage-type symptoms were twice as frequent as voiding symptoms. The general pattern of bothersome symptoms (from the most common: frequency of urination and nocturia, to the least commonly reported symptom of straining) were similar to the pattern observed in the current study.

The present study identified factors associated with both storage and voiding LUTS, and others that were specific to LUTS type. The absence of a relationship between age and either storage or voiding LUTS , was at odds with most previously published data (see [199] for review), possibly because of the inclusion of a comprehensive range of health-related, physical, lifestyle and socioeconomic factors in the analysis. While some

functional decline of the lower urinary tract undoubtedly occurs with ageing, data from the present study suggests there are other, arguably stronger, factors (abdominal fat mass, plasma glucose, obstructive sleep apnoea, HDL cholesterol, and energy intake) determine symptoms. The factors positively associated with storage LUTS were increased abdominal fat mass, plasma glucose and low HDL cholesterol, increased probability of OSA, and retirement. The association of abdominal fat mass with storage LUTS was independent of any effect of BMI. In a previous study of 45-79 year old Scandinavian men, a positive association was observed between waist-to-hip ratio and frequency of urination, nocturia and urgency. This study also reported an association between BMI and storage LUTS, but relied on self-measured height, weight, and waist circumference [38]. Any independent effect of abdominal adiposity on storage LUTS could be mediated by several (potentially interrelated) factors, all with previously reported relationships to LUTS. These include increased sympathetic nerve activity [200], inflammation [201], and impaired regulation of nitric oxide production, similar to what occurs in the vasculature under similar circumstances [202]. This latter mechanism is supported by observations that PDE5 inhibitors are of benefit to men reporting LUTS (see [203] for review). The relationship observed between elevated fasting plasma glucose in men with storage LUTS provides further evidence that impaired glucose tolerance is involved in the pathophysiology of overactive bladder [204]. Although the inverse relationship between HDL cholesterol and storage LUTS did not reach significance, the observed trend was similar to a finding in a large cross-sectional study of men from the NHANES cohort, where an inverse relationship between HDL levels and total LUTS was observed [205]. Our data adds further weight to recent observations of an association between OSA and storage LUTS [206], in addition to the often-reported association

between apnea and LUTS secondary to BPH. Previous studies have shown an increased frequency of micturition, and in particular nocturia, were associated with increased nightime urine output and the apnea hypopnea index in men with OSA [207]. Furthermore, there is data emerging that treatment of OSA with CPAP can reduce or eliminate nocturia in men [208]to the extent some clinical guidelines now recommend the treatment of OSA in men presenting with LUTS. Taken together, these associations suggest that storage LUTS is a feature of the metabolic syndrome, and when nocturia and frequency predominate, the presence of OSA should be considered.

Factors found to associate with significant voiding LUTS in this analysis were the presence of BPH, erectile or thyroid dysfunction, probability of OSA, and also peak urine flow, total energy intake, and higher household income. The higher total energy intake (with trends towards higher saturated fat and lower fibre intake) in men with significant voiding symptoms was independent of any relationship with either BMI or waist circumference. In a large-scale cross-sectional analysis of men from the Health Professionals Follow-up Study there was a moderate association between energy and total fat intake and BPH [56]. In accordance with our observations, there was no role of adiposity in this relationship. Recent data from the Boston Area Community Health (BACH) study demonstrated a similar relationship between energy intake and total LUTS, but also reported an association between polyunsaturated fat intake and total LUTS [197].

The significance of, and explanation for, the observation that men in the highest income bracket were more likely to record moderate to severe voiding symptoms is

unclear. Data from other cohort studies is inconsistent; both increased [209] and reduced [198] LUTS have been reported with higher socioeconomic status. In contrast, the relationship between voiding LUTS and ED is well established. In the Multinational Survey of the Aging Male (MSAM-7), for example, the presence of LUTS was the strongest predictor of erectile dysfunction (ED) [88]. Associations between physician-diagnosed thyroid dysfunction and voiding LUTS have not to our knowledge been reported. There are a number of plausible mechanisms whereby thyroid dysfunction may affect the lower urinary tract, including effects on autonomic nerve activity [210], and modulation of the number of β2 adrenergic receptors and the rate of prostate cancer growth by triiodothyronine (T3) in vitro [211]. Elevated serum T3 has also recently been found in a small sample of men referred for BPH/ prostate cancer treatment [212].

The strengths of this study include the use of a large random sample of men from a broad age group, similar in characteristics to men from the general Australian population[195], comprehensive clinical, demographic, and bio-psychosocial data and the separation of storage and voiding LUTS. The limitations of this study include the use of cross-sectional data, an inability to control for fluid intake, and the reliance on self-report for some lifestyle and medical factors.

In summary, while storage LUTS appear most strongly related to components of the metabolic syndrome (abdominal fat mass, plasma glucose and low HDL cholesterol), voiding LUTS were predominantly associated with conditions such as benign prostatic enlargement (BPE), urine flow and erectile function. Lifestyle modifications focussed on

a reduction in abdominal obesity may provide an effective strategy to reduce the burden of LUTS.

7.6 Author's comment

The preceding study was one of only two Australian studies among community-dwelling men that examined the prevalence of LUTS, and the first one to separately examine the prevalence of storage and voiding LUTS separately. We thought it important to examine the current population burden of this condition given the noted effects on both individual quality of life and the economic impact on the healthcare system (Chapter 2). Furthermore, given an ageing demographic and secular increases in many of the known risk factors for LUTS (e.g. obesity) (Chapter 1), a current estimate of the population-prevalence of LUTS in men was warranted. Finally, given recent studies demonstrating an increasing amount of risk factors associated with LUTS in men and attempts to view LUTS 'beyond the bladder', we had sought to examine the relative contribution of a range of risk factors to the presence of both storage and voiding LUTS in men.

Our findings of an overall prevalence of LUTS of 18.2% of all men examined (aged 35-80 years) was slightly higher than the most recent survey of LUTS in Australian men (16.2% [213]) (likely due to the use of different methodology) and lower than that previously reported from a survey of men from the same geographic region (26% [42] over 15 years ago (likely due to the inclusion of men with confounding conditions such as prostate and bladder disorders). We were able to demonstrate a much higher prevalence rate of storage (28.2%) compared with voiding (12.6%) symptoms, a finding supported by many of the cohort studies published after the preceding paper that have differentiated by LUTS cluster type [214 - 217].

Our multivariate modelling demonstrated that while many of the risk factors of storage and voiding LUTS are shared, there were some identified that were unique to either LUTS cluster type. In general, storage LUTS were associated with risk factors indicative of poorer metabolic control (e.g. increased abdominal fat mass, plasma glucose, low HDL cholesterol and OSA). Voiding LUTS were particularly prevalent among men with a complex of other age-related conditions such as BPH, poor urine flow, erectile and thyroid dysfunction.

Given the findings from this study, our next investigation of LUTS in men sought to examine the incidence and progression of both storage and voiding LUTS in men, and the factors that predicted these changes, using data from our 5-year follow up clinic visits.

Through the editing process for the proceeding manuscript and at the request of the examiners for this thesis, a number of issues were omitted from the previous chapter that are now listed below:

Autonomic nervous system and LUTS in men

Autonomic hyperactivity (AH) occurs through the dysregulation of parasympathetic and sympathetic tone. Our own data and those of others [218] [219] [76] have shown that LUTS are connected to the metabolic syndrome (MetS). Given MetS is a known outcome of AH [220] and recent identification of various subtypes of α 1-adrenergic receptors in the male bladder, prostate, and penile tissue [221], it has therefore been suggested that AH may lead to the development of LUTS. While we were able to demonstrate in the preceding study that many of the components of MetS (obesity, and elevated plasma glucose and

lipids) were associated with the presence of storage LUTS no tests of autonomic function were performed at this clinic. However, a sub-section of FAMAS participants did have some measurements of autonomic function performed as part of a later polysomnographic testing session, allowing us to further explore any association between AH and LUTS in this cohort of men using repeat data.

Thyroid dysfunction and LUTS

Our finding of an association between thyroid dysfunction and a higher voiding LUTS score was unique (and a discussion of possible mechanisms is included in the preceding chapter). Of those examined, only n=26 reported being diagnosed with some form of thyroid dysfunction, with 46% reporting hypothyroidism and 35% reporting hyperthyroidism (19% were unaware what type of thyroid condition they had) based on data taken from a later survey of the same participants. The resultant cell sizes were too small to allow any meaningful examination of the relative contribution of hypo vs. hyperthyroidism to the observed effect on voiding function in the preceding study. However, the available literature suggests that autonomic dysfunction may again link voiding dysfunction with hyperthyroidism in particular, as studies have demonstrated patients with hyperthyroidism have increased β-adrenergic activity [222]. Again, this will be explored further using a larger dataset that includes FAMAS men.

CHAPTER 8

Clinical and biopsychosocial determinants of sexual dysfunction in middle-aged and older Australian men

Sean Martin, B Sc [1,2] , Evan Atlantis Ph D [1,2] , Kylie Lange B Sc [2], Matthew T Haren Ph D [1,3] , Anne Taylor Ph D [2,4], Gary Wittert MD FRACP [1,2] and Members of the Florey Adelaide Male Ageing Study

[1] Freemasons Foundation Centre for Men's Health, University of Adelaide, Adelaide, South Australia

[2] Discipline of Medicine, University of Adelaide, Adelaide, South Australia

[3] SANSOM Institute, Division of Health Sciences, University of South Australia, Adelaide, South Australia

[4] Population Research and Outcomes Studies, Discipline of Medicine, University of Adelaide, Adelaide, South Australia

Published: Journal of Sexual Medicine, 2012 July 3 (Epub)

Statement of Authorship

Sean A. Martin (Candidate)

Roles: Corresponding Author; Conception and Design; Acquisition of Data; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Matthew T. Haren

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Anne W. Taylor

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Kylie Lange

Roles: Design; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Gary Wittert

Roles: Principal Investigator; Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Evan Atlantis

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

8.1 Abstract

Introduction: Erectile dysfunction (ED) and other related sexual dysfunctions in men have recently been shown to associate with a range of conditions and biopsychosocial factors. However, few studies have been able to control for these related factors simultaneously.

Aim: To determine the prevalence of and associated risk factors for ED and low solitary and dyadic sexual desire.

Main Outcome Measures: Erectile function (International Index of Erectile Function-erectile function) and sexual desire (Sexual Desire Inventory 2), as well as associated socio-demographic, lifestyle, biological, and clinical risk factors.

Methods: Data were collected from 1,195 randomly selected, community-dwelling men as part of the Florey Adelaide Male Ageing Study.

Results: The prevalence of ED, low solitary, and dyadic sexual desire was 17.7%, 67.7%, and 13.5%, respectively. Increasing age, abdominal fat mass, obstructive sleep apnea risk, and the absence of a regular partner were associated with both degrees of ED severity. Insufficient physical activity, low alcohol consumption, and hypertension were associated with mild ED only, and voiding lower urinary tract symptoms, diabetes, and lower plasma testosterone were independently associated with moderate to severe ED. Increasing age, lower alcohol consumption, insufficient physical activity, and a diagnosis of depression, anxiety, or insomnia were associated with both low dyadic and solitary sexual desire. Post-school qualifications and lower plasma testosterone were associated with low dyadic desire, whereas lower education and income, unemployment, and migration were associated with low solitary sexual desire. The

absence of a regular partner and post-school qualifications were associated with higher solitary sexual desire.

Conclusions: While ED and low dyadic and solitary sexual desire share some risk factors, we were able to demonstrate that unique factors exist for each of these domains. Attention should first be given to addressing these modifiable risk factors.

8.2 Introduction

Recent reviews of male sexual dysfunction have demonstrated that while a wealth of information is available for erectile dysfunction (ED), comparatively little is known of the prevalence and risk factors for other sexual dysfunctions in men. Community-based studies indicate that the prevalence of ED among all men is between 19% and 63%, and rises to between 68% and 87% in those over 60 years, depending on the setting in which the study was performed [94]. In Australia, only limited population-based data on the prevalence of ED are available. In a nationwide telephone survey of Australian males aged over 40 years, 21.3 % of men reported a significant degree of ED [44]. A number of factors that associate with ED, independent of age, have been identified. These include diabetes [223], cardiovascular disease [224], psychological disorders [225 129], musculoskeletal disease [226], lifestyle factors [227 77], altered muscle mass and strength [228], endocrine disorders [229], medication usage [230], and deteriorating social position [231]. Although a number of cross-sectional studies have documented a decrease in sexual desire with increasing age, most have not assessed the overall prevalence of, and risk factors associated with, varying types of sexual desire. In those studies where these risk factors have been assessed, it is apparent that many of the same disease processes and risk factors that are associated with ED are also associated with sexual desire, for example ageing [232], hypertension [233], smoking [146], endocrine disorders [137], and medication usage [146]. One of the limitations of these studies has been the use of inventories with a limited number of items [149], enrolment of clinical or convenience samples [227], and a small sample size [234]. Recent observations have also suggested that

differing domains of sexual desire among men (e.g. desire for sexual activity with a partner or self) may be susceptible to different rates of change and risk factors [235]. The objective of this study was to determine the prevalence of and independent risk factors for ED, and both dyadic and solitary sexual desire among 1,195 men aged 35-80 years who participated in the population-based Florey Adelaide Male Ageing Study (FAMAS).

8.3 Methods

8.3.1 Study design and population

Data were obtained from the Florey Adelaide Male Ageing Study (FAMAS), a randomly-selected population-based study of males, aged 35-80 years at recruitment and residing in the northern and western suburbs of Adelaide, Australia. Details of the FAMAS design, procedures and participants have been published elsewhere [177]. Comparisons with the Australian Census 2001 data showed that FAMAS participants matched the population for most key demographics, although younger groups and never-married men were under-represented and older participants were over-represented [177].

All protocols and procedures were approved by the Royal Adelaide Hospital Research Ethics Committee and, where appropriate, the Aboriginal Health Research Ethics Committee of South Australia. All participants provided written, informed consent prior to their inclusion in the study.

8.3.2 Sexual dysfunction outcomes

During FAMAS clinic visits, a separate questionnaire assessing sexual health and function was completed in private. This included the Sexual Desire Inventory 2 (SDI-2, [139]), a 14 item self-reported measure with participants indicating the strength and frequency of sexual desire over the past month. For the frequency-items, participants chose one out of the seven options, ranging from 'not at all' to 'more than once a day'. For the strength items, participants scored their sexual desire on a 9-point Likert scale,

ranging from 0 (no desire) to 8 (strong desire). The SDI-2 has a test–retest reliability over 1 month of .76. Factor analysis has demonstrated the presence of two domains within the SDI-2: dyadic sexual desire (the desire to engage in sexual behaviour with a partner) and solitary sexual desire (the desire to engage in sexual behaviour with one's self). In the present study, low dyadic and solitary sexual desire was defined as a score of ≤ 16 and ≤ 6, respectively. This was adopted from the approach of Beck et al. who examined low sexual desire in men aged 18-54 years, using an item that measures similar domains of sexual desire as used in the present study [236]. Overall, this corresponds to an average response of less than once a week for frequency items and in the lowest tertile range for strength items for each domain [139]

Erectile dysfunction was assessed by the International Index of Erectile Function (IIEF, [97]), a 15 item self-report measure assessing various domains of erectile function over the past month. In the present study, only the erectile function (EF) domain of the IIEF was included in this analysis. The IIEF-EF has a test–retest reliability over 1 month of .87. The intercourse satisfaction (IS) domain has low specificity [97] and because of sensitivity concerns we did not include questions on orgasmic function. Those respondents with an IIEF-EF score of 0-16 were categorised as moderate to severe, 17-25 as mild-mild/moderate (herein referred to as 'mild', and those with a score of 26 or greater as no ED.

8.3.3 Additional covariates

In addition to sexual health and function, a number of other measures were included in the present study, involving a combination of standardised self-report measures and

biomedical assessment. Details of these have been published previously [177]. Briefly, information on age, education, marital, occupational and smoking status was assessed by self-report questionnaire completed prior to clinic attendance, using validated measures [177]. This also involved questions relating to physician-diagnosed and family history of major chronic disease. Medication usage was determined by self-report and consented data linkage with a national pharmaceutical registry. Symptoms of depression were assessed using the Beck Depression Inventory (1A; [184]). The probability of obstructive sleep apnoea (OSA) was determined using a multivariable prediction equation that accounts for self-report symptoms (frequency of loud snoring, breathing cessation, and snorting and gasping, [186]). Dietary macronutrient composition was assessed through use of a self-administered semi-quantitative food frequency questionnaire [187]. Leisure-time physical activity was measured with items from a national activity survey [185].

On arrival at the clinic visit, an 8-12 hour fasting blood sample was taken by venipuncture and immediately refrigerated and transported to a NATA certified laboratory for hormonal measurement [177]. Height, weight, waist and hip measurements, blood pressure and handgrip strength were also measured during the 90 minute clinic visit [177].

Finally, participants had whole body and regional (including abdominal) body fat and lean mass measured by dual energy x-ray absorptiometry (DEXA) using the LUNAR DPX+ pencil beam or Prodigy DF fan beam densitometer (both, GE Lunar Corporation, Wisconsin USA).

8.3.4 Statistical analysis

Initial descriptive analyses between selected independents and outcome measures (dyadic & solitary SD, mild & moderate/severe EF) were conducted using chi-square (categorical) and t-tests (continuous). Independents were selected on the basis of demonstrated or suspected associations with the outcome. For the final regression models, relative risks and 95% confidence intervals were estimated by binary and multinomial logistic regression. Firstly, the relative risk of each independent on the outcome was examined to determine individual main effects. Next, regression models were fitted with the independent variable and age to get age-adjusted relative risks. Age was then checked as a modifier for each of the independent variables by fitting against age and the age- independent interaction. Age was considered a modifier for an independent variable if the interaction had a p-value < 0.005 (to account for the multiple testing). Those variables whose age-adjusted relative risks had a p value <0.25 were included in the final multivariate model.

Given the established relationship between erectile function and hypertensive medications [237], an additional sensitivity analysis was performed between erectile function and the major anti-hypertensive medications classes (see Table 3) was performed.

For prevalence estimates, data were weighted according to the inverse of their probability of selection from the target population.

All data were analysed using PASW Statistics 17.0 (SPSS Inc. Chicago, USA).

8.4 Results

Table 8-1. Distribution of selected factors by dyadic (with partner) sexual desire score (SDI-II) in a cohort of Australian men (n=1195).

Variable		*Low Sexual Desire (Partner)*		*Regular Sexual Desire (Partner)*		*p*
		%	Count	%	Count	
Age Group	35-44 years	1.6%	4	98.4%	258	**0.000**
	45-54 years	4.1%	13	95.9%	305	
	55-64 years	11.8%	35	88.2%	261	
	65-80 years	32.8%	89	67.2%	182	
	All years	13.5%	141	85.4%	1026	
Any post-school qualification	Yes	17.9%	98	82.1%	724	
	No	12.5%	40	87.5%	281	**0.009**
Household Income (Category)	Low	25.3%	96	74.7%	284	
	Middle	7.5%	30	92.5%	371	
	High	2.6%	9	97.4%	339	**0.000**
Work Status (Employed/Not)	Not Employed	25.2%	104	74.8%	309	
	Employed	4.8%	35	95.2%	698	**0.000**
Partner (Y/N)	No Partner					
	Partner					
Country of Birth	Other	13.9%	53	86.1%	328	
	Australia	11.2%	86	88.8%	680	0.236
Smoking (Current)	Yes	10.6%	27	89.4%	227	
	No	12.6%	112	87.4%	779	0.670
LTPA (Suff. / Insuff.)	Insufficient	13.9%	81	86.1%	503	
	Sufficient	10.3%	58	89.7%	505	**0.006**
Alcohol (>2 std drinks/day)	No	14.3%	103	85.7%	618	
	Yes	8.5%	36	91.5%	390	**0.002**
Fat Free Mass Index (kg/m2)		18.8	15.7, 22.2	20.3	16.1, 22.6	**0.044**
Abdominal Fat Mass Index (kg/m2)		13.0	8.41, 16.89	11.1	6.14, 15.47	**0.008**
Hand Grip (Dominant; kgF)		43.0	31, 57	50.0	36, 65	**0.010**
Total Testosterone (nmol/L)		11.8	4, 21	14.3	7, 24	**0.011**
SHBG (nmol/L)		41.6	19, 77	34.5	15, 63	**0.015**
LH (IU/L)		8.0	2, 32	5.8	2, 12	**0.009**
Total PSA (ug/L)		2.2	0.4, 7.2	1.8	0.3, 5	**0.008**
Probability of OSA		0.669	0.252, 0.939	0.566	0.185, 0.905	**0.006**
Storage LUTS		4	0, 10	3	0, 8	**0.038**
Voiding LUTS		3	0, 15	2	0, 8	**0.050**

Angina	Yes	29.6%	21	70.4%	50	**0.000**
	No	11.0%	118	89.0%	958	
Anxiety	Yes	18.6%	19	81.4%	83	**0.035**
	No	11.5%	120	88.5%	925	
Depression (combined; dichot)	Yes	16.7%	44	83.3%	220	**0.002**
	No	10.8%	95	89.2%	788	
Diabetes (combined; dichot)	Yes	19.9%	28	80.1%	113	**0.008**
	No	11.0%	111	89.0%	895	
High cholesterol (combined; dichot)	Yes	12.3%	95	87.7%	679	**0.894**
	No	11.8%	44	88.2%	329	
Hypertension (combined; Y/N)	Yes	6.1%	34	93.9%	525	**0.000**
	No	17.9%	105	82.1%	483	
Insomnia	Yes	21.4%	25	78.6%	92	**0.002**
	No	11.1%	114	88.9%	916	
Osteoarthritis	Yes	20.4%	22	79.6%	86	**0.030**
	No	11.3%	117	88.7%	922	
Prostate Cancer	Yes	38.5%	10	61.5%	16	**0.000**
	No	11.5%	129	88.5%	992	
Other Cancer	Yes	20.0%	18	80.0%	72	**0.007**
	No	11.4%	121	88.6%	936	
Anxiolytics	Yes	29.0%	18	71.0%	44	**0.000**
	No	11.2%	121	88.8%	964	
Cardiovascular	Yes	20.0%	91	80.0%	365	**0.000**
	No	6.9%	48	93.1%	643	
Genitourinary	Yes	25.7%	9	74.3%	26	**0.000**
	No	11.7%	130	88.3%	982	
Sedatives	Yes	26.5%	27	73.5%	75	**0.000**
	No	10.7%	112	89.3%	933	
Other medication	Yes	26.5%	22	73.5%	61	**0.002**
	No	11.0%	117	89.0%	947	

LH = luteinizing hormone; LTPA = leisure-time physical activity; LUTS = lower urinary tract symptom; OSA = obstructive sleep apnea; PSA = prostate-specific antigen; SDI-2 = Sexual Desire Inventory 2; SHBG = sex hormone-binding globulin

Of all respondents, 0.9% (n=11) of men identified as being exclusively homosexual, with a further 0.7% (n=8) men identifying as bisexual (4.5% of respondents (n=52) chose not to identify their sexuality). The characteristics of respondents in relation to sexual desire (dyadic and solitary) are shown in Table 8-1 and Table 8-2. Overall, 13.5% of all men examined had low dyadic sexual desire, and 67.7% of participants had low solitary sexual desire. The proportion of respondents with low sexual desire increased with age.

Among men aged 65-80, less than a third reported low sexual dyadic desire (compared with 89.4% for solitary desire in men from the same age group). In contrast, among men in the youngest age group, only 1.6% reported a low dyadic sexual desire, whereas 50% aged 35-80 years reported a low solitary sexual desire.

Table 8-2. Distribution of selected factors by solitary (with self) sexual desire score (SDI-II) in a cohort of Australian men (n=1195).

Variable		*Low Sexual Desire (Solitary)*		*Regular Sexual Desire (Solitary)*		*p*
		%	Count	%	Count	
Age Group	35-44 years	50.0%	134	50.0%	134	**0.000**
	45-54 years	60.4%	194	39.6%	127	
	55-64 years	75.2%	228	24.8%	75	
	65-80 years	89.4%	253	10.6%	30	
	All years	67.7%	809	30.6%	366	
Any post-school qualification	Yes	67.4%	567	32.6%	274	
	No	72.1%	238	27.9%	92	**0.019**
Household Income (Category)	Low	79.2%	316	20.8%	83	
	Middle	66.5%	272	33.5%	137	
	High	58.6%	205	41.4%	145	**0.000**
Work Status (Employed/Not)	Not Employed	82.1%	455	17.9%	77	
	Employed	61.2%	354	38.8%	289	**0.000**
Partner (Y/N)	No Partner	56.4%	119	43.6%	92	
	Partner	71.7%	690	28.3%	273	**0.000**
Country of Birth	Other	72.8%	283	27.2%	106	
	Australia	66.9%	526	33.1%	260	**0.036**
Smoking (Current)	Yes	67.4%	178	32.6%	86	
	No	69.3%	631	30.7%	279	0.554
LTPA (Suff. / Insuff.)	Insufficient	71.2%	423	28.8%	171	
	Sufficient	66.4%	386	33.6%	195	0.047
Alcohol (>2 std drinks/day)	No	72.8%	537	27.2%	201	
	Yes	62.2%	272	37.8%	165	**0.000**
Fat Free Mass Index (kg/m2)		19.3	16.1, 22.7	19.2	15.9, 22.3	0.744
Abdominal Fat Mass Index (kg/m2)		11.4	6.04, 16.01	10.9	6.03, 15.59	0.448
Hand Grip (Dominant; kgF)		49.0	33, 64	51.0	36, 65	0.300
Total Testosterone		13.6	7, 24	15.8	8, 21	**0.010**

(nmol/L)						
SHBG (nmol/L)		36.7	16, 69	32.7	15, 58	**0.055**
LH (IU/L)		6.4	2, 13	5.6	2, 11	**0.039**
Total PSA (ug/L)		2.1	0.3, 6	1.4	0.3, 4.2	**0.028**
Probability of OSA		0.604	0.215, 0.924	0.526	0.167, 0.898	**0.046**
Storage LUTS		3	0, 8	3	0, 8	0.838
Voiding LUTS		2	0, 9	2	0, 8	0.750
Angina	Yes	83.8%	62	16.2%	12	**0.004**
	No	67.8%	747	32.2%	354	
Anxiety	Yes	67.0%	71	33.0%	35	**0.005**
	No	49.0%	638	51.0%	431	
Depression (combined; dichot)	Yes	73.4%	201	26.6%	73	**0.046**
	No	67.5%	608	32.5%	293	
Diabetes (combined; dichot)	Yes	77.6%	118	22.4%	34	**0.012**
	No	67.5%	691	32.5%	332	
High cholesterol (combined; dichot)	Yes	70.2%	556	29.8%	236	**0.097**
	No	66.1%	253	33.9%	130	
Hypertension (combined; Y/N)	Yes	59.6%	338	40.4%	229	**0.000**
	No	77.5%	471	22.5%	137	
Insomnia	Yes	80.0%	100	20.0%	25	**0.004**
	No	67.5%	709	32.5%	341	
Osteoarthritis	Yes	81.8%	90	18.2%	20	**0.002**
	No	67.5%	719	32.5%	346	
Prostate Cancer	Yes	88.5%	23	11.5%	3	**0.029**
	No	68.4%	786	31.6%	363	
Other Cancer	Yes	77.2%	71	22.8%	21	**0.073**
	No	68.1%	738	31.9%	345	
Anxiolytics	Yes	78.6%	55	21.4%	15	**0.070**
	No	68.2%	754	31.8%	351	
Cardiovascular	Yes	78.1%	370	21.9%	104	**0.000**
	No	62.6%	439	37.4%	262	
Genitourinary	Yes	91.4%	32	8.6%	3	**0.003**
	No	68.2%	777	31.8%	363	
Sedatives	Yes	84.9%	90	15.1%	16	**0.000**
	No	67.3%	719	32.7%	350	
Other medication	Yes	79.8%	71	20.2%	18	**0.002**
	No	68.0%	738	32.0%	348	

LH = luteinizing hormone; LTPA = leisure-time physical activity; LUTS = lower urinary tract symptom; OSA = obstructive sleep apnea; PSA = prostate-specific antigen; SDI-2 = Sexual Desire Inventory 2; SHBG = sex hormone-binding globulin

Table 8-3 compares the characteristics of respondents with normal erectile function to those with varying degrees of erectile dysfunction. Overall, 17.7% of all men had significant erectile dysfunction (moderate ED or greater). Mild ED was present in 35.2% of respondents. Erectile function was normal in 29.3% of men. Of men aged 35 - 44 years 50% had normal erectile function, and 28.8% and 16.2% were found to have mild and moderate / severe ED respectively. By contrast, among men in the oldest age group, only 9% where found to have normal erectile function, whereas 53.6% and 37.3% had mild and moderate / severe ED.

