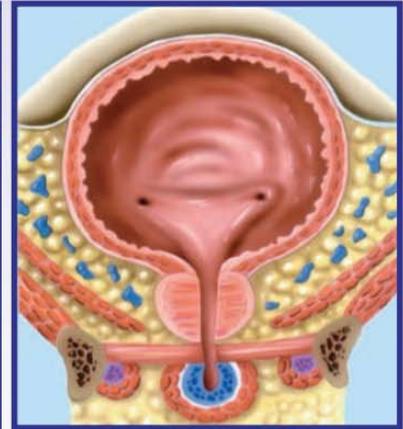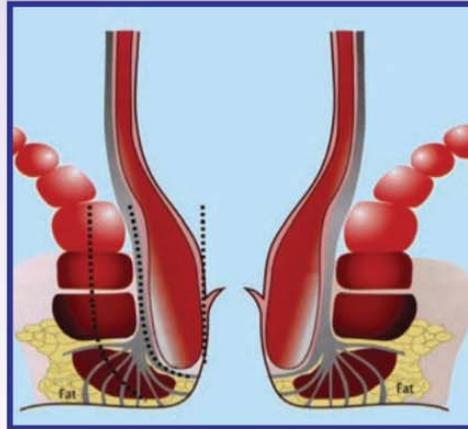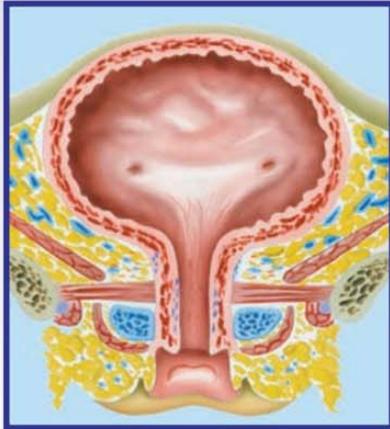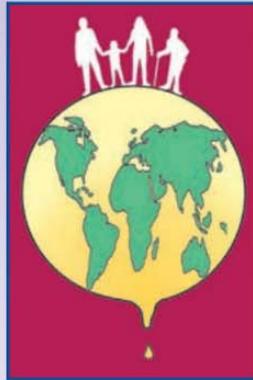# INCONTINENCE

EDITORS

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eau European Association of Urology

5th EDITION 2013

ICUD

> The great tragedy of science :
> The slaying of a beautiful hypothesis by an ugly fact
> Thomas Huxley (1825-1895)

Committee 1

Epidemiology of Urinary Incontinence (UI) and other Lower Urinary Tract Symptoms (LUTS), Pelvic Organ Prolapse (POP) and Anal Incontinence (AI)

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CONTENTS

Epidemiology of Urinary Incontinence (UI) and other Lower Urinary Tract Symptoms (LUTS), Pelvic Organ Prolapse (POP) and Anal Incontinence (AI)

IAN MILSOM

D. ALTMAN, R. CARTWRIGHT, M.C. LAPITAN, R. NELSON, U. SILLÉN, K. TIKKINEN

A. INTRODUCTION

In this report we focus on the epidemiology (distribution and determinants) of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal incontinence (AI). We also discuss important topics such as differences between epidemiological and clinical approaches to health problems, help seeking behaviour, and methodological issues for this research.

We have included a section on overactive bladder and nocturia which are commonly occurring LUTS. A worldwide estimation of the current and future number of individuals with LUTS [1,2] including UI and overactive bladder (OAB) is also included at the end of this chapter.

The epidemiological population under study for this review will mainly be community dwelling non-institutionalised persons. The review will include discussion of the prevalence, incidence, natural history, and presence of racial and ethnic differences. We also review correlates and potential risk factors that have been revealed in epidemiological studies. Progress has clearly been made during the 4 years since our previous report when the 4th International Consultation on Incontinence (4th ICI) was published. Some new important areas have been studied with increasing regularity and quality. We have searched the literature for relevant new articles, thus reviewing a large number of high-quality and population based studies, as well as clinical trials that might include relevant epidemiological data. Because of an abundant number of studies, only a small fraction can be presented in a text like this. Other studies not presented here may have equally useful information, but lack of space precluded their inclusion.

Summary points:

- This review includes discussion of the prevalence, incidence, natural history, and presence of racial and ethnic differences in the epidemiology of UI, OAB, nocturia, POP and AI.

- Correlates and potential risk factors that have been revealed in epidemiological studies are also reviewed.

B. BASIC EPIDEMIOLOGICAL CONSIDERATIONS

Epidemiology is the scientific study of the distribution and determinants of disease in people. *Descriptive epidemiology* is the description of disease prevalence, incidence, (and mortality) by persons, place and time, while the term *analytical epidemiology* describes the search for determinants of disease risk. The discovery of risk factors and protective factors may then in turn lead to primary or secondary prevention.

In order to collect knowledge about risk factors or natural history, observational studies are needed. Cohort studies and case-control studies are the most common. However, caution is always needed when interpreting the results from such studies, as associations found in epidemiological studies may not be the same as causes. Longitudinal study designs and appropriate control for confounding factors are preferred, as these increase the validity of epidemiologic studies. For practical and ethical reasons, experimental designs are seldom used.

Recommendations and conclusions should always be based on the best available evidence. Studies of interventions, and studies of risk factors generally cannot be randomised because they relate to inherent human characteristics or practices, and exposing subjects to harmful risk factors is unethical. No uniform guidelines for assessing the results of observational studies exist, and the level of evidence for risk factors from observational studies should be judged on the soundness of the exclusion of alternative explanations by statistical and other controls. But some initiatives for how to report meta-analyses of observational studies have been taken [3].

