

# Lower urinary tract symptoms in women – aspects on epidemiology and treatment

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# ABSTRACT

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## Lower urinary tract symptoms in women – aspects on epidemiology and treatment

Lower urinary tract symptoms (LUTS) are common conditions that compromise a person's quality of life and result in increased health care costs for society.

The aims of this thesis were to describe the prevalence and natural course of different LUTS in women (*Paper I*), to assess prevalence changes over time (*Paper II*), and to evaluate the importance of genetic factors on LUTS (*Paper III*). The long-term results of the Stamey needle colposuspension for female stress urinary incontinence were also assessed (*Paper IV*).

***Paper I:*** In this population-based, longitudinal study the very same women (n=1081) were assessed regarding the prevalence, progression and remission of various LUTS in 1991 and 2007, using a postal questionnaire. The proportion of women reporting urinary incontinence (UI), overactive bladder (OAB), nocturia and daytime voiding frequency of  $\geq 8$  times/day increased markedly over time. Both incidence and remission for most symptoms were considerable.

***Paper II:*** The prevalence of LUTS, help-seeking behaviour, treatment and quality of life were compared in two population-based surveys of women performed in 1991 (n=2911) and 2007 (n=3158) using a similar questionnaire. The reported prevalence of UI and OAB was unchanged over time as was help-seeking due to UI. In 2007, more women stated that the presence of UI limited their daily life.

***Paper III:*** Questionnaire-based national cohort survey evaluating the prevalence of LUTS in Swedish twins born 1959-1985 (n=25 364). Heritability was assessed in female twins. LUTS were more common in women than in men. The strongest genetic effects were observed for UI and nocturia and the lowest for OAB without incontinence where environmental effects dominated. Shared environment accounted for nearly one third of the total variation for OAB without incontinence and for one fifth of the variation for stress UI. Non-shared environmental effects were in the range of 45-65% for the various LUTS.

***Paper IV:*** Twenty-four women, treated by the Stamey method for stress UI, were followed up by means of a questionnaire, urodynamic assessment and a standardised quantification test. Time to follow-up was 63 months. Approximately half of the women considered themselves continent at follow-up. The mean postoperative leakage was significantly reduced as compared to preoperatively. Most women were satisfied with the result of the operation.

***Conclusions:*** These studies showed that the prevalence of UI and OAB in women has been largely unchanged in the last 16 years. UI, OAB and other LUTS constitute dynamic conditions. The prevalence of symptoms increases with increasing age, but both progression and remission over time are common. The strongest genetic effects were observed for conditions involving UI and for nocturia while the lowest genetic effects were observed for OAB, where environmental factors were more important. The Stamey procedure may be used in a selected group of women with genuine stress UI and stable detrusor with acceptable long-term results and patient satisfaction.

***Keywords:*** Urinary incontinence; Overactive bladder; Lower urinary tract symptoms; Epidemiology; Prevalence; Incidence; Progression; Remission; Twins; Genetic; Heritability; Stress urinary incontinence; Stamey

# LIST OF PUBLICATIONS

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- I. Longitudinal population-based survey of urinary incontinence, overactive bladder and other lower urinary tract symptoms in women.**  
Anna Lena Wennberg, Ulla Molander, Magnus Fall, Christer Edlund, Ralph Peeker and Ian Milsom.  
*Eur Urol* 2009;55(4):783-791.
- II. Lower urinary tract symptoms: Lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007.**  
Anna Lena Wennberg, Ulla Molander, Magnus Fall, Christer Edlund, Ralph Peeker and Ian Milsom.  
*Accepted for publication, BJUI, 15 January 2009.*
- III. The heritability of lower urinary tract symptoms (LUTS).**  
A population-based survey in a cohort of adult Swedish twins.  
Anna Lena Wennberg, Daniel Altman, Cecilia Lundholm, Åsa Klint, Anastasia Iliadou, Ralph Peeker, Magnus Fall, Nancy L Pedersen and Ian Milsom.  
*Manuscript.*
- IV. Stamey's abdominovaginal needle colposuspension for the correction of female genuine stress urinary incontinence.**  
Long-term results.  
Anna Lena Wennberg, Christer Edlund, Magnus Fall and Ralph Peeker.  
*Scand J Urol Nephrol* 2003;37(5):419-423.

# ABBREVIATIONS

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BTX-A	Botulinum Toxin A
DiHA	Dextranomers in Hyaluronan
DO	Detrusor Overactivity
DZ	Dizygotic
EMG	Electromyography
GSI	Genuine Stress Incontinence
ICI	International Consultation on Incontinence
ICS	International Continence Society
ISD	Intrinsic Sphincter Dysfunction
LUTS	Lower Urinary Tract Symptoms
MUI	Mixed Urinary Incontinence
MZ	Monozygotic
OAB	Overactive Bladder
OAB dry	Overactive Bladder without Urinary incontinence
OAB wet	Overactive Bladder with Urinary incontinence
PFMT	Pelvic Floor Muscle Training
QoL	Quality of Life
RCT	Randomised Controlled Trial
RTX	Resiniferatoxin
STR	Swedish Twin Registry
SUI	Stress Urinary Incontinence
TOT	Trans Obturator Tape
TVT	Tensionfree Vaginal Tape
UI	Urinary Incontinence
UUI	Urge Urinary Incontinence
VAS	Visual Analogue Scale

## Historical background

Lower Urinary Tract Symptoms (LUTS) are common conditions that may be encountered in men and women of all ages and by clinicians from many different disciplines. These symptoms have widespread human and social implications, causing discomfort, shame and loss of self-confidence [1-4]. There has been a growing interest in various LUTS in recent years as a consequence of better diagnostic and treatment options, as well as an increased awareness of the negative impact for the individual sufferer.

However, the issue is not new. Annotations regarding incontinence have been found on Egyptian papyrus rolls from 2000 BC and directions for treatment of enuresis have been found from 1550 BC (Kahun gynaecological papyrus approx. 1825 BC, Ebers papyrus approx. 1550 BC). Pelvic floor exercises as a means of treating urinary incontinence were popularised by Kegel in 1948 [5], but have actually been an important part of exercise programmes in Chinese Taoism for more than 6000 years. The first classification of urinary incontinence (UI) is said to have been drawn up by Goldberg already in 1616 [6]. Surgical treatment of UI, mainly female stress urinary incontinence, has been performed since the later part of the 19<sup>th</sup> century. Over the years more than a hundred different surgical methods have been tried, developed or rejected. The first techniques were vaginal operations often combined with the correction of a vaginal

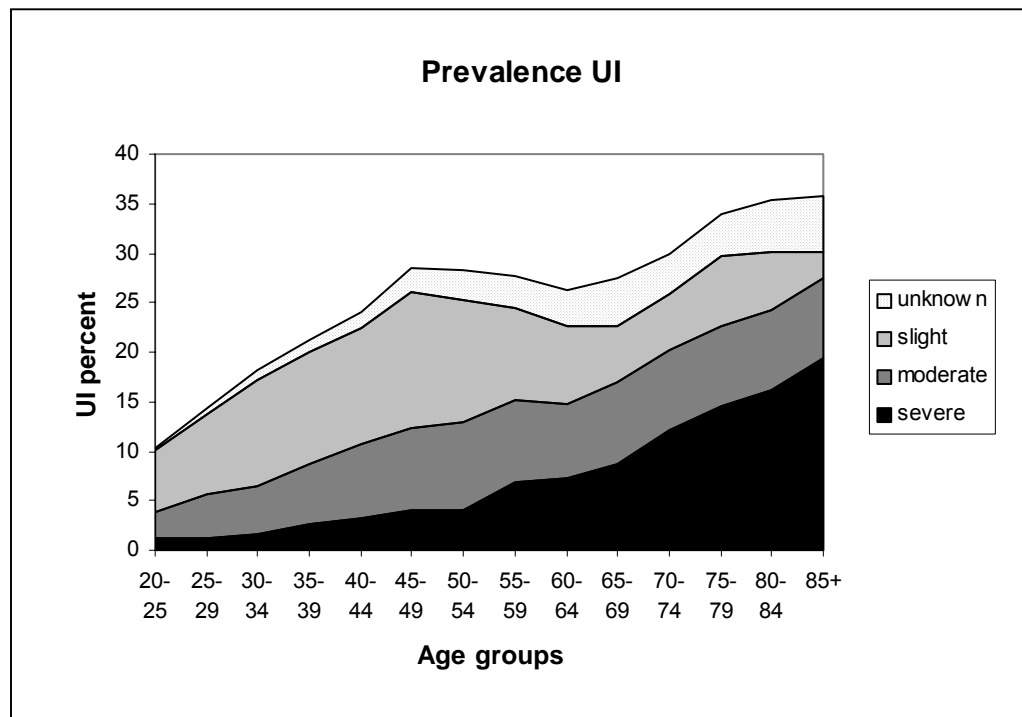
prolapse, such as the procedure described by Kelly 1914 [7, 8], and the main objective was to restore visible anatomical defects. In the 1940<sup>s</sup> sling-operations were routine and in the -50<sup>s</sup> abdominal vesico-urethral suspensions were brought forward (Marschall-Marchetti-Krantz, Lapidés). In 1961 Burch published his work on the open colposuspension technique [9] which is by many still considered as “the golden standard” for the correction of female genuine stress incontinence. In order to minimise the surgical trauma inflicted, abdominovaginal needle suspensions of the bladder neck, such as the Stamey method, were introduced in the 1960<sup>s</sup> and -70<sup>s</sup> [10]. Concurrently, urodynamic investigational methods developed and new theories about the pathophysiological background to the symptoms were presented. In the early years of 1990 Ulmsten and Papa Petros revolutionised the field with their “integral theory” [11] and the subsequent introduction of the tension-free vaginal tape (TVT) procedure [12]. This minimal-invasive technique rapidly gained popularity and is alongside with the Burch procedure one of the dominating surgical methods used for the treatment of female stress urinary incontinence at present. In the last decades, we have also gained important new knowledge regarding the overactive bladder symptom complex and there has been an increased focus on research aiming to improve overactive bladder treatment.

## Epidemiology

The term LUTS was introduced in 1994 in order to describe the patients' complaints without implying their cause [13]. Traditionally, focus has been on UI in women and on other LUTS, known as "prostatism", in men. The new term subsequently proved to be relevant since large population-based surveys in recent years have shown that bladder control symptoms are neither sex-, nor age- or disease-specific.

Urinary incontinence is, nevertheless, still the most familiar LUTS in women. Estimates of prevalence range from a few percent to around 50% in different studies [14]. The wide variation in the reported

prevalence can be explained by various reasons such as the use of different definitions, the heterogeneity of different study populations and also population sampling procedures. Large cross-sectional population-based samples have however concluded that the prevalence of any female urinary incontinence ranges from 20% to 40% in young and middle-aged women, and then steadily increases with age (Figure 1) [16]. Approximately half of the incontinence is stress type (SUI), about 10% urge urinary incontinence (UII) and one third mixed incontinence (MUI). Stress leakage occurs more frequently in younger women whereas urge and mixed urinary incontinence are more prevalent in the older ages [14-17].



(Reprinted by permission from J Clin Epid [16])

**Figure 1.** Prevalence of UI by age and severity.



Similarly to UI, the estimated prevalence of other LUTS varies considerably between different surveys. In the EPIC study [18], which was a large European population-based survey of UI, Overactive bladder (OAB) and other LUTS, 66% of the participating women reported at least one LUTS. The most common LUTS, in both men and women, was nocturia (48.6% men, 54.5% women), which, in women, was followed by UI and urgency (13.1% and 12.8% respectively). The overall prevalence of OAB, in the EPIC study, was 11.8%. Other large surveys from Europe and the United States have estimated the prevalence of OAB to approximately 17% [19, 20] in both men and women.

Møller *et al.* described “bothersome LUTS” as LUTS occurring more often than weekly, and found a prevalence of almost 28% in 40-60-year-old Danish women [21]. Several other authors have described the bother of various LUTS and their negative impact on quality of life. Nested case-control data from the EPIC study showed that more than half of the individuals reporting OAB were bothered by their symptoms and that the use of “coping strategies” was common [22]. UI has been shown to have a negative effect on physical activities, confidence, self-perception and social activities, UUI and MUI being more detrimental than SUI in this respect [2, 4, 17]. In a recent study, Coyne *et al.* also reported greater rates of co-morbidities and depression as well as significantly worse health-related quality

of life and lower work productivity in individuals with OAB symptoms as compared to controls [23]. Nevertheless, several investigations have shown that only a small number of women actually seek help from the medical health care system [24-26].

Longitudinal studies on LUTS in women are scarce and only few epidemiological data are available on the development or the natural history of urinary incontinence or other LUTS (Table 1) [15, 27-37]. The annual overall incidence of UI seems to gather between 1-9% while estimates of remission vary from 4-30%. At present there are only very few population-based studies describing the natural course of other LUTS in the same women. Møller *et al.* followed a random sample of 2284 middle-aged Danish women for 1 year and reported 10% incidence and 28% remission of LUTS [33]. McGrother *et al.* presented rather similar figures (15% and 23% respectively) during one year in a large population-based survey [32], while Heidler *et al.* in a selected population of women without urinary incontinence found annual incidence and remission proportions of 5.3% and 4.6% [29]. As for long-term longitudinal studies on LUTS in women, there are no such studies published hitherto.

A detailed knowledge of the natural history of LUTS in women may help to target treatment resources, to provide ideas for preventive steps in the future and to interpret long-term medical trials.

**Table 1.** Longitudinal studies of UI, OAB and other LUTS.

First author, publication year	Country	Study design	Evaluated symptoms	Progression	Regression	Duration of follow-up
Herzog 1990 [30]	USA	Prospective population based study, men and women $\geq 60$ yrs	UI	Women: 1-yr incidence = 20% Men: 1-yr incidence = 10%	Women: 1-yr remission = 12% Men: 1-yr remission = 30%	1+2 yrs
Burgio 1991 [15]	USA	Prospective population based study, women 42-50 yrs	UI	Cummulative incidence (at least monthly UI) = 8%	Not reported	3 yrs
Nygaard 1996 [34]	USA	Prospective population based study, women $\geq 60$ yrs	UI	Baseline to 3 yrs: SUI = 24% UUI = 20% 3 to 6 yrs: SUI = 21% UUI = 28%	Baseline to 3 yrs: SUI = 29% UUI = 32% 3 to 6 yrs: SUI = 25% UUI = 22%	3+6 yrs
Holtedahl 1998 [31]	Norway	Prospective population based study, women 50-74 yrs	UI	1-yr incidence 1%	No cases of remission	1 yrs
Samuelsson 2000 [35]	Sweden	Prospective population based study, women 20-59 yrs	UI	Cummulative incidence = 14% Mean annual incidence = 3%	5-yrs remission = 28% Mean annual remission = 6%	5 yrs
Møller 2000 [33]	Denmark	Prospective population based study, women 40-60 yrs	LUTS	1-yr incidence = 10%	1-yr remission = 28%	1 yrs
McGrother 2004 [32]	UK	Population-based study, men and women $\geq 40$ yrs	LUTS (storage symptoms)	Women: 1-yr incidence = 15% Men: 1-yr incidence = 14%	Women: 1-yr remission = 23% Men: 1-yr remission = 26%	1 yrs
Hägglund 2004 [28]	Sweden	Prospective population based study, women 22-50 yrs	UI	Cummulative incidence = 17% Mean annual incidence = 4%	4-yrs remission = 16% Mean annual remission = 4%	4 yrs
Heidler 2007 [29]	Austria	Prospective cohort study, continent women $\geq 20$ yrs	LUTS other than UI	Mean annual incidence = 5%	Mean annual remission = 5%	6.5 yrs
Wehrberger 2006 [37]	Austria	Prospective cohort study, women $\geq 20$ yrs	UI	Cummulative incidence = 26% Mean annual incidence = 4%	6.5-yrs remission = 19% Mean annual remission = 3%	6.5 yrs
Donaldson 2006 [27]	UK	Prospective, population based study, women $\geq 40$ yrs	OAB, SUI	OAB: 1-yr incidence = 7% 2-yrs incidence = 6% 3-yrs incidence = 7% SUI: 1-yr incidence = 7% 2-yrs incidence = 6% 3-yrs incidence = 6%	OAB: 1-yr remission = 35% 2-yrs remission = 34% 3-yrs remission = 34% SUI: 1-yr remission = 39% 2-yrs remission = 39% 3-yrs remission = 34%	3 yrs
Townsend 2007 [36]	USA	Prospective cohort study, women 36-55 yrs	UI	Cummulative incidence = 14% Mean annual incidence = 7%	2-yrs remission = 14%	2 yrs

## Classifications

The International Continence Society (ICS) is a worldwide organisation working to increase the knowledge and awareness of various problems associated with bladder control. The standardisation Subcommittee of the International Continence Society is continuously working to standardise the terminology of Lower Urinary Tract Dysfunction.