Table 8-3. Distribution of selected factors by combined erectile function (IIEF-EF) score in a cohort of Australian men (n=1195).

Variable		*Normal EF*		*Mild ED*		*Moderate / Severe ED*		*p*
		% / $\bar{x}$	*N / 95% CI*	*% / $\bar{x}$*	*N / 95% CI*	*% / $\bar{x}$*	*N /95% CI*	
Age Group	35-44 years	55.0%	143	28.8%	75	16.2%	42	**0.000**
	45-54 years	40.0%	122	41.3%	126	18.7%	57	
	55-64 years	27.8%	70	52.0%	131	20.2%	51	
	65-80 years	9.0%	15	53.6%	89	37.3%	62	
	All years	29.3%	350	35.2%	421	17.7%	212	
Any post-school qualification	Yes	37.9%	268	39.7%	281	22.3%	158	
	No	29.8%	81	50.4%	137	19.9%	54	**0.009**
Household Income (category)	Low	18.3%	51	46.6%	130	35.1%	98	
	Middle	35.0%	127	45.5%	165	19.6%	71	
	High	50.8%	167	37.1%	122	12.2%	40	**0.000**
Work Status (Employed/Not)	Not Employed	14.8%	43	50.2%	146	35.1%	102	
	Employed	44.3%	306	39.8%	275	15.9%	110	**0.000**
Partner (Y/N)	No Partner	24.5%	38	31.0%	48	44.5%	69	
	Partner	37.5%	310	45.2%	373	17.3%	143	**0.000**
Country of Birth	Other	31.9%	102	45.6%	146	22.5%	72	
	Australia	37.4%	248	41.5%	275	21.1%	140	0.233
Smoking (current)	Yes	40.3%	89	38.9%	86	0.0%	0	
	No	34.1%	259	44.1%	335	20.8%	46	0.223
LTPA (Suff. / Insuff.)	Insufficient	34.8%	170	47.1%	230	21.8%	166	
	Sufficient	36.4%	180	38.6%	191	18.0%	88	**0.007**
Alcohol (>2 std	Yes	35.4%	213	40.4%	243	25.1%	124	

drinks/day)								
	No	36.0%	137	46.7%	178	29.3%	146	**0.025**
Fat Free Mass Index (kg/m2)		19.4	(16.1, 22.8)	19.3	(16.2, 22.4)	19.1	(16, 23.3)	0.544
Abdominal Fat Mass Index (kg/m2)		10.86	(7.88, 11.39)	11.38	(7.14, 14.78)	11.94	(7.48, 13.37)	**0.038**
Hand Grip (Dominant; kgF)		53	(40, 66)	49	(36, 63)	47	(34, 63)	**0.010**
Total Testosterone (nmol/L)		14.9	(8, 24)	14.2	(8, 24)	12.7	(7, 23)	**0.041**
SHBG (nmol/L)		31.3	(15, 55)	35.7	(15.5, 66.5)	36.7	(18, 72)	**0.035**
LH (IU/L)		5.8	(2, 12)	6.4	(2, 13)	8.0	(2, 32)	**0.009**
Total PSA (ug/L)		1.1	(0.3, 3)	2.2	(0.3, 5.2)	2.4	(0.4, 6.2)	**0.008**
Probability of OSA		0.506	(0.277, 0.769)	0.584	(0.409, 0.712)	0.611	(0.386, 0.704)	**0.006**
Storage LUTS		2	(0, 7)	3	(0, 7)	4	(0, 9)	**0.038**
Voiding LUTS		1	(0, 5)	2	(0, 8)	3	(0, 10)	**0.050**
Angina	Yes	20.0%	8	50.0%	20	30.0%	12	**0.002**
	No	36.3%	342	42.5%	401	21.2%	200	
Anxiety	Yes	25.6%	21	42.7%	35	31.7%	26	**0.032**
	No	36.5%	329	42.8%	386	20.6%	186	
Depression (combined)	Yes	29.0%	63	41.0%	89	30.0%	65	**0.002**
	No	37.5%	287	43.3%	332	19.2%	147	
Diabetes (combined)	Yes	20.8%	21	49.5%	50	29.7%	30	**0.003**
	No	37.3%	329	42.1%	371	20.6%	182	
High cholesterol (combined)	Yes	33.5%	222	43.8%	290	22.7%	150	0.134
	No	39.9%	128	40.8%	131	19.3%	62	
Hypertension (combined)	Yes	40.4%	207	42.7%	219	17.0%	87	**0.000**
	No	30.4%	143	43.0%	202	26.6%	125	
Insomnia	Yes	23.6%	21	48.3%	43	28.1%	25	**0.037**
	No	36.8%	329	42.3%	378	20.9%	187	
Osteoarthritis	Yes	26.8%	22	47.6%	39	25.6%	21	0.214
	No	36.4%	328	42.4%	382	21.2%	191	
Prostate Cancer	Yes	7.7%	1	61.5%	8	30.8%	4	**0.062**
	No	36.0%	349	42.6%	413	21.4%	208	
Other Cancer	Yes	20.0%	13	49.2%	32	30.8%	20	**0.013**
	No	36.7%	337	42.4%	389	20.9%	192	
Anxiolytics	Yes	13.6%	6	50.0%	22	36.4%	16	**0.003**
	No	36.6%	344	42.5%	399	20.9%	196	
Cardiovascular	Yes	21.1%	74	49.6%	174	29.3%	103	**0.000**
	No	43.7%	276	39.1%	247	17.2%	109	
Genitourinary	Yes	15.4%	4	38.5%	10	46.2%	12	**0.000**
	No	36.2%	346	42.9%	411	20.9%	200	
Sedatives	Yes	20.4%	11	51.9%	28	27.8%	15	0.054
	No	36.5%	339	42.3%	393	21.2%	197	
Other medications	Yes	16.4%	12	53.4%	39	30.1%	22	**0.002**

	No	37.1%	338	42.0%	382	20.9%	190	

CI = confidence interval; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function; LH = luteinizing hormone; LTPA = leisure time physical activity; LUTS = lower urinary tract symptom; OSA = obstructive sleep apnea; PSA = prostate-specific antigen; SHBG = sex hormone-binding globulin

Figure 8-1 (below) shows the multi-adjusted regression estimates for low dyadic (C) and solitary sexual desire (D).Those factors independently associated with both low solitary and dyadic desire included age over 54 years, low income, depression and insomnia. Factors associated with low dyadic desire only included low leisure time physical activity, anxiety, and the presence of a post school qualification, which by contrast was associated with higher solitary desire. Low solitary desire was associated with consumption of less than two standard drinks of alcohol per day, the presence of hypertension and the use of genitourinary medications. Only men taking genitourinary medications (as defined by the WHO ATC classification system) were found to be at an increased risk of low solitary desire.

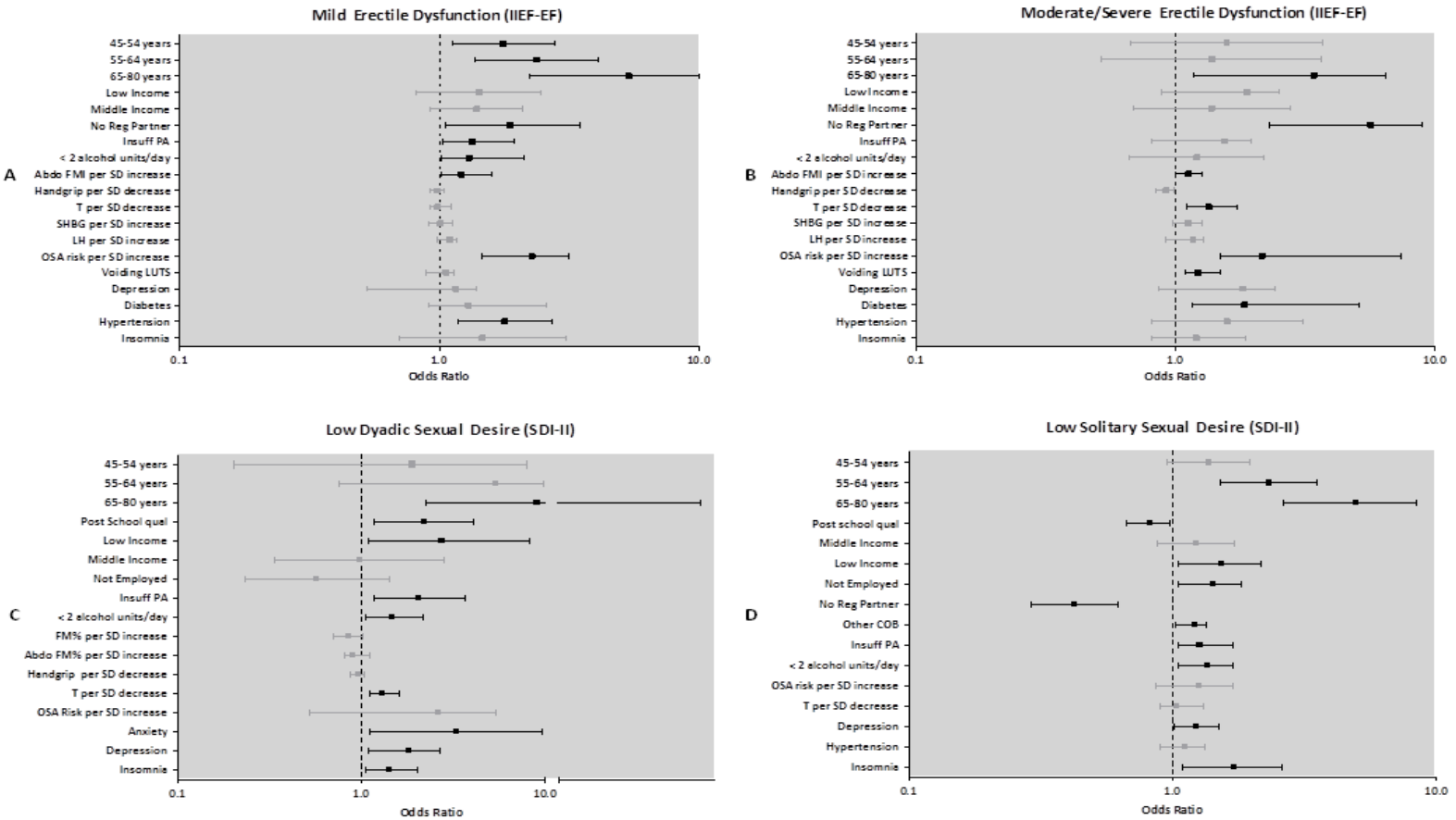


Figure 8-1. Data are presented as ORs (95% CI) for mild (A) and moderate / severe (B) erectile function (referent category: normal EF (IIEF)), low partner (C) and solitary (D) sexual desire (referent category: normal sexual desire (SDI-II), and low sexual satisfaction (E) and activity (F) (referent category: normal satisfaction & activity (IIEF)). All predictors with an age-adjusted p- value of < 0.1 were included in the final multi-adjusted model. Referent categories for categorical predictors (not shown) were: 35 - 44 years, high income, no post-school qualifications, regular partner, sufficient physical activity, > 2 standard alc. drinks/day, no lifetime diagnosis of anxiety, depression, diabetes, hypertension, insomnia. For continuous predictors, odds ratios represent a one unit standard deviation increase or decrease. The final multivariable models were also adjusted for any anxiolytic, cardiovascular or genitourinary medication usage.

Figure 8-1 shows the multi-adjusted estimates for both mild and moderate/severe ED. Factors found to be independently associated with both mild and moderate / severe ED included increasing age (for men aged over 45 and 65 years for mild and moderate /severe ED, respectively), no regular partner, higher abdominal fat mass, obstructive sleep apnea, and the use of cardiovascular medications. Factors associated with mild ED only included consuming less than two standard drinks of alcohol per day, low leisure-time physical activity, higher plasma luteinizing hormone, and hypertension. Moderate and severe ED was independently associated with lower handgrip strength, higher plasma testosterone, diabetes, depression, insomnia, and the use of genitourinary medications.

8.5 Discussion

This study has examined the effect of multiple socio-demographic, lifestyle, biological and clinical factors on male sexual dysfunction. By taking this broad approach we have been able to assess the relative contribution of many putative confounders of male sexual function using standardised measures in a representative sample of middle-aged to elderly community-dwelling Australian men. To our knowledge, it is the first study of its kind to compare the prevalence of both dyadic and solitary sexual desire among such a sample of men.

One in seven men (13.5%) of all ages reported low dyadic sexual desire; 1.6% in the youngest age group and 32.8% in the oldest. In contrast, over two-thirds (67.7%) of all men in the present study reported low solitary sexual desire, 50.0% in the youngest and 89.4% in the eldest age groups, respectively. In a previous study, approximately a decade ago, 28% of men aged 40-79 years from the same geographic region as the current study reported low sexual desire based on a single item measure when surveyed by mail [238]. Similarly, in a more recent nationwide mail survey of 5990 men aged over 40 years, 25.8 % of respondents reported low sexual desire, again using a single item question. In a survey of US men aged 18-59 years using the Brief Male Sexual Inventory (BMSI), low sexual desire was reported in 14.7% of participants [239]. The BMSI includes multiple measures of sexual desire, which do not differentiate between partnered or solitary sexual desire. Of the other major measures of sexual function in men, the full version of the IIEF also assesses sexual desire. In the present study, only dyadic sexual desire significantly correlated with the sexual desire domain

of the full-version of the IIEF (IIEF-SD; r=0.78; data not shown). Further, when categorised as in the present study, the proportion of men with low sexual desire as assessed by the questions relating to sexual desire on the IIEF-SD, was closest to the observed prevalence of low dyadic sexual desire (18.5% of all men).

The factors associated with low sexual desire in this study differed to the extent they affected either dyadic or solitary sexual desire. Increasing age, low alcohol consumption, insufficient physical activity, and a diagnosis of depression, anxiety or insomnia were all associated with both low dyadic and solitary sexual desire, albeit to varying extents. Having a post-school qualification and lower plasma testosterone were found to associate with low dyadic desire, whereas lower education and income, unemployment, being born outside of Australia were associated with low solitary sexual desire only. The absence of a regular partner and a post-school qualification were associated with higher solitary sexual desire.

The relationship between age and the measured domains of sexual desire varied. As compared to the youngest age group, only men aged over 55 years had lower solitary desire, whereas low dyadic desire was seen in the eldest age group only. It has previously been documented that under normal circumstances sexual desire is retained until late in life in both male humans and animals [240]. The preference for partnering is striking, and retained into very old age. While is it easy to deduce why the absence of a regular partner may lead to higher solitary sexual desire, the reasoning for an association with higher education is unclear. Previous research in this area has exclusively examined the association between education and overall sexual desire. In

most cases, higher educational status was found to associate with overall sexual desire in men [109], [234], [146], with one study finding no influence of educational status [241]. Interestingly, if the same measure for sexual desire as this latter study (the IIEF-SD) is used in our cohort, we also find no association between educational status and sexual desire; but as indicated the IIEF-SD appears to relate to dyadic rather than solitary sexual desire .

Alcohol consumption has previously been shown to have a varied impact on sexual desire, with cohort studies demonstrating either an increased risk [242], decreased risk [243] or no effect [227]. In the present study, alcohol consumption was analysed based on the current recommendation for alcohol intake for adults (2 standard drinks/day; [244]), with men who reported consuming less than this amount, shown to be at an increased risk of both reduced dyadic and solitary sexual desire. These findings are, to our knowledge, the first to suggest a benefit of moderate alcohol consumption on both domains of sexual desire. Insufficient physical activity was associated with both low dyadic and solitary sexual desire, in keeping with previous studies examining physical activity and sexual function [77], [121]. An obesity-driven disruption to androgen production has been suggested to adversely affect sexual desire [245], however no independent effect of elevated fat mass (either total or abdominal as measured by DEXA) on sexual desire was observed in this study. Few studies have been able to simultaneously control for both physical activity, body composition and androgen status as in the present study, suggesting other beneficial effects of regular exercise (such as reduced emotional distress [246]) may account for this observation. Our data are consistent with findings from the Boston Area Community Health Survey (BACH), where an independent effect

of both physical activity and plasma testosterone on a multi-adjusted model of libido was demonstrated [229], although dyadic and solitary sexual desire were not examined separately. The discrepancy in this study of low plasma testosterone on partnered, as compared to solitary sexual desire, is consistent with the observation that adequate androgen levels are more important for the formation of satisfactory sexual partnerships than purely regulation of mechanical sexual function [81]. The association between a physician-diagnosis of depression, anxiety or insomnia and both low dyadic and solitary desire observed in this study were in agreement with the long-established links between psychological distress and sexual desire [247]. Data from this study also showed unemployed men and those from the lowest income stratum were at a higher risk of low solitary sexual desire only. In a study examining the risk factors associated with different sexual activities in 1410 US men aged 18 to 59 years, the likelihood of masturbating at least once per month was reduced in men of low social status (defined by income and occupational indices) [143]. This was purported to result from increased psychosocial stress, an observation that is supported by our finding of both low solitary and dyadic desire in men with conditions such as depression, anxiety and insomnia. We were also able to demonstrate an association between being born out of Australia and low solitary sexual desire, possibly because of an increased likelihood of self-report by Australian men [248].

The prevalence of moderate ED or greater observed in the present study (17.7% of all men) is consistent with that seen in comparable studies (see [104] for review). Results from the BACH survey over the same period found an almost identical proportion of ED of similar severity (17.3 %) [249]. Apart from the well-established effect of age on ED [104],

we examined the relative contribution of various covariates to both mild and moderate to severe ED. While some associations were common to mild, as well as moderate to severe ED (abdominal fat mass, OSA, no regular partner), others were limited to those men with mild ED (insufficient physical activity, low alcohol consumption, hypertension) or moderate / severe ED only (voiding LUTS, diabetes, lower plasma testosterone). Our data confirm the previously noted association between obesity and ED (see [250] for review). The relationship between elevated visceral adiposity and ED persists after adjustment for all covariates. Obstructive sleep apnoea risk was shown to be the most significant factor associated with ED, irrespective of severity.

The relationship between erectile dysfunction and lack of a regular partner is well established (see [94] for review). In particular, 63% of widowed men across all ages in this study reported some degree of ED (data not shown); data from the Massachusetts Male Ageing Study identified widowhood as the strongest predictor of incident ED [251]. The increased risk of ED in men with either insufficient physical activity or low alcohol consumption adds weight to recent recommendations from the International Consultation on Sexual Dysfunctions that such lifestyle factors should be addressed before treatment for ED is considered, particularly in the case of younger men with milder symptoms [252]. While excessive alcohol consumption can have a deleterious effect on male sexual function, our data add to the emerging view that moderate alcohol consumption may be protective for normal erectile function [243].

Table 8-4. Contribution of composite hypertensive factors to mild erectile function (IIEF-EF) score in a cohort of Australian men.

Variable	*Mild ED*		*Multi-adjusted OR*	
	%	*N*	OR	95% CI
Hypertension (combined)	**42.7%**	**239**	**1.787**	**1.178, 2.712**
Hypertension (Elevated systolic or diastolic BP)	19.0%	102	**1.673**	**1.051, 2.612**
Hypertension (Antihypertensive use)	14.3%	87	**1.442**	**1.023, 2.658**
Hypertension (Physician diagnosis of HT)	9.4%	50	1.441	0.981, 2.721
Angiotensin II Inhibitors	4.2%	21	**1.348**	**1.113, 2.158**
ACE Inhibitors	2.3%	10	**1.316**	**1.081, 2.057**
α-blockers	2.1%	11	NS	NS
β-blockers	4.0%	20	**1.292**	**1.003, 2.699**
Calcium channel blockers	2.3%	10	**1.342**	**1.103, 2.051**
High ceiling diuretics	1.1%	6	**1.300**	**1.020, 2.651**
Thiazides	2.2%	12	**1.333**	**1.099, 2.458**
Other low ceiling diuretics	0.2%	1	NS	NS
Smooth muscle relaxants	0.2%	1	NS	NS
Vasodilators	1.0%	5	NS	NS
Other HT meds	0.6%	3	NS	NS

CI = confidence interval; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function; LH = luteinizing hormone; LTPA = leisure time physical activity; LUTS = lower urinary tract symptom; OSA = obstructive sleep apnea; PSA = prostate-specific antigen; SHBG = sex hormone-binding globulin

In the present study, hypertension was associated with mild ED only. Few previous studies have assessed hypertensive symptoms (both measured and self-report) against severity of ED, while controlling for medication use. Burchardt and colleagues had demonstrated that measured and self-reported hypertension was associated with severe ED only [253], however this is likely to have been confounded by an inordinately high proportion of men with severe ED within the study population (45.2%) and did not control for the use of hypertensive medications. When the derived hypertension variable from the present study is broken into its constituent parts (either physician-

diagnosed hypertension, elevated systolic or diastolic BP, or use of antihypertensive medication), the largest contributors to this observed effect on mild ED are measured BP, current antihypertensive use, and previous diagnosis of hypertension, respectively (Table 8-4). Of the hypertensive medications included, (in order of effect size), angiotensin II inhibitors, calcium-channel blockers, thiazides, ACE inhibitors, high-ceiling diuretics, and beta-blockers were found to significantly contribute to the medication-mediated effect on mild ED (Table 8-4).

Our finding of an association with voiding urinary symptoms and moderate / severe ED is consistent with emerging evidence that suggests a common mechanism (and effective management strategies) between the two conditions [254]. The presence of diabetes was also associated with moderate /severe ED only, a relationship documented in previous longitudinal studies [255] [109]. The observation of an increased severity of ED in men with lower plasma testosterone is consistent with the established effect of testosterone on penile endothelial and smooth muscle function (see [256] for review).

The strengths of this study include the use of a comprehensive set of clinical, demographic, and bio-psychosocial data in assessing the risk factors associated with both low dyadic and solitary sexual desire and erectile dysfunction in men. The use of a relatively large random sample of men from a broad age group, similar in characteristics to men from the general Australian population, is a further strength.

The limitations of this study include the use of cross-sectional data and a subsequent inability to infer causality and address overlapping symptomology, an absence of empirical support for the chosen cut-points for low sexual desire, only 1.6% of men

identifying as either homosexual or bisexual, and the reliance on self-reported measures to assess some lifestyle and medical factors.

This study has confirmed the role of established (physical activity, alcohol consumption), as well as introducing novel risk factors (e.g. OSA, visceral adiposity) that should be addressed before further medical intervention. The direction and relative importance of these relationships will be the focus of future investigations using follow-up data.

8.6 Author's comment

The preceding study examined the prevalence and risk factors of another common condition of the ageing male (erectile dysfunction). To our knowledge this was also the first time that this was also performed for both low dyadic and solitary sexual desire in a community-based cohort of men. As discussed (Chapter 5) dyadic sexual desire refers to the '*interest in or wish to engage in sexual activity with another person, or a desire for intimacy and sharing with another person*', while solitary sexual desire refers to an '*interest in engaging in sexual behaviour with oneself and may involve a wish to refrain from intimacy and sharing with others*' [139]. These constructs are thought to measure a more global aspect of sexual desire than most other measures of commonly used in epidemiological studies (e.g. the sexual desire domain of the IIEF, the Sexual Arousability Inventory) [139], however the clinical utility of these distinctions remains in dispute [257].