Studies of disease frequency should rely on a very specific definition of the condition under investigation. The absence of unifying definitions for the conditions reviewed here is a fundamental problem which has not been resolved. Definitions used and problems associated with them are discussed in the subsections for the particular populations below.

Prevalence is defined as the probability of experiencing a symptom or having a condition or a disease within a defined population and at a defined time point. The concept is important for establishing the distribution of the condition in the population and for projecting the need for health and medical services.

Incidence is defined as the probability of developing the condition under study during a defined time period. Incidence is usually reported for one-, two- or five-year time intervals.

Even in many of the recent studies reviewed analyses are very simple. Often only proportions or percentages are used to describe differences in different subgroups. Many analyses do not control for confounders (by stratification or multivariate analysis techniques). There is an obvious need for more advanced epidemiological analyses of risk factors and comorbidity, and strength of associations should be determined by relative risks and odds ratios.

The relative risk (RR) estimates the magnitude of an association between exposure and a condition, and indicates the likelihood of having the condition in the exposed group relative to those who are not exposed (e.g. do not have the risk factor). A RR of 1.0 indicates that the rates in the exposed and non-exposed groups are identical and thus that there is no association between the exposure and the condition in that specific dataset. A value greater than 1.0 indicates a positive association or an increased risk. A RR of 2.5 for UI indicates that there is a 2.5 times increased risk or that the persons in question are 150 percent more likely to have incontinence than those without the risk factor.

The odds ratio (OR) is the odds for having a risk factor in persons with a condition divided by the odds among those without the condition. An OR of 2.5 for UI my be interpreted as meaning that in this sample the odds in favour of having incontinence are 2.5 times higher among those with the risk factor than among those without.

For a condition with high prevalence, like UI or POP, OR and RR will not be identical, but in practice the results can be interpreted similarly. Results should always be given with a 95% confidence interval (CI).

Words like well established and established may be used about risk factors and findings with a high level of evidence in the literature. For less documented findings words like " indications of" or " data are suggestive" may be used.

Summary points:

- Descriptive epidemiology reports disease incidence, prevalence (and mortality) by persons, place and time.

- Analytical epidemiology searches for determinants of disease risk. There is a need for good longitudinal cohort studies.

- Variations in definitions and measurement issues are fundamental, and lead to problems with assessing the findings in epidemiological studies.

- There is a need for more advanced epidemiological analyses of risk factors and comorbidity using multivariable techniques, and strength of associations should be determined by relative risks and odds ratios.

C. EPIDEMIOLOGY OF ENURESIS AND UI IN CHILDREN

I. GENERAL COMMENTS AND DEFINITIONS

The International Children's Continence Society (ICCS) has issued new recommendations regarding terminology of bedwetting or *nocturnal enuresis* (NE) [4]. NE is now the term for all urinary incontinence during sleep taking place in discrete episodes, regardless of the presence or absence of concomitant daytime symptoms. *Monosymptomatic nocturnal enuresis* (MNE) denotes bedwetting without any other LUTS symptoms, and *non-monosymptomatic nocturnal enuresis* (NMNE) should be used for those with any concomitant LUTS.

NE is caused by relative nocturnal polyuria [5] and/or nocturnal bladder over-activity [6], combined with the lack of arousal at the time when the bladder needs to be emptied. The most important cause is, of course, the lack of arousal, otherwise the child would have had nocturia.

Any other leakage of urine in children during both the day and night is referred to as UI, just as it is in the adult population. UI with no obvious cause, i.e. without neurological or congenital anatomic alterations, is often seen together with other urinary symptoms such as frequency, urgency and infections. Altogether these symptoms are referred to as functional LUT dysfunction, which is the term used to describe the entire spectrum of functional filling-voiding disturbances. Several sub-classifications have been used for children who present with varying degrees of "functional" urinary symptoms. Some are based on urodynamic patterns, others on clinical presentation.

According to recent definitions by the ICCS [4], based on symptoms and flow-residual studies rather than invasive urodynamic investigations, incontinence as a result of a filling-phase dysfunction, is in most cases due to an OAB, which can also be referred to as "urgency syndrome" and "urge incontinence". Children with OAB usually have detrusor overactivity, but this label cannot be applied to them without cystometric evaluation. When incontinence is the result of a voiding-phase dysfunction, the diagnosis is often dysfunctional voiding (DV), which is induced by increased activity in the sphincter and pelvic floor during voiding. It is subdivided into staccato and fractionated voiding, and the terms cannot be applied unless repeat uroflow measurements have been performed. Voiding postponement (VD) is another common LUT dysfunction causing UI in children, but differs from the other since it is induced by a habitual postponement of voiding and not a LUT dysfunction per se.

NE and UI due to functional LUT dysfunction are the wetting problems addressed in this chapter. Both can be either primary (the child has not been dry for more than six months) or secondary (the wetting has recurred after a dry period lasting more than six months). If the complaints are secondary, they may signify psychological, neurological or even structural anomalies and therefore require careful consideration.

The healthy infant is socially incontinent but physiologically continent, because micturitions (about once every hour) are discrete and there is no leakage of urine between micturition [7]. Bladder control develops during the first four to six years of life and is a highly complex process, which is still not fully understood. Most children are toilet trained by the age of three years, although there is huge social and cultural variation. By the age of five years, the child is normally able to void at will and to postpone voiding in a socially acceptable manner [8]. By this age, night-time and daytime involuntary wetting becomes a social problem and a cause for therapeutic intervention.

II. PREVALENCE OF NOCTURNAL ENURESIS (NE)

As bladder control is something that develops over time, longitudinal studies are the best way of defining the dynamics of this process. Studies giving us the prevalence for all children between five and 15 years of age, for example, are not appropriate, as all the developmental stages are clustered together. It is therefore better to give the prevalence for an age cohort, such as seven-year-olds. Furthermore, random sampling should preferably be used in order to be able to say anything about the population. These problems associated with understanding epidemiology were summarised by Krantz [9], who also reviewed the epidemiological studies that had been published by 1993.