Lower urinary tract symptoms (LUTS) are defined from the individuals' perspective and are divided in three groups according to the current standards recommended by the ICS; *storage, voiding and post micturition symptoms*. Most women with LUTS belong to the first group - storage symptoms. These include, among others, *increased daytime frequency, nocturia, urgency, OAB and urinary incontinence*. The ICS definitions of these symptoms are as follows [38]:

**Urinary incontinence (UI)** is the complaint of any involuntary leakage of urine.

**Stress urinary incontinence (SUI)** is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.

**Urge urinary incontinence (UII)** is the complaint of involuntary leakage accompanied or immediately preceded by urgency.

**Mixed incontinence (MUI)** is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.

**Increased daytime frequency** is the complaint by the patient who considers that he/she voids too often by day.

**Nocturia** is the complaint that the individual has to wake at night one or more times to void.

**Urgency** is the complaint of a sudden compelling desire to pass urine, which is difficult to defer.

Urgency, with or without urge incontinence, usually with frequency and nocturia can be described as the **Overactive bladder syndrome (OAB)**.

## Etiology and pathogenesis

### Stress urinary incontinence

A prerequisite for urinary continence is that the urethral closure pressure exceeds the intravesical pressure. When the relation is the opposite, the bladder will empty, voluntarily or involuntarily. Urethral closure pressure depends on many factors; an adequate neuromuscular control, adequate pelvic floor muscle function, urethral support by the pelvic floor, the vaginal and fascial components together with different components of the

urethra itself such as the epithelium, connective tissue, vascular plexa and smooth as well as striated musculature. All these factors are closely linked to each other via a complex arrangement of ligaments. Urinary leakage will occur if either the supportive tissues in the region of the urethra and the bladder neck are denervated or otherwise damaged, or if there is a dysfunction in the urethra itself.

Stress urinary incontinence is the most prevalent type of involuntary leakage in women and is by far more common in women than in men due to the anatomical differences between men and women. Several different theories behind the pathogenesis of female SUI have been published four of which will be presented below:

### **1) The intra-abdominal pressure equalization theory**

This theory was introduced in the 1960<sup>s</sup> and was dominating for a long period of time. It hypothesizes that the increase in abdominal pressure during straining is passively transmitted to the proximal (intra-abdominal) part of the urethra, and thus contributes to the urethral closure pressure at physical stress. Urethral hypermobility would, according to this theory, position this high pressure zone of the urethra below the pelvic floor during straining and stress leakage would occur as a consequence of incomplete transmission of intraabdominal pressure to the proximal part of the urethra [39]. Several surgical procedures, introduced at this time, consequently aim at elevating

the bladder neck or the proximal urethra to secure a better transmission of intra-abdominal pressure. Later studies have however shown that there is an active component to the increase in urethral pressure rather than just a passive pressure transmission and the relationship between the actual position of the urethra and SUI has been questioned [40].

### **2) The integral theory**

The integral theory states that “stress symptoms, urge symptoms, and symptoms of defective flow may all derive, for different reasons, from laxity in the vagina or its supporting ligaments, as a result of altered connective tissue” [11]. The theory proposes that the anterior vaginal wall, through its connection to pubourethral ligaments and pelvic musculature, transmits specific pelvic muscle contractions which open or close the bladder neck and the urethra. The two most important elements are the fixation of the urethra to the pubourethral-vaginal ligaments and the fixation of the urethra to the suburethral vaginal wall, the so called anterior forces. The vaginal wall is also linked to the pubococcygeus and levator ani muscles, constituting forces working in the posterior direction. Defects or slackness of any of these structures can cause SUI as a result of an imbalance between anterior and posterior forces, but laxity of the pubourethral ligaments and suburethral hammock are thought to be especially important in causing SUI. The integral theory is currently the dominating pathophysiological theory behind SUI together with the “hammock hypothesis”.

### 3) The hammock hypothesis

The “hammock concept” does not contradict the integral theory but gives more emphasis to the supportive layer underlying the urethra. This anatomically based theory postulates that the tissues posterior to the proximal urethra, composed of the anterior vaginal wall and the endopelvic fascia, constitute a hammock-like supportive layer against which the urethra is compressed during strain. The stability of the suburethral layer depends on an intact connection of the vaginal wall and endopelvic fascia to the arcus tendineus fascia pelvis and the levator ani muscles. In stress incontinent women the supportive hammock is thought to be defective and unable to provide strong enough support to compress the urethra when intra-abdominal pressure rises [41].

### 4) Intrinsic sphincter dysfunction, ISD

The female urethral wall consists of an outer layer of striated muscle fibres, and an inner layer of smooth muscle fibres, lined by the mucosa, submucosal vessels and connective tissues. The mucosa and vessels help to form a watertight seal. Two urethral sphincteric mechanisms are involved in controlling urine flow in women:

- The smooth muscle sphincter consists of the smooth muscle layer of the bladder neck and the proximal urethra. This sphincter, which is a physiological and not an anatomical sphincter, is under involuntary control and keeps the bladder

and upper urethra closed during the storage phase.

- The striated muscle sphincter, the so called rhabdosphincter, is part of the outer layer of the female urethra. This sphincter is, together with the smooth muscle component, responsible for upholding a continuous urethral pressure at rest and during bladder filling, but it is also under voluntary control. It consists of an inner portion (the intrinsic striated sphincter) and an extrinsic portion which is part of the pelvic floor musculature [42].

In women who have been subjected to obstetric trauma, extensive pelvic surgery or irradiation stress urinary incontinence may occur as a consequence of a dysfunction in the urethra itself, so called intrinsic sphincter dysfunction (ISD). ISD can also result from neurological or congenital disease [43]. The urethral pressure in these cases is low and in its most pronounced form the condition is characterised by a permanent open bladder neck and urethra, incapable of resisting expulsive forces. The amount leaked is usually substantial and often manifests already at low physical activity. The prevalence of ISD increases with increasing age and studies on apoptosis have revealed an age-correlated increase in apoptotic activity in the rhabdosphincter musculature [44]. In later years, ISD as a sole diagnosis has, however, been questioned. It is probable that hypermobility and intrinsic sphincter dysfunction in many cases are interrelated and occur simultaneously [45].

### **Overactive bladder (with or without incontinence)**

Urgency and OAB are believed to originate in the bladder or from more or less prominent neurological disorders. The neural regulation of bladder filling and micturition is very complex involving both voluntary control mechanisms and involuntary reflex loops. The superior control of the micturition cycle is exerted by the so-called pontine micturition centre which is under influence of the cerebral cortex and several other brain areas. The cerebral voluntary control is mainly inhibitory and responsible for the micturition reflex. An injury to this circuit may result in an insufficient cortical inhibition and thereby bladder control dysfunction [46].

Abnormalities of bladder smooth muscle have also been related to the occurrence of bladder overactivity, for instance in cases of bladder outlet obstruction. Prolonged obstruction could lead to partial nerve damage as well as metabolic effects on the muscle cells through the production of free radicals and lipid peroxidises [47].

Many women present with a mixture of urinary symptoms related to urinary incontinence and several studies have, in fact, shown an association between different kinds of UI and OAB suggestive of a common pathophysiological pathway. Mattiasson and Teleman demonstrated an overactive opening mechanism of the urethra during the filling phase and a more effective opening of the bladder outlet during micturition in all incontinent

women irrespective of UI type [48]. Gunnarsson and Mattiasson showed a decreased ability to activate vaginal wall/pelvic musculature during short contraction, measured by surface electromyography (EMG), in women with all kinds of incontinence, in contrast to healthy controls [49]. A common pathophysiological pathway is also suggested in the integral theory. According to this theory the laxity of the suburethral vagina and its supporting ligaments may not only cause UI but in addition urge symptoms and symptoms of defective flow. The proposed mechanism is that the slackness of the pubourethral ligaments and anterior vaginal wall allows urine to pass into the proximal urethra and induces a premature micturition reflex by stimulating stretch receptors in the bladder neck, thus causing urgency [11]. Another interesting observation, which might support the presence of a common pathophysiological mechanism, is that several treatment alternatives aiming to treat SUI also may have a favourable effect on urge or mixed symptoms [50-53].

### **Risk factors**

The main risk factors for urinary incontinence are age, pregnancy/childbirth (especially the first delivery) and overweight [16, 54-56].

Although pregnancy itself seems to be a risk factor, the mode of delivery has been shown to influence the risk of UI. In

women who have had vaginal deliveries, the risk of UI is about twice the risk for nulliparous women, while the relative risk for women who have had caesarean sections is approximately 1.5 [55]. The increased risk of UI due to vaginal delivery might be explained by stretching of the pelvic floor tissues or ischaemic trauma to the distal branches of the pudendal nerve causing denervation of the intrinsic urethral sphincter. The effect of parturition is, however, elicited by age [55]. When specifically studying the effect of parity or delivery on the different subtypes of UI the data is divergent. Rortveit *et al.* found an association with parity or mode of delivery for SUI as well as MUI, but not for UUI [55, 56]. Viktrup *et al.*, however, showed an increase of both SUI and UUI after vaginal delivery [57], which was sustained by Altman *et al.* who, in addition to increased SUI, found a significant increase in the frequency of urinary urgency after vaginal delivery independent of age [58].

Other suggested risk factors include smoking, chronic obstructive pulmonary disease, diabetes and neurological disease, previous hysterectomy and possibly also hereditary factors [54, 59-62].

There is little evidence as yet available regarding the relative importance of hereditary factors for the development of LUTS. Family history studies have found a two- to threefold greater prevalence of

SUI among first-degree relatives of women with SUI compared to first-degree relatives of continent women [63-65]. Furthermore, the genetic influence on SUI and pelvic organ prolapse has been studied in female Swedish twins, showing that genetic factors contributed to approximately 40% of the variation in liability for both disorders [66]. There is, however, a need of further studies to evaluate the importance of genetic factors for UI, OAB and other LUTS. It is probable that different subgroups of UI are differently related to genetic and environmental factors [67].

While a wide variety of risk factors for the occurrence of UI have been identified, more information regarding the risk factors for OAB and other LUTS is still needed. OAB symptoms increase with increasing age and are often accompanied by urinary incontinence (OAB wet) [19]. Neurological diseases, such as Parkinsonism, multiple sclerosis, adult normal pressure hydrocephalus as well as cerebrovascular disease are markedly related to OAB symptoms. However, in many cases, the patient may demonstrate bladder overactivity without any overt neurological disease [68]. It is conceivable that these individuals still suffer from discrete pelvic floor nerve damage or subtle disorders in the parts of the central nervous system responsible for micturition control [69, 70].

## **Diagnostic measures**

When a patient presents with any LUTS, an investigation is initiated to objectify, diagnose and eventually treat her symptoms. The basic examination aims at discovering underlying causes, suggesting a diagnosis and selecting patients for specialist care.

### **History**

A careful history at the beginning of the consultation is central and will form the base for the coming assessment. The history should include information concerning previous pregnancy and delivery, pathological conditions, surgical interventions, radiotherapy to the pelvic region, neurological diseases and previous trauma. Current medication is of interest. Direct questioning concerning the urinary symptoms and leakage is of paramount importance. When and how often do the symptoms appear? When did it all start? Are there any provoking events or situations? It is also important to understand the patient's subjective perception of her symptoms, how they affect her quality of life and what her expectations of treatment are.

### **Gynaecological examination**

A gynaecological examination, including cough provocation test, provides information on skin changes, vaginal atrophy, concomitant prolapse and other possible conditions, such as diverticula, tumours or myomas. Urethral hyper-

mobility and urinary leakage upon provocation can be assessed. A negative cough provocation test does, however, not exclude urinary leakage. In cases of urinary leakage at straining a Bonney's test can be performed. If the leakage ceases when the bladder neck is stabilised digitally (=positive Bonney's test) this is an indication of hypermobility rather than sphincteric dysfunction. It is, however, difficult to lift the bladder neck without compressing the urethra and thus the value of Bonney's test is uncertain.

### **Neurological examination**

Bladder dysfunction may be the initial sign of a neurological disease, e.g. multiple sclerosis [69, 70]. A brief neurological examination concerning anal sphincter tonus, perineal sensitivity as well as sensitivity and other neurological manifestations in the lower extremities can give valuable information. Thorough neurological testing is, however, difficult to perform and interpret and, hence, serious or progressive symptoms should prompt a consultation by a neurologist.

### **Micturition chart**

A self-administered micturition chart, or volume/frequency chart, gives information concerning the number of micturitions and volume voided at each micturition. It also gives information on the number of leakage episodes, the daily urine volume and the patient's fluid intake. The micturition chart is thus a valuable instrument that should be included in the basic investigation.



**Pad test**

A pad test is generally used in order to objectify a leakage and measure its magnitude. This information can also be obtained by a standardised quantification test (below).

**Standardised quantification test [71]**

The bladder is filled with a catheter to a specified volume (half the cystometric capacity) and the patient performs the following exercises wearing a pre-weighed pad:

1. Coughing strongly 5 times
2. Running on the spot for one minute
3. Washing hands under running cold water for one minute
4. Jumping on the spot with the feet together for half a minute
5. Jumping on the spot with the feet apart and together for half a minute

The amount of leakage is determined by weighing the pads, and the voided volume is measured.

**Urine examination**

A simple urinary test should be included in the basic investigation to exclude urinary tract infection and detect haematuria.

The abovementioned diagnostic measures constitute the base for assessing urinary symptoms and leakage. If the symptoms are complicated, the diagnosis is difficult or if complementary information is needed to plan certain interventions, any of the following examinations may be indicated:

**Post-voiding residual volume**

Post-voiding residual volume is measured either with a catheter post micturition or by a bladder scan. This investigation is important to exclude possible urinary retention.

**Urethroscopy**

A sudden onset of urgency symptoms and urinary leakage or concomitant bleeding increases the risk of an underlying urinary tract tumour. In such cases, an endoscopic examination of the urethra and the bladder should be undertaken. The examination also gives an opportunity to reveal inflammatory disorders of the lower urinary tract.