SECTION III

PREDICTORS OF THE PROGRESSION AND IMPROVEMENT OF LOWER URINARY TRACT SYMPTOMS & SEXUAL DYSFUNCTION IN MEN

CHAPTER 9

Role of modifiable risk factors in the progression and remission of Lower Urinary Tract Symptoms (LUTS) in men

Sean Martin[1, 2], Kylie Lange[2], Matthew T Haren[1,3], Anne W. Taylor [4], Gary Wittert[1,2] and Members of the Florey Adelaide Male Ageing Study

[1] Freemasons Foundation Centre for Men's Health, University of Adelaide, Adelaide, South Australia

[2] School of Medicine, University of Adelaide, Adelaide, South Australia

[3] SANSOM Institute, Division of Health Sciences, University of South Australia, Adelaide, South Australia

[4] Population Research and Outcomes Study, University of Adelaide, Adelaide, South Australia

Submitted: Journal of Urology

(Modified version published Journal of Urology, Jun 11, 2013)

Statement of Authorship

Sean A. Martin (Candidate)

Roles: Corresponding Author; Conception and Design; Acquisition of Data; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Kylie Lange

Roles: Design; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Matthew T. Haren

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Anne W. Taylor

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Gary A. Wittert

Roles: Principal Investigator; Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

9.1 Abstract

Purpose: To determine the change in total, storage and voiding lower urinary tract symptoms (LUTS) and factors associated with the progression and improvement of symptom-type.

Methods: After exclusion of men with prostate or bladder cancer and/or surgery, progression and improvement of storage and voiding LUTS was assessed using the AUA-SI in 1,103 men, aged 35-80 years at baseline and 862 men, at 5-year follow-up clinics.

Results: Overall, 39.8% (n=308) and 32.3% (n=250) of all men examined during follow-up clinics exhibited progression in their storage and voiding LUTS, while 33.1% (n=256) and 23.4% (n=181) of all men showed improvement in their storage and voiding LUTS. In final adjusted regression models, higher bother, physical activity, and physical well-being at baseline were found to predict improvement of both storage and voiding LUTS, while higher income, HDL cholesterol, and lower triglycerides predicted improvement of storage LUTS only. Being widowed, higher income and estradiol, and depression at baseline predicted the progression of both storage and voiding LUTS, while higher abdominal fat mass, glucose, and OSA risk predicted storage LUTS progression only. Higher age, lower HDL cholesterol, and previous BPH, and erectile dysfunction at baseline were found to predict the progression of voiding LUTS only.

Conclusions: LUTS is a dynamic condition in men that may progress or remit over time; progression appears largely driven by deteriorating metabolic state and modifiable risk factors. Accordingly, these should be a point of primary intervention for men with LUTS given the additional benefits on cardio-metabolic risk reduction.

9.2 Introduction

The prevalence of lower urinary tract symptoms (LUTS) in men has been extensively described in different populations [258]. However, there remain relatively few longitudinal studies that are able to examine the natural progression of this common condition [34, 110, 259-261], despite its known influence on reducing quality of life and increasing health care expenditure [262]. Recent studies examining LUTS onset and progression in men have shown a varying incidence rate [34, 110, 259-261], but all demonstrated an accelerated onset with age. Male LUTS is a dynamic condition [259, 261], yet few studies exist that examine the rate of improvement in addition to LUTS onset. In a study of elderly men from the Osteoporotic Fractures in Men (MrOS) Study with clinically significant LUTS at baseline, over a quarter had reported a significant improvement of their symptoms at follow-up [259]. An earlier study of Swedish men aged 45-99 years showed that 20.2% and 9.5% of men had remitting urinary incontinence (UI) and overactive bladder (OAB), respectively; however no other LUTS were examined [260].

Recent findings from population-based studies have identified a wide range of risk factors and health conditions that associate with LUTS in men [110], suggesting the lower urinary tract is susceptible to systemic influences outside of the prostate. Furthermore, these associations vary according to specific clusters of urinary symptoms [263]. Storage symptoms such as frequency, urgency, and nocturia have shown independent associations with increased abdominal mass [264], hypertension [62], plasma glucose [61] and sleep apnea [207]. Voiding symptoms such as reduced flow, difficulty in initiating

micturition, hesitancy, post-micturition dribble, and a sense of incomplete emptying have been shown to associate with metabolic, endocrine and lifestyle factors [72], sexual dysfunction [265] and medication usage [266]. These findings suggest that troublesome LUTS may resolve following the modification of certain risk factors or conditions. To date however, few studies have simultaneously examined the contribution of many of these factors to the progression and improvement of LUTS-type in men.

The objective of this study therefore was to determine the natural progression and improvement of both storage and voiding LUTS, and identify the predictors of this change, in a cohort of community-dwelling men.

9.3 Methods

9.3.1 Study design and population

Data were obtained from the Florey Adelaide Male Ageing Study (FAMAS), a randomly-selected population-based study of males residing in the northern and western suburbs of Adelaide, Australia. The design and protocols for this study have been described in detail elsewhere [177].

A total of 1,195 men aged 35 – 80 at recruitment completed a baseline telephone interview and clinic visit (T1) between 2002 and 2005. Comparisons with the Australian Census 2001 data showed that FAMAS participants matched the population for most key demographics [177]. Follow-up clinic visits using identical protocols were conducted between 2007 to 2010 (T2), as near as practical to five years post the subjects initial visit (mean follow-up period 5.0 ± 0.2 years).

All protocols and procedures were approved by the Royal Adelaide Hospital Research Ethics Committee. All participants were required to give written, informed consent prior to their inclusion in the study.

9.3.2 Lower urinary tract symptoms

The seven-item American Urology Association – Symptom Index (AUA-SI) was used to evaluate the presence of LUTS. Men were classified as having significant LUTS if their total LUTS score was ≥ 7. Subjects were classified as having storage symptoms if the sum of their score on AUA-SI items 2, 4 and 7 was ≥ 4 (and their score on item 4 (urgency) was > 1) and having voiding symptoms if the sum of their score on AUA-SI items 1, 3, 5 and 6 was 5. For the purposes of this analysis LUTS progression was

defined as new reports of significant symptoms from T1 to T2 for either total (≥ 7), storage (≥ 4), and voiding (≥ 5) LUTS, and LUTS remission as the disappearance of significant symptoms from T1 to T2.

A portable analyser (UROCAP-II, Laborie Technologies, Ontario, Canada) was used to evaluate participants' urine flow. Peak recorded urinary flow was adjusted by volume (Qmax (vol)).

9.3.3 Demographic factors, health status & medication usage

As previously reported [177], information on age, education, marital, occupational and smoking status was assessed by self-report questionnaire completed prior to clinic attendance, using validated measures [182]. Questions relating to physician-diagnosed and family history of major chronic disease were included. Medication usage was determined by self-report and data linkage with a national medication registry. The presence of depression was assessed using the Beck Depression Inventory (BDI-1A [184]), or a report of physician-diagnosed depression and/or use of anti-depressant medication. The probability of obstructive sleep apnoea (OSA) was determined using a multivariable prediction equation [186]). Dietary macronutrient composition was assessed through use of a self-administered semi-quantitative food frequency questionnaire [187]. Leisure-time physical activity (LTPA) was measured with items from a national activity survey (1999 National Physical Activity, Armstrong 2000).

9.3.4 Plasma assays

On arrival at the clinic visit, an 8-12 hour fasting blood sample was taken by venipuncture and immediately refrigerated before being stored at -80˚C prior to assay.

A validated stable-isotope dilution liquid chromatography–tandem mass spectrometry (LC–MS/MS; [267]) was used to measure serum total testosterone (TT) (LOQ: 0.01 nmol/L; inter-assay CV: 9.3% at 0.43 nmol/L; 8.6% at 1.66 nmol/L, 4.0% at 8.17 nmol/L) and estradiol (E2) (LOQ: 15 pmol/L; inter-assay CV: 14% at 23 pmol/L; 4.0% at 83 pmol/L, 6.0% at 408 pmol/L). Plasma HDL, LDL cholesterol, and triglycerides were measured enzymatically using a Hitachi 911 (Boehringer, Germany; inter-assay CV: triglyceride 3%, total cholesterol 2.3%, HDL 6.7% and LDL 3.7%). Plasma glucose determined using an automated chemistry analyser system (Olympus AU5400, Japan; inter-assay CV: 2.5% at 3.5 mmol/L and 3.0% at 19.6 mmol/L). Glycated haemoglobin (HbA1c) was measured by high-pressure liquid chromatography (HPLC) using a spherical cation exchange gel (CV 2% at 6% of total haemoglobin). All assays were preformed in NATA-certified laboratories on the day of the clinic visit (see [177] for summary).

9.3.5 Body composition

Height, weight, waist and hip measurements (as per (Norton & Olds , 2000)), blood pressure and handgrip strength were also measured during the 90 minute clinic visit [177]. Whole body and regional (including abdominal) body fat and lean mass measured by dual energy x-ray absorptiometry (DEXA) using the equivalent LUNAR DPX+ pencil beam or Prodigy DF fan beam densitometer [190]; GE Lunar Corporation, Wisconsin USA).

9.3.6 Statistical analysis

For the present analysis, men at baseline or follow-up visit with a history of bladder (n = 11) or prostate cancer (n = 53) or surgery (n = 42) and those with a current self-reported urinary tract infection (n = 7), were excluded from analysis. In addition, men

who voided less than 100 ml (n = 17) were also removed from this analysis. For prevalence comparisons, all data were weighted according to the inverse of their probability of selection from the target population during the respective Census wave (T1: 2002; T2: 2007). For the initial multinomial logistic regression model, independents were selected on the basis of demonstrated or suspected associations with the outcome (LUTS progression, LUTS remission and equivocal LUTS). Interactions between each independent and / or related covariates (e.g. age, BMI) were also tested for their effects on the outcome measure. Predictors were included in the final regression model if they demonstrated an age-adjusted association with a p value of ≤ 0.1. All data were analysed using PASW Statistics 17.0 (SPSS Inc. Chicago, USA).

9.4 Results

9.4.1 Study population

Table 9-1. Descriptive characteristics of analytic sample of a cohort of Australian men during baseline (2002-5) and follow-up clinic visits (2007-10).

	Baseline 2002-2005		**Follow-up 2007-2010**		
	Mean / %	SD / N	Mean / %	SD / N	*p*
Age Group (years)					
35-44	24.5%	270	**21.7%**	**175**	**0.001**
45-54	28.9%	319	26.1%	210	
55-65	26.2%	289	26.4%	213	
65-80	20.4%	225	**25.9%**	**208**	
Urinary Tract					
Storage LUTS	2.8	2.5	**3.0**	**2.6**	**0.002**
Voiding LUTS	1.8	3.1	**2.2**	**3.2**	**0.001**
Total LUTS	4.6	4.9	**5.1**	**5.1**	**0.001**
Storage LUTS (overall)	1.26	1.26	1.31	1.11	0.760
Nocturia	1.41	1.16	1.51	1.21	0.321
Urgency	1.11	0.91	1.05	1.20	0.876
Frequency	1.22	1.41	1.31	1.28	0.260
Voiding LUTS (overall)	1.45	1.51	1.61	1.22	0.167
Incomplete Emptying	1.31	1.06	1.35	1.12	0.112
Intermittent Stream	1.41	1.26	1.31	1.02	0.243
Weak Stream	1.31	1.44	1.42	1.12	0.566
Straining	1.53	1.16	1.61	1.12	0.201
Peak Urin. Flow (mL/sec)	1.05	0.50	**0.82**	**0.41**	**0.001**
PSA (nmol/L)	1.8	1.5	**2.1**	**1.8**	
BMI	27.0	4.2	**28.8**	**4.5**	**0.018**
Abdo. FM%(DEXA)$^{\Delta}$	32.7	8.2	**34.7**	**5.2**	**0.050**
Hand Grip (Domin.; Nm)	49.6	9.1	**42.2**	**9.2**	**0.001**
Systolic BP (mmHg)	136	18	138	20	0.255
Diastolic BP (mmHg)	84	8	**81**	**9**	**0.041**
Demographics					
Married / Partner	81.2%	895	81.6%	729	0.092
Separated / Divorced	11.0%	121	9.2%	89	
Widowed	2.4%	26	3.2%	30	
Never married	5.4%	60	4.9%	46	
Post-school qualif.	72.2%	216	75.4%	700	0.200
No post-school qualify.	27.6%	86	24.3%	205	

FT	53.0%	585	**44.7%**	**414**	**0.005**
PT/Casual	9.5%	105	9.5%	88	
Unemployed	2.7%	30	2.3%	21	
Retired	26.3%	290	**36.8%**	**335**	
Other	8.4%	93	5.7%	53	
Household Income Low	32.4%	351	30.3%	250	0.119
Middle	36.1%	392	36.9%	308	
High	31.5%	342	32.7%	272	
Lifestyle Factors					
Sufficient PA □	45.7%	489	**35.5%**	**290**	**0.021**
Low PA □	27.0%	293	21.7%	221	
Sedentary □	27.3%	311	**32.8%**	**329**	
Current smoker	23.1%	255	**16.2%**	**151**	**0.001**
Non-current smoker	76.9%	847	**83.1%**	**771**	
Clinical Measures					
Glucose (mmol/L)	4.9	1.3	**5.5**	**1.6**	**0.009**
HbA1c (%)	5.7	0.8	5.9	0.8	0.241
Insulin(IU/L)	11	10	12	11	0.568
Triglycerides (mmol/L)	1.8	1.3	1.8	1.6	0.357
LDL chol. (mmol/L)	3.5	0.9	3.1	1.0	0.011
HDL chol. (mmol/L)	1.2	0.3	1.0	0.3	0.138
Total T (nmol/L)	17.4	6.6	**16.1**	**5.7**	**0.001**
DHT	1.75	0.84	**1.64**	**0.69**	**0.001**
SHBG (nmol/L)	35.1	16.6	**38.9**	**17.2**	**0.002**
E2 (pmol/L)	91.5	40.5	**93.0**	**37.4**	**0.010**
T3 (pmol/L)	4.3	0.8	4.3	0.8	0.561
T4 (pmol/L)	14.7	2.5	**15.2**	**2.7**	**0.002**
TSH (mIU/L)	1.77	1.41	1.79	1.66	0.097
Health Conditions ϕ					
PCS (SF36; Aus) $^{\infty}$	47.9	9.6	**44.2**	**10.4**	**0.005**
MCS (SF36; Aus) $^{\infty}$	50.4	9.5	**46.3**	**11.7**	**0.006**
OSA Probability <80% $^{+}$	78.5%	824	**77.0%**	**751**	**0.022**
≥ 80% $^{+}$	20.5%	247	**22.1%**	**171**	
Erectile Function (IIEF-5)	14.5	7.3	**14.9**	**7.4**	**0.042**
Solit. Sex.Desire (SDI-II)	6.1	5.7	6.2	5.5	0.466
DyadicSex.Desire (SDI-II)	40.6	15.4	**35.1**	**16.3**	**0.039**
Angina	5.3%	59	**7.5%**	**69**	**0.049**
Anxiety	9.2%	101	9.4%	87	0.569
Asthma	12.2%	135	12.3%	114	0.891
Depression	12.1%	134	12.2%	113	0.359
Diabetes	8.9%	98	**12.8%**	**118**	**0.001**
BPH	5.4%	60	**7.2%**	**59**	**0.001**
High chol.	31.9%	352	**38.6%**	**357**	**0.001**
High BP	26.6%	293	**37.5%**	**347**	**0.001**

Insomnia	10.1%	111	8.3%	77	0.108
Osteoarthritis	8.7%	96	**11.4%**	**105**	**0.012**
Other Cancer	7.1%	78	**11.1%**	**103**	**0.023**
Medications ⊕					
Adrenergics	13.2%	159	**17.1%**	**133**	**0.008**
Anticholinergics	4.6%	55	**6.7%**	**49**	**0.029**
Antithrombotics	15.7%	189	15.1%	149	0.244
Dermatologicals	20.1%	242	21.5%	217	0.117
5-α reductase inhibitors	2.2%	23	2.9%	23	0.068
Glucocorticoids	5.6%	67	6.7%	49	0.116
NSAIDS	11.1%	139	**16.2%**	**141**	**0.023**
Statins	13.8%	163	**16.4%**	**143**	**0.042**

Table 9-1 details the descriptive characteristics of participants at each time point. The mean total AUA-SI score was approximately 0.5 points higher in participants at the follow-up visits, and higher mean storage and voiding AUA-SI scores were also observed at follow-up. There was no difference in degree of bother in storage or voiding LUTS between the two waves, but participants at the follow-up visits had higher plasma PSA levels, and peak urinary flow was reduced. At follow-up visits, men were less likely to be in full-time employment and more likely retired. There was no difference between the two waves in marital, education and income status. Participants at follow-up had higher BMI, abdominal fat mass percentage (as measured by DEXA) and lower diastolic BP, handgrip strength, and levels of LTPA. Plasma glucose, sex-hormone binding globulin, estradiol and free thyroxine (T4) concentrations were higher at follow-up, while total testosterone and dihydrotestosterone were lower. Men from the follow-up visits had lower physical and mental component summary score (based on responses to the SF-36), and higher probable sleep apnea, erectile dysfunction and lower dyadic sexual desire scores. More men at follow-up had physician-diagnosed angina, diabetes, BPH, elevated cholesterol and blood pressure,

osteoarthritis and non-prostatic cancers, and were more likely to be taking adrenergics, anticholinergics, non-steroidal anti-inflammatory drugs and statins (Table 9-1).

9.4.2 LUTS Prevalence

Table 9-2. Prevalence of total, storage and voiding LUTS in cohort of Australian men during baseline (2002-5) and follow-up clinic visits (2007-10).

Age Group	Total LUTS - Mild		Total LUTS Moderate		Total LUTS Severe		Storage LUTS		Voiding LUTS	
Baseline	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
35 – 39	86.6	97	12.5	14	0.9	1	24.1	27	7.1	8
40 – 49	86.7	274	11.7	37	1.6	5	23.4	74	8.9	28
50 – 59	87.8	294	11.0	37	1.2	4	23.4	79	8.6	29
60 – 69	71.8	153	25.8	55	3.3	7	33.6	72	20.1	43
70 – 80	68.5	85	25.0	31	7.3	9	46.0	57	25.0	31
All ages	**81.8**	**903**	**15.8**	**174**	**2.4**	**26**	**28.0**	**309**	**12.6**	**139**
Follow-Up										
40 – 49	78.4	120	20.9	32	0.4	1	30.9	47	13.2	20
50 – 59	76.5	140	20.8	38	2.7	5	33.3	61	16.9	31
60 – 69	78.4	145	19.5	36	2.2	4	30.8	57	14.1	26
70 – 79	76.7	99	18.6	24	4.7	6	33.6	43	19.5	25
80 – 85	62.7	25	27.0	4	7.2	8	39.0	16	23.8	10
All ages	**75.0**	**533**	**20.7**	**143**	**4.3**	**24**	**32.5**	**224**	**16.3**	**112**

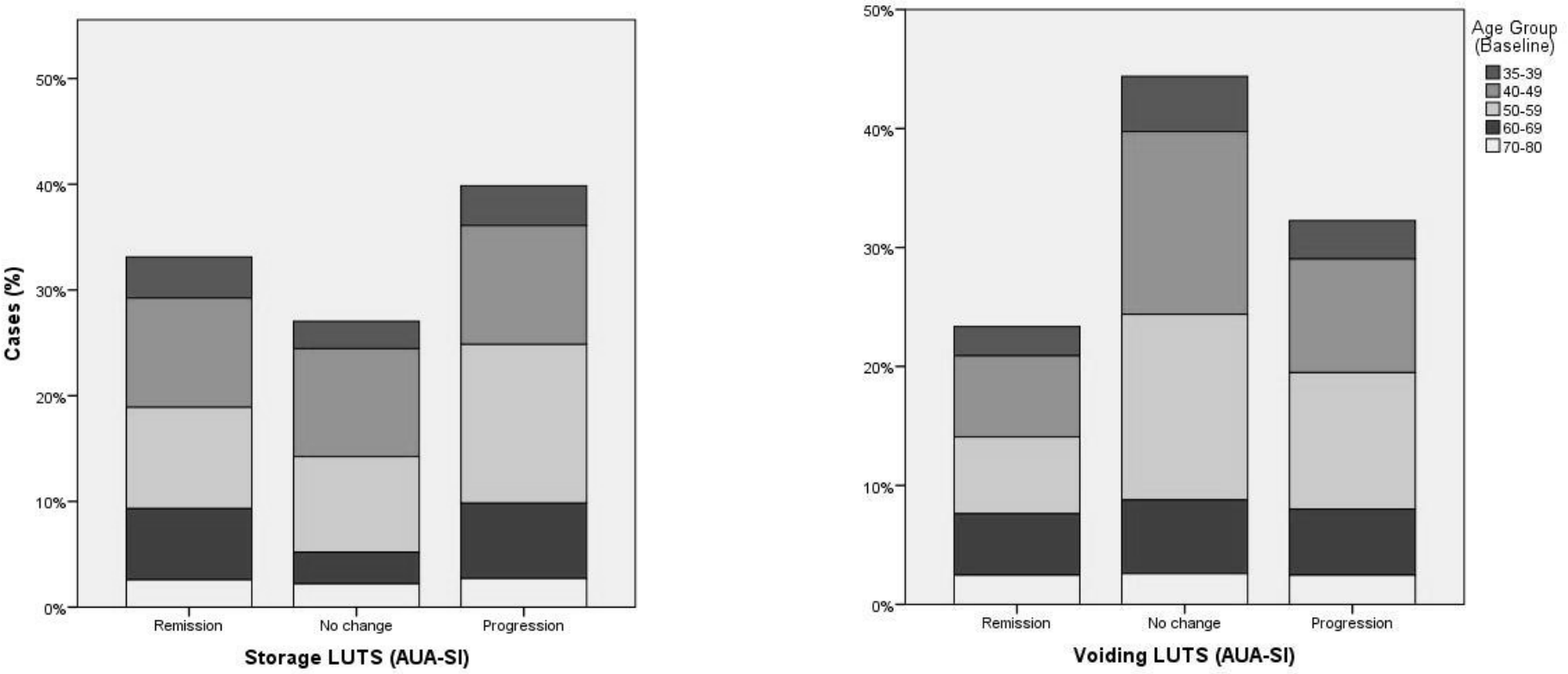
Between baseline and follow-up visits, the proportion of men who reported mild LUTS symptoms had decreased from 81.8% of all men at baseline to 75.0% at follow-up (most notably in men aged less than 59 years at baseline) while the proportion of men reporting moderate (20.7% of all men at follow-up, c.f. 15.8% at baseline) and severe symptoms (4.3% of all men at follow-up, c.f. 2.4% at baseline) had increased. Increases in moderate symptoms had occurred in all but the oldest age group, while increases in severe symptoms were only observed in the oldest age group.

The proportion of men reporting significant storage (≥4 AUA-SI score) and voiding (≥ 5 AUA-SI score) LUTS increased to 32.5% and 16.3% of all-aged men, respectively. In

comparison to men observed at baseline, those participants aged 40-49 , 50-59 and 60-69 years at follow-up were found to have the greatest increase in significant storage and voiding symptoms.