One explanation for the variation in prevalence in different studies is the fact that some studies include only monosymptomatic enuresis (MNE), whereas others also include what is defined as non-monosymptomatic enuresis (NMNE). Another explanatory factor is that the frequency of enuretic episodes differs or is not taken into account in some studies. Moreover, most epidemiological studies link primary and secondary enuresis together.

1. PREVALENCE OF ALL NIGHT WETTING (MNE+ NMNE) ACCORDING TO AGE

Longitudinal cohort studies should be the ideal when analysing epidemiology in childhood NE, as there is a successive reduction in prevalence. Only a few of these studies are available [10-15] and cross-sectional studies at different ages therefore have to be used.

Most studies investigate cohorts of children in an age span of six to 12 years of age, for example, and give the prevalence for the entire group. Some of them also give the age-related prevalence [13, 16-26] which is summarised in **Table 1**. Cross-sectional studies of a specific age are also included [27-31] in **Table 1**.

In most studies (Table 1), the prevalence for seven-year-olds was between 7% and 10%. In two studies, the prevalence was higher; 15.1% and 16.4% for Turkish [20] and Korean [18] children respectively, despite the fact that the inclusion criteria were very similar in all the studies dealing with seven-year-olds (NE=night wetting once/month or more), apart from the studies by Hellström [27] (once/3 months or more) and Järvelin [28] (once/6 months or more). The prevalence of more frequent wetting (once/week or more) was lower compared to the prevalence for all wetting (once/month or more) by age, which have been illustrated in **Figure 1**.

In nine studies at age seven years [12,16,19,21-24,27-28], (Table 1) the numbers of both non-enuretic and enuretic children were given and the definitions

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Table 1. Prevalence of nocturnal enuresis (NE) (= Monosymptomatic nocturnal enuresis (MNE) + Non-monosymptomatic nocturnal enuresis (NMNE) together) grouped according to age.

Author and year	Prevalence of NE (%)		
	7 years	11-12 years	16-17 years
Chiozza [16]	6.8	2	
Järvelin [28]	8		
Spee-van der Wekke [18]	8	4.6	
Cher [19]	9.3	1.7	
Hellström [27, 29]	9.5		0.5
Ferguson [12]	10.3		
Kanaheswari [25]	10.3	3.3	
Serel [20]	15.1	4	
Lee [21]	16.4	4.5	
Swithinbank [30, 31]		4.7	1.1
Soderstrom [23]	7.0	2.6	
Kajiwara [22]	10.1	3.7	
Yeung [24]	10.1	2.0	1.7
Butler[15]	14.2		
Su [26]		1.9	

for enuresis were similar (MNE and NMNE, wetting once/1-3 months or more). A prevalence of 10% was obtained by meta-analyses of these studies (cohort of 14372 seven-year-old children, of whom 1422 were enuretic). Only four studies included groups of children that were chosen at random from the population [16,21,24,28].

At age 11-12 years, the prevalence of NE had decreased and from the studies shown in **Table I** the prevalence varied between 1.7% and 4.7%. In seven of the studies, the number of

non-enuretics and enuretics were available and the definition of NE was similar (once/month or more), apart from Swithinbank's [30] study (once/3 months or more). In these studies, the total number of children included was 8947, while the number of children with NE was 278, giving a prevalence of 3.1%. So, of those children with NE at age seven years, almost 15% spontaneously grow out of the wetting every year. In a recent Japanese study a higher resolution rate was reported in children with MNE compared to NMNE in children 7 to 12 years of age (21% and 15%, respectively) [22]. Similar results were found in a study from Hong Kong in which the proportion of children with NMNE was significantly greater in adolescent boys than in boys aged 5-10 years (32% vs 14.6%), even if the total prevalence of NE was decreasing as in other studies [24].

The variation in the prevalence of NE at 11-12 years between the studies is less than that seen at age seven years. The highest prevalence is no longer found in Turkey or Korea, as was the case at age seven years, but instead comes from a non-randomised cross-sectional study of 11- to 12-year-old schoolchildren (n=1145) in the UK (4.7%). It can therefore be suggested that the high prevalence seen in the studies from Turkey and Korea at age seven is not due to differences in genetic predisposition, but rather to phenotypic differences, such as the age of toilet training and the subsequent attainment of bladder control, socio-economic status, or cultural differences.

At age 16-17, three cross-sectional studies show a further reduction in prevalence to 0.5-1.7%. Two of the studies re-investigated children who had