**Urodynamics**

Cystometry is the most important of the urodynamic procedures. Through fine catheters inserted in the bladder and vagina or rectum the intravesical and intra-abdominal pressures can be measured during filling and micturition. The examination gives a good picture of the integrity of the parts in the neural system responsible for micturition control, but also a good impression concerning the detrusor function as well as the true compliance of the wall of the urinary bladder. A “bladder cooling test” can give additional information about involuntary detrusor contractions and help discriminate between upper and lower motor neurone lesions [72].

Important to note, however, is that, although the diagnosis *detrusor over-activity* (DO) requires urodynamic measurement, OAB is a clinical and not a urodynamic diagnosis. Patients with OAB may or may not display premature detrusor contractions upon filling cystometry and, conversely, a dysfunctional detrusor activity may be found in non-symptomatic individuals.

### **Urography, computer tomography and/or ultrasound**

These investigations are indicated when there is a macroscopic bleeding from the urinary tract, when a tumour is suspected or to check the upper urinary tract in the case of bladder outlet obstruction.

## **Treatment options**

### **Behavioural treatment**

The simplest behavioural treatment consists of different life-style modifications such as fluid restriction, weight loss and smoke cessation [73-75]. In disabled patients or patients with cognitive insufficiency, toilet assistance, routine voiding schemes or awareness training, so-called prompted voiding, can be of good help. Bladder training, whereby the individual is provided strategies to improve bladder control and prolong the interval between micturitions, has also been shown to have good short- and long-term effect on urge/urge incontinence and mixed urinary incontinence [76-79].

### **Pelvic floor muscle training**

The aim of pelvic floor muscle training (PFMT) is to enable the pelvic floor muscles to regain as much strength as possible in order to maintain continence in physically provocative situations. It may also improve the actions of neuromuscular connections and reflexes in the region of the bladder and urethra [52]. It is primarily a technique to treat stress urinary incontinence, although in some cases patients with mixed or urge symptoms may also benefit from pelvic floor exercises [50, 52]. A training programme should always be introduced by a physiotherapist or urotherapist and should include instructions to correctly identify the pelvic floor muscles, exercises towards strength and endurance as well as training in provocative situations. In current practice, PFMT is advocated as first-line treatment for UI in women with an estimated improvement in 60-70 per cent of the patients [80-82]. The obvious clinical role of PFMT has, however, been questioned lately, based on the arguments that substantial evidence from well-powered randomised controlled trials is lacking [83].

### **Biofeedback**

Biological feed-back is a technique whereby the patient, by the help of technical support, is made conscious of unaware events in her body. A sound or a light connected to a scale indicates either the strength of the pelvic muscle contraction, registered by a vaginal

squeeze device, or the activity in the nerves registered by surface EMG. Biofeedback, in combination with PFMT, can be useful in women who have difficulties in identifying and contracting the pelvic musculature. The effect of this technique in addition to PFMT alone has, however, not been shown to be significantly better in patients with SUI [84] but may have a better effect when treating women with OAB [53]. In patients with urge urinary incontinence urodynamic measures have been tried to make patients recognise and respond with inhibition to detrusor contractions [76, 85]. Still, the method is time-consuming and evidence of the effect is scarce.

### **Pharmacological treatment**

**Oestrogen** substitution has been recommended for the treatment of UI in post-menopausal women. Low-dose, vaginally administered oestrogens may be of benefit for the irritative symptoms of urgency, frequency and UUI. The effect is however rather a result of the reversal of urogenital atrophy than a direct action on the lower urinary tract. Several randomised controlled studies in postmenopausal women with incontinence have, on the contrary, shown that hormone therapy either has no effect or actually worsens pre-existing incontinence [86-88].

**Anticholinergic/antimuscarinic** medication constitutes together with behavioural therapy first-line treatment of urgency/OAB and UUI. Antimuscarinics reduce

detrusor contractions by inhibiting muscarinic receptors on the surface of smooth muscle cells and urothelial cells in the urinary bladder. Many other organs, besides the bladder, express muscarinic receptor activity, so adverse effects are common (e.g. dry mouth, blurred vision and constipation). Several antimuscarinic drugs are available, each with a different specificity to bladder muscarinic receptors, thus producing different adverse effect profiles. To limit undesired side-effects alternative routes of administration (e.g. transdermal or intravesical) and extended release oral formulations have been developed for certain compounds [89, 90].

**Duloxetine** is a selective serotonin/norepinephrine reuptake inhibitor which is thought to increase pudendal nerve signalling to the striated urethral sphincter, and hence increase its tonus. Although duloxetine in randomised controlled trials (RCTs) has been shown to reduce the number of incontinence episodes in women with SUI [91, 92], the clinical use has been limited due to side-effects (mainly nausea) and low compliance.

**Desmopressin** (a vasopressin analogue) can be used to treat nocturia, provided that other reasons of frequent nocturnal micturitions, such as cardiac failure, diabetes and renal failure, are excluded. Hyponatremia may occur as a consequence of fluid retention and patient surveillance regarding weight gain or deranged serum sodium levels is important.

### **Intravesical treatment regimens**

The antimuscarinic substance **Oxybutynin** is available for intravesical administration in patients with detrusor overactivity (DO) [90]. This route of administration may result in symptom amelioration, while side effects are reduced. However, the intravesical route is inconvenient unless the patient already performs intermittent self-catheterisation. Other substances used for intravesical regimens in the treatment of severe DO are **Capsaicin**, **Resiniferatoxin** (RTX) and **Botulinum toxin subtype A** (BTX-A). RTX is a potent analogue of capsaicin and belongs to a group of substances known as vanilloids. These compounds act by desensitising the vanilloid type 1 receptor (TRPV 1) and inactivating C-fibres responsible for mediation of noxious stimuli and initiating painful bladder sensations [93, 94]. Capsaicin and RTX have been shown to reduce symptoms in patients with detrusor overactivity, but RCT's are scarce and more information is needed on long-term efficacy and side-effects [95, 96]. BTX-A selectively blocks the release of acetylcholine from nerve-endings and intramuscular injections into the detrusor have been used to treat neurogenic detrusor overactivity. This chemical denervation is not permanent and the injection therapy must be repeated with regular intervals (approximately 4-6 months). The results have been promising, but little is known about long-term side effects [97-99]. Patient counselling regarding self-catheterisation before the treatment is necessary since bladder emptying failure is common.

### **Electrical stimulation**

Functional electrical stimulation with vaginal, rectal or external transducers has been used for many years to treat SUI, MUI and OAB symptoms. The basis for this kind of management is to activate the pelvic floor muscle fibres and to reinforce existing inhibitory reflexes from the vaginal and anal region. It can be used either as a single treatment or in combination with PFMT. Treatment protocols vary in terms of stimulation pulse frequency, intensity and duration depending on the type of incontinence and equipment used. When treating urgency symptoms the aim of the treatment is to activate reflex mechanisms that have an inhibitory effect on the bladder. Experimental studies have indicated that frequencies of 5-10 Hz are optimal while intensity should be close to the maximum that the patient can tolerate. The stimulation is given in 20-minute sessions, one to several times a week for five to six weeks. When SUI is to be treated the aim is to activate the slow as well as the fast twitch fibres in the pelvic floor musculature. This requires a higher frequency, around 50 Hz, lower intensity and a longer stimulation period (8-14 hours every night or day for three to four months). A similar kind of long-term treatment can sometimes also be offered to treat OAB. The best results of functional electrical stimulation have been demonstrated when treating urgency symptoms [53, 100-102] but it has also been questioned whether the short-term treatment is really cost-effective as a single treatment in routine practice due to

poor results in the long term [103].

Voiding dysfunctions that are refractory to conservative treatment, particularly severe UUI, urinary frequency and idiopathic non-obstructive retention can also be treated by sacral neuromodulation, often referred to as sacral nerve stimulation. This implies direct stimulation of sacral nerve roots at the level of S3 or S4 by permanently implanted electrodes. There are arguments that the stimulation operates through the afferent nerves all the way up to the level of the cortex cerebri, like in peripheral electrostimulating methods, but the exact mode of action remains to be elucidated [104]. The method is safe, but expensive and should be reserved for selective cases [105].

### **Surgical treatment**

First-line treatment for female SUI is usually conservative. In cases refractory to conservative measures, surgery is generally advocated. Many surgical procedures have been described over the last century. Based on the pathophysiological theories presented earlier, the general surgical approaches for the correction of female SUI today are: correction of urethral hypermobility, enhancing or strengthening the urethral support or strengthening the intrinsic sphincter mechanism.

#### **1) Correction of urethral hypermobility**

Procedures to suspend and stabilise the bladder neck and proximal urethra in a high retropubic position, thereby prevent-

ing their descent during periods of increased intra-abdominal pressure, include pubovaginal sling procedures, vesico-urethral suspensions (e.g. Marschall-Marchetti-Krantz, Lapedes) and abdominovaginal colposuspension techniques (e.g. Burch). The Burch procedure [9], in which the anterior vaginal wall is sutured to Cooper's ligament bilaterally, is by many considered as "the golden standard" for the correction of female SUI. The procedure can be performed as an open or laparoscopic operation with similarly good results [106]. Needle suspensions of the bladder neck, such as the Stamey method, are minimal-invasive, abdominovaginal techniques in which the bladder neck is sutured to the abdominal musculature or rectus fascia by the use of specially designed long needles [10, 107, 108]. Most needle suspensions are performed under endoscopic control. As for the Stamey suspension, the initial results of this procedure were promising, but did not always seem to be maintained at long-term follow-up. Reports on long-term results are, however, somewhat conflicting [109-112].

#### **2) Strengthening the urethral support**

Following the integral theory and the hammock hypothesis, modern surgical therapy of female SUI is focused on providing additional support at the mid-urethra to restore continence (e.g. TVT or TOT). In the TVT-procedure, a polypropylene sling is placed beneath the mid-urethra in a tension-free manner, through a retropubic route, using specially designed troacars. The method is minimal-invasive

and several publications have reported on its simplicity, safety and efficacy [113-116]. However, in order to avoid the risk related to the blind passage of troacars through the retropubic space, a transobturator route to sling placement has been developed (TOT) [117]. The TOT-sling passes through the obturator foramina and beneath the mid-urethra, thus preserving the principle of mid-urethral support while avoiding the potential risks of TVT-placement. The TOT method is theoretically safer, with less risk of serious complications such as bladder perforation and injury to the bowel and major blood vessels. At present, the published experience from RCT's shows no significant differences in cure rate or complications rate between the two techniques [118-120].

Although mid-urethral sling procedures are effective and generally associated with less morbidity than colposuspension and pubovaginal slings, they have potential disadvantages. These are mostly related to the blind passage of needles and troacars through body tissues, postoperative voiding dysfunction and complications of using a synthetic sling material [116, 121-124].

### **3) Strengthening the intrinsic sphincter mechanism**

Surgical techniques to support a damaged sphincter mechanism comprise pubovaginal sling procedures including TVT [125], periurethral injections of a bulking agent [126] or implantation of an artificial

sphincter [127].

A sling procedure implies the placement of a sling around the urethra through an incision in the abdominal wall on either side. Biological or artificial sling materials can be used. Pubovaginal slings enhance the bladder outlet resistance through two mechanisms. During an increase in the intrabdominal pressure the sling is drawn upwards and thereby increases the intraurethral pressure (active mechanism). The sling also supports the urethra and the bladder neck, thus increasing the passive resistance. Common complications of the sling procedures are voiding difficulties including urinary retention and, for artificial slings, erosion into the urethra or rejection of the graft [128-130].

Periurethral injection of various expansion substances is a minimal-invasive option to treat ISD by creating an artificial cushioning around the urethra. Several compounds have been tried for this purpose, e.g. Teflon, silicone, collagen, autologous fat and dextranomers in hyaluronan (DiHA). Teflon and silicone both have the disadvantage of possible distant migration, collagen may cause allergy and is rapidly degraded and injection of autologous fat may cause fat-embolism. DiHA seems to be a more favourable substance, but blind injection by the use of an implanter has been associated to the development of sterile abscesses. Cure rates of around 50% using periurethral injections have been reported [126, 131-135]. Considering the difficulty

in treating sphincter insufficiency, especially iatrogenic, an attempt with injection therapy may be justified.

The artificial urinary sphincter is a mechanical device applied around the urethra, which compensates for urethral sphincter insufficiency by compressing the urethra. The equipment consists of a silicone inflatable cuff positioned around the urethra, a pressure-regulating balloon placed in the abdominal cavity and a pump placed in the labium majus in women or in the scrotum in men. The patient regulates the opening of the sphincter during micturition by squeezing the pump, which in turn decompresses the urethral cuff. The success rate is high, but the procedure is more risky in women and the equipment is expensive. Malfunction over time is common [127, 136]. Implantation of an artificial sphincter should thus be considered a last resort procedure.

### **Major reconstructive surgery for refractory OAB**

Surgical management is generally not first-line treatment for UUI. Nevertheless, some patients with mixed incontinence may benefit from a conventional

incontinence operation [51] in accordance with the integral theory.

In severe cases of urge urinary incontinence, refractory to conservative measures, a clam cystoplasty might lead to symptom resolution [137, 138]. This is a procedure in which the bladder is split transversally in two halves down to the trigone. Between them, an antimesenterically opened section of the small intestine is interponated. In this way, dysfunctional detrusor contractions are damped. The procedure increases bladder capacity and reduces intravesical pressure upon detrusor contraction by neutralisation of the pressure wave. Bladder emptying can, however, be unsatisfactory and clean intermittent self-catheterisation is necessary in approximately one third of the cases postoperatively. Other common side effects are increased bowel frequency, vitamin B12-deficiency and sporadic urinary tract infections. For very severe cases, in which it is not possible to achieve an acceptable function via reconstruction of the lower urinary tract, a urinary diversion may sometimes be the only remaining option.





## AIMS OF THE STUDY

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The overall aims of this thesis were to describe the prevalence and natural course of different LUTS in women, to assess possible changes in the prevalence of various LUTS over time, and to evaluate potential genetic influence on the prevalence of LUTS.

### **SPECIFIC AIMS:**

- To describe the natural course (prevalence, progression and remission) of UI, OAB and other LUTS in women through a population-based longitudinal study.
- To assess possible time-trends regarding the prevalence of various LUTS, health care seeking and treatment due to UI in women.
- To estimate the prevalence of UI, OAB and other LUTS in a large population of Swedish twins.
- To assess the relative contribution of genetic and environmental factors for the occurrence of LUTS in women.
- To evaluate long-term results of the Stamey abdominovaginal colposuspension for the correction of female stress urinary incontinence.



## METHODS

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In 1991, a population based survey of UI was conducted in Gothenburg, Sweden [17]. Every fourth woman (n=2911) from the total female population aged  $\geq 20$  years, resident in the Central District of Gothenburg, was randomly selected from the Swedish Population Register and invited by letter to complete a questionnaire regarding UI and other LUTS, e.g. frequency, urgency and nocturia (Appendix 1). The women's quality of life (QoL) was assessed using a visual analogue scale. Medication being taken at the time was recorded, as was reproductive history and demographic parameters considered to be relevant. Validation of the questionnaire, including a detailed medical history and examination, was made in 1991 in a sub-sample of women (n=140) complaining of UI, and UI was confirmed in 98%.