9.4.3 LUTS improvement and progression

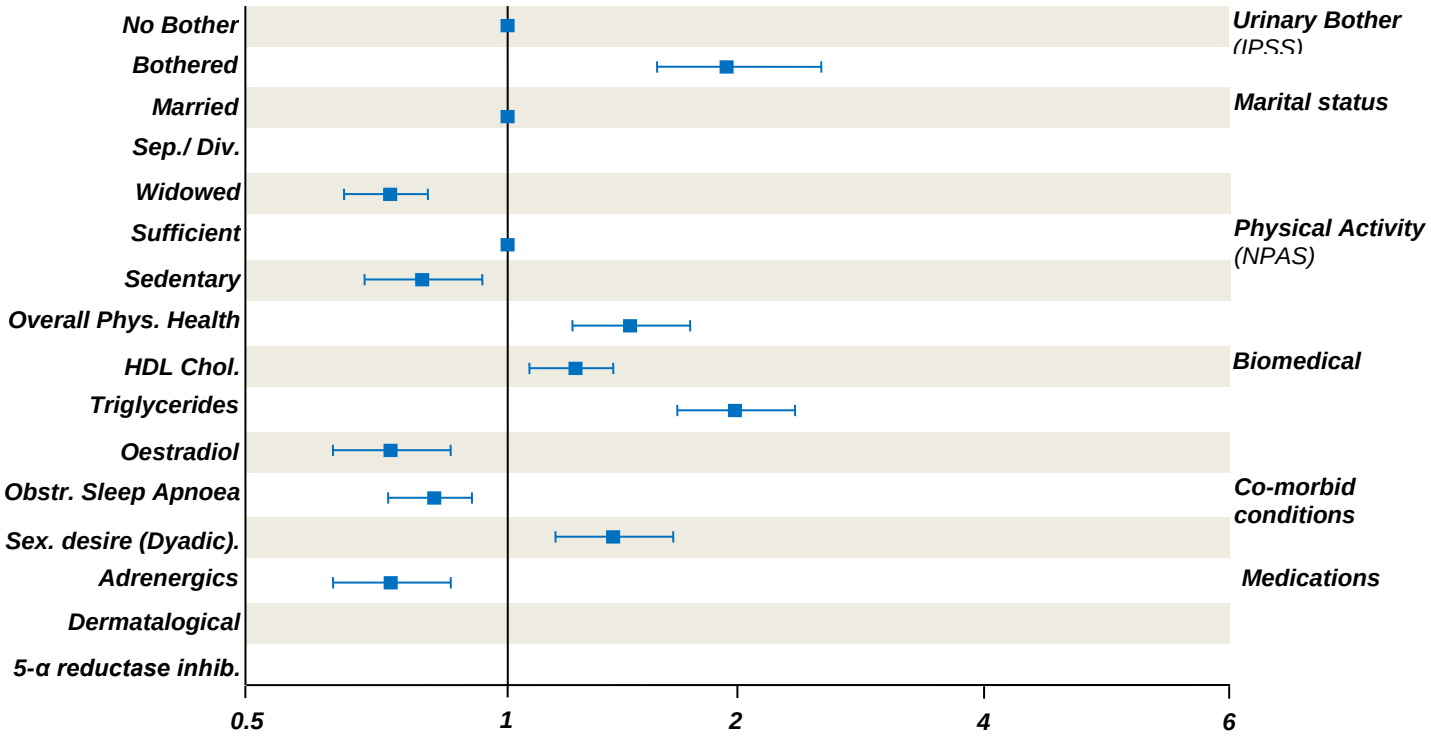
Figure 9-1
Change in Voiding and Storage Lower Urinary Tract Symptoms (LUTS) in a cohort of Australian men during baseline (2002-5) and follow-up (2007-10) clinic visits

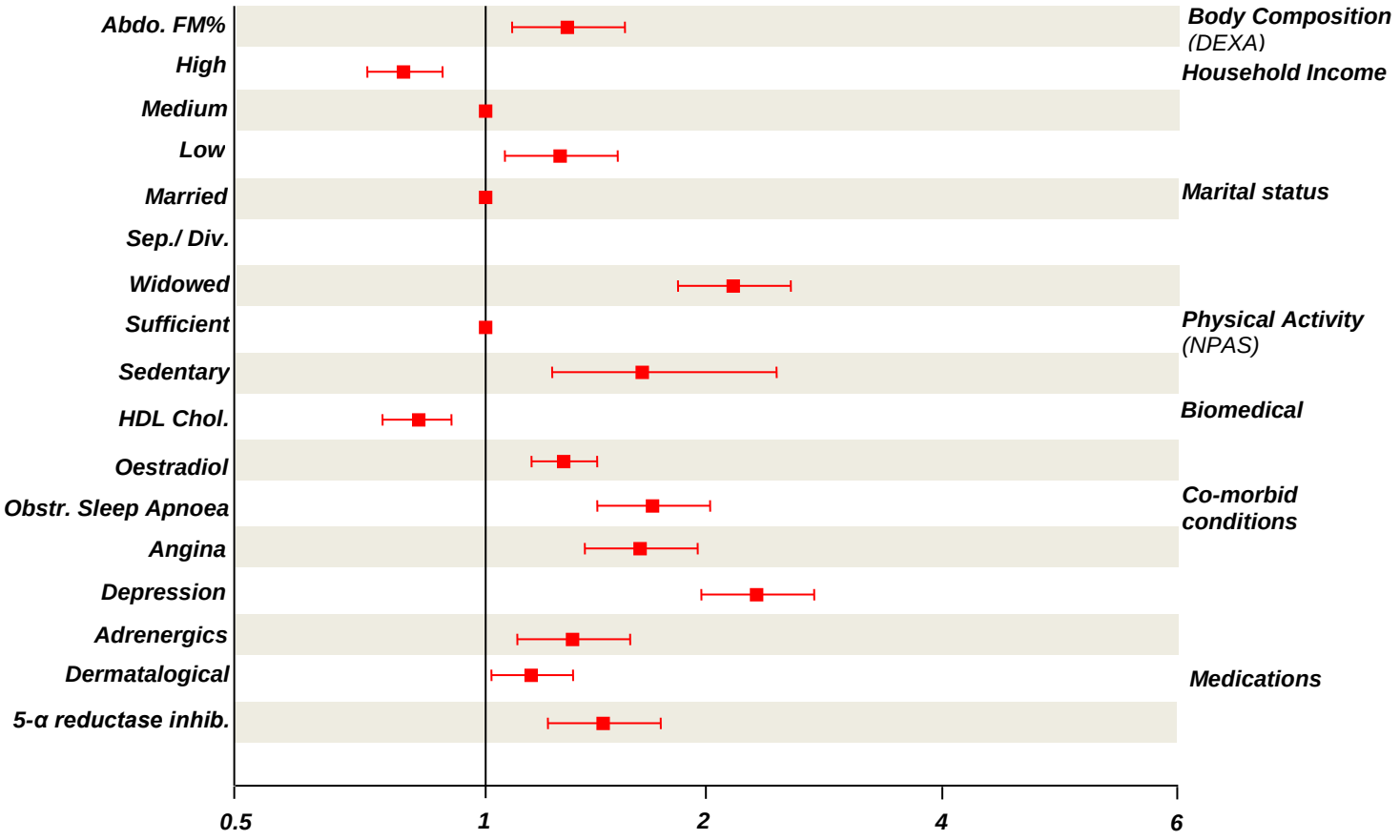


Progression was defined as new reports of significant symptoms from T1 to T2 for storage (≥ 4), and voiding (≥ 5) LUTS, and LUTS remission as the disappearance of significant symptoms from T1 to T2

Of the men examined during follow-up visits, 27.0% (n=209) reported a stable storage LUTS score between visits (-1 to 1 point absolute change in storage symptom AUA-SI score), whereas 33.1% (n=256) and 39.8% (n=308) reported an improvement (change in AUA-SI score of ≤ 2) and progression (change in AUA-SI score of ≥ 2), respectively. For voiding symptoms, 44.0% (n=344) of participants, reported stable AUA-SI score between visits (-2 to 2 point absolute change in voiding symptom AUA-SI score), and 23.4% (n=181) and 32.3% (n=250) of men exhibited either a regression (change in AUA-SI score of ≤ 3) or progression (change in AUA-SI score of ≥ 3) of voiding symptoms (Fig. 9-1).

Fig 9-2. Final multi-adjusted models for progression or remission of storage LUTS incl. a range of social, lifestyle and biomedical variables.



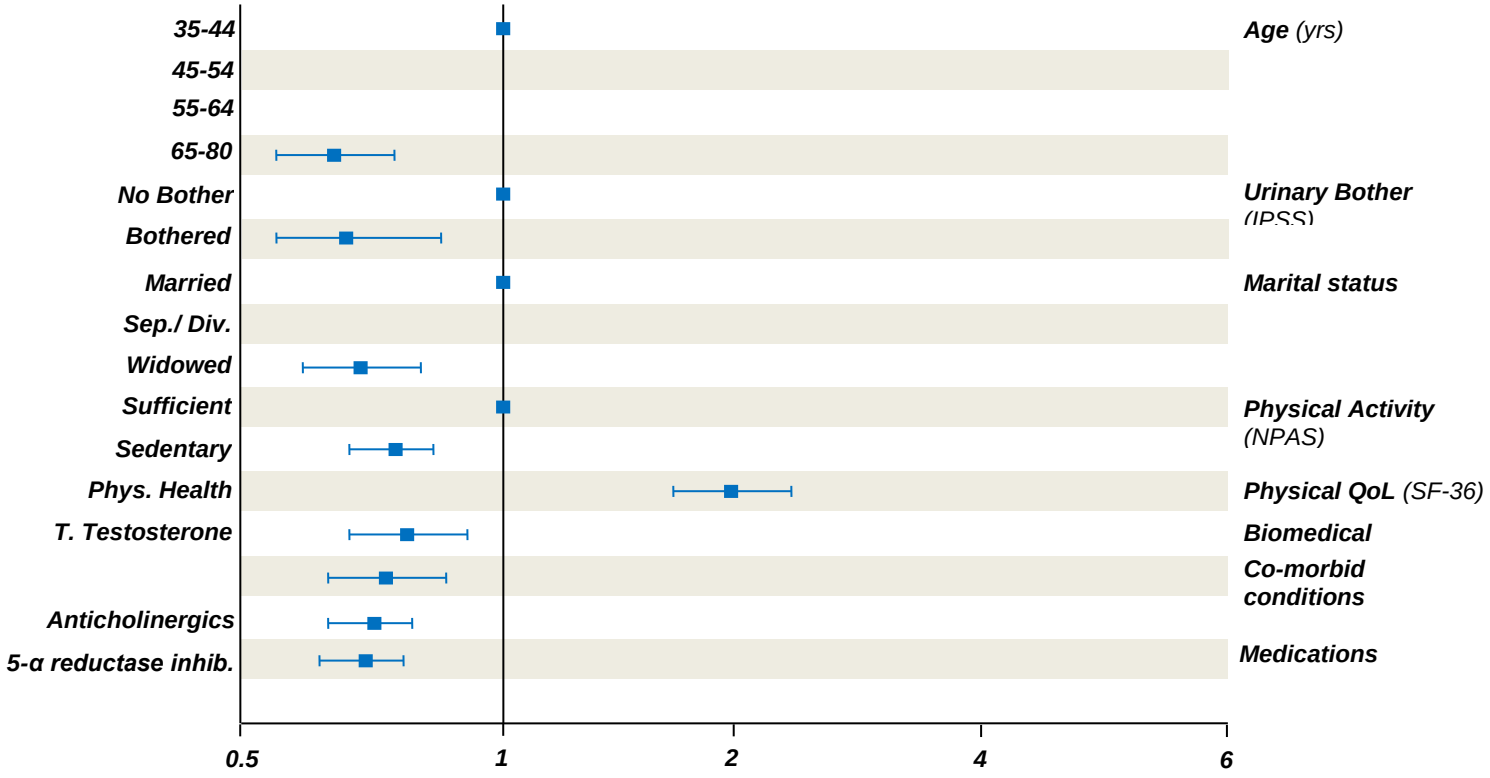


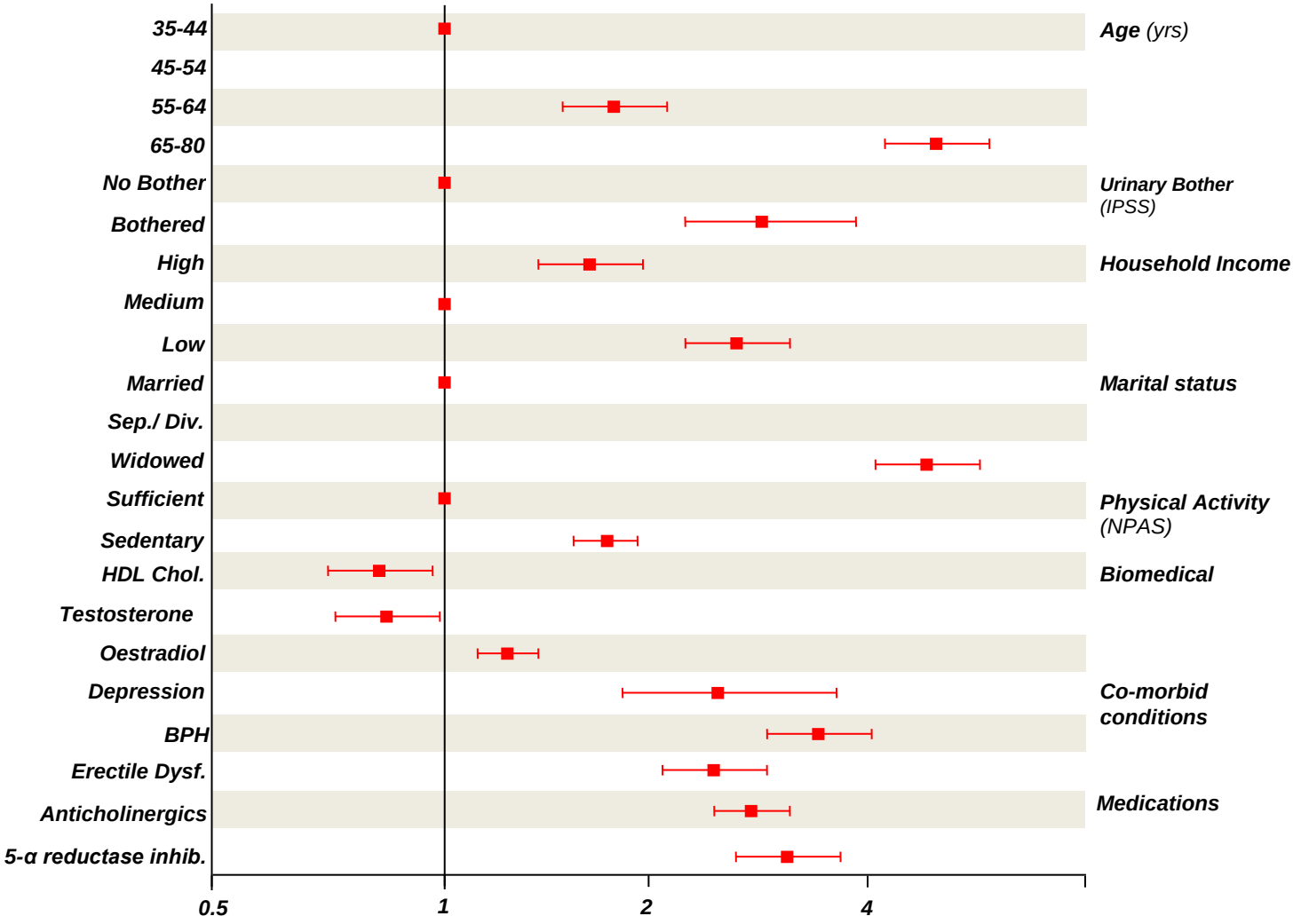
Independent variables with a univariate association with the dependent of p ≤0.1, were included in the final models if the age-adjusted association had a p- value of ≤0.1 , with those Pictured OR's represent the likelihood of symptom remission (blue bars) or progression (red bars) at 5yr clinic for storage LUTS for each of the variables listed, when compared with stable LUTS. For each categorical factors the referent category appears on the 1 line, an OR left of this line indicates less likely to occur, whereas an OR to the right indicates more likely. For each continuous variable the ORs represent the change in the likelihood of either symptom remission or progression per SD increase. Some variables were predictors of both remission and regression.

Figures 9-2 and 9-3 illustrate in a multi-adjusted model the baseline predictors of the improvement and progression of storage and voiding LUTS. When accounting for all other variables, being widowed, sedentary, lower plasma HDL cholesterol and higher estradiol, obstructive sleep apnea risk, and the use of adrenergic medications at baseline predicted both improvement and progression of storage symptoms. While having higher urinary bother, physical well-being, triglycerides, and sexual desire were baseline predictors of improvement alone. Higher abdominal fat mass, lower income, a

diagnosis of angina or depression, and the use of dermatological medications or 5-α reductase inhibitors were found to be predictors of storage progression only. For voiding symptoms, higher age, urinary bother, being widowed and sedentary, lower plasma testosterone, a diagnosis of BPH, and using anti-cholinergic or 5-α reductase inhibitors at baseline predicted both improvement and progression of symptoms. While only a higher degree of physical well-being at baseline predicted improvement of voiding symptoms alone, and both higher and lower household income, lower plasma HDL cholesterol, and higher estradiol, and a diagnosis of depression and erectile dysfunction at baseline were found to be predictors of voiding symptom progression only.

Fig 9-3. Final multi-adjusted models for progression or remission of voiding LUTS incl. a range of social, lifestyle and biomedical variables .





Independent variables with a univariate association with the dependent of p ≤0.1, were included in the final models if the age-adjusted association had a p- value of ≤0.1 , with those Pictured OR's represent the likelihood of symptom remission (blue bars) or progression (red bars) at 5yr clinic for voiding (B) LUTS for each of the variables listed, when compared with stable LUTS. For each categorical factors the referent category appears on the 1 line, an OR left of this line indicates less likely to occur, whereas an OR to the right indicates more likely. For each continuous variable the ORs represent the change in the likelihood of either symptom remission or progression per SD increase. Some variables were predictors of both remission and regression.

9.5 Comment

These data confirm the considerable extent to which LUTS affects men in the broader community, document the different rate of change between storage and voiding-type symptoms, and suggest that both storage and voiding LUTS may remit as well as progress. Importantly these data highlight the presence of discriminating factors that predict either the remission or progression of both storage and voiding LUTS.

In the present study, one in four men without clinically-significant urinary symptoms at baseline had developed LUTS at the follow-up visit. This increased to almost a third of all men with storage-type symptoms, with only one in six men showing significant voiding symptoms. The incidence of all LUTS observed in this cohort (total LUTS: 1.38% of cases/yr; storage LUTS: 0.82% of cases/yr; voiding LUTS: 0.76% of cases/yr) is substantially lower than those previously reported in other cohort studies [34, 110, 259-261]. There are a few explanations for this observation. First, LUTS onset occurs more frequently in older men [258]. The average age at baseline of FAMAS participants in this study was 52.1 years. Thus the much higher rate of incident total LUTS observed in the Mr. OS survey (14.5% of cases / yr) could be attributed to the higher mean age within the cohort (73 years) [259]. In the case of results published from the Olmsted County study [261], the authors did not exclude men with confounding urinary conditions (bladder and prostate cancer/surgery, UTIs), which limits comparisons with the present study.

When controlling for a wide range of factors, a pattern of predictors of remission and progression emerged for both storage and voiding LUTS. For storage symptoms, having

a higher urinary bother, HDL cholesterol, sexual desire and overall physical well-being, with lower triglycerides at baseline were found to predict the remission of storage LUTS alone, while higher abdominal fat mass, lower income, angina or depression, and the use of dermatological medications and 5-α reductase inhibitors at baseline were found to predict progression of storage symptoms only. In the case of voiding symptoms, only a higher degree of physical well-being at baseline predicted the remission of voiding symptoms, while both higher and lower household income, lower plasma HDL cholesterol, and higher estradiol, depression and erectile dysfunction at baseline were predictors of voiding symptom progression only.

The demonstration of men with higher levels of urinary bother at baseline being more likely to report voiding dysfunction at follow-up is unsurprising and consistent with the available literature [26, 262]. In contrast to this general pattern, men from the present study with remitting storage LUTS were more likely to report significant bother at baseline. This may reflect the higher degree of bother associated with storage symptoms, as evidenced in the present study by the higher mean AUA bother score and use of adrenergic medications. This is supported by previous research that demonstrates men are more likely to seek treatment for storage symptoms (e.g. nocturia) and consider voiding dysfunction an inevitable consequence of ageing [26].

Recent observations in other cohort studies have suggested that physical activity has a protective effect on the likelihood of LUTS in men (see [268] for review). These observations have mostly occurred in cross-sectional studies, with some unable to control for highly interrelated variables (e.g. obesity). Recently, longitudinal data from the Mr. OS cohort have confirmed the protective effect of physical activity on LUTS [269],

however this is the first study that demonstrates that physical activity predicts both the remission and progression of symptoms in both storage and voiding LUTS.

Widowed men have long been known to be at an increased risk of a variety of conditions, such as erectile dysfunction, diabetes, and depression [270]. In the present study, widowhood remained one of the strongest predictors of the remission and progression of both storage and voiding LUTS. While some prospective cohort studies have demonstrated a similarly sized effect of widowhood on the development of total LUTS, to our knowledge this is one of the first demonstrations of an effect of being widowed on both storage and voiding symptoms in a cohort study including younger men.

There is a substantial body of evidence that demonstrates the association between depression and LUTS cross-sectionally in men [271], yet few prospective studies have been available to examine the direction of this relationship. Our data concurs with the only previous prospective study to have examined the relationship between LUTS and depression [272], showing an elevated risk of LUTS progression in depressed men independent of other lifestyle and medical factors. Furthermore, we demonstrated that the presence of depression at baseline (defined as either self-report, BDI score, and/or anti-depressant usage) preceded the progression of both storage and voiding symptoms this community-based cohort of men.

The finding of an elevated plasma estradiol in men leading to an increase in both storage and voiding symptoms is of particular clinical interest. Previous attempts in other cohort studies have been hampered by the use of assays with low accuracy in detecting a hormone that occurs in very low concentrations in men. In fact, only one known cross-sectional study has used liquid chromatography-tandem mass

spectrometry in assessing estradiol and LUTS in men [59]. We have further demonstrated an influence of elevated estradiol on both storage and voiding LUTS in men. Recent work demonstrating the importance of estrogen receptor signalling in cells isolated from the bladder, prostate, and urethra [273], together with the previously known role of estrogens in regulating cardiac endothelium function in males [274], suggest a potential role of storage and voiding symptoms as upstream predictors of cardiac disease in men.

The strengths of this study include the use of a comparatively large random sample of men from a broad age group, similar in characteristics to men from the general Australian population [177], a comprehensive bio-psychosocial dataset (including the use of a state-of-the-art mass spectrometer to analyse sex hormones) and the use of conservative estimates of remitting, stable and progressing urinary symptoms for both storage and voiding LUTS. The limitations of this study include the availability of two time points only, and the reliance on self-report measures for most chronic conditions and demographic data.

9.6 Conclusion

In middle-aged and older men, the natural history of LUTS is a dynamic process that includes both remission and progression of symptoms. This study is one of only a few studies that have been able to identify unique, modifiable factors that predict remission and progression over a significant period of time. Given the demonstrated high prevalence of LUTS among men of this age and its associated burden in an ageing demographic, attention should be paid to addressing such factors before further medical or surgical treatment for troubling urinary symptoms.

CHAPTER 10

Predictors of sexual dysfunction incidence and improvement in men

Sean A. Martin [1, 2], Evan Atlantis [3], Kylie Lange [4], Anne W. Taylor [5], Peter O'Loughlin [6], Gary A. Wittert [1,2] and Members of the Florey Adelaide Male Ageing Study (FAMAS)

[1] Freemasons Foundation Centre for Men's Health, University of Adelaide, Adelaide, South Australia

[2] Discipline of Medicine, University of Adelaide, Adelaide, South Australia

3 School of Nursing and Midwifery, University of Western Sydney, Sydney, New South Wales

[4] Centre of Clinical Research Excellence (CCRE) in Nutritional Physiology, Interventions and Outcomes, University of Adelaide, Adelaide, South Australia

[5] Population Research and Outcomes Studies, Discipline of Medicine, University of Adelaide, Adelaide, South Australia

[6] Chemical Pathology, SA Pathology, Adelaide, South Australia

Submitted: Annals of Internal Medicine

(Modified version resubmitted to Journal of Sexual Medicine, Aug 2013)

Statement of Authorship

Sean A. Martin (Candidate)

Roles: Corresponding Author; Conception and Design; Acquisition of Data; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Evan Atlantis

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Kylie Lange

Roles: Design; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Anne W. Taylor

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Peter O'Loughlin

Roles: Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

Gary Wittert

Roles: Principal Investigator; Sought and Obtained Funding; Analysis and Interpretation of Data; Drafting the Article; Revising It for Intellectual Content; Final Approval of the Completed Article

Signed ..... Date .....

10.1 Abstract

Background: There is limited information available from community-based studies about the incidence, and improvement, of sexual dysfunction in middle aged and elderly men.

Objective: To describe the incidence and remission, and associated biopsychosocial predictors, of erectile dysfunction (ED) and low solitary and dyadic sexual desire.

Design: Population-based cohort study.

Setting: Community-dwelling men from Adelaide, Australia.

Subjects: Men aged 35-80 years at baseline who attended baseline (2002-5) and follow-up clinic visits (2007-10).

Measurements: Erectile function (IIEF-EF) and sexual desire (SDI- 2), as well as associated socio-demographic, lifestyle, biological, and clinical risk factors by clinical examination and self-report questionnaire.

Results: At follow-up, 34.5% (n=179) men had developed ED, while 35.0% (n=45) of men with ED at baseline subsequently improved. For low solitary and dyadic sexual desire, 24.2% (n=90) and 8.0% (n=60) of men reported incident cases, while 15.3% (n=68) and 21.8% (n=17) of men reported improved symptoms at follow-up. In final regression models, age and diabetes at baseline were both independent predictors of incident and improved ED at follow-up, while lower income, abdominal fat mass, alcohol intake, voiding LUTS and depression were associated with ED progression only. Being never married, widowed, and unemployment at baseline was associated with both deterioration and improvement of dyadic desire at follow-up, while increasing age, retirement, insufficient physical activity and low alcohol intake was associated

with deteriorating dyadic desire only, and lower income, depression and insomnia, cancer, abdominal fat mass, OSA risk, and plasma testosterone were associated with reduced likelihood of dyadic desire improvement at follow-up. Being never married, employment, and alcohol intake at baseline was associated with both deterioration and improvement of solitary desire, while lower plasma testosterone, storage LUTS and hypertension were associated with deteriorating solitary desire only, and higher income, not being sedentary or depressed at baseline were associated with improvements in solitary desire at follow-up.

Limitations: Participants were predominantly Caucasian and did not include younger age groups.

Conclusions: Sexual dysfunction in aging men is a dynamic disorder. This data highlights the common relationship between several modifiable risk factors for a range of conditions and ED and low sexual desire. Consequently, ED and low sexual desire may act as sentinel markers of chronic disease.

10.2 Introduction

Erectile dysfunction (ED) and loss of sexual desire are among the most common sexual dysfunction syndromes in men. Based on nationally representative data sources, it is estimated that the 12-month prevalence of at least one sexual dysfunction is between 30% and 70% in sexually active men in high-income countries [143]. On average, this estimation increased markedly with age. Sexual dysfunction is associated with a marked decrement in health-related quality of life [275], increased risk of developing depression [276], and is a useful prognostic indicator in cardiovascular disease (CVD) [122].

Historically, declining sexual function in men has been considered as an inevitable consequence of the ageing process rather than a medical dysfunction [277]. However, a substantial portion of this decline could be partially due to the accumulation of co-morbidities with age, and these may be amenable with timely therapeutic intervention. For instance, several medical conditions and related treatments that interfere with sexual function include depression, diabetes and CVD [276]. Furthermore, ED in particular has recently been shown to be associated with a variety of medical conditions including diabetes [223], cardiovascular [224], as well as musculoskeletal disease [226], mood disorders [225-77], declining muscle mass and strength [228], endocrine disorders [108], medication usage [230], and deteriorating social position [231]. Co-morbid sexual dysfunction with any of these medical conditions would complicate treatment options, and likely worsen their prognosis. For instance, men with ED typically have lifestyle risk factors [227].

Thus, it is important to know whether the complex association between sexual dysfunction and medical conditions is causal or consequential. Longitudinal associations between sexual and medical conditions could strengthen the overall evidence of causality, but have not been adequately assessed by previous studies. We aimed to determine the modifiable risk factors for and clinically relevant consequences of sexual dysfunction in a regionally representative sample of Australian men.

10.3 Methods

10.3.1 Study population

Data were obtained from the Florey Adelaide Male Ageing Study (FAMAS [177], a longitudinal study of 1195 randomly-selected men living in the north-west region of Adelaide, and aged 35 years and over at recruitment.

Baseline clinic assessments occurred between 2002 and 2005 (T1), and follow-up clinic visits, using identical protocols, between 2007 and 2010 (T2).

Approval for the research was obtained from the Royal Adelaide Hospital Research Ethics Committee and the Aboriginal Health Research Ethics Committee.

10.3.2 Sexual dysfunction variables

Dyadic and solitary sexual desire

Sexual desire was assessed with the Sexual Desire Inventory 2 (SDI-2, [139]), which separately measures dyadic sexual desire (defined as interest in or a wish to engage in sexual activity with another person and desire for intimacy) and solitary sexual desire (defined as an interest in engaging in sexual behaviour by oneself, or a wish to refrain from intimacy) [139]. In the present study, low dyadic and solitary sexual desire was defined as a score of ≤ 16 and ≤ 6, respectively [278].