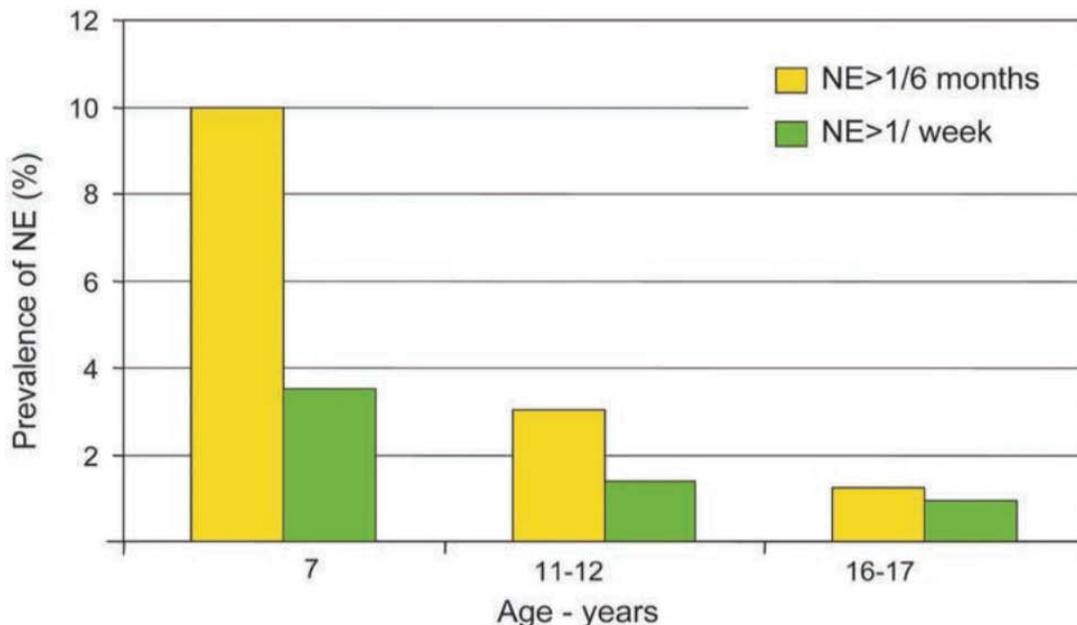Figure 1. Prevalence of nocturnal enuresis (NE) by frequency of enuretic episodes and age. The data were obtained from metaanalyses of the epidemiological studies included in table III.1. NE>1 episode/6months: at 7 years [16, 19, 21-25, 27-28,], 11-12 years [16, 19, 21-24, 30] and 16-17 years [24, 29, 31]. NE>1 episode/ week: at age 7 years [23, 24, 27, 28], 11-12 years [23, 24, 30] and 16-17 years [24, 29].

previously been studied; at age seven years [29] and 11-12 years [30] respectively. The prevalence when the cohorts were added together was 1.3% (cohort=3819, NE=51) [24,29,31], which gives a spontaneous cure rate of 11% a year among those who wet at age 11-12 years.

In a study of 13,081 adults randomly sampled in the Netherlands [32], an overall prevalence of NE of 0.5% was found. There was no significant difference between age groups. Primary NE was reported by 50% of the men and 19% of the women, indicating that a small group of the enuretic children remain enuretic as adults.

2. PREVALENCE OF MONOSYMPTOMATIC ENURESIS (MNE)

Very few studies make a distinction between MNE and NMNE and it is therefore difficult to obtain relevant figures for MNE (**Table 2**). In two studies from Scandinavia dealing exclusively with seven-year-olds, there was agreement between the studies; 6.4% [28] and 7.4% [27]. Recently, a Japanese study gave similar figures for MNE; 6.2% at age 7 years. In this latter study MNE corresponded to approximately 60% of all NE in ages from 7 to 12 years [19]. When it comes to studies in which all ages were mixed (5-12 years), four studies were identified in which those without daytime voiding problems could be identified.

However, the difference in prevalence of MNE varied in these studies; 3.5% [17], 6.9% [33], 9.4% [21] and 15% [34].

3. PREVALENCE OF NE VERSUS GENDER

Almost all epidemiological studies of NE report a higher prevalence in boys than in girls, with a ratio of 2:1 in western countries [16-23,26-28,30,33-35]. It appears that the gender difference diminishes

Table 2. Prevalence of Monosymptomatic nocturnal enuresis (MNE) at age seven years and overall (including all ages).

Author and year	Prevalence of MNE (%)	
	Age 7 years	All ages included
Järvelin [28]	6.4	
Hellström [27]	7.4	
Kanaheswari [25]	9.0	6.2
Lee [21]	13.6	9.4
Yeung [17]		3.5
Neveus [33]		6.9
Bower [34]		15.0
Kajiwara [22]	6.2	3.5

with age and becomes less visible and less proven among older children [29,31,36] (**Figure 2**).

4. PREVALENCE OF NE VERSUS ETHNICITY

In a study from The Netherlands [18], a higher prevalence was reported in the Turkish/Moroccan group (14%) than in the Dutch children (6%) (OR 3.76 (95%CI 1.98-7.12)). An equally high prevalence was found in a Turkish study of children with NE [20] at age seven years (15.1%). In a study from Korea [18], the same high prevalence at age 7 years was identified (16.4%). However, other studies from South-East Asia had comparable [19,22,24] or even lower levels of prevalence to those in western countries. In fact, two Chinese studies have shown a low prevalence of nocturnal enuresis [17,37], 3.6% and 4.3% for children aged 4-12 and 6-16 respectively, which they attribute to earlier nocturnal urinary control in Chinese children, due to earlier toilet training.

5. PREVALENCE OF NE VERSUS FREQUENCY OF WET NIGHTS AND AGE

Yeung et al [24]showed in a large epidemiological study that the relative proportion of subjects with frequent bed-wetting increased with age. Overall 82% of the adolescents had >3 wet nights/week versus enuretic children aged 5-10 (42%) (**Figure 3**). Such a relationship is also evident in fig 1, in which the proportion of children with severe NE increase with age, even if the total number decrease. Further support for severe NE to remain in a higher proportion as compared to children with infrequent bedwetting was shown in a recent study [15]. Findings in epidemiological studies also show a correlation between severity of the NE and NMNE [15-16,38], meaning that NE in adolescents often are combined with LUT dysfunction.

III. POTENTIAL RISK FACTORS FOR NE

Several risk factors have been established or suggested by epidemiological studies and the most important ones will be discussed here.

1. DAYTIME UI AND LUT DYSFUNCTION

Daytime UI, a symptom of LUT dysfunction, has in epidemiological studies been shown to be the strongest predictor for NE (OR 4.8 (2.9-7.9)) and has been identified in a third of the patients (NMNE) [38]. However, poor concordance was revealed (kappa 0.25), which confirmed the two to be separate entities that should be evaluated and treated separately.