In *Paper I*, the participants from 1991 who were still alive and available in the Swedish Population Register in 2007 (n=1408) were asked by letter to complete a similar questionnaire as in 1991. If no reply was received follow-up letters were mailed after approximately one and three months.

In *Paper II*, a new group of 3158 women aged 20 years or above (every fourth), resident in the same urban district in 2007, was randomly selected from the Swedish Population Register and was invited to complete the same postal questionnaire. Follow-up letters were mailed after approximately two and three months to

those who did not answer the first invitation.

We (re-)assessed the data on UI, OAB and other LUTS from 1991 and the data obtained in 2007 according to the current definitions approved by the International Continence Society (ICS) 2002. In *Paper I* longitudinal comparisons of the data from the same women participating in the study in 1991 and 2007 was made. In *Paper II* comparisons between the two cross-sectional samples were performed.

*Paper III* is a national, population-based, cross-sectional survey of UI, OAB and other LUTS in a cohort of Swedish twins born in 1959-1985 (n=42 582) identified through the Swedish Twin Register (STR). The twins were contacted by letter in 2005 and invited to participate in a web-based survey in order to screen for common complex diseases and common exposures. Those not responding to the web questionnaire were phoned and offered the possibility of answering the survey through a telephone interview. The questionnaire comprised a section of questions relating to lower urinary tract function. Prevalence rates of UI, OAB, nocturia and frequency were determined according to the ICS definitions. Twin similarity and heritability of these symptoms were estimated in female twins.

*Paper IV* is a retrospective study in which 24 out of 37 women consecutively operated on at the Dept. of Urology, Sahlgrenska University Hospital, with the

Stamey needle colposuspension method for the treatment of SUI, between October 1992 and March 1999, were followed up.

*The inclusion criteria were:*

1. Preoperatively stable detrusor
2. Preoperatively normal filling-cystometry
3. Preoperatively normal urethroscopy
4. Preoperatively objectively confirmed urinary leakage on a standardised quantification test

Women were only excluded if the above criteria were not fulfilled or if information

on any of these preoperative investigations was missing. All patients had gone through a standardised surgical procedure and had been subjectively evaluated after 6 months by the surgeon. Long-term follow up was performed at a minimum of 24 months postoperatively. The patients were requested to complete a questionnaire with questions about UI, comorbidities, complications and satisfaction of the Stamey operation during a personal (or a telephone) interview (Appendix 4). They were also asked to undergo a filling cystometry and a new standardised quantification test.

# METHODOLOGICAL CONSIDERATIONS

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## Ethics

The study protocol of *Papers I, II and IV* was approved by the Research Ethics Committee at Sahlgrenska Academy, Gothenburg University, Sweden. *Paper III* was approved by the Research Ethics Committee at Karolinska Institute, Stockholm, Sweden.

## The study populations

*Paper I:* Originally randomly selected, 1081 women who participated in a population-based survey of UI in the central district of Gothenburg in 1991.

*Paper II:* Randomly selected samples of 2248 and 2402 women aged 20 years or above resident in the central district of Gothenburg in 1991 and 2007, respectively. The mean age in 1991 was  $48.1 \pm 20.4$ , range 20-98 years and in 2007  $46.2 \pm 20.0$ , range 19-101 years.

*Paper III:* 10 184 male and 12 850 female twins, aged 20-46 years, from a national population-based cohort of twins.

*Paper IV:* 24 of the 37 women, operated on with the Stamey method during the period in question, were included in the follow-up. Seven women were excluded since pre-operative standard urodynamics and/or a standardised quantification test were not retrieved. In addition, one

woman was excluded because of preoperatively revealed detrusor over-activity. Of the remaining women, six were either dead, unavailable or did not agree to participate. Mean age at the time of the operation was 54.7 years (range 34-80 years).

## The definitions

In *Papers I-III* the definitions established by the ICS 2002 [38] were used with one exception. Frequency was assessed in 1991 as the number of daytime micturitions, irrespective of the women's subjective perception, and thus it was not possible to compare 'increased daytime frequency' in *Papers I and II* according to the current ICS definition. The mean number of daytime micturitions and the percentage of women reporting eight or more micturitions per day were compared in 1991 and 2007. In *Paper III*, the above case definitions of frequency were reported in addition to the ICS definition of frequency.

Nocturia has previously been shown to be the most prevalent LUTS, occurring in about 50 per cent of all men and women [18]. In addition to the ICS definition of nocturia (one or more episodes per night), we also assessed nocturia defined as two or more micturitions per night (*Papers I-III*).

UI was defined as “any involuntary leakage of urine” according to the 2002 ICS definition. The standardisation sub-committee of the ICS also recommends that UI in each circumstance should be further described according to type, frequency and severity [38]. UI symptoms in *Papers I and II* were grouped according to how frequently they occurred, i.e. daily, 2-3/week, 1/week and 1/month. In the analyses in *Paper I*, we compared the women reporting at least weekly urinary loss to those with symptoms occurring some time per month in order to identify the women who were most likely to be bothered by their symptoms, as suggested by Møller *et al.* [21]. Similar answer alternatives, to classify the severity of urinary leakage, were also provided in the questionnaires of *Papers III and IV*. Yet, from an individual’s perspective, substantial infrequent wetting might be as bothersome as a few drops every day.

Participants reporting UI were classified as having stress urinary incontinence (SUI) if involuntary leakage occurred during effort and urge urinary incontinence (UUI) if loss of urine was preceded by urgency or uncontrollable voiding with little or no warning. Participants reporting both SUI and UUI symptoms were classified as having MUI. In *Papers I and II* there was a minor change in the answer alternatives to classify incontinence type between 1991 and 2007 which might have influenced the possibility to make adequate comparisons (Appendix 2).

According to the ICS definition of OAB the only obligatory symptom is urgency. However, it often occurs in association with frequency, nocturia and/or urinary incontinence. OAB in *Papers I-III* was defined as a positive answer to the question on urinary urgency, with (OAB wet) or without (OAB dry) subsequent urinary leakage. The terms OAB wet and OAB dry have certain disadvantages and they are not official ICS terminology. Nevertheless, the literature in recent years has been generously endowed with these terms. We could have used the term OAB with incontinence and OAB without incontinence. For study purposes UUI was not separated from SUI in these specific analyses.

In *Paper IV* stress urinary incontinence is referred to as Genuine Stress urinary Incontinence (GSI), which implies urinary leakages on stress provocation without urodynamically demonstrable detrusor contractions. Some of the patients in this study, in fact, had a preoperative history of mixed urinary incontinence with a dominating stress component. However, all had stable detrusors without objectively confirmed urge incontinence upon filling cystometry or on provocation test. A description of pre- and postoperative urge symptoms in the study group is provided in the results section (Table 6).

## The questionnaires

A questionnaire is an objective method designed to measure subjective phenomena such as symptoms and quality of life (QoL). The reliability and validity of the questionnaire is thus important and should be scientifically verified. Reliability includes factors such as internal consistency and test-retest reliability whereas validity includes

content, construct and criterion validity. Based on the degree of verification, the International Consultation on Incontinence (ICI) has recommended certain questionnaires, for the use in research and clinical practice, when evaluating LUTS and the impact of LUTS on QoL [139]. The highly recommended (Grade A) questionnaires are presented in Table 2 [140-152].

**Table 2.** ICI highly recommended (Grade A) questionnaires for the assessment of UI alone or in the presence of other LUTS, including OAB.

<b>Combined symptoms and QoL impact of UI</b>	
Men and women	ICIQ [141]
Women	Bristol Female LUTS-SF [142] SUIQQ [147]
<b>Combined symptoms and QoL impact of OAB</b>	
Men and women	OAB-q [143]
<b>Symptoms of UI (LUTS)</b>	
Women	Urogenital Distress Inventory [149] UDI-6 [152] Incontinence Severity Index [148] BFLUTS [145]
<b>QoL impact of UI</b>	
Men and women	Quality of life in persons with UI (I-QOL) [144] SEAPI-QMM [151]
Women	Kings Health Questionnaire (KHQ) [146] Incontinence Impact Questionnaire (IIQ) [149] IIQ-7 [152] Urinary incontinence Severity Score (UISS) [150] Contlife [140]

A shortcoming of *Papers I-II and IV* is that none of these studies was based on validated internationally accepted questionnaires.

In *Papers I and II* the questionnaire of 2007 was identical to that of 1991 apart from four minor modifications as specified in Appendix 1 and 2. Disease specific validated questionnaires were rare in the early 90<sup>s</sup>. The used questionnaire was constructed and validated in 1991, but not according to the above principles. Minor modifications was necessary in 2007 due to the long time interval between the surveys, but major modifications or the use of a modern validated questionnaire in 2007 would have precluded adequate comparisons between 1991 and 2007.

The entire questionnaire used in *Paper III* contained approximately 1300 questions, in 34 sections relating to numerous health conditions, dietary information and quality of life, frequency of exercising and social factors [153]. The questionnaire was constructed using a branching format, meaning that the participants were only asked follow-up questions if they responded positively to key initial questions. The section on lower urinary tract function consisted of four introductory questions, nine questions on urinary incontinence, six questions on micturition frequency and five questions on urinary urgency, adopted from a validated epidemiological survey on female incontinence (Appendix 3) [16]. Extensive questionnaires generally lower the degree of participation. The average

time to answer the questionnaire in *Paper III* was 80-85 minutes, and in this context the response rate of almost 60% must be considered very good.

The lack of a validated questionnaire in *Paper IV* may, at least partly, be weighed up by the associated personal interview and the urodynamic assessment on follow-up. The interviews, in this study, were performed by the same interviewer who had no previous relation to the patients.

## Visual Analogue Scale

The Visual Analogue Scale (VAS) was first introduced to measure pain [154]. The scale consists of a 100 mm line where the two end-points represent extremes of the variable and the subject will choose a point representing her actual status. In the context of urinary incontinence, the VAS-scale has previously been used as diagnostic tool to discriminate detrusor instability from SUI [155, 156] and to assess subjective distress related to UI [157]. Stach-Lempinen *et al.* compared the VAS instrument to other QoL-instruments for urinary incontinent women and concluded that it is valid, reproducible and responsive to treatment of UI in women [158].

In *Papers I and II* the women were requested to rate their opinion of their QoL by a mark on a 100 mm VAS-scale. One extremity of the scale represented healthy/feeling good and the other extremity on the scale represented ill/



feeling bad. VAS scores were obtained by measuring the distance from zero to the mark. When rating their VAS, the women were not specifically asked to relate their QoL to possible UI/LUTS and thus the impact of such symptoms on QoL could not be assessed by using this scale only. The women were, however, also asked if they considered their incontinence to cause limitations in their social life.

## The Swedish Twin Registry

The Swedish Twin Registry was first established in the 1950<sup>s</sup> to study the effect of smoking and alcohol consumption on cancer and cardiovascular disease while controlling for genetic predisposition. It now includes more than 170 000 twins in three different cohorts (cohorts of twins born 1886-1925, 1926-1958 and 1959-1990) and it is a unique resource for the evaluation of numerous illnesses. Data collection through questionnaires has previously been made from the two older cohorts, and was completed in 2005 from the youngest cohort. Part of the data obtained from this cohort constitutes the base of *Paper III*. Information on zygosity is essential for twin studies. The methods used for assigning zygosity in the STR have been validated with DNA as having 98% accuracy [153]. The data in the STR can be used for several purposes; to study the relative importance of genetic and environmental influences on a phenotype (quantitative genetic analyses and heritability estimation), to investigate the importance of a presumed risk factor after

controlling for genetic and early environmental effects (co-twin control analyses) and finally to perform conventional epidemiological studies. The first and the last principles were addressed in *Paper III*.

## The Stamey Procedure

The Stamey bladder neck suspension, evaluated in *Paper IV*, was performed as a standard procedure that was strictly adhered to in all cases [10]. All patients were operated on by the same surgeon. The anterior vaginal wall was incised longitudinally and separated from the urethra by careful dissection. Two small transverse incisions were made in the skin just above the symphysis pubis to the left and right of the midline, and bluntly dissected down to the rectus abdominis. A Stamey needle was passed through one of the small suprapubic incisions down to the vagina, and was threaded to position a 2/0 prolene or dermalone suture close to the bladder neck at that side. The needle was passed again about 1 cm laterally and used to pick up the other end of the same suture, forming a loop. A 5 mm Dacron tube was left over the suture to add resistance to the tissue around the bladder neck. This manoeuvre was repeated on the other side. When both sutures were positioned satisfactorily, the anterior vaginal wall was closed, the sutures were individually tied above the anterior sheath of the rectus abdominis muscle and the skin was closed. Care was taken using repeat endoscopic control to verify that the

slung was correctly positioned and that there had been no perforation into the bladder.

but the activity did not cause any urinary leakage.

## Standardised quantification test

In *Paper IV* a standardised quantification test was performed as described on page 17 to objectify any urinary leakage. Four of the five activities used in this test reveal stress urinary leakage while one (washing hands under running cold water) is more likely to provoke urgency or urgency incontinence. The patients' subjective perception of the provoking action should thus be noted during the test. In our material, one patient experienced a sensation of urgency during hand-washing,

## Statistical methods

An overview of the statistical methods used in this thesis is presented in Table 3.

Descriptive data are presented as number of individuals, mean, range, standard deviation and proportions. Prevalence was calculated as a percentage of the eligible responders (*Papers I-III*). Incidence was calculated as the percentage of those who were not cases at baseline becoming incident cases on follow-up. Remission was calculated as the percentage of cases at baseline ceasing to be cases on follow-up (*Paper I*).

**Table 3.** Statistical methods used in papers I-IV.

Methods	I	II	III	IV
<i>Descriptive statistics</i>				
Mean	x	x	x	x
Range	x	x	x	x
Frequencies (%)	x	x	x	x
Probandwise concordance rates			x	
Tetrachoric correlations			x	
<i>Analytical statistics</i>				
One sample t-test	x			
Duncan's multiple range test	x			
Wilcoxon rank sum test		x		x
Fisher's exact test		x		
Anova		x		
Generalised estimating equations			x	
Quantitative genetic analysis (ACE-model)			x	

One sample t-test was used to compare normally distributed paired data (*Paper I*). The non-parametric Wilcoxon rank sum test was used for paired comparisons where data were not considered to be normally distributed (*Papers II and IV*). Fishers exact test was used for dichotomous variables (*Papers II*) and generalised estimating equations were used for dichotomous variables to account for correlations within twin pairs (*Paper III*). All tests were two-sided and  $p < 0.05$  was considered as statistically significant. Analysis of variance with Duncan's multiple range test for post hoc comparisons was used in the analysis of possible differences between QoL-assessments in *Paper I*.

In *Paper III*, twin similarity was assessed using probandwise concordance rates and tetrachoric correlations, for monozygotic (MZ) and dizygotic (DZ) female twin pairs, respectively. By comparing MZ twins with identical genotype and DZ who on average share 50% of their segregating genes, conclusions can be drawn about the relative importance of genetic and environmental factors. A genetic influence is suggested if MZ twin are more concordant for the disease than DZ twins, whereas evidence for environmental effects comes from MZ twins who are discordant for the disease. Heritability estimates the degree of twin similarity, that is explained by genetic effects, whereas shared and non-shared environmental effects include all nongenetic influences. Quantitative genetic analyses for estimates of variance

components (genetic, shared and non-shared environment) and their confidence intervals were obtained by structural equation modelling (ACE-model).