Erectile dysfunction

The erectile function (EF) domain of the full-scale International Index of Erectile Function (IIEF, [97]) was used to assess erectile function. Those respondents with an IIEF-EF score of 6-10 were categorised as having severe ED; 11-16 as moderate ED; 17-25 as

mild-mild/moderate (herein referred to as 'mild'), and those with a score of 26 or greater as no ED [97]. We further categorised participants with no or mild ED as having 'Normal EF' and those with either moderate or severe ED as having 'Significant ED' in line with previous validatory studies [279].

10.3.3 Other covariates

Height, weight, blood pressure and handgrip strength were measured [177] along with a whole body and regional (including abdominal) body fat and lean mass assessment by dual energy x-ray absorptiometry (DEXA) [190].

Information on age, education, marital, occupational status, and smoking behaviour was assessed by questionnaire, which included questions relating to physician-diagnosed and family history of major chronic disease [177]. Depression was assessed using the Beck Depression Inventory v.1A; [184]. The probability of obstructive sleep apnoea (OSA) was determined using a multivariable prediction questionnaire [186]. In addition to self-report, information relating to medication usage was obtained from Medicare Australia. Dietary macronutrient composition (including alcohol consumption) was assessed with a self-administered semi-quantitative food frequency questionnaire [187]. Leisure-time physical activity was measured with items from a national activity survey [280].

Plasma assays

A fasting, morning blood sample was taken at each visit, immediately refrigerated and transported to a NATA certified laboratory assay within 4- hours [177]. Serum total

testosterone (TT) and estradiol (E2) were measured by a high-sensitivity chromatography–tandem mass spectrometry (LC–MS/MS) [177] (TT: LOQ: 0.01 nmol/L; inter-assay CV: 9.3% at 0.43 nmol/L; 8.6% at 1.66 nmol/L, 4.0% at 8.17 nmol/L; E2: LOQ: 15 pmol/L; inter-assay CV: 14% at 23 pmol/L; 4.0% at 83 pmol/L, 6.0% at 408 pmol/L). Plasma HDL, LDL cholesterol, and triglycerides were measured enzymatically using a Hitachi 911 autoanalyser (IA-CV: triglyceride 3%, total cholesterol 2.3%, HDL 6.7% and LDL 3.7%), glucose determined using an automated hexokinase assay (IA-CV: 2.5% at 3.5 mmol/L and 3.0% at 19.6 mmol/L), glycated haemoglobin (HbA1c) was measured by high-pressure liquid chromatography (HPLC) using a spherical cation exchange gel (IA-CV 2% at 6% of total haemoglobin) [177].

10.3.4 Statistical analyses

Subjects were excluded if they had self-reported prostate cancer (n=47) or orchidectomies (both uni- and bilateral; n=6), or were receiving gonadotropin-releasing hormones (n=7), anti-androgen therapy, or testosterone therapy (n=11).

Incidence of low dyadic and solitary sexual desire was defined as those men without symptoms at T1, presenting with an SDI-II score of ≤ 16 (low dyadic desire) and ≤ 6 (low solitary desire) at T2. ED incidence was defined as those men with normal ED at T1, presenting with an IIEF-EF score of ≤ 16 (significant ED) at T2. Improvement was defined as the absence of significant symptoms at T2 in those men who reported low dyadic and solitary desire and significant ED at T1.

Initial descriptive analyses between selected independents and outcome measures (incidence and improvement of low dyadic and solitary desire and significant ED) were

conducted using chi-square (categorical) and t-tests (continuous). Independents were selected on the basis of demonstrated or suspected associations with the outcome. For the final regression models, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by binary logistic regression. Firstly, the OR of each independent on the outcome was examined to determine individual main effects. Next, regression models were fitted with the independent variable and age to get age-adjusted OR. Age was then checked as a modifier for each of the independent variables by fitting against age and the age- independent interaction. Age was considered a modifier for an independent variable if the interaction had a p-value < 0.005 (to account for the multiple testing). Those variables whose age-adjusted relative risks had a p value <0.25 were included in the final multivariate model.

All data were analysed using PASW Statistics 17.0 (SPSS Inc. Chicago, USA).

10.4 Results

10.4.1 Erectile function and sexual desire at baseline and follow-up

Table 10-1. Improvement and progression of ED & low dyadic and solitary sexual desire symptoms from baseline (2002-5) to follow-up clinic visits (2007-10)

	Follow-up status			
Baseline Status	**Improved**	**Stable**	**Progression**	**Total (n)**
Significant ED % (n)	35.0 (45)	65.0 (84)		129
Normal EF % (n)		65.4 (339)	34.6 (179)	518
Low Dyadic Desire % (n)	21.8 (17)	78.2 (61)		78
Normal Dyadic Desire % (n)		92.0 (586)	8.0 (60)	646
Low Solitary Desire % (n)	15.3 (68)	84.7 (325)		393
Normal Solitary Desire % (n)		75.8 (232)	24.2 (90)	322

Data are presented as % (n) of participants at follow-up who had improved, remained stable or progressing erectile dysfunction (ED_IIEF), and low dyadic or solitary sexual desire (SDI-II) by baseline status. Note: Participants who failed to complete all items of the IIEF-EF (n=153), SDI-II (Dyadic) (n=86) & SDI-II (Solitary) (n=95) were excluded from analysis.

Of the men with normal erectile function at baseline, 34.5% (n=179) had significant ED at follow-up, while 35.0% (n=45) with ED at baseline improved at follow-up. Of the men with normal dyadic and solitary sexual desire at baseline, there was a deterioration in 8.0% (n=60) and 24.2% (n=90) of men, respectively. Of those men with low dyadic and solitary sexual desire at baseline, 21.8% (n=17) and 15.3% (n=68) were significantly improved at follow-up.

10.4.2 Predictors ED, low dyadic and solitary sexual desire incidence and improvement

Table 10-2. Descriptive characteristics of men who attended 5-year follow up visits (2007-10) by erectile dysfunction progression or improvement (IIEF-ED)

		ED progression		No ED progression		**ED improvement**		No ED improvement	
		% / x	**N / SD**	% / x	N / SD	**% / x**	**N / SD**	% / x	N / SD
Age Group	**35-44 years**	16.7%*****	19	33.2%	150	9.9%*****	19	24.5%	13
	45-54 years	30.7%	35	34.5%	156	16.8%*****	32	43.4%	23
	55-64 years	25.4%	29	25.7%	116	28.8%	55	28.3%	15
	65-80 years	27.2%*****	31	6.6%	30	44.5%	85	3.8%	2
Marital status	**Married / Partner**	92.1%	105	89.8%	404	73.3%*****	140	64.2%	34
	Separated / Divorced	5.3%	6	6.0%	27	11.5%	22	22.6%	12
	Widowed	0.0%	0	0.9%	4	5.8%	11	3.8%	2
	Never married	2.6%	3	3.3%	15	9.4%	18	9.4%	5
Post-school qualification	**Bachelor degree or higher**	22.4%*****	17	18.4%	61	18.1%*****	26	26.1%	12
	Trade / Apprenticeship	25.0%	19	33.8%	112	29.9%	43	32.6%	15
	Certificate / Diploma	48.7%	37	43.2%	143	45.1%	65	39.1%	18
	Other	3.9%	3	4.5%	15	6.9%	10	2.2%	1
Work Status	**FT**	50.9%*****	58	70.7%	319	29.3%*****	56	58.5%	31
	PT / Casual	11.4%	13	8.4%	38	11.0%	21	11.3%	6
	Unemployed	1.8%	2	1.3%	6	4.2%*****	8	22.8%	12
	Retired	31.6%*****	36	11.5%	52	11.5%*****	22	26.4%	14
	Other	4.4%	5	8.0%	36	9.4%	18	11.3%	6
Household	**High**	35.7%*****	40	42.9%	192	14.8%*****	28	32.7%	17

Income									
	Middle	28.6%*****	32	41.7%	187	31.2%	59	46.2%	24
	Low	35.7%*****	40	15.4%	69	54.0%*****	102	21.2%	11
Country of Birth	**Australia**	76.3%*****	87	68.1%	308	65.4%*****	125	77.4%	41
	Other	23.7%*****	27	31.9%	144	34.6%*****	66	22.6%	12
Body measures	**Whole Fat Mass (%)**	28.2	5.9	26.5	6.1	27.0	6.7	26.8	6.9
	Abdominal Fat Mass (%)	36.0*****	7.1	32.4	7.7	33.9	8.6	33.9	8.9
	Hand Grip (Dominant)	50	9	52	8	46	9	50	8
Smoking (current)	**Yes**	14.0%	16	22.0%	99	18.3%*****	35	24.5%	13
	No	86.0%*****	98	78.0%	351	81.7%	156	75.5%	40
Physical Activity	**Low**	57.5%*****	67	50.0%	226	48.2%*****	92	35.8%	19
	Sufficient	42.5%*****	48	50.0%	226	51.8%*****	99	64.2%	34
Alcohol (>2 std drinks/day)	**No**	52.6%*****	60	58.0%	262	70.2%*****	134	60.4%	32
	Yes	47.4%*****	54	42.0%	190	29.8%	57	39.6%	21
Endocrine	**Total testosterone (nmol/L)**	17.6	5.8	17.4	5.9	16.4	5.7	18.2	11.3
	Dihydrotestosterone (nmol/L)	1.66	0.68	1.72	0.8	1.69	0.72	1.84	1.36
	Estradiol (pmol/ L)					91.5*****	37.8	103.6	56.9
Health Conditions									

	Probability of OSA	0.62*****	0.21	0.53	0.23	0.43*****	0.20	0.63	0.26
	Storage LUTS	17.5%	20	14.4%	65	22.5%	43	24.5%	13
	Voiding LUTS	17.6%*****	20	9.5%	43	20.9%	40	17.0%	9
	Angina	15.8%*****	20	2.4%	11	10.5%	20	1.9%	1
	Anxiety	8.8%	10	6.6%	30	9.4%	18	13.2%	7
	Depression	25.9%*****	31	18.6%	84	26.7%	51	30.2%	16
	Diabetes	19.3%*****	22	5.1%	23	9.1%*****	17	22.6%	12
	High cholesterol	67.5%	77	66.2%	299	27.7%*****	53	45.2%	24
	Insomnia	9.6%	11	8.0%	36	12.0%*****	23	18.9%	10
	Osteoarthritis	12.3%*****	14	5.5%	25	15.2%	29	1.9%	1
	Prostate Cancer	3.5%	4	0.0%	0	5.8%	11	0.0%	0
	Other Cancer	6.1%	7	4.6%	21	12.0%	23	5.7%	3
Medications									
	Adrenergics	12.3%	14	8.0%	36	21.5%	41	13.2%	7
	Anticholinergic	3.5%	4	1.8%	8	7.9%	15	3.8%	2
	Antipsychotics	0.9%	1	0.2%	1	2.6%	5	0.0%	0
	Genitourinary	2.6%	3	1.3%	6	5.8%	11	3.8%	2
	Glucocorticoids	5.3%	6	5.5%	25	7.3%	14	3.8%	2

*Data are presented as % (n) of participants at follow-up who had ED progression or ED improvement (IIEF-EF) (shaded columns include all other participants). Note: Participants who failed to complete all items of the IIEF-EF (n=153) were excluded from analysis. * $p \leq 0.05$*

Table 10-2 compares the baseline characteristics of men who had either incident or improved ED at follow-up. Men with incident ED were more likely to be from the eldest age group (65-80 years), separated or divorced, retired, from lower gross income households, and less likely to be from the youngest age group (35-44 years), married or with a partner, and in full-time work than men with no ED at baseline. Men with ED at follow-up were also more likely to have higher abdominal fat mass (as measured by

DEXA), drink less than two standard units of alcohol per day, a higher risk of obstructive sleep apnea (OSA), storage and voiding lower urinary tract symptoms (LUTS), angina, anxiety, depression, diabetes, high cholesterol, insomnia and cancer (other than prostate), and have lower measured handgrip strength and leisure-time physical activity levels at baseline. Adrenergic, anti-cholinergic, and glucocorticoid usage at baseline was associated with ED at follow-up.

Table 10-3. Descriptive characteristics of men who attended 5-year follow up visits (2007-10) by low dyadic sexual desire progression or improvement (SDI-II).

		Low dyadic progression		No low dyadic progression		**Low dyadic improvement**		No low dyadic improvement	
		% / x	**N / SD**	% / x	N / SD	**% / x**	**N / SD**	% / x	N / SD
Age Group	**35-44 years**	5.9%	1	1.6%	1	28.6%	193	7.8%	4
	45-54 years	17.6%	3	10.9%	7	34.0%	229	11.8%	6
	55-64 years	35.3%	6	31.3%	20	26.4%	178	17.6%	9
	65-80 years	41.2%	7	56.3%	36	11.0%	74	62.7%	32
Marital status	**Married / Partner**	88.2%	15	79.7%	51	85.6%	575	82.4%	42
	Separated / Divorced	5.9%	1	9.4%	6	8.3%	56	7.8%	4
	Widowed	0.0%	0	3.1%	2	1.5%	10	3.9%	2
	Never married	5.9%	1	7.8%	5	4.6%	31	5.9%	3
Post-school qualification	**Bachelor degree or higher**	14.3%	2	11.1%	5	20.1%	100	17.9%	7
	Trade / Apprenticeship	28.6%	4	20.0%	9	34.2%	170	15.4%	6

	Certificate / Diploma	50.0%	7	64.4%	29	41.4%	206	56.4%	22
	Other	7.1%	1	4.4%	2	4.2%	21	10.3%	4
Work Status	**FT**	41.2%	7	17.2%	11	64.3%	433	17.6%	9
	PT / Casual	11.8%	2	12.5%	8	9.5%	64	3.9%	2
	Unemployed	0.0%	0	1.6%	1	2.4%	16	2.0%	1
	Retired	41.2%	7	59.4%	38	15.9%	107	60.8%	31
	Other	5.9%	1	9.4%	6	7.9%	53	15.7%	8
Household Income	**High**	17.6%	3	8.1%	5	38.4%	256	21.6%	11
	Middle	41.2%	7	29.0%	18	39.9%	266	25.5%	13
	Low	41.2%	7	62.9%	39	21.6%	144	52.9%	27
Country of Birth	**Australia**	58.8%	10	67.2%	43	69.3%	467	72.5%	37
	Other	41.2%	7	32.8%	21	30.7%	207	27.5%	14
Body measures	**Whole Fat Mass (%)**	24.0	8.1	28.1	7.1	26.7	6.2	28.3	6.1
	Abdominal Fat Mass (%)	31.4	11.2	35.2	8.8	33.6	7.8	35.2	8.2
	Hand Grip (Dominant)	49	7	43	8	51	9	47	8
Smoking (current)	**Yes**	11.8%	2	14.1%	9	21.6%	145	5.9%	3
	No	88.2%	15	85.9%	55	78.4%	527	94.1%	48
Physical Activity	**Low**	64.7%	11	57.8%	37	49.0%	330	41.2%	21
	Sufficient	35.3%	6	42.2%	27	51.0%	344	58.8%	30
Alcohol (>2 std drinks/day)	**No**	76.5%	13	70.3%	45	58.3%	393	68.6%	35

	Yes	23.5%	4	29.7%	19	41.7%	281	31.4%	16
Endocrine	**Total testosterone (nmol/L)**	16.5	4.4	15.8	6	17.5	6.50	15.9	5.2
	Dihydrotestosterone (nmol/L)	1.69	0.49	1.65	0.69	1.73	0.86	1.71	0.78
	Estradiol (pmol/ L)	91.4	36.6	89.8	28.4	96.7	42	106.4	51.3
Health Conditions									
	Probability of OSA	0.58	0.26	0.68	0.21	0.55	0.23	0.66	0.20
	Storage LUTS	29.4%	5	25.0%	16	16.0%	108	21.6%	11
	Voiding LUTS	35.3%	6	23.4%	15	11.0%	74	17.6%	9
	Angina	0.0%	0	10.9%	7	3.9%	26	15.7%	8
	Anxiety	5.9%	1	12.5%	8	7.7%	52	9.8%	5
	Depression	17.6%	3	28.1%	18	21.1%	142	21.6%	11
	Diabetes	5.9%	1	18.8%	12	8.8%	59	21.6%	11
	High cholesterol	29.4%	5	20.3%	13	32.3%	218	29.4%	15
	Insomnia	5.9%	1	20.3%	13	8.6%	58	11.8%	6
	Osteoarthritis	5.9%	1	17.2%	11	7.0%	47	19.6%	10
	Prostate Cancer	5.9%	1	6.3%	4	0.6%	4	9.8%	5
	Other Cancer	29.4%	5	10.9%	7	5.5%	37	15.7%	8
Medications									
	Adrenergics	11.8%	2	25.0%	16	9.6%	65	21.6%	11
	Anticholinergic	5.9%	1	12.5%	8	2.4%	16	5.9%	3
	Antipsychotics	0.0%	0	3.1%	2	0.4%	3	2.0%	1
	Genitourinary	0.0%	0	7.8%	5	2.2%	15	3.9%	2
	Glucocorticoids	11.8%	2	10.9%	7	5.0%	34	3.9%	2

*Data are presented as % (n) of participants at follow-up who recorded improvement or progression of low dyadic sexual desire (SDI-II (Dyadic)) (shaded columns include all other participants). Note: Participants who failed to complete all items of the SDI-II (Dyadic) (n=86) were excluded from analysis. * $p \leq 0.05$*

Men who had deteriorating dyadic desire at follow-up were older, had obtained higher education levels, retired, or from lower income households. Such men were also less likely to be married or be in full-time work (Table 10-3). Men who had deteriorating solitary sexual desire were also more likely to be older, married, have lower levels of education, from lower income households, be been born outside of Australia and less likely to work full-time (Table 10-4). Men with deteriorating dyadic sexual desire were also more likely to have higher abdominal fat mass, be current smokers, have less than two standard units of alcohol per day, a higher risk of obstructive sleep apnea (OSA), storage and voiding lower urinary tract symptoms (LUTS), angina, anxiety, depression, diabetes, insomnia and osteoarthritis. Whereas men with deteriorating solitary desire were more likely to have higher whole and abdominal fat mass, be current smokers, have low levels of leisure-time physical activity, a higher risk of obstructive sleep apnea (OSA), angina, anxiety, depression, diabetes, insomnia and osteoarthritis. Men with deteriorating dyadic sexual desire had greater use of adrenergic, anti-cholinergic, and genito-urinary medications and men with deteriorating solitary desire reported greater use of adrenergic medications at baseline (Table 10-4).

Table 10-4. Descriptive characteristics of men who attended 5-year follow up visits (2007-10) by low solitary sexual desire progression or improvement (SDI-II).

		Low solitary progression		No low solitary progression		**Low solitary improvement**		No low solitary improvement	
		% / x	**N / SD**	% / x	N / SD	**% / x**	**N / SD**	% / x	N / SD
Age Group	**35-44 years**	26.5%	18	40.5%	109	27.2%	22	13.6%	54
	45-54 years	26.5%	18	33.5%	90	38.3%	31	26.8%	106

	55-64 years	29.4%	20	19.3%	52	25.9%	21	31.1%	123
	65-80 years	17.6%	12	6.7%	18	8.6%	7	28.5%	113
Marital status	**Married / Partner**	72.1%	49	79.9%	214	84.0%	68	89.6%	355
	Separated / Divorced	19.1%	13	11.2%	30	9.9%	8	4.5%	18
	Widowed	1.5%	1	1.1%	3	1.2%	1	3.0%	12
	Never married	7.4%	5	7.8%	21	4.9%	4	2.8%	11
Post-school qualification	**Bachelor degree or higher**	13.5%	7	26.7%	54	19.7%	13	15.2%	43
	Trade / Apprenticeship	42.3%	22	33.2%	67	33.3%	22	28.0%	79
	Certificate / Diploma	40.4%	21	38.6%	78	39.4%	26	50.0%	141
	Other	3.8%	2	1.5%	3	7.6%	5	6.7%	19
Work Status	**FT**	61.8%	42	67.7%	182	71.6%	58	46.2%	183
	PT / Casual	10.3%	7	11.9%	32	6.2%	5	8.6%	34
	Unemployed	1.5%	1	3.0%	8	1.2%	1	2.3%	9
	Retired	20.6%	14	10.8%	29	11.1%	9	33.8%	134
	Other	5.9%	4	6.7%	18	9.9%	8	9.1%	36
Household Income	**High**	29.9%	20	44.2%	119	43.0%	34	26.6%	104
	Middle	44.8%	30	37.5%	101	36.7%	29	36.8%	144
	Low	25.4%	17	18.2%	49	20.3%	16	36.6%	143
Country of Birth	**Australia**	75.0%	51	71.7%	193	64.2%	52	67.7%	268
	Other	25.0%	17	28.3%	76	35.8%	29	32.3%	128
Body measures	**Whole Fat Mass (%)**	26.1	6.7	26.5	6.2	26.6	6.7	27.3	6.2
	Abdominal Fat Mass (%)	33.5	8.7	33.5	7.7	33.2	7.7	34.2	8.0

	Hand Grip (Dominant)	50	8	52	9	51	10	49	9
Smoking (current)	**Yes**	19.1%	13	23.1%	62	18.5%	15	18.7%	74
	No	80.9%	55	76.9%	206	81.5%	66	81.3%	322
Physical Activity	**Low**	48.5%	33	45.7%	123	60.5%	49	49.5%	196
	Sufficient	51.5%	35	54.3%	146	39.5%	32	50.5%	200
Alcohol (>2 std drinks/day)	**No**	55.9%	38	53.2%	143	48.1%	39	68.2%	270
	Yes	44.1%	30	46.8%	126	51.9%	42	31.8%	126
Endocrine	**Total testosterone (nmol/L)**	16.7		18.1	7.5	16.8	5.7	16.8	5.8
	Dihydrotestosterone (nmol/L)	1.73	1.7	1.75	0.97	1.75	0.82	1.69	0.74
	Estradiol (pmol/ L)	103.5	0.78	98.5	51.1	88.4	32.8	96.9	36
Health Conditions									
	Probability of OSA	0.55	0.23	0.53	0.24	0.51	0.22	0.60	0.22
	Storage LUTS	22.1%	15	14.9%	40	18.5%	15	17.7%	70
	Voiding LUTS	14.7%	10	10.0%	27	9.9%	8	14.4%	57
	Angina	4.4%	3	2.6%	7	2.5%	2	7.3%	29
	Anxiety	8.8%	6	8.9%	24	8.6%	7	7.6%	30
	Depression	17.6%	12	20.1%	54	23.5%	19	23.2%	92
	Diabetes	16.2%	11	6.3%	17	7.4%	6	13.6%	54
	High cholesterol	36.8%	25	34.2%	92	32.1%	26	27.8%	110
	Insomnia	10.3%	7	7.8%	21	6.2%	5	12.4%	49
	Osteoarthritis	2.9%	2	4.8%	13	6.2%	5	12.4%	49

	Prostate Cancer	2.9%	2	0.0%	0	0.0%	0	3.3%	13
	Other Cancer	4.4%	3	3.7%	10	4.9%	4	9.8%	39
Medications									
	Adrenergics	16.2%	11	8.9%	24	6.20%	5	14.9%	59
	Anticholinergic	2.9%	2	1.9%	5	2.50%	2	5.3%	21
	Antipsychotics	2.9%	2	0.7%	2	0.00%	0	0.8%	3
	Genitourinary	0.0%	0	1.1%	3	4.90%	4	3.8%	15
	Glucocorticoids	5.9%	4	7.1%	19	3.70%	3	5.6%	22
Other sexual measures	**Erectile dysfunction**	23.7%	14	25.0%	66	13.30%	10	21.6%	69
	Low Dyadic	2.9%	2	1.1%	3	3.70%	3	17.7%	70
	Low Solitary								
	Orgasmic Function	8.5	3.9	7.8	4.1	8.1	3.6	6.4	2.9
	Intercourse Satisfaction	9.1	5.5	8.4	5	10.5	5.6	8.1	4.4
	Overall Satisfaction	7.2	3.1	7.1	2.8	7.4	2.0	7.2	3.1

*Data are presented as % (n) of participants at follow-up who recorded improvement or progression of low solitary sexual desire (SDI-II (Solitary)) (shaded columns include all other participants). Note: Participants who failed to complete all items of the SDI-II (Solitary) (n=95) were excluded from analysis. * p ≤ 0.05*

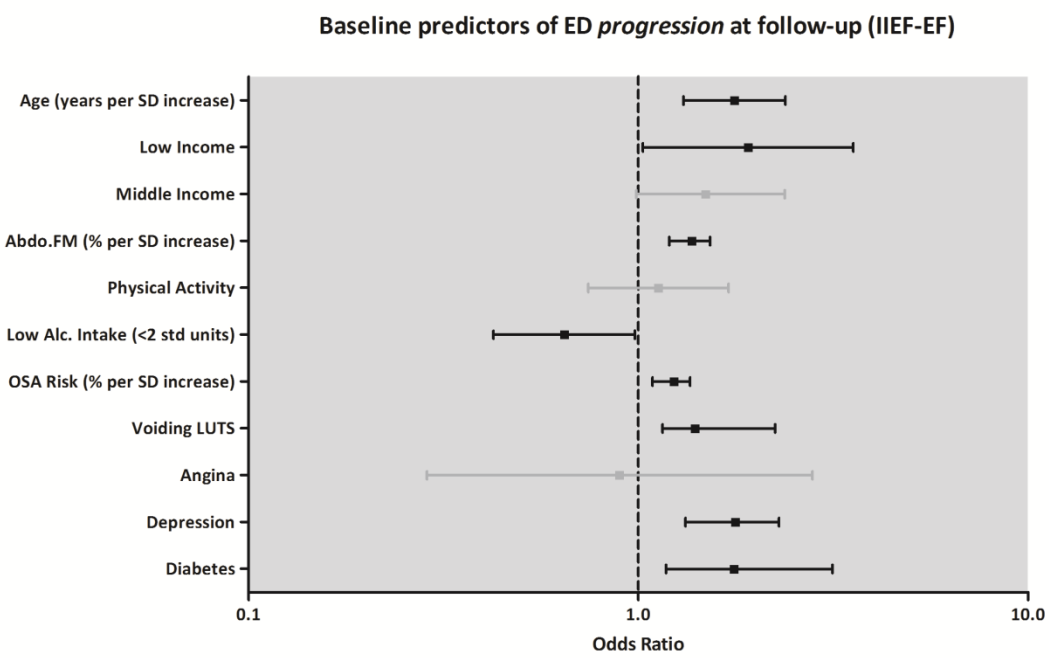
10.4.3 Multi-adjusted models of ED and low dyadic and solitary sexual desire

In multiple adjusted regression models (Figure 10-1), the independent predictors of incident ED were increasing age, residing in a lower income household, higher abdominal fat mass (by DEXA), being employed, moderate alcohol intake, having diabetes , voiding LUTS, increased OSA risk, angina, depression, and dyslipidemia at

baseline. Predictors of ED improvement included lower age, not being unemployed or having diabetes, voiding LUTS, angina and dyslipidemia.