2. FAMILY HISTORY

NE is a hereditary disorder and this has been demonstrated in many studies (for example, [16,17,20,28,33,34,39]. The mode of inheritance appears to be autosomal dominant. Järvelin [28]

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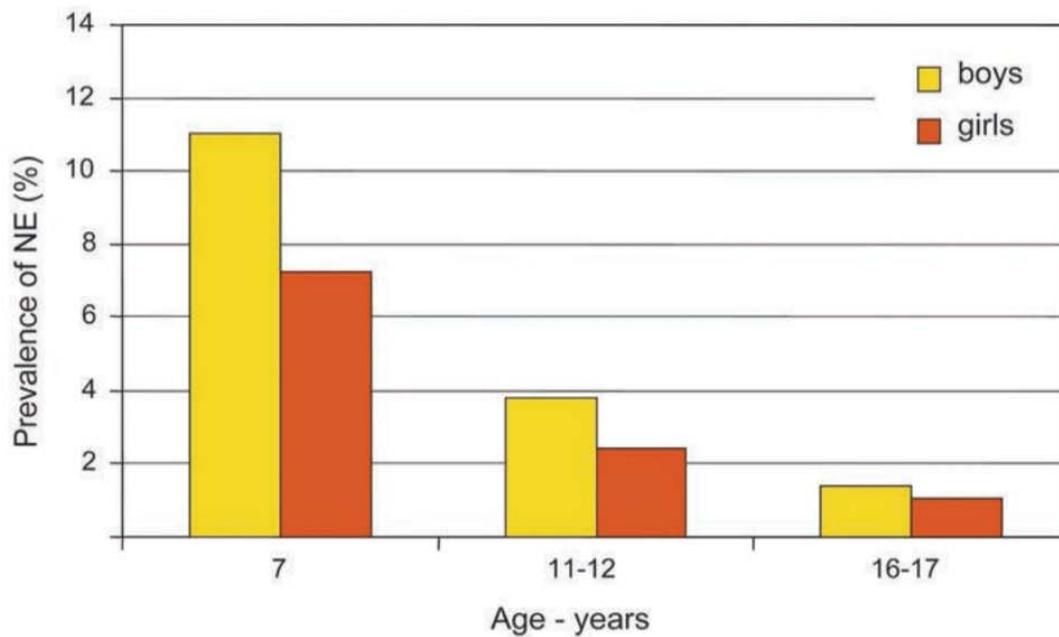
Figure 2. Prevalence of nocturnal enuresis (NE) >1 episode/6months, by gender and age. The prevalence data were obtained from metaanalyses of the following epidemiological studies: at age 7 [16, 22-24, 27, 28], age 11-12 [16, 22-24, 30] and age 16-17 [24, 29, 31].
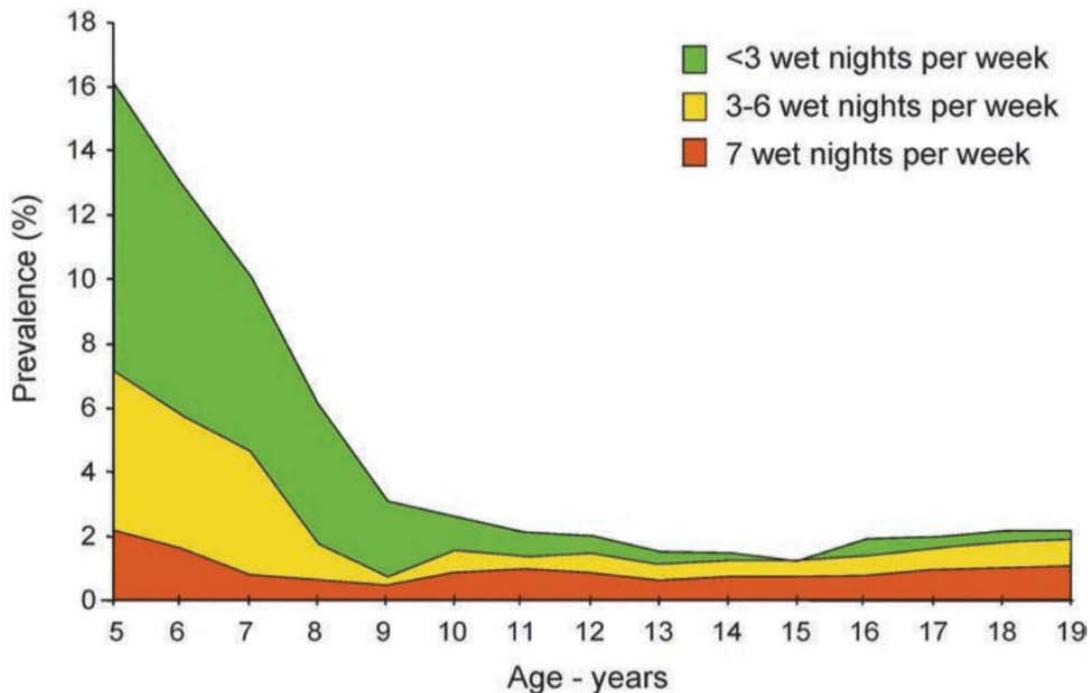
Figure 3. Prevalence of nocturnal enuresis by frequency of enuretic episodes and age. Data from [21].

showed that, if both parents were enuretics as children, the RR (95% CI) for the child to have NE was 16 (6.3-20.1), while if only one was enuretic, the RR was 7.8 (5.1-9.8). It has recently been shown that the risk for the child to have hereditary NE is increased with the severity of the enuresis. Children with severe NE (>2 episodes/week) were combined with odds ratio for maternal NE 3.63 (2.56-5.14), whereas mild and moderate NE (<2 episodes/week) had 2.14 (1.74-2-64) [40]. The association with paternal NE was less pronounced, but a similar increased association

to severe NE was observed. Using molecular genetic methods, foci have been found on chromosomes 13, 12, 8 and 22 [41-42. A picture of pronounced heterogeneity for both genotype and phenotype emerges [43].