In *Papers I and II* it might have been valuable to include confidence intervals as a measure of uncertainty, since it allows the reader to judge whether the results are clinically important or not. However, given the large number of observations in these studies, the confidence limits can be expected to be reasonably narrow.

When reporting the results of the post-operative standardised quantification test in *Paper IV* it might have been informative to include the median as a measure of location in addition to the mean. In this case, the post-operative values varied between 0-165 g and the mean was 19 g, while the median would have been zero.

Statistical analyses were performed using the SAS 9.1 statistical software package, SAS Institute Inc, Cary, NC, USA (*Papers I-III*), MX, a structural equation-based program (*Paper III*) and the StatView 5.0, Abacus Concepts Inc., Berkeley, CA, USA (*Paper IV*).



## RESULTS

Table 4 shows the prevalence estimates of various LUTS in *Papers II and III* compared to prevalence estimates in a number of other large population-based surveys [16, 18, 20, 21, 26, 32].

**Table 4.** The prevalence of UI and other LUTS in women; a comparison of the prevalence estimates in Papers II-III and estimates of other large population-based surveys.

	Irwin (EPIC) [16]	McGrother [32]	Møller [21]	Hannestad (Epincont)	Hunskaar [26]	Stewart (NOBLE)	Paper II 1991	Paper II 2007	Paper III
Age (yrs)	≥18	≥40	40-60	≥20	≥18	≥18	≥20	≥20	20-46
Participants (N)	*)	50 002	3208	27 936	17 080	5204	2248	2402	12 850
UI (ICS) (%)	13		16	25	35		17	18	7
Nocturia (ICS) (%)	54	40					42	47	61
Nocturia ≥2/night (%)	24	14					31	29	23
Frequency (ICS) (%)	7								18
Frequency ≥8/24 h (%)		36					15	20	27
OAB (urgency) (%)	13	7-8				17	18	18	9
OAB dry (%)	7					7	11	8	7
OAB wet (%)	6					9	7	10	2

\*) Number of women not specified. Total number of participants (men + women) 19 165.

## Paper I

The questionnaire was returned by 1081 of the 1408 women still available for re-assessment (Response rate, 77%).

### Urinary incontinence

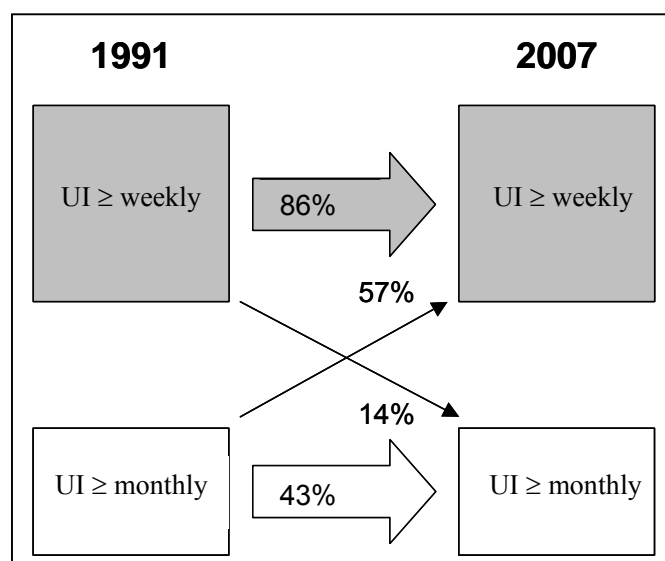
The overall prevalence of urinary incontinence increased from 15% in 1991 to 28% in 2007 ( $p < 0.001$ ). The most pronounced increase (18%,  $p < 0.001$ ) occurred among women who were 20-34 years at the primary assessment. The incidence and regression of urinary incontinence within the same women between 1991 and 2007 were 21% and 34%, respectively. Among women with persistent UI, only 14% of the women with incontinence occurring more than weekly in 1991 reported an amelioration of their symptoms in 2007, whereas 57% of those who leaked some time per month in 1991 reported at least weekly

incontinence in the 2007 assessment (Figure 2).

Thirteen per cent of all women reported having consulted a doctor about their incontinence in 1991 as compared to 30% in 2007 ( $p < 0.001$ ). Of the women who reported resolution of UI in 2007 ( $n = 51$ ), fourteen (27%) stated that they had sought health care due to incontinence and nine (18%) had undergone an incontinence operation.

### Urgency and nocturia

The overall prevalence of urgency and nocturia (ICS definition) in the same women assessed in 1991 and 2007 increased by 9% and 20% ( $p < 0.001$ ), respectively. The overall incidence and remission rates of urgency were 20% and 43%. The progression from 0-1 micturiations/night to 2 or more times was 36% and the corresponding regression was 38%.



**Figure 2.** Progression and regression of UI frequency in the same women assessed in 1991 and 2007.

## OAB

The overall percentage of women reporting OAB symptoms increased from 17% in 1991 to 26% in 2007 ( $p < 0.001$ ).

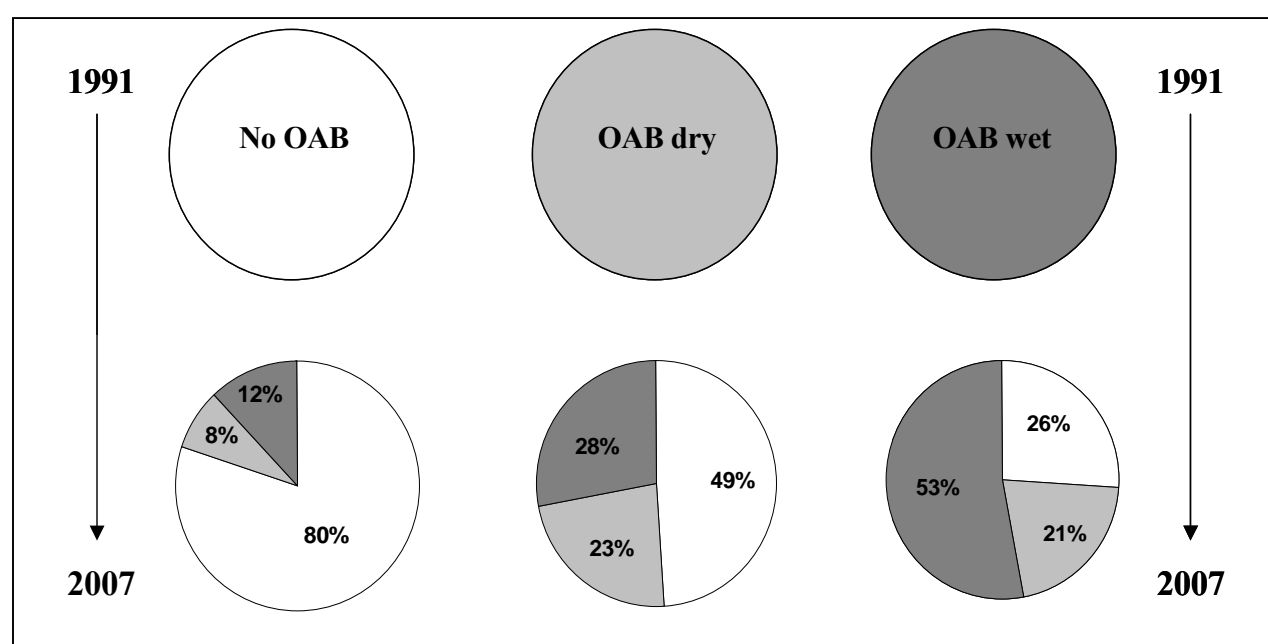
There was no significant change in the prevalence of OAB dry (11% and 10%, respectively) but the proportion of women reporting OAB wet increased from 6% to 16% ( $p < 0.001$ ) Figure 3 describes the progression or regression of OAB symptoms within the same women between 1991 and 2007.

## Micturition frequency

There was a minor increase in the mean number of daytime micturitions between 1991 and 2007 ( $5.5 \pm 1.9$  in 1991 to  $5.8 \pm 2.3$  in 2007 ( $p < 0.001$ )). The proportion of women reporting daytime frequency of eight or more times per day increased by 3% from 1991 to 2007 ( $p < 0.05$ ).

## Quality of life

The general prevalence of co-morbidities increased significantly over the years in all age groups. Fifty-one per cent of the women were on any medication in 2007 as compared to 20% in 1991 ( $p < 0.001$ ). Reported quality of life, as measured by the VAS scale, deteriorated with increasing age between the two assessment points (VAS 16 vs 24,  $p < 0.001$ ). The reported quality of life did, however, not differ between women who were continent in 1991 and remained continent upon follow-up as compared to women with incident incontinence. Neither did we observe any difference in the self-reported quality of life change between 1991 and 2007 in women who denied OAB symptoms on both occasions as compared to women with new onset OAB dry or wet.



**Figure 3.** Progression and regression of OAB in the same women in 1991 and 2007.

## ***Paper II***

In 1991 and 2007, the questionnaire was completed and returned by 77% and 76% of the invited women, respectively. No woman completed both surveys. There were no major differences between respondents and non-respondents in the two groups with regard to age, civil status and nationality. The cohort of women in 2007 comprised a greater percentage of younger women than in 1991 ( $48.1 \pm 20.4$ , range 20-98 years (1991),  $46.2 \pm 20.0$ , range 19-101 years (2007)). An Analysis of Variance (ANOVA) however showed that this disparity did not affect the results. The distribution of possible risk factors differed in some aspects between the cohorts. In 2007, the average BMI of the responders was greater than in 1991 (23.6 versus 22.5), there was a significantly lower proportion of smokers (14% versus 30%,  $p < 0.001$ ) and more women reported UI heredity than in 1991 (29% versus 16%,  $p < 0.001$ ). There was, however, no difference between 1991 and 2007 regarding parity, number of gynaecological operations and childhood enuresis in the two cohorts.

### **Urinary incontinence**

The proportion of women with UI did not differ significantly between the two assessments (17% and 18%, respectively). Apart from women aged 65-79 years who reported more urinary incontinence in 2007 than 1991 (33% vs 25%,  $p < 0.05$ ) there were, when stratifying for age, no significant differences between the

assessments in the other age groups. Neither was there any difference in the average frequency of leakage amongst incontinent women in the two cohorts. Daily leakage was, however, more common in 1991 (42% vs 33%,  $p < 0.05$ ), whereas urinary leakage 2-3 times per week was more common in 2007 (22% vs 15%,  $p < 0.05$ ).

### **Nocturia**

Nocturia (ICS definition) was extremely common at both assessments with a detectable difference (42% and 47% respectively,  $p < 0.001$ ). The greatest differences were observed in women younger than 65 years. About one third of the women reported two or more nocturnal micturitions in both 1991 and 2007 (31% and 29% respectively, NS).

### **Micturition frequency**

Daytime voiding frequency of eight or more times a day was reported by more women in 2007 than in 1991 (15% and 20% respectively,  $p < 0.001$ ). When grouped according to age, there were significant differences in women  $< 50$  years and in those aged  $\geq 80$  years.

### **Urgency and overactive bladder**

The overall prevalence of OAB/urgency was unchanged between 1991 and 2007 (18%). The prevalence of OAB dry decreased slightly (11% versus 8%,  $p < 0.01$ ) whereas the prevalence of OAB wet increased (7% vs 10%,  $p < 0.001$ )



between the two assessments. The most pronounced differences for OAB dry were seen in the youngest women. For OAB wet there was a trend towards more marked differences in all of the older groups but significant differences could only be detected in the upper middle-aged (50-64 years).

### **Help-seeking pattern/behaviour and quality of life**

The women were also asked if they had attended medical services for the treatment of UI. No overall difference in help-seeking was detected, but there was a trend towards increased help-seeking in older women in 2007 compared to 1991, with a significant difference in those aged 65-79 years (20% of the women 2007 vs 12% in 1991,  $p<0.01$ ). Physiotherapy had been provided more often in 2007, but there was no difference in the proportion of women having received drugs,

incontinence aids or surgical treatment. Interestingly, the proportion of women  $\geq 80$  years who had had surgery for UI had more than tripled in 2007 (24% vs 7%,  $p<0.05$ ), while the proportion of those  $\geq 80$  years who reported to have been prescribed drugs in 2007 was less than half of that in 1991 (19% vs 42%,  $p<0.05$ ).

In general, self-reported QoL was significantly better for women participating in 1991 than in 2007 (VAS 18 as compared to 23,  $p<0.01$ ). Incontinent women, as well as women with urgency, reported poorer QoL as compared to women without urinary symptoms in both cohorts. Thirteen per cent and 29% ( $p<0.001$ ) of the women with UI in 1991 and 2007, respectively, stated that the presence of urinary incontinence limited their social life. This trend was maintained throughout the age groups.

### Paper III

In total, 25 365 twins completed the questionnaire (response rate 59.6%).

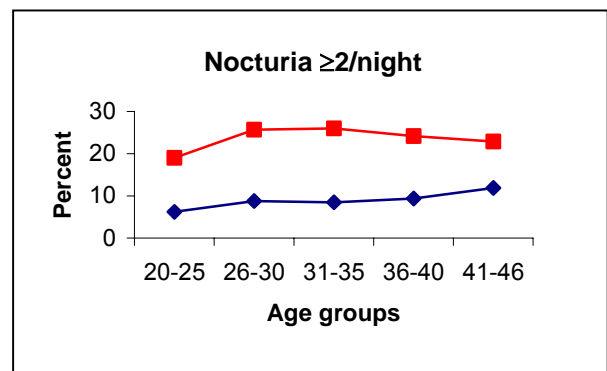
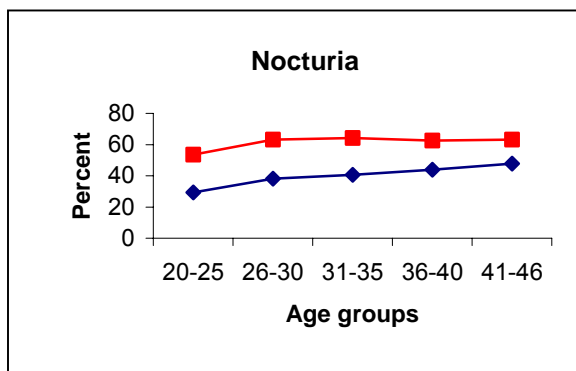
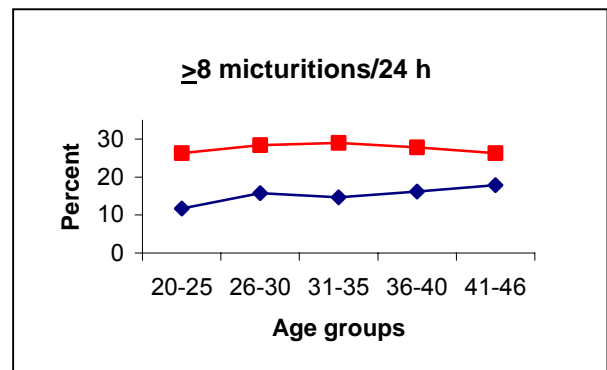
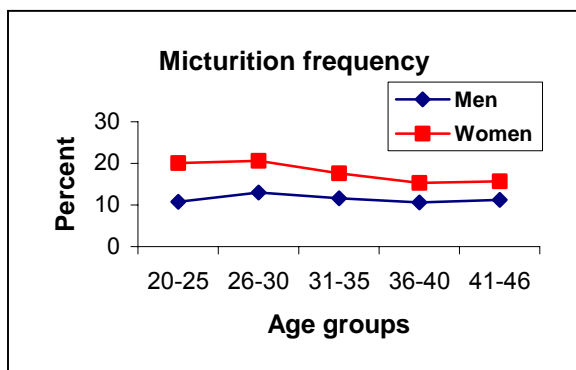
#### Prevalence of LUTS

Comparisons of the prevalence of LUTS in twins grouped according to age and gender are presented in Figures 4-11.