In the final model of deteriorating dyadic sexual desire (Figure 10-2), the independent predictors were increasing age, being widowed or never married, unemployment, retirement, insufficient physical activity and low alcohol intake. Baseline predictors of dyadic desire improvement included not residing in lower income households, and the absence of depression, insomnia, cancer, lower abdominal fat mass and OSA risk, and a higher plasma testosterone.

In final models of deteriorating solitary sexual desire (Figure 10-2), independent predictors included never being married, unemployment, low alcohol intake, a lower plasma testosterone, and the presence of storage LUTS and hypertension at baseline. Baseline predictors of improved solitary sexual desire included being employed at baseline, being married, moderate alcohol intake, not being from a low income household, being sedentary and depression.



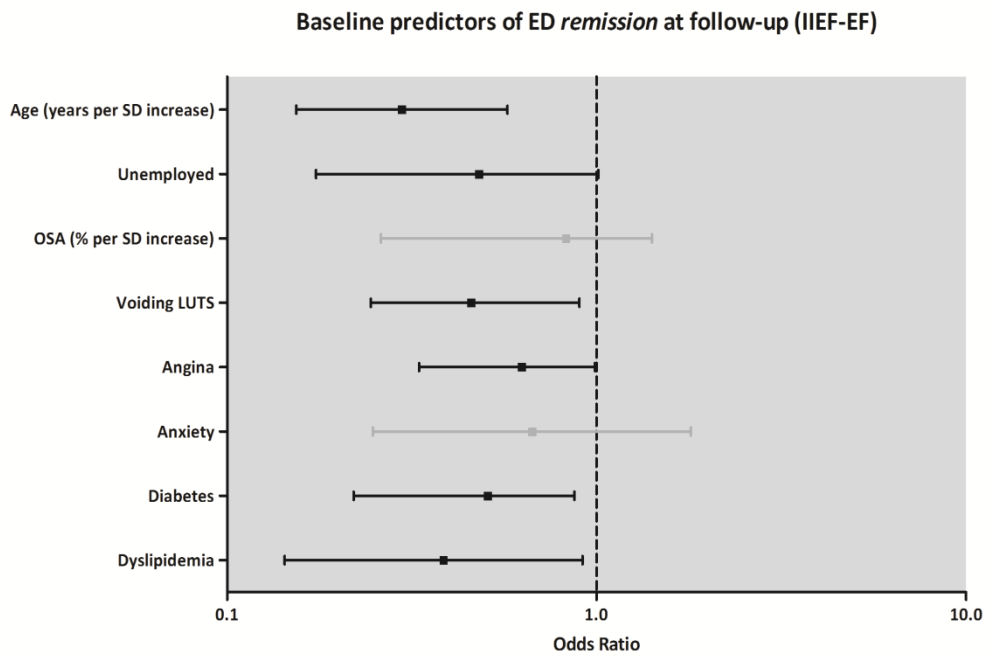


Figure 10-1. **Baseline predictors of incident (progression) & improved (remission) ED at follow-up.** Data are presented as ORs (95% CI) from binary logistic regression models. All predictors with an age-adjusted p- value of < 0.1 were included in the final multi-adjusted model.

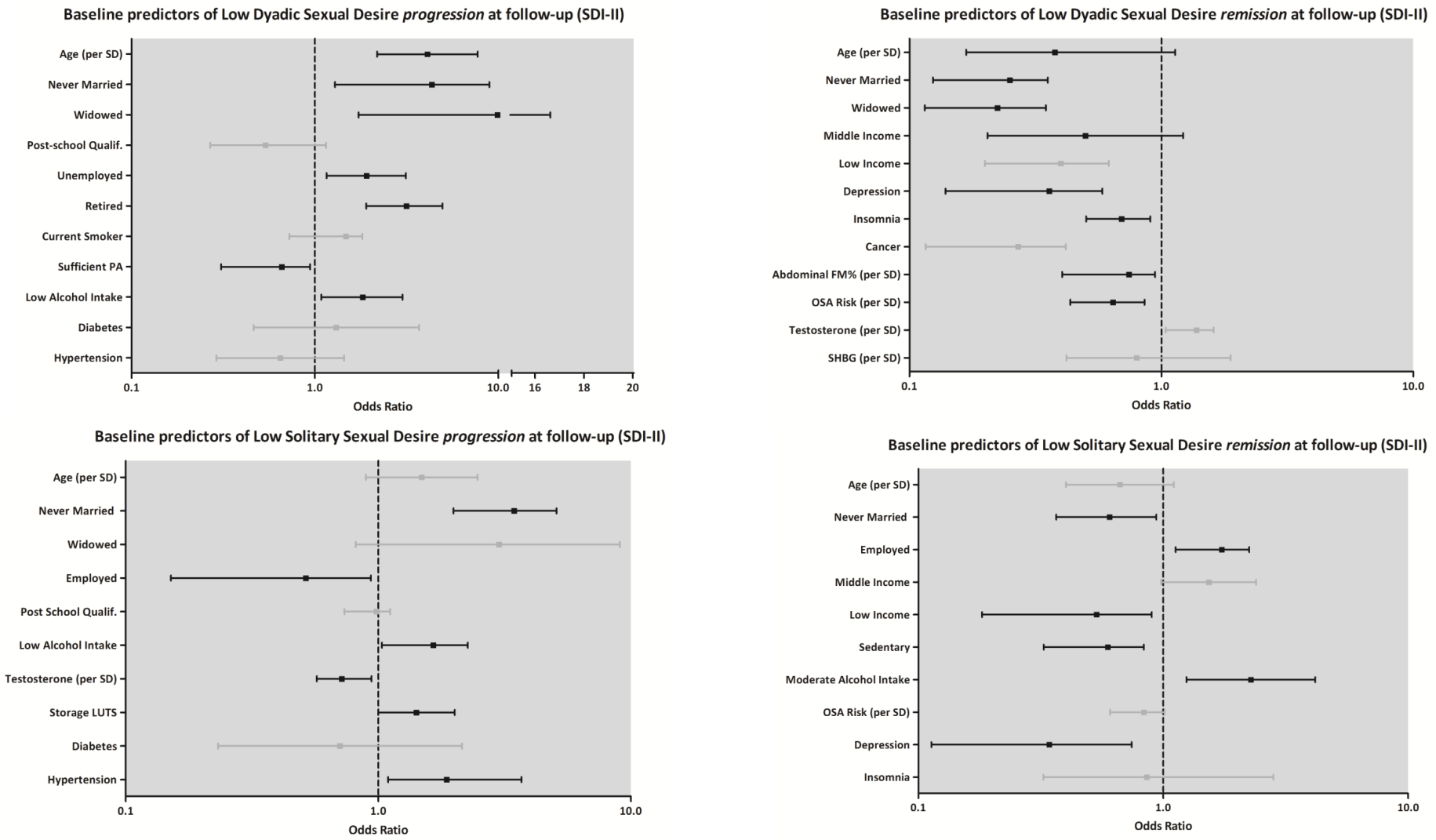


Figure 10-2. **Baseline predictors of deteriorating & improving dyadic & solitary sexual desire at follow-up.** Data are presented as ORs (95% CI) from binary logistic regression models. All predictors with an age-adjusted p- value of < 0.1 were included in the final multi-adjusted model.

10.5 Discussion

Erectile dysfunction (ED)

The incidence rate observed in the present study (32 cases per 1000 person-years) is consistent with the 26 per 1000 person-years observed in the Massachusetts Male Aging Study (MMAS), which has a similar age range (FAMAS: 35-80 years, cf. MMAS: 35-69 years) and demographic profile of participants [149]. Previous estimates of ED incidence in other population-based studies has varied from 12 to 66 cases per 1000 person-years [251], [281], [112]. The ages of the men in these studies ranged from 26 to 83 years of age, and higher rates were seen in older cohorts; e.g. 66 cases per 1000 person-years in the Brazilian Men's Health Study (60-83 years [112]). Lower incidence rates were also observed in studies that only used two questions to assess ED (cf. a discriminant analysis of 15 questions using the IIEF) [109].

We found that similar proportions of men experienced improvement (35.0%) as reported incident ED (34.6%). The rate of improvement is comparable to that seen in the MMAS where 33% of men had improvement of ED symptoms between visits [232]. Data from other studies also provide evidence that ED may spontaneously remit. For example, 11 of 128 (9%) diabetic men, and 7 of 45 (16%) of those without vascular complications, regained erectile function after five years [282].

In multiple-adjusted models, increasing age, lower household income, unemployment, higher abdominal fat mass and OSA risk at baseline were all associated with an increased risk of ED at follow-up. A number of chronic conditions were also predictors

of subsequent ED, including angina, diabetes, depression, dyslipidemia and voiding LUTS, with varying magnitudes of effect.

The relationship between increasing age and increasing prevalence of ED is well established. Our data suggest that for every 10.6 years increase in age, there was a 2.6-fold increase in the likelihood of incident ED and 1.92-fold decrease in the likelihood of ED improvement at follow-up. This is similar to the magnitude of change observed in the MMAS, with an OR of 2.4 and 0.58 for incident ED and improvement respectively [232]. Others have speculated that this effect of age may include the influence of other factors that accumulate in ageing men (poor lifestyle choices, increased chronic conditions and medication use) [112]. After controlling for such factors in this study, age remained one of the strongest determinants of ED. In experimental studies age-related declines in the regulation of blood flow [283], and declining nitric oxide release [284] have been demonstrated. It remains unclear to what extent an unmeasured burden of environmental, behavioural or disease related factors mediate the effect of increasing age. Clearly since a significant number of men retain erectile function even into advanced age, it is unlikely that increasing age in and of itself has an invariant effect.

There is a well-established relationship between low socio-economic status (SES) and increased risk of cardiovascular disease (CVD) [285]-[286]. ED is a marker of underlying CVD [122] and therefore it is not surprising that we found a positive association between SES and ED. In cross-sectional studies ED has been shown to be independently associated with occupational status [107], [287], and household income [229]. Results from the current study indicate that ED was 2.7- times more likely to be present at follow-up in men from low income households, and was less likely to improve in those who were unemployed. Our data support those of the MMAS, which found that incident ED was

less likely in men from higher educational backgrounds. In the MMAS, it was proposed that the relationship between education and ED could, in part, be explained by disposable income [229]. In contrast, we find that the relationship between education and ED is independent of income.

Our data confirm the association between obesity and ED observed in previous longitudinal studies (see [250] for review). Even after adjustment for other covariates, improvements in ED symptoms were less likely in men with elevated visceral adiposity (by DEXA). Diet-induced weight loss has been shown to improve erectile function [288]. Recent cross-sectional [278], [289] and clinical [290] studies demonstrate an independent association between obstructive sleep apnea (OSA) and ED. In the current study the symptoms of OSA preceded the development of ED, and were independent of other measured risk factors. Treatment of severe OSA with continuous positive airway pressure (CPAP) therapy has been shown to substantially improve erectile function [291]. In cross-sectional studies, moderate alcohol intake (one to two standard drinks per day), as compared to lifetime abstainers [116,292], although there is some conflicting data [293]. The protective effect of moderate alcohol consumption shown in the current study is consistent with a previous large-scale observational study that suggested a beneficial effect of mild alcohol consumption for erectile function [294]. Moreover, even heavy alcohol consumption does not appear to have an independent adverse effect on erectile function [77].

Our finding that men with angina were less likely to show an improvement in erectile function accords with the known influence of various cardiovascular diseases (CVDs) on erectile function [122] and with ED being an established predictors of future CVD [295]. Diabetes likewise has a well-established link with ED [223], and this was confirmed in the

present study, with diabetic men being at both an increased and decreased risk of incident and improved ED, respectively.

In previous cross-sectional studies, ED and voiding LUTS have been shown to have common risk factors [278], [237] and pathophysiological mechanisms, including enlarged prostate [296], systematic inflammation [297] and elevated lipids [298]. To our knowledge the current data are the first demonstration of significant voiding LUTS preceding the development of ED in a prospective cohort study. On average, significant voiding LUTS appeared 5.6 years earlier in men than ED, suggesting targeting men who present with troubling voiding symptoms is an important strategy in reducing the burden of ED and subsequent CVD.

Cross-sectional studies demonstrate a clear relationship between depression and ED [299-300]. In the present study, of all of the chronic conditions, depression was the strongest predictor of incident ED. As far as we are aware, only one previous study, the MMAS, has examined the longitudinal relationship between depression and ED [108]. In that study depressive symptoms at baseline did not predict incident ED. However, the presence of related psychosocial traits (e.g. general nervousness, lack of control) at baseline were found to predict incident ED, suggesting other psychogenic factors not included in the current analysis may confound the interpretation. There is increasing evidence for an association between chronic inflammation and depression [301] and therefore it is plausible that a pro-inflammatory environment may serve as a common pathophysiological mechanism for both depression and ED.

Dyadic and solitary sexual desire

Although approximately 25% of men developed low solitary sexual desire at follow-up, only 8.0% of men had developed low dyadic desire. By contrast, solitary and dyadic desire improved in 21.8% and 15.3% of men, respectively. Previous prospective studies [149],[109] have also found that sexual desire was relatively well preserved into old age, although these studies did not distinguish between dyadic and solitary desire (although the MMAS did report a decreased masturbatory frequency in older men). Data from the present study concurs with our previous cross-sectional observations [278], and others [146] showing a marked preference for partnering that is maintained well into older age.

In the multiple-adjusted models, marital status at baseline was found to be a strong predictor of both deterioration and improvement of dyadic desire. Not being engaged in the workforce, insufficient physical activity and low alcohol intake predicted the deterioration of dyadic desire only, while the presence of depression, insomnia, cancer, higher abdominal fat mass and OSA risk and lower plasma testosterone were all found to reduce the likelihood of improvements in dyadic sexual desire. For solitary sexual desire, marital and employment status and low alcohol consumption at baseline were found to predict both deterioration and improvement. Lower testosterone, storage LUTS and hypertension at baseline was also predictive of deterioration of solitary desire, while depression, lower income, physical activity and alcohol intake at baseline were shown to reduce the likelihood of improvement in low solitary desire. The examination of explanatory variables in previous longitudinal studies of changes in sexual desire in men has been limited. In separate analyses of men from the Olmsted

County Study of Urinary Symptoms and Health Status, both diabetes [302] and lower testosterone [303] were found to predict lower sexual desire at follow-up. The relationship between testosterone and sexual desire in men has been well-established in cross-sectional [304]-[305] and clinical studies [306]. However, recent observations that diabetic men are less likely to report regular sexual desire in a large-scale cross-sectional survey of Danish men [146] were not repeated in our longitudinal analyses. While diabetic men were at an increased age-adjusted risk of both low dyadic and solitary sexual desire, this effect was not maintained in our final, fully-adjusted models. Given recent observations from the European Male Ageing Study (EMAS) that show low sexual desire in men with type 2 diabetes is consequent upon decreased serum testosterone [307], this is most likely as a result of our ability to control for varying testosterone levels in men.

The strengths of our study include a longitudinal design and the ability to simultaneously evaluate a wide range of risk factors, a population-based sample that allows for risk factors to be examined in the community, rather than being conducted in those who present for medical care, and the concurrent evaluation of ED, and more than one domain of sexual desire. The limitations of this study include the reliance on self-report for some lifestyle and medical factors. While representative of their target population, study participants were predominantly Caucasian and 35-80 years old (at recruitment). Consequently, these findings may not be applicable to other ethnic populations and age groups.

Taken together, these data highlight the relationship between remediable risk factors for a range of chronic diseases that are related to ED and low sexual desire. Moreover,

ED and low sexual desire may precede the development of many of these abnormalities, and should be considered sentinel markers of chronic disease.

SECTION IV

CONCLUSIONS AND GENERAL DISCUSSION

11.1 Introduction

This chapter concludes the thesis with a general discussion of the key findings and their significance. Implications for translation are discussed and several options for further research into lower urinary tract symptoms (LUTS) and sexual health and function in men are suggested.

11.2 Lower urinary tract symptoms (LUTS)

The prevalence of uncomplicated lower urinary tract symptoms (LUTS) in an urban cohort of community-based Australian middle-aged to elderly men was 18.2% overall. The prevalence of storage and voiding LUTS was 28.0% and 12.6%, respectively, with a specific pattern of age independent behavioural and disease-related risk factors associated with each (Chapter 3); many amenable to intervention.

In a longitudinal analysis of the cohort (Chapter 5), one in four men without clinically-significant urinary symptoms at baseline had developed LUTS at the follow-up visit; almost a third of all men developed storage-type symptoms, and one in six men significant voiding symptoms. Also, 33.1% and 23.4% of men showed improvement in their storage and voiding LUTS, respectively. Multi-adjusted models of storage and voiding LUTS revealed specific predictors of this change. For storage symptoms, having higher urinary bother, HDL cholesterol, sexual desire and overall physical well-being, and lower triglycerides at baseline were found to predict the remission of storage LUTS. Higher abdominal fat mass, lower income, angina or depression, the use of corticosteroids, anti-psoriatic medications and 5-α reductase inhibitors at baseline were found to predict progression of storage LUTS. In the case of voiding symptoms, only a higher degree of physical well-being at baseline predicted the remission of symptoms. At baseline, higher as well as lower household income, lower plasma HDL cholesterol, and higher serum estradiol, depression, and erectile dysfunction predicted the progression of voiding symptoms.

11.2.1 Implications for translation

From a clinical perspective, these findings reinforce recent suggestions that it is reasonable to consider the impact of LUTS "beyond the bladder" [26], as a marker of risk for cardio-metabolic disease, and associated with remediable risk factors that should be investigated.

The findings from this thesis are consistent with, but also have implications for, current consensus statements on the treatment of LUTS. The most recent practice recommendations from the International Consultation on New Developments in Prostate Cancer and Prostate Diseases (ICPCPD) [308] indicates that the treatment of LUTS in men needs to be considered on the basis of "whether the patient presents with predominant storage-type (or irritative) or voiding-type (or obstructive) symptoms, or a possible mix of both" (p.17). In the management algorithm presented as part of the ICPCPD there is a recommendation that lifestyle modifications be considered prior to pharmacological treatment, including reduction of alcohol consumption, smoking, and obesity (all of which, with the exception of smoking, were found to be predictive of worsening LUTS in the present study). In addition, data from this thesis, taken together with those of others [309], [310], [309] suggest that increasing physical activity may alleviate LUTS, particularly storage-type symptoms [311]. Both recently published guidelines for the management of male LUTS from the UK's National Health Service (NHS) [312] and the European Association of Urology (EAU) [313] list a range of conditions that should be considered and addressed prior to further treatment for LUTS (incl. BPH, prostatitis, diabetes, obstructive sleep apnea). Data from this thesis in combination with other studies [314] [314] [276], suggests that depression should be added to this list.

11.3 Erectile dysfunction (ED) and low sexual desire

The prevalence of ED, low solitary and dyadic sexual desire was 17.7%, 67.7%, and 13.5%, respectively (Chapter 4). Increasing age was associated with a higher prevalence of ED, low dyadic and solitary sexual desire. Nevertheless more than two-thirds of men in the eldest age group reported “normal” dyadic sexual desire (compared to approximately 30% for solitary sexual desire), indicating that the desire for partnering is maintained well into older age. Accordingly ED should be asked about and managed irrespective of age.

In the longitudinal analysis of ED and low sexual desire (Chapter 6), the incidence rate for ED (32 cases per 1000 person-years) was consistent with other similarly-designed cohort studies. A comparable rate for low solitary sexual desire (26 cases per 1000 person-years) was observed. However, the incidence of low dyadic sexual desire was much lower (8 cases per 1000 person-years). At follow-up, ED and low dyadic and solitary sexual desire improved in 35%, 22% and 15%, respectively. Increasing age remained a strong predictor of the likelihood of ED progression or remission. Age was not a predictor of either incident or remission of low solitary desire, and only a weak predictor of incident low dyadic sexual desire. Physical comorbidities (angina, anxiety, diabetes, voiding LUTS) were the dominant factors affecting erectile function, while psychosocial and demographic factors (depression, insomnia, widowhood, unemployment, and income) were predominantly responsible for changes in dyadic and solitary sexual desire. The influence of the modifiable risk factors, such as higher abdominal fat mass, sleep apnea, alcohol intake, plasma lipids and testosterone,

diabetes and physical activity was clearly evident in the longitudinal follow-up of ED and sexual desire, emphasizing the need to address such risk factors as a primary approach.

11.3.1 Implications for translation

The most recent consensus statement on ED management from the EAU [122], suggested that "Lifestyle changes and risk factor modification must precede or accompany ED treatment" is an A-grade level of recommendation supported by Level 1b grade of evidence. The current data indicate that the presence of obstructive sleep apnea should also be considered in patients presenting with ED particularly in light of recent findings demonstrating that CPAP therapy can improve erectile function [291].

There are no such clinical guidelines for the management of men who present with symptoms of low sexual desire. Generally, men who report to a physician complaining of low libido are investigated for hypogonadism, which includes a complex of other symptoms (mood disorders, fatigue, low muscle mass/strength, frailty) [94]. Despite the relatively low occurrence of truly hypogonadal men (between 2-5% of adult aged males [307]), an increasing amount is being spent by the pharmaceutical industry on direct marketing to encourage men who may be experiencing declines in libido to consult their physician [267]. One of the identified limiting factors in addressing men who present with low libido symptoms in the absence of other hypogonadal symptoms, has been "a lack of reliable evidence from epidemiological surveys suggesting of factors which may contribute to declining libido in the natural setting " [94].

Apart from hypogonadism a number of disorders have been clearly associated with reduced sexual desire including Parkinson's disease, epilepsy, insomnia, mood disorders such as depression and anxiety and medications such as anti-depressants [94]. In addition, the data in this thesis suggest that abdominal obesity, obstructive sleep apnea, excessive alcohol consumption, and absent physical activity may also be independent risk factors for low sexual desire and are amendable to modification [288] [311]. Furthermore, psychosocial factors (recent widowhood, unemployment, and low income) have also been identified as important contributors to lowered sexual desire, and should be considered in the assessment and management of patients with such sexual dysfunction.

11.4 Future research

The two primary questions arising from this research that require further investigation are:

11.4.1 Common mechanisms mediating LUTS and ED

Multiple epidemiological studies in addition to the studies presented in this work have shown that LUTS and ED are related, independent of age or other co morbidities, such as diabetes or hypertension. We have proposed a unifying hypothesis whereby smooth muscle dysfunction in the bladder and proximal urethra mirrors that which occurs in the vascular smooth muscle [315] and involves similar mechanisms to those mediating endothelial dysfunction (i.e. inflammation, insulin resistance, abnormal glucose metabolism and elevated saturated fatty acids.). A role for inflammatory markers in particular appears likely [201] and warrants further investigation. This is of particular interest since there is now evidence that inflammation also contributes to the pathophysiology of depression which is strongly associated with both LUTS [314] and low SD [316].

The role of other of factors such autonomic dysfunction (consequent on obesity, sleep apnoea, thyroid dysfunction, or medication use), sex steroids (affected by obesity, depression, thyroid dysfunction, medication use or endocrine disruptors such as bisphenol-A and phthalates), hypoxia (sleep apnoea), and atherosclerosis require further investigation.

11.4.2 LUTS / SD as markers of future risk for diabetes mellitus and cardiovascular disease

There is now a reasonable body of evidence to suggest that ED is an early marker for cardiovascular events such as heart attack and stroke [317]. From the discussion above it could be expected that LUTS may serve as an early marker of subsequent cardiovascular disease and diabetes mellitus.

ED and LUTS are both overtly noticeable and inconvenient to men. Screening patients for either of these conditions by asking simple questions such as those contained within this thesis will reveal their presence, and should prompt further investigation for other risk factors in a primary care setting. In a public health context, drawing attention to the link between these symptoms and disease risk may prompt men into seeking appropriate care, particularly since proper management of the identified risk factors has been shown to ameliorate these conditions. Given the evidence that weight loss [288] and management of sleep apnoea [291] are effective in improving SD, ED and LUTS, the case for translation into practice seems compelling, and further research is warranted as to feasibility and efficacy.

11.4.3 Additional areas for further investigation include:

i) The relationship between LUTS and ED and health care service utilisation (including use and types of primary health care services, medication patterns);

ii) The impact of LUTS /ED on other aspects of quality of life (including relationships; mood disorders; productivity);

iii) Relationships between sleep architecture / sleep disorders / fatigue on LUTS, ED and low sexual desire;

iv) Given the demonstrated large proportion of men with remediable relapsing symptoms, what is the long term outcome on LUTS / ED by targeting these specific risk factors?

v) Although we have speculated that the effect of abnormal thyroid function may be mediated by effects on autonomic nerve function and /or sex steroids, the precise mechanisms responsible for the relationship between altered thyroid function and LUTS remains to be determined.

vi) Determine the rate of and predictors for the incidence and remission of other sexual dysfunctions for which there is comparatively little data available (e.g. orgasmic function, intercourse satisfaction and overall sexual satisfaction).