3. PSYCHOPATHOLOGY

There are evident connections between childhood enuresis and mental well-being 13-14,37,39,44-47]. Evidence is accumulating to show that psychological consequences are probably caused by the enuresis and not a cause of primary NE, which has

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been thought for a long time [45]. The findings presented by Feehan [14] support this latter statement, as he only found an association between psychopathology and secondary NE, while children with primary NE did not display a connection of this kind.

4. DEVELOPMENTAL DELAY AND ADHD

Children with developmental delay and mental retardation have been shown to have a higher prevalence of NE [12,18,28,48]. Spee-van der Wekke [18] found that children who were given special education in school, including both those with and without mental retardation, had an OR of 3.74 (95%CI 2.32-6.03) for NE.

Perinatal events such as toxaemia and low birth weight, possibly involving an increased risk of minor neurological dysfunction, have also been shown to be associated with NE [12,28,39]. A connection between NE and minor neurological dysfunction of this kind has also been shown by Lunsing [49] in 12-year-old enuretic children. Furthermore, children with attention deficit hyperactivity disorders (ADHD) are more likely to have enuresis than the general child population [46,50-52].

5. SLEEP AND AROUSAL

The main pathology behind NE in children is the inability to wake up to the sensation of a full bladder. Parents often say that their enuretic child " sleeps very deeply". Some recent studies support this view. By using auditory signals [53], computerised EEG [54] or questionnaires [33], a defect in arousal has been largely validated. In the study by Neveus [33], the odds ratios were significantly high for a high arousal threshold (2.7), pavour nocturnus (2.4) and confusion when awoken from sleep (3.4). Computerised EEG energy analysis has indicated both greater depth of sleep and impaired arousal in enuretics [55]. Difficult arousal from sleep has also been shown in children with NE compared to children with isolated day-wetting problems and controls, by using a scoring system in a questionnaire [56].

6. SOCIO-CULTURAL FACTORS

Differences in the prevalence of NE [17,20-21,37,57] at early ages in different parts of the world are probably partly due to socio-cultural differences and not to differences in genetic predisposition [18]. It has been suggested that socio-economic status correlates with NE in some studies [16,46], whereas in others no correlation was found [12].

7. OTHER RISK FACTORS

Obstructive sleep apnoea (OSA) has been associated with enuresis in some patients [58]. In an epidemiological study association between severe OSA and NE in girls was shown [26], but when including both sexes and all forms of OSA no difference was seen. In another study dealing with OSA patients versus controls, a significant correlation between NE and OSA was found (OR 5.1 (2.4-10.7) [59]. Removal of large adenoids or tonsils causing upper airway obstruction in children with NE significantly reduced or cured NE [60]. Constipation (see co-morbidity below) may cause secondary NE or make primary NE persist [58]. Enkopresis was shown as a risk factor for NE in an epidemiological study (OR 2.7 (1.6-4.4)), while no association with constipation could be identified [38]. Sexual abuse must also be included among the factors that may lead to NE [62]. Organic conditions such as infravesical obstruction and neuropathic bladder may also present as NE. In most cases, however, additional symptoms are present to make detection possible. Type1 diabetes was reported to be a risk factor for secondary MNE due to the polyuria seen at presentation [63].

IV. PREVALENCE OF FUNCTIONAL INCONTINENCE IN CHILDREN

In children with functional LUT dysfunction, OAB is far more common than dysfunctional voiding. In a urodynamic study of 1,000 patients with functional LUT dysfunction, approximately two-thirds had an OAB and one-third had dysfunctional voiding [64]. Based on clinical information, another study comprising 226 children revealed that 76% were considered to have an OAB and only 1% dysfunctional voiding. The difference illustrates that different inclusion criteria influence the rate of prevalence [65].

When considering the total prevalence of UI (all frequencies of UI included) (**Table 3**), there was a variation between 3.2% and 9% in different studies at the age of seven years. In the earliest studies the prevalence was lower (3.2%-5.0%), whereas in the studies performed later in the 2000 [21, 23, 66-68], the prevalence was higher 6.3%-9.0%. One explanation for the difference was probably an increased recognition of the problem in the population through information via media etc. At 11-13 years the reported prevalence varied between 1.1% and 12.5%. Swithinbank's study [30] showed a very high prevalence (12.5%) and differed most from the rest (1.1%-4.2%). The difference could probably partly be explained by different limits for frequency of UI (occasionally [30] vs once/month or more). The fact that the studies were performed in different parts of the world was also a possible explanatory factor (UK and Korea).

The frequency of UI decreased with age (**Table 3**), which was clearly demonstrated in the subjects with frequent episodes of UI (>1/week) (**figure 4**). The prevalence at 7 years, 11-13 years and 15-17 years was 2.6%, 1.1% and 0.3% respectively. There were only two authors who investigated the same cohort of children on two occasions; Hellström [27, 29] in Sweden and Swithinbank [27, 28] in the UK.