In this cohort, aged 20-46 years, the prevalence of various LUTS was in general more prevalent in women than in men (Figures 4-11). When comparing the age groups, the prevalence of OAB increased in male twins and nocturia increased in both male and female participants ( $p < 0.001$ ). There was no evident age-dependant change in frequency, defined according to the ICS definition in male twins while micturition frequency decreased with age in female

twins ( $p < 0.001$ ). In twins of both sexes, there was, however, an increase in micturition frequency in nominal terms (number of micturitions/24 hours) with increasing age and in the proportion of participants reporting frequency defined as  $\geq 8$  micturitions/24 hours ( $p < 0.001$ ). There was also an increase in the percentage number of individuals who reported  $\geq 2$  nocturnal micturitions and this was particularly apparent in male twins ( $p < 0.001$ ).

All types of UI were more prevalent in women than in men ( $p < 0.001$ ) and all subtypes increased with increasing age in women ( $p < 0.001$ ), but not in men. The most pronounced increase was an increase in the prevalence of SUI from 1.0% in women aged 20-25 years to 10.3% in women aged 41-46 years.



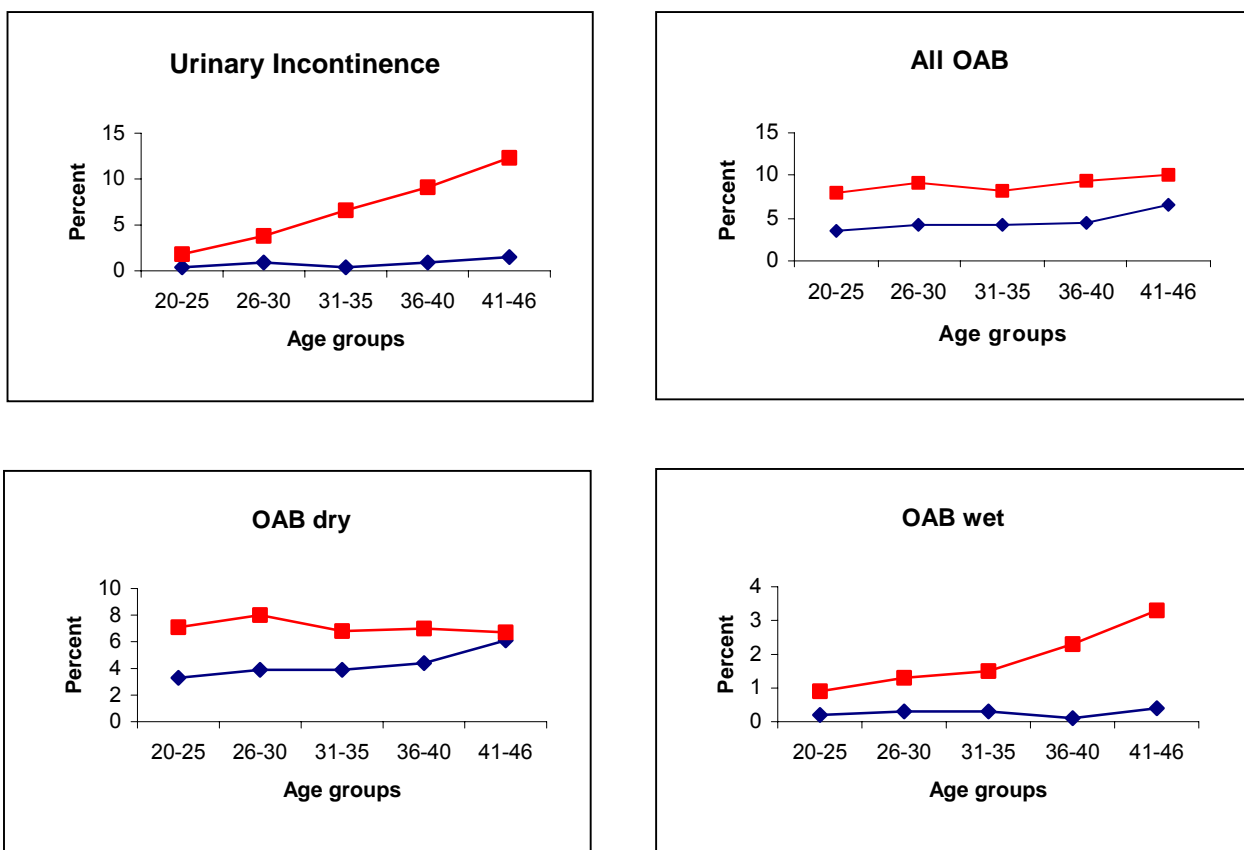
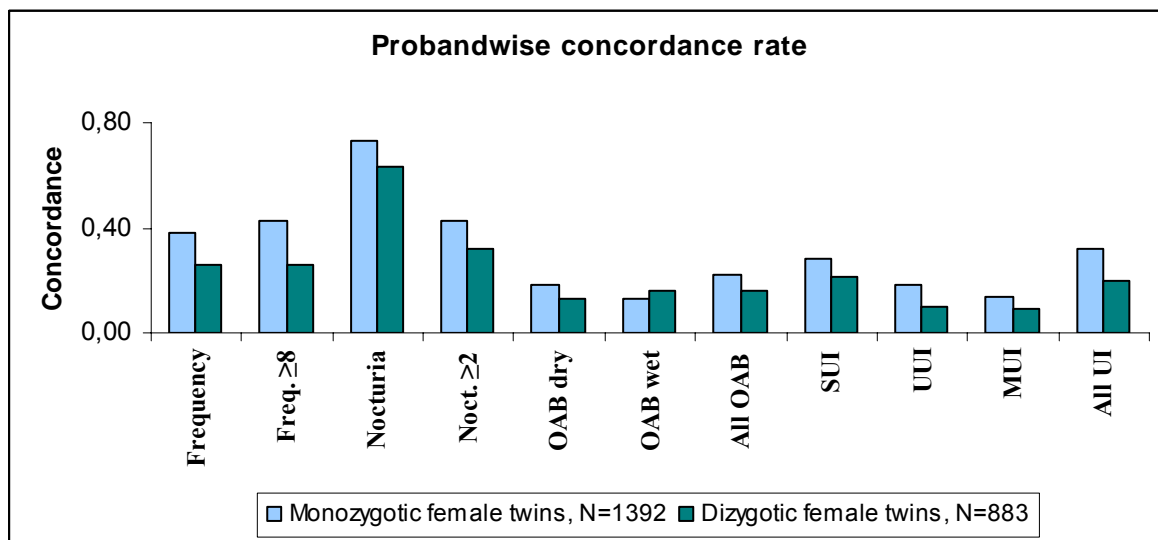


Figure 4-11. Prevalence of LUTS according to age and gender.

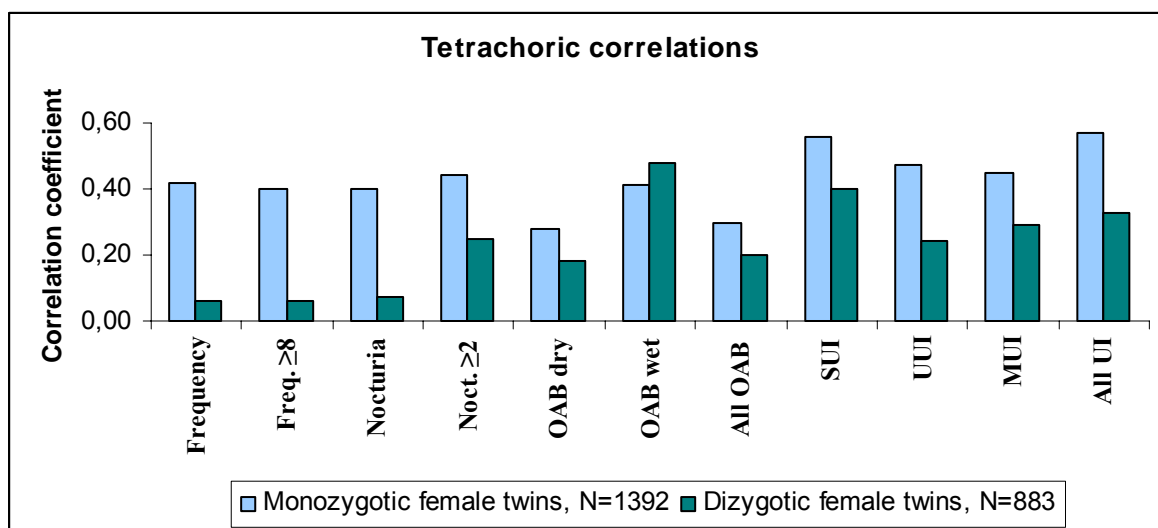
### Twin similarity and heritability

The prevalence of LUTS, in particular UI and OAB, was low in male twins and there were insufficient male cases to compute measures of similarity or heritability estimates in men. Thus, estimates are presented for women only. Thirteen hundred and ninety-two monozygotic (MZ) and 883 dizygotic (DZ) same sex female twin pairs with known zygosity

were identified. Comparisons of probandwise concordance rates and tetrachoric correlations according to zygosity are shown in Figures 12 and 13. With the exception of OAB wet, indicators of twin similarity were higher among monozygotic compared to dizygotic twins for frequency, nocturia, OAB (all), OAB dry and UI (all subtypes), which indicates genetic effects.



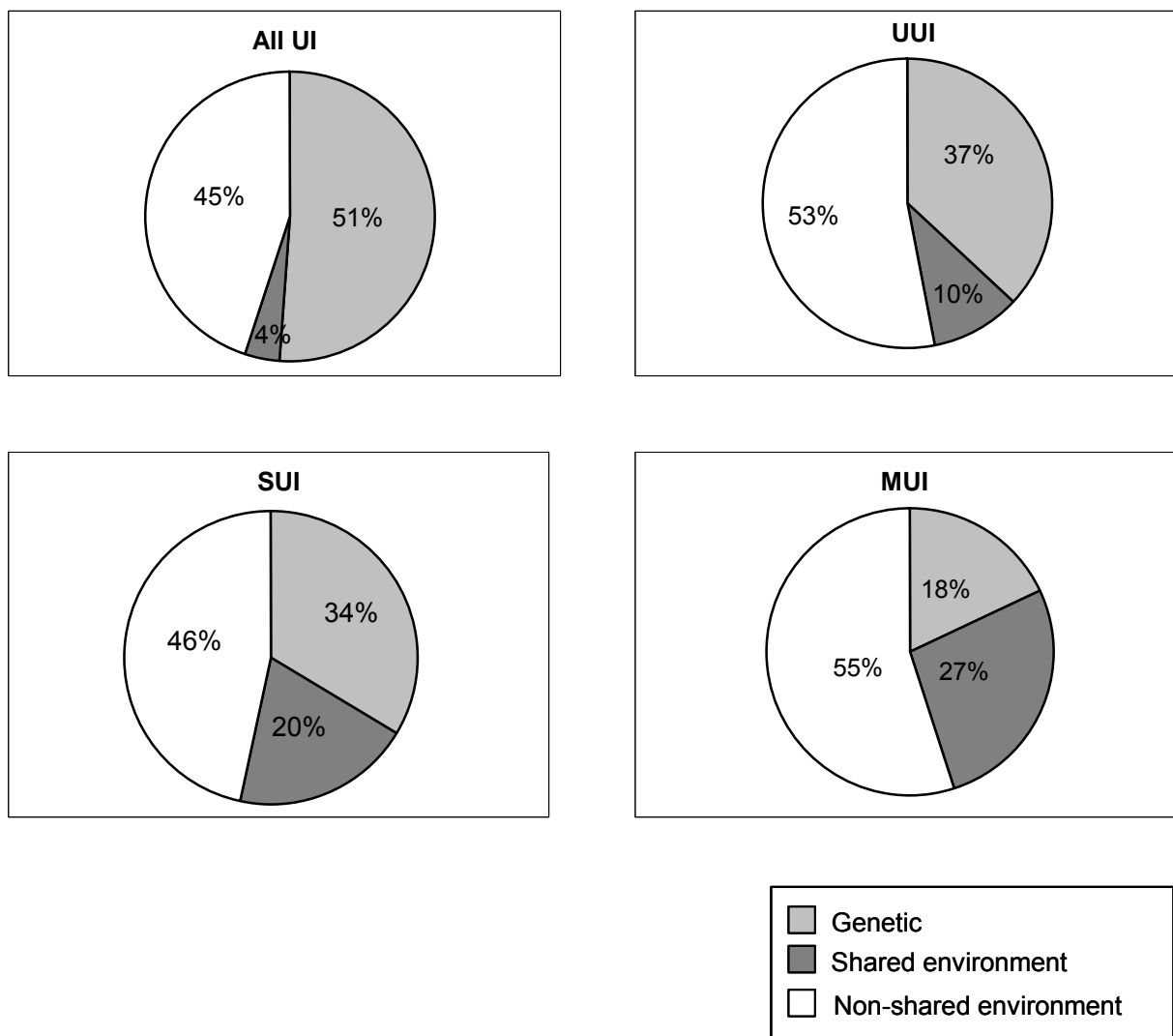
**Figure 12.** Probandwise concordance rates for LUTS in twins grouped according to zygosity.



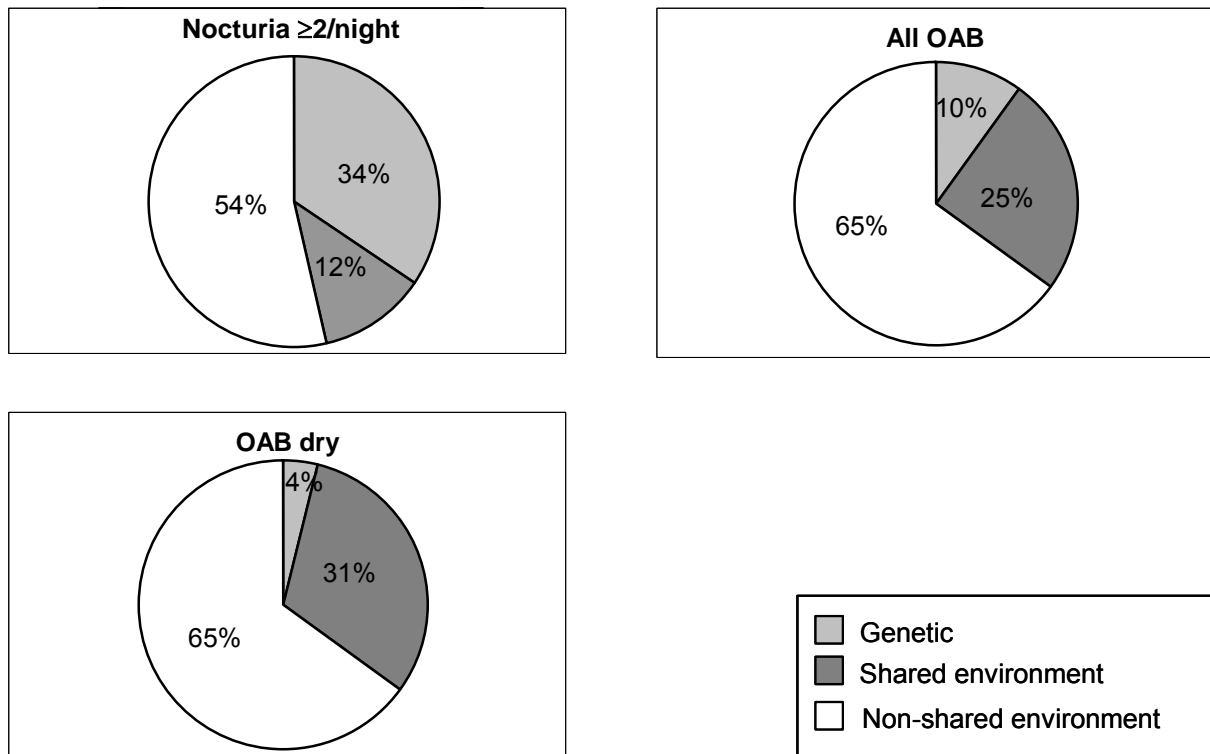
**Figure 13.** Tetrachoric correlations for LUTS in twins grouped according to zygosity.