REFERENCES

1. ABS: Population Projections, Australia, 2004 to 2101 Canberra: Australian Bureau of Statistics, vol. (cat. no. 3222.0), 2008

2. AIHW: Australia's health 2008. Canberra: Australian Institute of Health and Welfare, vol. Cat. no. AUS 99., 2008

3. Gregory, A. T., Lowy, M. P., Zwar, N. A.: Men's health and wellbeing: taking up the challenge in Australia. Med J Aust, **185:** 411, 2006

4. AIHW: The health of Australia's males. Edited by A. I. o. H. a. Welfare. Canberra, 2011

5. AIHW: Australia's health 2012. Edited by A. I. o. H. a. Welfare. Canberra, 2012
6. AIHW: Changes in life expectancy and disability in Australia 1998 to 2009. . Edited by A. I. o. H. a. Welfare. Canberra, 2012

7. Mathers, C. D., Vos, E. T., Stevenson, C. E. et al.: The burden of disease and injury in Australia. Bull World Health Organ, **79:** 1076, 2001

8. AIHW: Chronic diseases and associated risk factors in Australia, 2006. . Edited by A. I. o. H. a. Welfare. Canberrra, 2006

9. King, D. E., Mainous, A. G., Geesey, M. E.: Turning back the clock: adopting a healthy lifestyle in middle age. Am J Med, **120:** 598, 2007

10. Connell, R. S. T., Walker L, Wood J, Butland D, Fisher J, Bowyer J.: Men's health: A research agenda and background report. Edited by D. o. H. a. A. Care. Canberra, 2007

11. Cameron, E., Bernardes, J.: Gender and Disadvantage in Health: Men's Health for a Change. Sociology of Health & Illness, **20:** 673, 1998

12. Holden, C. A., Allan, C. A., McLachlan, R. I.: Windows of opportunity: a holistic approach to men's health. Med J Aust, **192:** 708, 2010

13. NCHS: Health, United States, 2011: With Special Feature on Socioeconomic Status and Health. Edited by N. C. f. H. Statistics. Hyattsville, MD., 2012

14. White, A., Cash, K.: The European Men's Health Forum: A report on the state of men's health across 17 European countries. Brussels, Belgium: The European Men's Health Forum, 2003

15. AIHW: Logie H, H. R. P. A.: Longitudinal studies of ageing: Implications for future studies. Edited by A. I. o. H. a. Welfare. Canberra, vol. AIHW cat. no. AGE 42., 2004

16. Samet, J. M., Munoz, A.: Evolution of the cohort study. Epidemiol Rev, **20:** 1, 1998

17. Willett, W. C., Colditz, G. A.: Approaches for conducting large cohort studies. Epidemiol Rev, **20:** 91, 1998

18. Fletcher, R.: Testosterone Poisoning or Terminal Neglect? The Men's Health Issue. Edited by D. o. t. P. Library. Canberra: AGPS, 1996

19. Reynard, J., Brewster, S., Biers , S.: Basic physiology of bladder and urethra. Oxford, U.K.: Oxford Medicine, 2007

20. Moore, K. N., Agur, A.: Essential Clinical Anatomy, Third Edition. Philidelphia: Lippincott Williams & Wilkins, 2007

21. Abrams, P., Cardozo, L., Fall, M. et al.: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology, **61:** 37, 2003

22. Abrams, P.: Managing lower urinary tract symptoms in older men. BMJ, **310:** 1113, 1995

23. Abrams, P.: New words for old: lower urinary tract symptoms for "prostatism". BMJ, **308:** 929, 1994

24. Chapple, C. R., Patel, A. K.: Lower urinary tract symptoms in men. BMJ, **334:** 2, 2007

25. Lepor, H.: The pathophysiology of lower urinary tract symptoms in the ageing male population. Br J Urol, **81 Suppl 1:** 29, 1998

26. Chapple, C. R.: Lower urinary tract symptoms revisited. Eur Urol, **56:** 21, 2009

27. Barry, M. J., Fowler, F. J., Jr., O'Leary, M. P. et al.: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol, **148:** 1549, 1992

28. Kelleher, C., Cardozo, L., Khullar, V. et al.: A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol **104:** 1374, 1997

29. Basra, R., Artibani, W., Cardozo, L. et al.: Design and validation of a new screening instrument for lower urinary tract dysfunction: the bladder control self-assessment questionnaire (B-SAQ). Eur Urol, **52:** 230, 2007

30. Wagner, T. H., Patrick, D. L., Bavendam, T. G. et al.: Quality of life of persons with urinary incontinence: development of a new measure. Urology, **47:** 67, 1996

31. Wein, A. J.: The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. J Urol, **174:** 608, 2005

32. Turner-Warwick, R., Whiteside, C. G., Worth, P. H. et al.: A urodynamic view of the clinical problems associated with bladder neck dysfunction and its treatment by endoscopic incision and trans-trigonal posterior prostatectomy. Br J Urol, **45:** 44, 1973

33. Irwin, D. E., Milsom, I., Hunskaar, S. et al.: Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol, **50:** 1306, 2006

34. Platz, E. A., Joshu, C. E., Mondul, A. M. et al.: Incidence and progression of lower urinary tract symptoms in a large prospective cohort of United States men. J Urol, **188:** 496, 2012

35. Coyne, K. S., Sexton, C. C., Irwin, D. E. et al.: The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int, **101:** 1388, 2008

36. McVary, K.: Lower urinary tract symptoms and sexual dysfunction: epidemiology and pathophysiology. BJU Int, **97 Suppl 2:** 23, 2006

37. Haltbakk, J., Hanestad, B. R., Hunskaar, S.: How important are men's lower urinary tract symptoms (LUTS) and their impact on the quality of life (QOL)? Qual Life Res, **14:** 1733, 2005

38. Andersson, S. O., Rashidkhani, B., Karlberg, L. et al.: Prevalence of lower urinary tract symptoms in men aged 45-79 years: a population-based study of 40 000 Swedish men. BJU Int, **94:** 327, 2004

39. Paick, J. S., Kim, S. W., Oh, S. J. et al.: Voiding patterns in men and women with lower urinary tract symptoms combined with nocturia. Int J Urol, **14:** 699, 2007

40. Peters, C. A.: Lower urinary tract obstruction: clinical and experimental aspects. Br J Urol, **81 Suppl 2:** 22, 1998

41. Chapple, C. R.: Lower urinary tract symptoms suggestive of benign prostatic obstruction--Triumph: design and implementation. Eur Urol, **39 Suppl 3:** 31, 2001

42. Pinnock, C., Marshall, V. R.: Troublesome lower urinary tract symptoms in the community: a prevalence study. Med J Aust, **167:** 72, 1997

43. Hughes, A. M., Sladden, M. J., Hirst, G. H. et al.: Community study of uncomplicated lower urinary tract symptoms among male Italien immigrants in Sydney, Australia. Eur Urol, **37:** 191, 2000

44. Holden, C. A., McLachlan, R. I., Pitts, M. et al.: Men in Australia Telephone Survey (MATeS): a national survey of the reproductive health and concerns of middle-aged and older Australian men. Lancet, **366:** 218, 2005

45. Lemack, G. E.: Defining the role of overactive bladder treatments in men with lower urinary tract symptoms. Nat Clin Pract Urol, **4:** 174, 2007

46. Sarma, A. V., McLaughlin, J. C., Jacobsen, S. J. et al.: Longitudinal changes in lower urinary tract symptoms among a cohort of black American men: the Flint Men's Health Study. Urology, **64:** 959, 2004

47. WHO: Obesity and overweight. Edited by W. H. Organization. Geneva, Switzerland: WHO Press, vol. Fact sheet N°311, 2012

48. Mongiu, A. K., McVary, K. T.: Lower urinary tract symptoms, benign prostatic hyperplasia, and obesity. Curr Urol Rep, **10:** 247, 2009

49. Irwin, D. E., Milsom, I., Kopp, Z. et al.: Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. Eur Urol, **56:** 14, 2009

50. Hong, S. K., Lee, S. T., Jeong, S. J. et al.: Chronic kidney disease among men with lower urinary tract symptoms due to benign prostatic hyperplasia. BJU Int, 2009

51. Carter, H. B., Landis, P., Wright, E. J. et al.: Can a baseline prostate specific antigen level identify men who will have lower urinary tract symptoms later in life? J Urol, **173:** 2040, 2005

52. St Sauver, J. L., Sarma, A. V., Hollingsworth, J. M. et al.: Associations between modest weight changes and onset and progression of lower urinary tract symptoms in two population-based cohorts. Urology, **78:** 437, 2011

53. Maserejian, N.: Dietary Macronutrients, Cholesterol, and Sodium and Lower Urinary Tract Symptoms in Men. European Urology, **Epub Aug 03 2008**, 2008

54. Ambrosini, G. L., Fritschi, L., de Klerk, N. H. et al.: Dietary patterns identified using factor analysis and prostate cancer risk: a case control study in Western Australia. Ann Epidemiol, **18:** 364, 2008

55. Bravi, F., Bosetti, C., Dal Maso, L. et al.: Macronutrients, fatty acids, cholesterol, and risk of benign prostatic hyperplasia. Urology, **67:** 1205, 2006

56. Suzuki, S., Platz, E. A., Kawachi, I. et al.: Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. Am J Clin Nutr, **75:** 689, 2002

57. McVary, K. T., Rademaker, A., Lloyd, G. L. et al.: Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol, **174:** 1327, 2005

58. Belanger, A., Locong, A., Noel, C. et al.: Influence of diet on plasma steroids and sex hormone-binding globulin levels in adult men. J Steroid Biochem, **32:** 829, 1989

59. Litman, H. J., Bhasin, S., O'Leary, M. P. et al.: An investigation of the relationship between sex-steroid levels and urological symptoms: results from the Boston Area Community Health survey. BJU Int, **100:** 321, 2007

60. Parsons, J. K., Carter, H. B., Partin, A. W. et al.: Metabolic factors associated with benign prostatic hyperplasia. J Clin Endocrinol Metab, **91:** 2562, 2006

61. Rohrmann, S., Smit, E., Giovannucci, E. et al.: Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). Int J Obes (Lond), **29:** 310, 2005

62. Joseph, M. A., Harlow, S. D., Wei, J. T. et al.: Risk factors for lower urinary tract symptoms in a population-based sample of African-American men. Am J Epidemiol, **157:** 906, 2003

63. Roberts, R. O., Jacobson, D. J., Girman, C. J. et al.: Insulin-like growth factor I, insulin-like growth factor binding protein 3, and urologic measures of benign prostatic hyperplasia. Am J Epidemiol, **157:** 784, 2003

64. Mills, I. W., Crossland, A., Patel, A. et al.: Atorvastatin treatment for men with lower urinary tract symptoms and benign prostatic enlargement. Eur Urol, **52:** 503, 2007

65. Sarma, A. V., St Sauver, J. L., Hollingsworth, J. M. et al.: Diabetes treatment and progression of benign prostatic hyperplasia in community-dwelling black and white men. Urology, **79:** 102, 2012

66. Rohrmann, S., Giovannucci, E., Smit, E. et al.: Association of IGF-1 and IGFBP-3 with lower urinary tract symptoms in the third national health and nutrition examination survey. Prostate, **67:** 1693, 2007

67. Neuhouser, M. L., Schenk, J., Song, Y. J. et al.: Insulin-like growth factor-I, insulin-like growth factor binding protein-3 and risk of benign prostate hyperplasia in the prostate cancer prevention trial. Prostate, **68:** 1477, 2008

68. Meigs, J. B., Mohr, B., Barry, M. J. et al.: Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. J Clin Epidemiol, **54:** 935, 2001

69. Gann, P. H., Hennekens, C. H., Longcope, C. et al.: A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia. Prostate, **26:** 40, 1995

70. Rohrmann, S., Crespo, C. J., Weber, J. R. et al.: Association of cigarette smoking, alcohol consumption and physical activity with lower urinary tract symptoms in older American men: findings from the third National Health And Nutrition Examination Survey. BJU Int, **96:** 77, 2005

71. Orsini, N., RashidKhani, B., Andersson, S. O. et al.: Long-term physical activity and lower urinary tract symptoms in men. J Urol, **176:** 2546, 2006

72. Parsons, J. K.: Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol, **178:** 395, 2007

73. Platz, E. A., Rimm, E. B., Kawachi, I. et al.: Alcohol consumption, cigarette smoking, and risk of benign prostatic hyperplasia. Am J Epidemiol, **149:** 106, 1999

74. Kang, D., Andriole, G. L., Van De Vooren, R. C. et al.: Risk behaviours and benign prostatic hyperplasia. BJU Int, **93:** 1241, 2004

75. Rohrmann, S., Fallin, M. D., Page, W. F. et al.: Concordance rates and modifiable risk factors for lower urinary tract symptoms in twins. Epidemiology, **17:** 419, 2006

76. Parsons, J. K.: Lifestyle factors, benign prostatic hyperplasia, and lower urinary tract symptoms. Curr Opin Urol, **21:** 1, 2011

77. Derby, C. A., Mohr, B. A., Goldstein, I. et al.: Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology, **56:** 302, 2000

78. Coyne, K. S., Kaplan, S. A., Chapple, C. R. et al.: Risk factors and comorbid conditions associated with lower urinary tract symptoms: EpiLUTS. BJU Int, **103 Suppl 3:** 24, 2009

79. Feldman, H. A., Goldstein, I., Hatzichristou, D. G. et al.: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol, **151:** 54, 1994

80. Feldman, H. A., Johannes, C. B., Derby, C. A. et al.: Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med, **30:** 328, 2000

81. Corona, G., Mannucci, E., Lotti, F. et al.: Impairment of couple relationship in male patients with sexual dysfunction is associated with overt hypogonadism. J Sex Med, **6:** 2591, 2009

82. Gorbachinsky, I., Akpinar, H., Assimos, D. G.: Metabolic syndrome and urologic diseases. Rev Urol, **12:** e157, 2010

83. Zitzmann, M., Nieschlag, E.: Androgens and vascular function. J Endocrinol Invest, **26:** 767, 2003

84. Shamloul, R., Ghanem, H. M., Salem, A. et al.: Correlation between penile duplex findings and stress electrocardiography in men with erectile dysfunction. Int J Impot Res, **16:** 235, 2004

85. Narla, V., Santos, R. D., Campbell, C. Y. et al.: Coronary Artery Calcification and Inflammation According to Various Metabolic Syndrome Definitions. J Cardiometab Syndr, **4:** 33, 2009

86. McVary, K. T.: Sexual dysfunction in men with lower urinary tract symptoms and benign prostatic hyperplasia: an emerging link. BJU Int, **91:** 770, 2003

87. Kaplan, S. A.: [The role of muscarinic receptor antagonists in the treatment of men with lower urinary tract symptoms secondary to BPH]. Actas Urol Esp, **31:** 86, 2007

88. Rosen, R., Altwein, J., Boyle, P. et al.: Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol, **44:** 637, 2003

89. Rohrmann, S., Nelson, W. G., Rifai, N. et al.: Serum sex steroid hormones and lower urinary tract symptoms in Third National Health and Nutrition Examination Survey (NHANES III). Urology, **69:** 708, 2007

90. Koritsiadis, G., Stravodimos, K., Mitropoulos, D. et al.: Androgens and bladder outlet obstruction: a correlation with pressure-flow variables in a preliminary study. BJU Int, **101:** 1542, 2008

91. Covey, H. C.: Perceptions and attitudes toward sexuality of the elderly during the Middle Ages. Gerontologist, **29:** 93, 1989

92. Jonas, U.: The history of erectile dysfunction management. Int J Impot Res, **13 Suppl 3:** S3, 2001

93. Regan, P., Berschield, E.: Sexual Desire: Historical Perspectives In: Lust: What we Know about Human Sexual Desire Los Angeles, USA.: SAGE Publications, Inc, 1999

94. Lewis, R. W., Fugl-Meyer, K. S., Corona, G. et al.: Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med, **7:** 1598, 2011

95. Andersson, K. E.: Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. Pharmacol Rev, **63:** 811, 2011

96. Dean, R. C., Lue, T. F.: Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am, **32:** 379, 2005

97. Rosen, R. C., Riley, A., Wagner, G. et al.: The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology, **49:** 822, 1997

98. Rosen, R. C., Seftel, A. D.: Validated questionnaires for assessing sexual dysfunction and BPH/LUTS: solidifying the common pathophysiologic link. Int J Impot Res, **20 Suppl 3:** S27, 2008

99. O'Leary M, P.: Lower urinary tract symptoms, erectile dysfunction, and hypogonadism. Rev Urol, **8:** 44, 2006

100. Feldman, H. A., Goldstein, I., Hatzichristou, D. G. et al.: Construction of a surrogate variable for impotence in the Massachusetts Male Aging Study. J Clin Epidemiol, **47:** 457, 1994

101. Friedman, S., Harrison, G.: Sexual Functioning Questionnaire. Archives of Sexual Behaviour, **13**, 1982

102. Althof, S. E.: Evidence based assessment of rapid ejaculation. Int J Impot Res, **10 Suppl 2:** S74, 1998

103. Althof, S. E., Buvat, J., Gutkin, S. W. et al.: Sexual satisfaction in men with erectile dysfunction: correlates and potential predictors. J Sex Med, **7:** 203, 2010

104. Lewis, R. W.: Epidemiology of sexual dysfunction in Asia compared to the rest of the world. Asian J Androl, **13:** 152, 2011

105. Jung, J. H., Jae, S. U., Kam, S. C. et al.: 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, **6:** 2299, 2009

106. Lewis, R. W., Fugl-Meyer, K. S., Corona, G. et al.: Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med, **7:** 1598

107. Chew, K. K., Stuckey, B., Bremner, A. et al.: Male erectile dysfunction: its prevalence in Western australia and associated sociodemographic factors. J Sex Med, **5:** 60, 2008

108. Hall, S. A., Shackelton, R., Rosen, R. C. et al.: Risk factors for incident erectile dysfunction among community-dwelling men. J Sex Med, **7:** 712, 2011

109. Gades, N. M., Jacobson, D. J., McGree, M. E. et al.: Longitudinal evaluation of sexual function in a male cohort: the Olmsted county study of urinary symptoms and health status among men. J Sex Med, **6:** 2455, 2009

110. Kok, E. T., Schouten, B. W., Bohnen, A. M. et al.: Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen Study. J Urol, **181:** 710, 2009

111. Shiri, R., Hakkinen, J., Koskimaki, J. et al.: Erectile dysfunction influences the subsequent incidence of lower urinary tract symptoms and bother. Int J Impot Res, **19:** 317, 2007

112. Moreira, E. D., Jr., Lbo, C. F., Diament, A. et al.: Incidence of erectile dysfunction in men 40 to 69 years old: results from a population-based cohort study in Brazil. Urology, **61:** 431, 2003

113. Thompson, I. M., Tangen, C. M., Goodman, P. J. et al.: Erectile dysfunction and subsequent cardiovascular disease. JAMA, **294:** 2996, 2005

114. Gratzke, C., Angulo, J., Chitaley, K. et al.: Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med, **7:** 445, 2010

115. Mirone, V., Imbimbo, C., Bortolotti, A. et al.: Cigarette smoking as risk factor for erectile dysfunction: results from an Italian epidemiological study. Eur Urol, **41:** 294, 2002

116. Nicolosi, A., Moreira, E. D., Jr., Shirai, M. et al.: Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology, **61:** 201, 2003

117. Nicolosi, A., Glasser, D. B., Moreira, E. D. et al.: Prevalence of erectile dysfunction and associated factors among men without concomitant diseases: a population study. Int J Impot Res, **15:** 253, 2003

118. Yoshiyama, M., de Groat, W. C.: The role of vasoactive intestinal polypeptide and pituitary adenylate cyclase-activating polypeptide in the neural pathways controlling the lower urinary tract. J Mol Neurosci, **36:** 227, 2008

119. Mak, R., De Backer, G., Kornitzer, M. et al.: Prevalence and correlates of erectile dysfunction in a population-based study in Belgium. Eur Urol, **41:** 132, 2002

120. Morillo, L. E., Diaz, J., Estevez, E. et al.: Prevalence of erectile dysfunction in Colombia, Ecuador, and Venezuela: a population-based study (DENSA). Int J Impot Res, **14 Suppl 2:** S10, 2002

121. Cheng, J. Y., Ng, E. M., Chen, R. Y. et al.: Alcohol consumption and erectile dysfunction: meta-analysis of population-based studies. Int J Impot Res, **19:** 343, 2007

122. Miner, M., Seftel, A. D., Nehra, A. et al.: Prognostic utility of erectile dysfunction for cardiovascular disease in younger men and those with diabetes. Am Heart J, **164:** 21, 2012

123. Fedele, D., Coscelli, C., Cucinotta, D. et al.: Incidence of erectile dysfunction in Italian men with diabetes. J Urol, **166:** 1368, 2001

124. Wabrek, A. J., Burchell, R. C.: Male sexual dysfunction associated with coronary heart disease. Arch Sex Behav, **9:** 69, 1980

125. Sjogren, K., Fugl-Meyer, A. R.: Some factors influencing quality of sexual life after myocardial infarction. Int Rehabil Med, **5:** 197, 2001

126. Chew, K. K., Finn, J., Stuckey, B. et al.: Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med, **7:** 192, 2010

127. Williams, K., Reynolds, M. F.: Sexual dysfunction in major depression. CNS Spectr, **11:** 19, 2006

128. Dunn, K. M., Croft, P. R., Hackett, G. I.: Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. J Epidemiol Community Health, **53:** 144, 1999

129. Araujo, A. B., Durante, R., Feldman, H. A. et al.: The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med, **60:** 458, 1998

130. Patil, S. P., Schneider, H., Schwartz, A. R. et al.: Adult obstructive sleep apnea: pathophysiology and diagnosis. Chest, **132:** 325, 2007

131. Shamloul, R., el Nashaar, A.: Idiopathic stuttering priapism treated successfully with low-dose ethinyl estradiol: a single case report. J Sex Med, **2:** 732, 2005

132. Derby, C. A., Barbour, M. M., Hume, A. L. et al.: Drug therapy and prevalence of erectile dysfunction in the Massachusetts Male Aging Study cohort. Pharmacotherapy, **21:** 676, 2001

133. Lundberg, G. D.: Daily tadalafil prevents erectile dysfunction in diabetic men. Medscape J Med, **10:** 127, 2008

134. Pfaus, J. G.: Pathways of sexual desire. J Sex Med, **6:** 1506, 2009

135. DeLamater, J. D., Sill, M.: Sexual desire in later life. J Sex Res, **42:** 138, 2005

136. Hull, E., Dominguez, J., Muschamp, J.: Neurochemistry of Male Sexual Behavior. In: Handbook of Neurochemistry and Molecular Neurobiology Edited by A. Lajitha. New York: Springer Link, 2007

137. Bancroft, J.: The endocrinology of sexual arousal. J Endocrinol, **186:** 411, 2005

138. APA: Diagnostic and statistical manual of mental disorders (4th ed., text ed). Washington: American Psychiatric Association 2000

139. Spector, I. P., Carey, M. P., Steinberg, L.: The sexual desire inventory: development, factor structure, and evidence of reliability. J Sex Marital Ther, **22:** 175, 1996

140. Bancroft, J., Janssen, E.: The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunction. Neurosci Biobehav Rev, **24:** 571, 2000

141. Hoon, E. F., Joon, P. W., Wincze, J. P.: An inventory for the measurement of female sexual arousability: the SAI. Arch Sex Behav, **5:** 269, 1976

142. Frank, E., Anderson, C., Rubinstein, D.: Frequency of sexual dysfunction in "normal" couples. N Engl J Med, **299:** 111, 1978

143. Laumann, E. O., Paik, A., Rosen, R. C.: Sexual dysfunction in the United States: prevalence and predictors. JAMA, **281:** 537, 1999

144. Mercer, C. H., Fenton, K. A., Johnson, A. M. et al.: Who reports sexual function problems? Empirical evidence from Britain's 2000 National Survey of Sexual Attitudes and Lifestyles. Sex Transm Infect, **81:** 394, 2005

145. Fugl-Meyer, K., Fugl-Meyer, A. R.: Sexual disabilities are not singularities. Int J Impot Res, **14:** 487, 2002

146. Eplov, L., Giraldi, A., Davidsen, M. et al.: Sexual desire in a nationally representative Danish population. J Sex Med, **4:** 47, 2007

147. Laumann, E. O., Glasser, D. B., Neves, R. C. et al.: A population-based survey of sexual activity, sexual problems and associated help-seeking behavior patterns in mature adults in the United States of America. Int J Impot Res, **21:** 171, 2009

148. Laumann, E. O., Nicolosi, A., Glasser, D. B. et al.: Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res, **17:** 39, 2005

149. Araujo, A. B., Mohr, B. A., McKinlay, J. B.: Changes in sexual function in middle-aged and older men: longitudinal data from the Massachusetts Male Aging Study. J Am Geriatr Soc, **52:** 1502, 2004

150. Najman, J. M., Dunne, M. P., Boyle, F. M. et al.: Sexual dysfunction in the Australian population. Aust Fam Physician, **32:** 951, 2003

151. Smith, A. M., Patrick, K., Heywood, W. et al.: Sexual practices and the duration of last heterosexual encounter: findings from the Australian longitudinal study of health and relationships. J Sex Res, **49:** 487, 2011

152. Kinsey, A. C., Pomeroy, W. R., Martin, C. E.: Sexual behavior in the human male. 1948. Am J Public Health, **93:** 894, 2003

153. Brotto, L. A.: The DSM diagnostic criteria for Hypoactive Sexual Desire Disorder in men. J Sex Med, **7:** 2015, 2010

154. Schiavi, R. C.: Normal aging and the evaluation of sexual dysfunction. Psychiatr Med, **10:** 217, 1992

155. Emmelot-Vonk, M. H., Verhaar, H. J., Nakhai-Pour, H. R. et al.: Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. Int J Impot Res, **21:** 129, 2009

156. Schiavi, R. C., Schreiner-Engel, P., White, D. et al.: Pituitary-gonadal function during sleep in men with hypoactive sexual desire and in normal controls. Psychosom Med, **50:** 304, 1988

157. Angst, J.: Sexual problems in healthy and depressed persons. Int Clin Psychopharmacol, **13 Suppl 6:** S1, 1998

158. Kafka, M. P.: Hypersexual disorder: a proposed diagnosis for DSM-V. Arch Sex Behav, **39:** 377, 2010

159. Papadopoulos, C., Beaumont, C., Shelley, S. I. et al.: Myocardial infarction and sexual activity of the female patient. Arch Intern Med, **143:** 1528, 1993

160. Angeleri, F., Angeleri, V. A., Foschi, N. et al.: The influence of depression, social activity, and family stress on functional outcome after stroke. Stroke, **24:** 1478, 1993

161. Boldrini, P., Basaglia, N., Calanca, M. C.: Sexual changes in hemiparetic patients. Arch Phys Med Rehabil, **72:** 202, 1991

162. Manolis, A., Doumas, M.: Antihypertensive treatment and sexual dysfunction. Curr Hypertens Rep, **14:** 285, 2012

163. Chitaley, K.: Type 1 and Type 2 diabetic-erectile dysfunction: same diagnosis (ICD-9), different disease? J Sex Med, **6 Suppl 3:** 262, 2009