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Table 3. Day urinary incontinence (UI) (including mixed day/night)

Author (ref)	Sample size	Prevalence (%)			
		<1/ week	>1/ week	Total day+ night	day only
Children 7 years:					
Järvelin [28]	Total: 2892			3.2[1]	1.8
	Boys: 1444			2.7	1.3
	Girls: 1445			3.7	2.3
Hellström [27]	Total: 3555	2.3	2.5	4.9[2]	2.7
	Boys: 1834	1.7	2.1	3.8	1.7
	Girls: 1721	2.9	3.1	6.0	3.7
Lee [21]	Total: 1325			6.7[3]	3.9
Kajiwara [66]	Total: 984			9.0[3]	9.0
	Boys: 532			9.2	9.2
	Girls: 452			8.9	8.9
Söderström [23]	Total: 715			6.3[3]	
	Boys: 367	3.0	3.8	6.8	
Joinson [67]	Girls: 348	3.2	2.6	5.8	
	Total: 8213			7.8[3]	
	Boys: 4222			6.9	
	Girls: 3991			8.8	
Swithinbank [68]	Total: 13973	6.4	0.9	7.3	
	Boys: 7217	6.0	0.7	6.8	3.3
	Girls: 3991	7.0	1.2	8.8	5.8
Children aged 11-13 years:					
Swithinbank [27]	Total: 1171	11.9	0.6	12.5[5]	
	Boys: 510	7.0	0.2	7.2	
	Girls: 661	15.7	0.9	16.6	
Lee [21]	Total: 913			1.1[3]	0.9
Kajiwara [66]	Total: 761			2.5[3]	
	Boys: 366			1.0	
	Girls: 395			3.9	
Söderström [23]	Total: 763			4.2[3]	
	Boys: 398	1.8	2.3	4.1	
	Girls: 365	3.0	1.3	4.3	
Children aged 15-17 years:					
Hellström [29]	Total: 651	1.5	0.3	1.8[2]	1.8
	Boys: 344	0.3	0.0	0.3	0.3
	Girls: 307	2.9	0.7	3.6	3.6
Swithinbank [31]	Total: 940			3.0[2]	
	Boys: 411			0.9	
	Girls: 529			4.7	

Episodes of UI: 1>1/6 months, 2>1/3 months, 3> 1/ month, 4>1/2 weeks, 5 occasionally

According to the studies by Hellström, the reduction from seven years to 17 years was 0.2% per year in those with wetting at least once a week and 0.3% when including all kinds of wetting. Swithinbank reported a far higher frequency for all kinds of wetting at age 11-12 years but not at 15-16 years and the reduction in his cohort of children was therefore approximately 2% per year.

UI was more common in girls in most studies, especially in the older age groups (**Table 3, figure 4**). From the prevalence found in the different studies, daytime UI could be suggested to be 1.5 times more common in girls than in boys at age seven years, whereas at age 16 years the difference was even more pronounced: 5-10 times more common in girls than in boys (**Table 3**). Overall in a population based study of 2856 children between 4.8-12.8 years, female gender was an independent risk factor for UI (OR 5.4 (2.6-11.1), [69].

1. PREVALENCE OF OVERACTIVE BLADDER (OAB)

In a Japanese study [66], the prevalence in children between 7 and 12 years of age, OAB was seen in 17.8%, with no significant difference between boys and girls. There was a gradual decrease in prevalence from 19.8% at the age of 7 years to 12.8% at 12 years.

2. COMORBIDITY:

a) Prevalence of NE

NE in combination with UI is denoted as NMNE as mentioned above. NE has been identified as an independent risk-factor for day-UI (OR 7.2 (3.4-15.2)) [69]. Association of NE to day UI was more often reported in children with frequent UI (≥ 2 episodes/ week), as compared to infrequent UI (< 2 episodes/ week) at 7.5 years [68]. In boys NE was seen in 70-80% of those with frequent day UI compared to about 50% in those with infrequent. Corresponding figures for girls was about 55% and 30%, respectively.

b) Prevalence of Bowel problems

Urinary and faecal incontinence often coexist in different combinations. Constipation in childhood is a very common condition and when functional faecal incontinence is seen, constipation is often the cause. The term encopresis can be used synonymously with functional faecal incontinence. An increasing number of epidemiological studies reporting the frequency of bowel problems are accumulating, either in terms of constipation or functional faecal incontinence, in children with daytime wetting. **Table 4** shows that the prevalence of bowel problems in day-wetting children approximately corresponded to a third of the children (21%-35%) [23,56,66-67,69-70], with even higher prevalence in the subgroup with dysfunctional voiding (43%) [70]. A significant association between day-wetting and bowel problems was shown [23]. These results support the new treatment concept of day-wetting children, with treatment of bowel problems as the first step. MNE, on the other hand, seldom have bowel problems (0%-1%), whereas in NMNE it is more common (16%-24%) [56,70].

In an epidemiological study from Japan including 5282 children, ages between 7-12 years, 81.5% were reported to have daily bowel movements. A significant higher prevalence of NMNE was found in those with constipation, compared to hose with regular daily bowel movements (3.4% vs 2.2%) [22].

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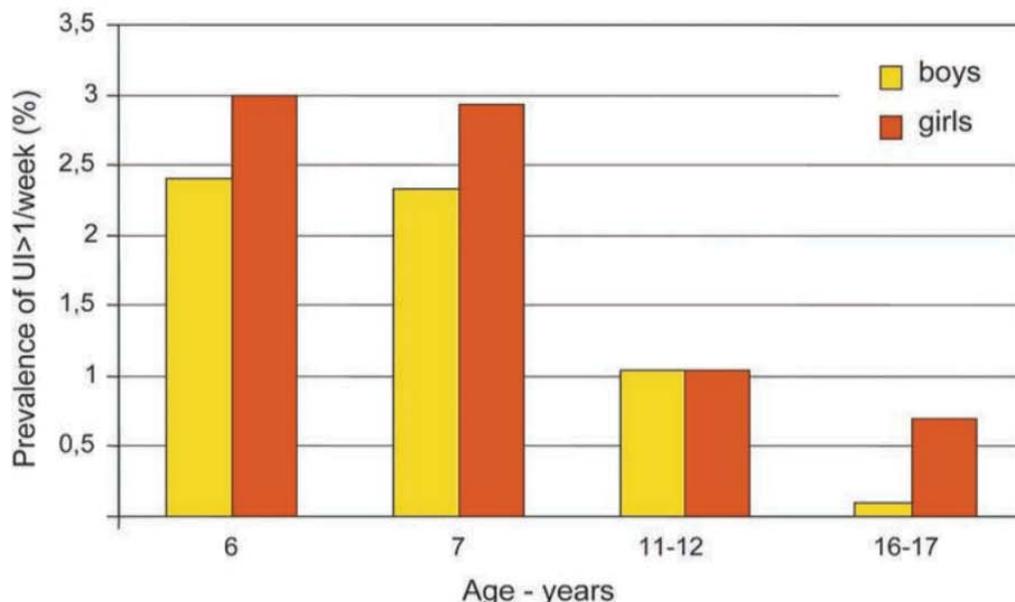
Figure 4. Prevalence of day UI (including mixed day/night) >1 episode/week by age and gender. Data are from: at age 6 years [71], 7 years [23, 27], 11-12 years [23, 30] and 16-17 years [29].