Figures 14-20 illustrate the heritability estimates derived from the ACE-model quantitative genetic twin analysis. The strongest genetic effects were observed for symptoms involving UI and for nocturia whereas the lowest genetic effects were observed for isolated OAB where environmental effects were more

important. Non-shared environmental effects were seen in the range of 45-65% for the various conditions. For OAB dry shared environment accounted for nearly one third of the total variation and for SUI one fifth of the total variation for the disorder could be attributed to shared environment.



**Figur 14-17.** Estimates of genetic and environmental effects from the quantitative twin analysis - ACE model.



**Figur 18-20.** Estimates of genetic and environmental effects from the quantitative twin analysis - ACE model.

## ***Paper IV***

All 24 study subjects participated in the personal interview and completed the questionnaire. Eighteen also agreed to undergo a full-scale cystometry, 16 of whom completed a second standardised quantification test.

### **Short-term follow-up**

All participating women reported subjective short-term amelioration of their SUI. There were no severe postoperative complications, except in one case where a urethrovaginal fistula was suspected because of postoperative vaginal discharge and pain. Micturition cystourethrography was, however, performed during which no fistula could be observed, one of the Stamey sutures was removed and the patient's symptoms resolved. Fourteen patients developed transient urinary retention necessitating prolonged treatment with a suprapubic catheter for a mean of 29 days, range 7-60 days

### **Long-term follow-up**

Time to follow-up ranged from 28-100 months (mean 63 months). The results are described in Table 5. At long-term follow-up 10 women (42%) were subjectively dry, 4 were improved but not completely dry and 9 had experienced a lasting improvement for 12-84 months (mean 37 months). In total, 23/24 (96%) reported initial improvement. In one patient, the leakage was aggravated by a severe incapacity to hold urine at night but she no longer suffered from SUI. The mean

postoperative leakage, yielded by the standardised quantification test, was 19 g, to be compared with a mean preoperative leakage of 100 g ( $p < 0.01$ ). On long-term evaluation, 13, 7 and 4 women reported excellent, good and poor outcome, respectively. In our material, there was no re-operation because of recurring SUI. Seventeen patients stated that they would recommend the Stamey procedure to a friend or a close relative with similar symptoms (i.e. SUI).

There were no major long-term complications of the surgical procedure. A substantial percentage (38%), however, reported on urge/urge incontinence after surgery (Table 6). In one patient the urodynamic assessment revealed phasic detrusor instability.

**Table 5.** Treatment results of the Stamey procedure.

Patient No	Duration of follow-up (months)	Leakage (g)		Postop complications	Subjective result		Leakage severity at long time follow-up	Long term satisfaction	Long-term urgency (UUI)
		Preop	Postop		Short term	Long term (months)			
1	46	350	2	Transient retention	Dry	Improved (36)	Light	Good	UUI
2	63	34	18	none	Dry	Improved (48)	Severe	Good	UUI
3	58	130		*1	Dry	Improved (48)	Light	Excellent	
4	35	125	0	None	Urgency	Impaired	Severe	Poor	UUI
5	35	112		*2	Dry	Dry	None	Excellent	
6	53	60		Transient retention	Dry	Dry	None	Excellent	
7	47	235		*3	Urgency	Improved	Moderate	Poor	UUI
8	28	88	0	Transient retention	Dry	Dry	None	Excellent	
9	64	27	0	None	Urgency	Improved (24)	Light	Good	UUI
10	53	120		Transient retention	Dry	Improved	Light	Good	
11	77	86	1	*4	Urgency	Improved	Light	Good	UUI
12	68	50	165 (see comment)	Transient retention	Dry	Improved	None	Excellent	
13	65	323	0	None	Dry	Improved (60)	Light	Excellent	
14	38	120		Transient retention	Dry	Dry	None	Good	
15	85	87		Transient retention	Dry	Dry	None	Excellent	
16	81	69	94	None	Dry	Improved (12)	Light	Poor	
17	81	110	0	Transient retention	Dry	Dry (84)	Light	Excellent	UUI
18	100	50	2	None	Dry	Dry	None	Excellent	
19	75	34	0	None	Dry	Dry	None	Excellent	
20	61	32	0	Transient retention	Urgency	Dry	None	Excellent	
21	46	28		Haematuria	Dry	Dry	None	Excellent	
22	81	19	8	Transient retention	Dry	Improved (24)	Moderate	Poor	
23	92	56	0	Transient retention	Dry	Dry	None	Excellent	
24	88	171	13	Transient retention	Dry	Improved	Light	Good	Urgency (detrusor instability)

\*1 Transient retention, suture extraction, urinary tract infection

\*2 Fever, thrombophlebitis right arm

\*3 Transient retention, urge, suture extraction, urinary tract infection

\*4 Urge, tenderness vaginal suture right side, suspected urethra fistula

Comment: Examination of this patient demonstrated a severe leakage, but she strongly denied similar problems in her everyday life



**Table 6.** Description of urgency symptoms pre- and postoperatively.

<b>Pat Nr</b>	<b>Preoperatively</b>	<b>6 months postop</b>	<b>longterm follow-up</b>
1			Urge incontinence
2	Urgency		Urge incontinence
4		Urgency	Urge incontinence
7		Urgency	Urge incontinence
9	Mixed incontinence	Urgency	Urge incontinence
11	Mixed incontinence	Urgency	Urge incontinence
12	Mixed incontinence		
17	Mixed incontinence		Urge incontinence
20	Urgency	Urgency	Urgency
24			Urgency (detrusor instability)



## GENERAL DISCUSSION

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The studies presented in this thesis describe the prevalence and the natural history of LUTS in women of different age and at different periods of time. *Paper III*, comprising approximately 25 000 individuals, is one of the largest of its kind to report population-based prevalence rates of LUTS including OAB and UI in young and middle-aged adults. In addition, the study design, utilising a large national cohort of twins, permits an evaluation of the relative importance of genetic factors as well as shared and non-shared environmental factors for the occurrence of LUTS.

The estimated prevalence of the various LUTS in this thesis (*Papers I-III*) is consistent with previous studies [16, 18, 20, 21, 26, 32]. A problem when assessing and comparing the results of different studies is the use of different definitions. Since 1991, even internationally accepted definitions, such as the definition of UI by the International Continence Society (ICS), have changed and new terms, e.g. overactive bladder (OAB), have been introduced. We used the current definitions proposed by the ICS 2002 [38], with the exception of daytime frequency, and we re-assessed previously obtained data identically. The use of validated symptom-specific questionnaires would have been preferable, but would have reduced the reliability of the comparisons in *Papers I-II*.

The majority of women with LUTS suffer from storage symptoms, which include

increased daytime frequency, nocturia, urgency and UI. In this thesis, we have chosen to focus on these symptoms, being the most common, and thus fail to identify individuals with symptoms falling into the other two categories

*Paper I* showed a marked overall increase in the prevalence of UI, urgency, OAB and nocturia when the same women were assessed in 1991 and 2007. There was considerable progression, but also remission for most symptoms. Women with frequent incontinence were unlikely to experience an amelioration of their symptoms over time. In addition, more than half of the women with more infrequent leakage in 1991 seemed to have worsened when re-assessed in 2007. This suggests that, despite the relatively high figure of remission for UI in this study (34%), clinically relevant urinary leakage seldom heals itself.

Interestingly, in *Paper I*, the proportion of women with UI in similar age groups was higher in 2007 than in 1991, which speculatively may mirror a true increase in the prevalence of UI over time amongst women of similar age. This speculation was, however, not substantiated by the results of *Paper II*, in which two populations of women from the same district of the city of Gothenburg were assessed with an interval of 16 years. An increased prevalence of UI over time could only be detected in women aged 65-79 years.

*Papers I-III* corroborate previous work in that the prevalences of UI and other LUTS were generally shown to increase with increasing age [16, 18, 19]. There are several possible explanations for this age-related increase (eg neurological and cerebrovascular disorders, pelvic tumours and pelvic floor weakness). In *Paper I* the increase in urinary leakage was most pronounced in women who were 20-34 years at the time of the first assessment. *Paper III* showed a similar increase of UI between the age groups 20-25 and 41-46 years, the increase being most apparent for SUI. The result is not surprising since this age span corresponds to a woman's most fertile period and to parturition, especially the first delivery, which is a well-known risk factor for the development of UI, particularly of SUI. In *Paper I*, other symptoms related to the control of bladder function showed a more pronounced increase later in life, probably reflecting the importance of other aetiologic mechanisms such as subtle neurological impairment, cerebrovascular disorders, and other comorbidities.

Presently, there are only a few other studies describing the progression and remission of UI and other LUTS in women. The estimates differ, depending not only on study procedures but also on the age of the participating women, the severity of symptoms and how symptoms have been assessed. As for UI, the reported annual overall incidence ranges from 1-9%, while estimates of remission vary between 4-30% [28, 34-36]. The great variation of estimates for remission

may reflect the difficulty in taking into account the effects of possible treatment. Møller *et al.* reported 10% incidence and 28% remission of LUTS [33] and McGrother *et al.* 15% and 23% [32], respectively, during one year. Heidler *et al.* in a selected population of women without urinary incontinence found annual incidence and remission proportions of 5.3% and 4.6% [29]. The calculated mean annual incidences and remission rates of the various LUTS in *Paper I* range between 0.5% and 3%. Given the long time interval between the assessments, such calculations are, however, misleading and have therefore not been presented. To measure the actual incidence *rate* more accurate data on individual follow-up time and drop-out is required. Ideally, measurements should be undertaken at regular intervals. Such data was unfortunately not available to us. Furthermore, we assessed each LUTS separately, in contrast to most other studies, which illustrate the difficulty in comparing the results of different surveys. The reasons why some women experienced symptom remission with increasing age remain unclear. A possible explanation might be the use of coping strategies, but in the present series it was also evident that many of the women reporting remission of symptoms also had been subjected to various interventions.

In the comparison between the two populations of women in *Paper II* we did not find any major changes in the proportions of women reporting various LUTS. Neither did we find any change

over time in the overall percentage of women who had consulted the health care system due to incontinence. Surprisingly, the treatment that had been provided was also unchanged with one exception, i.e. physiotherapy that had been offered significantly more often in 2007.

Since a number of important changes in the provision of medical care for UI, OAB and other LUTS have taken place between 1991 and 2007, we hypothesized that fewer women would currently be suffering from UI and LUTS today than 16 years ago. Several new antimuscarinics are now available. Our knowledge regarding the treatment of OAB symptoms has changed over the last 20 years from being a select specialist issue, to being common knowledge for nearly every urologist, gynaecologist and general practitioner. As for SUI, the introduction of the TVT operation has undoubtedly been of great importance, providing a fairly cheap, safe and fast means of correcting incontinence with a high success rate. We also hypothesised that, due to better awareness, more women would have contacted the health care system to discuss their symptoms, which was not the case.

Although the overall prevalence of UI did not change between the two assessments, the frequency of urinary leakage in incontinent women was slightly lower in 2007 than in 1991. This might perhaps, at least partly, mirror symptom amelioration due to better treatment. The age-related differences are probably the most interesting. When specifically studying

different age groups we found that it was more common among older women to have sought health care in 2007 than in 1991. In addition, women  $\geq 80$  years were more likely to have had surgery for UI in 2007 than 16 years ago, while the opposite was true for pharmacological treatment. It seems that older women today have higher demands of continence than previously, and also that surgeons are more prone to operate on older women. Presumably, the latter is a consequence of the introduction of new effective minimal-invasive surgical methods, such as the TVT procedure for SUI. Such information might be of importance for society in order to organise services accordingly.

Several previous investigations have shown that women do not always seek care for UI and LUTS. Reasons for not seeking help are mainly embarrassment or acceptance of the symptom as a normal consequence of aging or the belief that no treatment is available [159, 160]. Factors associated with help-seeking are age, duration and severity of symptoms plus having spoken to others. Routine health checks or consultations about other health problems might also serve as an opportunity for people to discuss their urinary problem [24, 161, 162]. Roe *et al.* also reported that knowledge about established continence services influenced help-seeking behaviour [162]. To a certain degree, the results of *Paper II* corroborate previous work, showing that help seeking behaviour is still poor despite advances in medical care and supposed provision of care, which, in some ways, is disappoint-

ing. Our results thus emphasise the importance for health care personal to ask about urinary problems and inform about what services are on offer.

The self-estimated QoL, in *Papers I and II*, was in general poorer in 2007 than in 1991. The deteriorating QoL in *Paper I* was not surprising since the women were older and of poorer health in general, than 16 years previously. What factors might have contributed to worsen generic QoL over the years, as demonstrated in *Paper II* is, however, difficult to understand. To answer this question properly qualitative studies would have to be undertaken. Several studies have emphasized the negative impact of UI and other LUTS on an individual's quality of life [2-4]. In *Paper II* incontinent women and women with urgency rated their QoL significantly worse than continent women and women without urgency, respectively. This has also been demonstrated by others using other QoL measures [2, 4, 163]. Significantly more incontinent women in 2007 in all age groups also considered their incontinence to have a negative impact on their social life. This might of course be a result of selection bias, but more likely an expression of how women currently are more active and have a lower tolerance for involuntary leakage than 16 years ago. In a longitudinal perspective, Hägglund *et al.* showed that changes in QoL scores over four years were significantly greater in women with persistent UI as compared to women with persistent continence, but any significant QoL change from baseline to follow-up

for incident and remission groups could not be demonstrated [28]. Similarly, we failed to demonstrate any QoL-difference in women considered as non-cases at both assessment points in comparison to incident cases. A possible explanation for the lack of significant differences in QoL for these groups could be the relative small number of subjects in each group.

The aetiology of LUTS is widely recognised to be multifactorial [164], but the importance of genetic and environmental influences is poorly understood. Evidence in support of a genetic influence on LUTS derives from studies on ethnic group diversity, studies on familial transmission of disease and twin studies [63-67, 165]. The majority of such studies have related to the symptom of urinary incontinence. A number of studies have suggested that Caucasian women are at increased risk of developing SUI compared to African-American women. Other studies have reported higher risk of symptoms associated with OAB in African-American women when compared to Caucasians [166-169]. Several cohort studies have evaluated the prevalence of UI in siblings and found a greater prevalence of UI among relatives of women with involuntary urinary leakage compared to relatives of continent women. Familial aggregation is, however, not invariably a result of genetic factors. Risk estimates derived from family members in most cases cannot distinguish between heritability and non-inherited factors in the family environment (shared environment), such as toilet training,

socioeconomic status, smoking habits, dietary/drinking habits and other life-style factors.