164. Bacon, C. G., Hu, F. B., Giovannucci, E. et al.: Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. Diabetes Care, **25:** 1458, 2002

165. Bancroft, J., Gutierrez, P.: Erectile dysfunction in men with and without diabetes mellitus: a comparative study. Diabet Med, **13:** 84, 1996

166. Michaelson, M. D., Cotter, S. E., Gargollo, P. C. et al.: Management of complications of prostate cancer treatment. CA Cancer J Clin, **58:** 196, 2008

167. Davison, B. J., Matthew, A., Elliott, S. et al.: Assessing couples' preferences for postoperative sexual rehabilitation before radical prostatectomy. BJU Int, **110:** 1529, 2012

168. Diaz, V. A., Jr., Close, J. D.: Male sexual dysfunction. Prim Care, **37:** 473, 2010

169. Amato, P., Buster, J. E.: Diagnosis and treatment of hypoactive sexual desire disorder. Clin Obstet Gynecol, **52:** 666, 2009

170. Thomas, D. R.: Medications and sexual function. Clin Geriatr Med, **19:** 553, 2003

171. Serretti, A., Chiesa, A.: Sexual side effects of pharmacological treatment of psychiatric diseases. Clin Pharmacol Ther, **89:** 142, 2011

172. Karraker, A., Delamater, J., Schwartz, C. R.: Sexual frequency decline from midlife to later life. J Gerontol B Psychol Sci Soc Sci, **66:** 502, 2011

173. Levy, J.: Sex and sexuality in later life stages. In: Sexuality across the life course. Edited by A. Rossi. Chicago: University of Chicago Press, 1984

174. Brecher, E.: Love, Sex, and Aging: A Consumers Union Report Little Brown & Co, 1986

175. Garde, K., Lunde, I.: Influence of social status on female sexual behaviour. A random sample study of 40-year-old Danish women. Scand J Prim Health Care, **2:** 5, 1984

176. Domenighetti, G., Tomada, A., Marazzi, A. et al.: Impact of job insecurity on sexual desire: an exploratory analysis. Swiss Med Wkly, **139:** 486, 2009

177. Martin, S. A., Haren, M. T., Middleton, S. M. et al.: The Florey Adelaide Male Ageing Study (FAMAS): design, procedures & participants. BMC Public Health, **7:** 126, 2007

178. Eastwood, B. J., Gregor, R. D., MacLean, D. R. et al.: Effects of recruitment strategy on response rates and risk factor profile in two cardiovascular surveys. Int J Epidemiol, **25:** 763, 1996

179. Dillman, D.: Dillman Protocol: Total Survey Design Method New York: Wiley-Interscience, 1978

180. Wilson, D. H., Starr, G. J., Taylor, A. W. et al.: Random digit dialling and Electronic White Pages samples compared: demographic profiles and health estimates. Aust N Z J Public Health, **23:** 627, 1999

181. Slattery, M. L., Edwards, S. L., Caan, B. J. et al.: Response rates among control subjects in case-control studies. Ann Epidemiol, **5:** 245, 1995

182. ABS: 2001 Census Dictionary. Canberra: Australian Bureau of Statistics, vol. 2901.0, 2001

183. Ware, J. E., Jr., Sherbourne, C. D.: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care, **30:** 473, 1992

184. Beck, A. T., Beck, R. W.: Screening depressed patients in family practice. A rapid technic. Postgrad Med, **52:** 81, 1972

185. Armstrong T, B. A., Davies J: Physical activity patterns of Australian adults. Results of the 1999 Physical Activity Survey. . Canberra: Australian Institute of Health and Welfare, 2000

186. Maislin, G., Pack, A. I., Kribbs, N. B. et al.: A survey screen for prediction of apnea. Sleep, **18:** 158, 1995

187. Hodge, A., Patterson, A. J., Brown, W. J. et al.: The Anti Cancer Council of Victoria FFQ: relative validity of nutrient intakes compared with weighed food records in young to middle-aged women in a study of iron supplementation. Aust N Z J Public Health, **24:** 576, 2000

188. Olds T, N. K., Australian Sports Commission.: Anthropometrica : a textbook of body measurement for sports and health courses. . Sydney, Australia: UNSW Press, 1996

189. Fuld, P. A., Masur, D. M., Blau, A. D. et al.: Object-memory evaluation for prospective detection of dementia in normal functioning elderly: predictive and normative data. J Clin Exp Neuropsychol, **12:** 520, 1990

190. Mazess, R. B., Barden, H. S.: Evaluation of differences between fan-beam and pencil-beam densitometers. Calcif Tissue Int, **67:** 291, 2000

191. Rosen, R. C., Giuliano, F., Carson, C. C.: Sexual dysfunction and lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Eur Urol, **47:** 824, 2005

192. Parsons, J. K., Bergstrom, J., Silberstein, J. et al.: Prevalence and characteristics of lower urinary tract symptoms in men aged > or = 80 years. Urology, **72:** 318, 2008

193. Roehrborn, C. G., Nuckolls, J. G., Wei, J. T. et al.: The benign prostatic hyperplasia registry and patient survey: study design, methods and patient baseline characteristics. BJU Int, **100:** 813, 2007

194. Coyne, K. S., Sexton, C. C., Kopp, Z. S. et al.: Rationale for the study methods and design of the epidemiology of lower urinary tract symptoms (EpiLUTS) study. BJU Int, **104:** 348, 2009

195. Martin, S., Haren, M., Taylor, A. et al.: Cohort profile: the Florey Adelaide Male Ageing Study (FAMAS). Int J Epidemiol, **36:** 302, 2007

196. PROS: Monitoring obesity in the South Australian population which survey type (telephone, face-to-face or biomedical)?, 2003

197. Litman, H. J., Steers, W. D., Wei, J. T. et al.: Relationship of lifestyle and clinical factors to lower urinary tract symptoms: results from Boston Area Community Health survey. Urology, **70:** 916, 2007

198. Li, M. K., Garcia, L. A., Rosen, R.: Lower urinary tract symptoms and male sexual dysfunction in Asia: a survey of ageing men from five Asian countries. BJU Int, **96:** 1339, 2005

199. Russell, S., McVary, K. T.: Lower urinary tract symptoms and erectile dysfunction: epidemiology and treatment in the aging man. Curr Urol Rep, **6:** 445, 2005

200. Jones, P. P., Davy, K. P., Alexander, S. et al.: Age-related increase in muscle sympathetic nerve activity is associated with abdominal adiposity. Am J Physiol, **272:** E976, 1997

201. Kupelian, V., McVary, K. T., Barry, M. J. et al.: Association of C-reactive protein and lower urinary tract symptoms in men and women: results from Boston Area Community Health survey. Urology, **73:** 950, 2009

202. de Groat, W. C., Yoshimura, N.: Afferent nerve regulation of bladder function in health and disease. Handb Exp Pharmacol**:** 91, 2009

203. Kohler, T. S., McVary, K. T.: The Relationship between Erectile Dysfunction and Lower Urinary Tract Symptoms and the Role of Phosphodiesterase Type 5 Inhibitors. Eur Urol, 2008

204. Klein, J. P., Waxman, S. G.: The brain in diabetes: molecular changes in neurons and their implications for end-organ damage. Lancet Neurol, **2:** 548, 2003

205. Rohrmann, S., Smit, E., Giovannucci, E. et al.: Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey. Urology, **64:** 504, 2004

206. Kemmer, H.: The relationship between sleep apnea and overactive bladder. Curr Urol Rep, **10:** 448, 2009

207. Umlauf, M. G., Chasens, E. R., Greevy, R. A. et al.: Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep, **27:** 139, 2004

208. Margel, D., Shochat, T., Getzler, O. et al.: Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. Urology, **67:** 974, 2006

209. Haidinger, G., Madersbacher, S., Waldhoer, T. et al.: The prevalence of lower urinary tract symptoms in Austrian males and associations with sociodemographic variables. Eur J Epidemiol, **15:** 717, 1999

210. Fliers, E., Klieverik, L. P., Kalsbeek, A.: Novel neural pathways for metabolic effects of thyroid hormone. Trends Endocrinol Metab, 2009

211. Ramberg, H., Eide, T., Krobert, K. A. et al.: Hormonal regulation of beta2-adrenergic receptor level in prostate cancer. Prostate, **68:** 1133, 2008

212. Lehrer, S., Diamond, E. J., Stone, N. N. et al.: Serum triiodothyronine is increased in men with prostate cancer and benign prostatic hyperplasia. J Urol, **168:** 2431, 2002

213. Holden, C. A., McLachlan, R. I., Pitts, M. et al.: Determinants of male reproductive health disorders: the Men in Australia Telephone Survey (MATeS). BMC Public Health, **10:** 96

214. Moreira, E. D., Jr., Neves, R. C., Neto, A. F. et al.: A Population-based survey of lower urinary tract symptoms (LUTS) and symptom-specific bother: results from the Brazilian LUTS epidemiology study (BLUES). World J Urol, 2013

215. Kupelian, V., McVary, K. T., Kaplan, S. A. et al.: Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston area community health survey. J Urol, **189:** S107, 2013

216. Latz, I., Weber, M., Korda, R. et al.: Lower urinary tract symptoms in relation to region of birth in 95,393 men living in Australia: the 45 and Up Study. World J Urol, **31:** 673, 2013

217. Choi, W. S., Lee, W. K., Lee, S. H. et al.: Is high-sensitivity C-reactive protein associated with lower urinary tract symptoms in aging men? Results from the hallym aging study. Korean J Urol, **53:** 335, 2012

218. Kupelian, V., McVary, K. T., Kaplan, S. A. et al.: Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston Area Community Health Survey. J Urol, **182:** 616, 2009

219. Kasturi, S., Russell, S., McVary, K. T.: Metabolic syndrome and lower urinary tract symptoms secondary to benign prostatic hyperplasia. Curr Urol Rep, **7:** 288, 2006

220. Grassi, G.: Sympathetic overdrive and cardiovascular risk in the metabolic syndrome. Hypertens Res, **29:** 839, 2006

221. Rahman, N. U., Phonsombat, S., Bochinski, D. et al.: An animal model to study lower urinary tract symptoms and erectile dysfunction: the hyperlipidaemic rat. BJU Int, **100:** 658, 2007

222. Chang, I. H., Oh, S. Y., Kim, S. C.: A possible relationship between testosterone and lower urinary tract symptoms in men. J Urol, **182:** 215, 2009

223. Malavige, L. S., Levy, J. C.: Erectile dysfunction in diabetes mellitus. J Sex Med, **6:** 1232, 2009

224. Shin, D., Pregenzer, G., Jr., Gardin, J. M.: Erectile dysfunction: a disease marker for cardiovascular disease. Cardiol Rev, **19:** 5

225. Nicolosi, A., Moreira, E. D., Jr., Villa, M. et al.: A population study of the association between sexual function, sexual satisfaction and depressive symptoms in men. J Affect Disord, **82:** 235, 2004

226. Newman, A. M.: Arthritis and sexuality. Nurs Clin North Am, **42:** 621, 2007

227. Bacon, C. G., Mittleman, M. A., Kawachi, I. et al.: Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med, **139:** 161, 2003

228. Cohen, P. G.: Aromatase, adiposity, aging and disease. The hypogonadal-metabolic-atherogenic-disease and aging connection. Med Hypotheses, **56:** 702, 2001

229. Hall, S. A., Esche, G. R., Araujo, A. B. et al.: Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab, **93:** 3870, 2008

230. Cirino, G., Fusco, F., Imbimbo, C. et al.: Pharmacology of erectile dysfunction in man. Pharmacol Ther, **111:** 400, 2006

231. Melnik, T., Soares, B. G., Nasselo, A. G.: Psychosocial interventions for erectile dysfunction. Cochrane Database Syst Rev**:** CD004825, 2007

232. Travison, T. G., Shabsigh, R., Araujo, A. B. et al.: The natural progression and remission of erectile dysfunction: results from the Massachusetts Male Aging Study. J Urol, **177:** 241, 2007

233. Suzuki, H., Tominaga, T., Kumagai, H. et al.: Effects of first-line antihypertensive agents on sexual function and sex hormones. J Hypertens Suppl, **6:** S649, 1988

234. Hintikka, J., Niskanen, L., Koivumaa-Honkanen, H. et al.: Hypogonadism, decreased sexual desire, and long-term depression in middle-aged men. J Sex Med, **6:** 2049, 2009

235. Brody, S.: The relative health benefits of different sexual activities. J Sex Med, **7:** 1336

236. Beck, J., Bozman, A., Qualtrough, B.: The experience of sexual desire: psychological correlates in a college sample. Journal of Sex Research, **28:** 443, 1991

237. Wein AJ , K. L., Novick AC, Partin AW , Peters CA: Physiology of penile erection and pathophysiology of erectile dysfunction In: Campbell-Walsh Urology. Edited by W. AJ. Philadelphia: Elsevier Inc, vol. 9th edn, pp. 718-49, 2007

238. Pinnock, C. B., Stapleton, A. M., Marshall, V. R.: Erectile dysfunction in the community: a prevalence study. Med J Aust, **171:** 353, 1999

239. O'Leary, M. P., Rhodes, T., Girman, C. J. et al.: Distribution of the Brief Male Sexual Inventory in community men. Int J Impot Res, **15:** 185, 2003

240. Rowland, D. L., Greenleaf, W. J., Dorfman, L. J. et al.: Aging and sexual function in men. Arch Sex Behav, **22:** 545, 1993

241. Reis, M. M., Abdo, C. H.: Prevalence of erectile dysfunction as defined by the International Index of Erectile Function (IIEF) and self-reported erectile dysfunction in a sample of Brazilian men who consider themselves healthy. J Sex Marital Ther, **36:** 87

242. Johnson, S. D., Phelps, D. L., Cottler, L. B.: The association of sexual dysfunction and substance use among a community epidemiological sample. Arch Sex Behav, **33:** 55, 2004

243. Chew, K. K.: Alcohol consumption and male erectile dysfunction: an unfounded reputation for risk? J Sex Med, **6:** 2340, 2009

244. NHMRC: Australian guidelines to reduce health risks from drinking alcohol. Canberra, 2009

245. Travison, T. G., Morley, J. E., Araujo, A. B. et al.: The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab, **91:** 2509, 2006

246. Salmon, P.: Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. Clin Psychol Rev, **21:** 33, 2001

247. Knapp, P. H.: Libido: a latter-day look. J Nerv Ment Dis, **142:** 395, 1966

248. Moreira, E. D., Jr., Glasser, D. B., Gingell, C.: Sexual activity, sexual dysfunction and associated help-seeking behaviours in middle-aged and older adults in Spain: a population survey. World J Urol, **23:** 422, 2005

249. Kupelian, V., Shabsigh, R., Araujo, A. B. et al.: Erectile dysfunction as a predictor of the metabolic syndrome in aging men: results from the Massachusetts Male Aging Study. J Urol, **176:** 222, 2006

250. Borges, R., Temido, P., Sousa, L. et al.: Metabolic syndrome and sexual (dys)function. J Sex Med, **6:** 2958, 2009

251. Feldman, H. A., Longcope, C., Derby, C. A. et al.: Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab, **87:** 589, 2002

252. Montorsi, F., Adaikan, G., Becher, E. et al.: Summary of the recommendations on sexual dysfunctions in men. J Sex Med, **7:** 3572

253. Burchardt, M., Burchardt, T., Baer, L. et al.: Hypertension is associated with severe erectile dysfunction. J Urol, **164:** 1188, 2000

254. Sandner, P., Neuser, D., Bischoff, E.: Erectile dysfunction and lower urinary tract. Handb Exp Pharmacol**:** 507, 2009

255. Hall, S. A., Shackelton, R., Rosen, R. C. et al.: Sexual activity, erectile dysfunction, and incident cardiovascular events. Am J Cardiol, **105:** 192

256. Aversa, A., Caprio, M., Rosano, G. M. et al.: Endothelial effects of drugs designed to treat erectile dysfunction. Curr Pharm Des, **14:** 3768, 2008

257. Goldey, K. L., van Anders, S. M.: Sexual arousal and desire: interrelations and responses to three modalities of sexual stimuli. J Sex Med, **9:** 2315, 2012

258. Irwin, D. E., Kopp, Z. S., Agatep, B. et al.: Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int, **108:** 1132, 2011

259. Parsons, J. K., Wilt, T. J., Wang, P. Y. et al.: Progression of lower urinary tract symptoms in older men: a community based study. J Urol, **183:** 1915, 2010

260. Malmsten, U. G., Molander, U., Peeker, R. et al.: Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years. Eur Urol, **58:** 149, 2010

261. Sarma, A. V., Jacobsen, S. J., Girman, C. J. et al.: Concomitant longitudinal changes in frequency of and bother from lower urinary tract symptoms in community dwelling men. J Urol, **168:** 1446, 2002

262. Wei, J. T., Calhoun, E., Jacobsen, S. J.: Urologic diseases in America project: benign prostatic hyperplasia. J Urol, **173:** 1256, 2005

263. Martin, S. A., Haren, M. T., Marshall, V. R. et al.: Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. World J Urol, **29:** 179, 2011

264. Moul, S., McVary, K. T.: Lower urinary tract symptoms, obesity and the metabolic syndrome. Curr Opin Urol, 2009

265. Morant, S., Bloomfield, G., Vats, V. et al.: Increased Sexual Dysfunction in Men with Storage and Voiding Lower Urinary Tract Symptoms. J Sex Med, 2008

266. Wuerstle, M. C., Van Den Eeden, S. K., Poon, K. T. et al.: Contribution of common medications to lower urinary tract symptoms in men. Arch Intern Med, **171:** 1680, 2011

267. Harwood, D. T., Handelsman, D. J.: Development and validation of a sensitive liquid chromatography-tandem mass spectrometry assay to simultaneously

measure androgens and estrogens in serum without derivatization. Clin Chim Acta, **409:** 78, 2009

268. Parsons, J. K., Kashefi, C.: Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. Eur Urol, **53:** 1228, 2008

269. Parsons, J. K., Messer, K., White, M. et al.: Obesity increases and physical activity decreases lower urinary tract symptom risk in older men: the Osteoporotic Fractures in Men study. Eur Urol, **60:** 1173, 2011

270. Barry, K. L., Fleming, M. F.: Widowhood: a review of the social and medical implications. Fam Med, **20:** 413, 1988

271. Cortes, E., Sahai, A., Pontari, M. et al.: The psychology of LUTS: ICI-RS 2011. Neurourol Urodyn, **31:** 340, 2012

272. Wong, S. Y., Hong, A., Leung, J. et al.: Lower urinary tract symptoms and depressive symptoms in elderly men. J Affect Disord, **96:** 83, 2006

273. Chavalmane, A. K., Comeglio, P., Morelli, A. et al.: Sex steroid receptors in male human bladder: expression and biological function. J Sex Med, **7:** 2698, 2010

274. Ling, S., Komesaroff, P., Sudhir, K.: Cellular mechanisms underlying the cardiovascular actions of oestrogens. Clin Sci (Lond), **111:** 107, 2006

275. Litwin, M. S., Nied, R. J., Dhanani, N.: Health-related quality of life in men with erectile dysfunction. J Gen Intern Med, **13:** 159, 1998

276. Atlantis, E., Sullivan, T.: Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. J Sex Med, **9:** 1497, 2012

277. Kinsey, A. C., Pomeroy, W. B., Martin, C. E.: Sexual behavior in the human male. Indiana: Indiana University Press, 1948

278. Martin, S., Atlantis, E., Wilson, D. et al.: Clinical and Biopsychosocial Determinants of Sexual Dysfunction in Middle-Aged and Older Australian Men. J Sex Med, 2012

279. Rosenberg, M. T., Staskin, D. R., Kaplan, S. A. et al.: A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. Int J Clin Pract, **61:** 1535, 2007

280. Armstrong, N., Welsman, J. R., Kirby, B. J.: Longitudinal changes in 11-13-year-olds' physical activity. Acta Paediatr, **89:** 775, 2000

281. Koskimaki, J., Hakama, M., Huhtala, H. et al.: Effect of erectile dysfunction on frequency of intercourse: a population based prevalence study in Finland. J Urol, **164:** 367, 2000

282. McCulloch, D. K., Young, R. J., Prescott, R. J. et al.: The natural history of impotence in diabetic men. Diabetologia, **26:** 437, 1984

283. Brindley, G. S.: Cavernosal alpha-blockade: a new technique for investigating and treating erectile impotence. Br J Psychiatry, **143:** 332, 1983

284. Kendirci, M., Trost, L., Sikka, S. C. et al.: The effect of vascular risk factors on penile vascular status in men with erectile dysfunction. J Urol, **178:** 2516, 2007

285. Hagger-Johnson, G., Mottus, R., Craig, L. C. et al.: Pathways from childhood intelligence and socioeconomic status to late-life cardiovascular disease risk. Health Psychol, **31:** 403, 2012

286. Chew, C., Halliday, J. L., Riley, M. M. et al.: Population-based study of antenatal detection of congenital heart disease by ultrasound examination. Ultrasound Obstet Gynecol, **29:** 619, 2007

287. Kalter-Leibovici, O., Wainstein, J., Ziv, A. et al.: Clinical, socioeconomic, and lifestyle parameters associated with erectile dysfunction among diabetic men. Diabetes Care, **28:** 1739, 2005

288. Khoo, J., Piantadosi, C., Duncan, R. et al.: Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. J Sex Med, **8:** 2868, 2011

289. Santos, T., Drummond, M., Botelho, F.: Erectile dysfunction in obstructive sleep apnea syndrome--prevalence and determinants. Rev Port Pneumol, **18:** 64, 2012

290. Szymanski, F. M., Filipiak, K. J., Hrynkiewicz-Szymanska, A. et al.: The high risk of obstructive sleep apnea--an independent risk factor of erectile dysfunction in ST-segment elevation myocardial infarction patients. J Sex Med, **8:** 1434, 2011

291. Taskin, U., Yigit, O., Acioglu, E. et al.: Erectile dysfunction in severe sleep apnea patients and response to CPAP. Int J Impot Res, **22:** 134, 2010

292. Akkus, E., Kadioglu, A., Esen, A. et al.: Prevalence and correlates of erectile dysfunction in Turkey: a population-based study. Eur Urol, **41:** 298, 2002

293. Green, J. S., Holden, S. T., Ingram, P. et al.: An investigation of erectile dysfunction in Gwent, Wales. BJU Int, **88:** 551, 2001

294. Moore, R. D., Smith, C. R., Kwiterovich, P. O. et al.: Effect of low-dose alcohol use versus abstention on apolipoproteins A-I and B. Am J Med, **84:** 884, 1988

295. Dong, J. Y., Zhang, Y. H., Qin, L. Q.: Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol, **58:** 1378, 2011

296. McVary, K. T.: Erectile dysfunction and lower urinary tract symptoms secondary to BPH. Eur Urol, **47:** 838, 2005

297. Blans, M. C., Visseren, F. L., Banga, J. D. et al.: Infection induced inflammation is associated with erectile dysfunction in men with diabetes. Eur J Clin Invest, **36:** 497, 2006

298. Toque, H. A., da Silva, F. H., Calixto, M. C. et al.: High-fat diet associated with obesity induces impairment of mouse corpus cavernosum responses. BJU Int, **107:** 1628, 2011

299. Hyde, Z., Flicker, L., Hankey, G. J. et al.: Prevalence and predictors of sexual problems in men aged 75-95 years: a population-based study. J Sex Med, **9:** 442, 2012

300. Kubin, M., Wagner, G., Fugl-Meyer, A. R.: Epidemiology of erectile dysfunction. Int J Impot Res, **15:** 63, 2003

301. Raison, C. L., Miller, A. H.: Is depression an inflammatory disorder? Curr Psychiatry Rep, **13:** 467, 2011

302. Burke, J. P., Jacobson, D. J., McGree, M. E. et al.: Diabetes and sexual dysfunction: results from the Olmsted County study of urinary symptoms and health status among men. J Urol, **177:** 1438, 2007

303. Gades, N. M., Jacobson, D. J., McGree, M. E. et al.: The associations between serum sex hormones, erectile function, and sex drive: the Olmsted County Study of Urinary Symptoms and Health Status among Men. J Sex Med, **5:** 2209, 2008

304. DeRogatis, L., Rosen, R. C., Goldstein, I. et al.: Characterization of hypoactive sexual desire disorder (HSDD) in men. J Sex Med, **9:** 812, 2012

305. Bhasin, S., Enzlin, P., Coviello, A. et al.: Sexual dysfunction in men and women with endocrine disorders. Lancet, **369:** 597, 2007

306. Allan, C. A., Forbes, E. A., Strauss, B. J. et al.: Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. Int J Impot Res, **20:** 396, 2008

307. Wu, F. C., Tajar, A., Beynon, J. M. et al.: Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med, **363:** 123, 2010

308. McConnell, J. D., Roehrborn, C. G., Bautista, O. M. et al.: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med, **349:** 2387, 2003

309. Penson, D. F., Munro, H. M., Signorello, L. B. et al.: Obesity, physical activity and lower urinary tract symptoms: results from the Southern Community Cohort Study. J Urol, **186:** 2316, 2011

310. Maserejian, N. N., Kupelian, V., Miyasato, G. et al.: Are physical activity, smoking and alcohol consumption associated with lower urinary tract symptoms in men or women? Results from a population based observational study. J Urol, **188:** 490, 2012

311. Khoo, J., Piantadosi, C., Worthley, S. et al.: Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. Int J Obes (Lond)

312. NHS: Lower urinary tract symptoms. The management of lower urinary tract symptoms in men. Edited by N. I. f. H. a. C. Excellence. London, vol. Clinical guideline 97, 2010

313. Oelke, M. C.: Guidelines on Conservative Treatment of Non-neurogenic Male LUTS. Edited by E. A. o. Urology, 2010

314. Milsom, I., Kaplan, S. A., Coyne, K. S. et al.: Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. Urology, **80:** 90, 2012

315. Wittert, G. A., Martin, S., Sutherland, P. et al.: Overactive bladder in men as a marker of cardiometabolic risk. Med J Aust, **197:** 379, 2012

316. Glina, S., Santana, A. W., Azank, F. et al.: Lower urinary tract symptoms and erectile dysfunction are highly prevalent in ageing men. BJU Int, **97:** 763, 2006

317. Shamloul, R., Ghanem, H.: Erectile dysfunction. Lancet, 2012