In *Paper III* it was possible to evaluate the relative contribution of genetic, shared and non-shared environmental factors for the occurrence of LUTS. The strongest genetic effects were observed for conditions involving UI, regardless of whether the involuntary loss of urine was associated with bladder overactivity or supposed pelvic floor weakness. Also for nocturia the genetic proportion of the total variation in liability was relatively high. The lowest estimates for genetic effects were observed for OAB where environmental effects dominated. Our data indicate that non-genetic familial effects, such as childhood micturition patterns and toilet training, might be involved in the causal mechanism of the overactive bladder symptom complex. The importance of childhood urinary symptoms for predicting adult overactive bladder symptoms has been postulated previously [170] and the results given in this study give further support to this hypothesis. However, it remains undecided exactly how dysfunctional voiding habits in childhood may give rise to overactive bladder later in life but it may involve life-style factors, compromised bladder storage volumes, disturbed local neurogenic bladder control as well as central nervous imprinting. Shared environmental effects also contributed to liability of developing stress urinary incontinence but were less pronounced. Our results are in agreement

with a previous study from the Swedish twin register, which suggested that heritability contributes to the liability of developing surgically managed pelvic organ prolapse and stress urinary incontinence. The authors presented evidence that for both disorders genetic and non-shared environmental factors equally contributed 40% of the variation in liability [66].

There is, however, also some contrasting data regarding the heritability of pelvic floor disorders and UI in other twin studies [67, 171, 172]. A Danish twin study of middle-aged and elderly twins found evidence for significant heritability for urge, but not for stress UI [67]. Another twin study presented data that genetics accounted for nearly 60% of the variation in bladder neck descent as measured by ultrasound [171]. However, it should be noted that most other twin studies are based on small groups of volunteers and are liable to bias since pairs who are concordant for the disease, are more likely to participate [173].

In *Paper II*, heredity as a risk factor for UI appeared more common in 2007 than in 1991. We believe that this finding reflects the general openness and awareness among people today for the problem of UI rather than a true increase. Still, such factors seemed to have a limited influence on the prevalence of complaints.

*Paper IV* showed that 23 out of 24 women (96%) operated on with the Stamey procedure reported an improvement of clinical symptoms for a mean of approxi-

mately three years and overall patient satisfaction in the long term was high (83%). The number of women who remained continent, however, decreased considerably over time. These are findings in keeping with those obtained by others but at variance with some reports [109-112, 174]. Previous studies on long-term results have reported success rates ranging from 33% at 10 years [174] to 93% at 7.5 years among patients with pure SUI [110].

Gofrit *et al.* found that the only significant factor that predicted the outcome of the Stamey procedure was the presence or absence of urgency or frequency preoperatively [110]. Also for the TVT operation, the type of incontinence has been shown to be an independent variable to predict the outcome of the procedure [175]. In the present study, the mean stress urinary leakage, as measured by a standardised quantification test, was significantly reduced at long-term follow-up, even among those who claimed to have recurrent incontinence. In many cases, relapse seemed to correspond to the presence of urgency/UUI rather than to SUI. It is known that undiagnosed urgency may be revealed after surgery for SUI, either as a result of the surgical procedure itself, or due to an existing urgency component being unmasked by successful treatment of the stress component [176]. Despite our efforts to include only women with SUI, it turned out that no less than 6 patients in fact had urgency and/or MUI preoperatively, although no urodynamically revealed DO.

Approximately half of the women who complained of urgency symptoms at long-term follow-up (five out of nine) had a preoperative history of urgency/MUI. Some of the “failures” could thus have been expected. Taking preoperative urgency symptoms into account, the “de novo” urgency prevalence, at long term after the Stamey procedure, was still high (21%) compared to, for example, the figure of 8% reported by Christensen *et al.* [109]. In this context it can also be noted that the estimated “de novo urge frequency” of the TVT procedure is 1-15% [113, 116, 177]

Considering the natural course of urgency as described in *Paper I*, and the long time that had passed since the operation for most patients, it is quite possible that the prevalence of urgency symptoms among the study subjects would have been similar on long-term follow-up regardless of the previous operation.

There are some drawbacks of Paper IV; it is a retrospective small study without a control group, it relies partly on a non-validated questionnaire and it lacks some of the consistency that we intended on beforehand. Moreover, the Stamey procedure is by most clinicians considered out of fashion due to previous reports on poor long-term results. A theoretically better methodology would be a RCT comparing the Stamey method to another minimal-invasive operational technique such as the TVT procedure. There are almost no previous prospective studies



evaluating the Stamey method and no RCT's. Christensen *et al.* retrospectively compared the long-term results of the Stamey procedure with those of the Burch procedure and found similar outcomes of both techniques [109]. Needle colpo-suspension techniques were, when they were introduced, valuable minimal invasive options to treat SUI in elderly and frail patients. This group, as well as others, may currently be offered a midurethral sling, such as the TVT operation. Despite initial fear of urethral erosions and voiding dysfunction in the long term, the TVT technique has proved to be a safe, effective and sustainable method. There

are few situations for which the Stamey method would be preferable, and hence, a RCT comparing these two procedures is unrealistic, although may be interesting. Nevertheless, it should be remembered that there is one advantage of the Stamey procedure over the TVT: the Stamey sutures are removable in contrast to the prolene tape, the latter being very difficult to remove. Such reversibility might be advantageous in e.g. stress incontinent patients with very low detrusor pressures where urinary obstruction is at risk, and can justify keeping the technique as part of the treatment armamentarium for urinary incontinence.



## CONCLUSIONS

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- LUTS are prevalent in women and the prevalence of these various symptoms increases with age in both men and women.
- UI and LUTS constitute dynamic conditions. There was a marked overall increase in the prevalence of UI, OAB and nocturia when the same women were assessed in 1991 and 2007. Both incidence and remission for most symptoms were considerable.
- The prevalence rates of UI and OAB have not changed during the last 16 years. Many women still do not seek help from the health care system and the help-seeking pattern has remained unchanged despite the fact that effective treatment in most cases can be offered nowadays.
- Both genetic and environmental factors contribute to the development of LUTS in women. The strongest genetic effects were observed for conditions involving UI and for nocturia and the lowest genetic effects were observed for OAB where environmental factors were more important. For OAB without incontinence shared environment accounted for nearly one third of the total variation. For stress urinary incontinence one fifth of the total variation for the disorder could be attributed to shared environment.
- The Stamey bladder neck suspension procedure may be used in a carefully selected population of women with genuine stress incontinence, intact urethral function and no demonstrable detrusor overactivity, with an acceptable long-term result and good patient satisfaction.



## GENERAL OUTLOOK AND FUTURE PERSPECTIVES

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According to an expert meeting in the United States in 2003, it was stated that the most important areas for future research regarding the epidemiology of lower urinary tract symptoms include further studies to identify risk factors and protective factors, studies to provide information on the relation of various LUTS to other co-morbidities, genetic epidemiology studies and health economic assessments [178].

When initiating *Paper I* we were hoping to be able to identify specific risk factors for the various LUTS; factors that were common for women with incident UI or other LUTS and for those with persistent continence/non-LUTS. Although the longitudinal design is optimal for this purpose, we soon realised that the number of study participants (and thus the power) would be insufficient to show any significant differences in this respect. In comparison, the number of women in *Paper III* is more than fourfold and, in addition, the STR contains an abundance of information on risk factors, lifestyle factors and co-morbidities, providing a unique source for longitudinal studies.

Collecting similar data at multiple times, from this relatively young population, would allow for an exclusive opportunity to track the onset of symptoms and to identify possible risk factors. The information available in the STR also offers an interesting possibility for future research concerning LUTS by the possibility of linkage to other registries, e.g. the national medical birth registry containing relevant information on pregnancy and childbirth.

Awareness of and treatment options for UI, OAB and other LUTS have improved rapidly in the last few years. Nevertheless, the available therapy is in some cases insufficient, side effects are common and many people still suffer from troublesome symptoms. Intensive research aiming at developing new drugs such as beta-3-stimulating compounds and sensory neurotransmitter antagonists for the treatment of OAB, as well as tissue engineering and the development of new surgical treatment possibilities are currently undertaken. In spite of all new technologies, many challenging areas of research remain for the future and the need of increased knowledge is obvious.



### Sammanfattning på svenska

Urininkontinens och andra nedre urinvägsbesvär är folkhälsoproblem som berör många kvinnor. Problem att kontrollera blåsan innebär ofta ett socialt handikapp och har i flera studier visats ha en negativ inverkan på en persons livskvalitet. Förekomsten av urininkontinens är väl studerad och vi vet utifrån olika tvärsnittstudier att mellan 20% och 50% av alla kvinnor drabbas av någon form av urinläckage. Störst är besvären i de högre åldersgrupperna. På senare år har man också alltmer börjat uppmärksamma andra urinvägsbesvär, såsom tvingande trängningssymptom och behov att tömma blåsan ofta eller vakna nattetid för att kasta vatten. Förekomsten av dessa nedre urinvägsbesvär bland kvinnor uppskattas vara i storleksordningen 20% till 40%. Det saknas däremot bra undersökningar som belyser hur olika typer av nedre urinvägsbesvär utvecklar sig över tiden.

Många kvinnor beskriver en blandning av olika nedre urinvägsbesvär och det finns flera studier som tyder på gemensamma uppkomstmekanismer. Flera riskfaktorer för att utveckla urininkontinens, överaktiv blåsa och andra nedre urinvägsbesvär är också gemensamma. Huvudsakliga riskfaktorer är ålder, neurologiska sjukdomar inklusive slaganfall, övervikt samt graviditet och förlossning. Ärftlighet kan också vara en viktig bidragande riskfaktor, men det finns få studier som behandlat detta. Den underliggande mekanismen bakom överaktiv blåsa är

oklar, men en mer eller mindre framträdande neurologisk dysfunktion tros vara orsaken. Såväl kvinnor som män med överaktiv blåsa har visat sig även i övrigt ha en högre sjuklighet än personer utan urinvägsbesvär. Likväl är det få som söker hjälp från hälso- och sjukvården, trots att effektiv behandling i många fall kan erbjudas.

Behandlingen när det gäller såväl ren ansträngningsinkontinens som trängningsinkontinens är i första hand konservativ och innefattar bland annat livsstilsförändringar och bäckenbottenträning. Läkemedel utgör framför allt en viktig del i behandlingen av trängningsinkontinens och överaktiv blåsa. Ren ansträngningsinkontinens kan ofta med fördel behandlas kirurgiskt när konservativa metoder haft otillräcklig effekt. Ett stort antal operationsmetoder har beskrivits. Den så kallade Stamey-metoden, där ett centimeterbrett parti av bäckenbotten på var sida om blåshalsen lyfts upp med U-formade suturer (stygn) via bukväggen, är ett minimalinvasivt ingrepp med god effekt på kort sikt. Långtidsresultaten har dock varit varierande och har i flera studier visat sig nedslående med hög recidivfrekvens.

För att få en uppfattning om huruvida olika typer av nedre urinvägsbesvär förändras hos en och samma individ har vi genomfört en populationsbaserad longitudinell studie där samma kvinnor, som 1991 deltog i en enkätstudie avseende sådana symptom, ombads besvara en

liknande enkät 16 år senare (2007). Målet med denna studie var att beskriva naturalförloppet vid kvinnlig urininkontinens, överaktiv blåsa och andra nedre urinvägsbesvär. I studien deltog 1081 kvinnor. Vi fann att de flesta symptom ökade med ökande ålder, men att både progression (försämring) och regression (förbättring) var vanligt förekommande. Kvinnor som hade frekvent urinläckage angav sällan förbättring.

Vi rekryterade också en ny slumpmässigt utvald grupp kvinnor från samma distrikt i centrala Göteborg och tillfrågade dem om deltagande i en ny tvärsnittstudie med samma frågeformulär. Resultaten av dessa båda tvärsnittsstudier, genomförda med 16 års mellanrum, har jämförts med avseende på förekomsten av nedre urinvägsbesvär, hjälpsökande och livskvalitet. I studierna 1991 och 2007 deltog 2248 kvinnor respektive 2402. Förekomsten av urininkontinens och överaktiv blåsa var oförändrad mellan de två undersökningarna, liksom andelen kvinnor som sökt hjälp för urinläckage. Förändringar över tid avseende förekomsten av övriga symptom var också liten. Den typ av behandling kvinnorna hade erbjudits 1991 respektive 2007 skilde sig framför allt på en punkt; nästan tre gånger så många kvinnor  $\geq 80$  år angav 2007 att de hade genomgått en inkontinensoperation jämfört med 1991.

Genom att jämföra hur sjukdomar fördelar sig mellan enäggstvillingar med identisk genuppsättning och tvåäggstvillingar som

har 50% av sitt genetiska material gemensamt kan man dra slutsatser om den relativa betydelsen av genetiska och icke-genetiska (gemensam och individuell miljö) faktorerens betydelse för sjukdomsförekomsten. Om sjukdomen förekommer hos båda tvillingarna i ett par oftare hos enäggstvillingar än hos tvåäggstvillingar pekar detta på att genetiska faktorer har betydelse. I ett samarbete med det svenska tvillingregistret, har uppgifter om bland annat urininkontinens och andra nedre urinvägsbesvär samlats in från 25 364 svenska tvillingar födda 1959-1985. Vi har undersökt förekomsten av urininkontinens, överaktiv blåsa och andra nedre urinvägsbesvär bland dessa män och kvinnor i åldrarna 20-46 år samt studerat genetiska och icke-genetiska faktorerens inverkan för uppkomsten av nedre urinvägsbesvär hos kvinnor. Nedre urinvägsbesvär var vanligare hos kvinnor än hos män, och förekomsten ökade med ökande ålder. Vi fann den största genetiska betydelsen för tillstånd som inbegrep urininkontinens liksom för nocturi, medan den genetiska inverkan var lägst för överaktiv blåsa utan inkontinens. Gemensam miljö uppskattades stå för ca 1/3 av den totala variationen för överaktiv blåsa utan samtidig inkontinens och för 1/5 av variationen för ansträngningsinkontinens. Fyrtiofem till sextiofem procent av de olika nedre urinvägsbesvären uppskattades bero på individuell miljö.

Den fjärde av våra studier är en långtidsuppföljning (minst 2 år) av



kvinnor som genomgått operation med Stameymetoden mot ren ansträngningsinkontinens. Uppföljningen utgjordes av ett frågeformulär, urodynamisk undersökning och ett standardiserat kvantifieringstest. Tjugofyra kvinnor kunde följas upp efter i medeltal 63 månader (28-100 månader). Fyrtiotvå procent av kvinnorna ansåg sig vara helt kontinenta vid uppföljningen.

Vid en objektiv värdering av kvinnornas läckage var detta signifikant lägre vid uppföljningen än före operationen, ett medelläckage på 19 gram jämfört med 100 gram preoperativt. Majoriteten av kvinnorna angav att de var nöjda eller mycket nöjda med resultatet av operationen.



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