V. POTENTIAL RISK FACTORS FOR DAY WETTING

1. FAMILY HISTORY

Day wetting, also including those subjects with mixed day and night wetting, has been shown to be correlated with hereditary factors, in parallel to what is known about children with NE. However, the number of studies is limited (**Table 5**). Like for NE hereditary factors have been shown to be more pronounced in those with severe UI (>2 episodes/week), especially when paternal day UI is present (**table 5**) [40].

Table 4. Comobidities. The prevalence of concommittant bowel problems in children with day-wetting and nocturnal enuresis.

Author	Number bowel problems in day-wetting group	OR (95%CI)	Number children bowel problems in NE	OR (95%CI)
Söderstrom 2004 [23]	35%	7.2 (4.1-12.7)		1.2 (0.6-2.5)[2] 2.0 (0.6-6.3)[3]
Kajiwara 2004 [66]	33%			
Von Gontard 2004 [70]	25%[4]		0%-16%[1]	
Chandra 2004 [56]	24%		1%-24%[1]	
Joinson 2006 [67]	33%			
Sureshkumar 2009 [69]	21%	3.3 (1.4-7.7)[2]		

Episodes of UI: 1>1/6 months, 2>1/3 months, 3> 1/ month, 4>1/2 weeks, 5 occasionally

2. PSYCHOPATHOLOGY

Children under stress as a result of marital separation, for example, have a higher incidence of diurnal or mixed UI, according to some authors [16,39,71]. Moreover, psychopathology investigated by Järvelin [39] using the Children's Apperception Test (CAT) revealed a significant increase in the signs of repression, including an inability to express one's emotions and feelings (p=0.027), when comparing day wetting children with controls. Neveus [33] found that daywetting children had more difficulty falling asleep (OR 2.4, CI 1.4-4) and he interpreted them as "anxious children". Lettgren [72] found a significant increase in attention problems and delinquent behaviour in a certain form of day-wetting children (voiding postponement) using the Child Behaviour Check List (CBCL, Achenbach). In a recent paper [73] similar results were found with the highest rate of psychiatric comorbidity in children with UI due to voiding postponement and the lowest in children with MNE. In the group with encopresis 65% were considered to have severe behavioural problems [70], meaning that children with both wetting and bowel problems are at the highest risk for psychopathology.

In a population-based study investigating psychological problems associated with day UI, 8213 children were included of whom 643 suffered from daytime wetting at median age 7.5 years [67]. Overall the results indicated a rate of psychological problems that was twice the rate reported for children with no daytime wetting, particularly notable was the increase in externalising problems. After adjustment for developmental delay, gender, stressful life events, variables associated with family socio-demographic background and soiling, there was still an independent association of daytime wetting and behaviour problems

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Table 5. Day wetting vs family history (including mixed day/night wetting).

Author	RR (95%CI)	OR (95%CI)	Positive history (%)
Järvelin [39]			
-enuresis in mother	10.1 (3.4-29.3)		
-enuresis in father	5.9 (1.9-17.8)		
Sureshkumar [71]			
daytime wetting in			
-male sibling		5.3 (1.6-18.2)	
-paternal lineage		9.3 (3.2-27.3)	
Chiozza [16]*			
-enuresis in parents		12.3	
Bower [34]			
-family history of enuresis			70**
Neveus [33]			
-family history		2.0 (1.1-3.7)	
Von Gontard [40]<2 episodes/week			
-maternal NE		1.2 (0.9-1.6)	
-paternal NE		1.3 (0.9-1.8)	
-maternal day UI		2.6 (1.4-5.1)	
-paternal day UI		5.5 (2.4-12.5)	
>2 episodes/week			
-maternal NE		2.1 (1.2-4.0)	
-paternal NE		2.1 (1.0-4.3)	
-maternal day UI		3.3 (0.8-13.7)	
-paternal day UI		10.1(2.3-44.1)	

*Only children with mixed day and night wetting, **compared with 45% in dry children

(OR 2.04, CI 1.67-2.51). In another epidemiological study UI was found to be associated with parenteral concerns about the child's social behaviour (OR 3.4 (1.4-8.3)), [69]. It is not clear whether the behavioural problems described in these studies are a cause or a consequence of daytime wetting.

3. MINOR NEUROLOGICAL DYSFUNCTION AND DEVELOPMENTAL DELAY

Children with minor neurological dysfunction have also been shown to have an increased rate of day wetting. Duel [50] found that children with ADHD are three times more likely to have day UI than controls (p<0.0005). Also in children with delayed maturation or with mental retardation, the risk of day wetting is increased (OR 1.9 and 4 respectively), according to studies by Järvelin [28]. Perinatal events, which can also be suggestive of minimal brain dysfunction, have also been shown to be over-represented in day-wetting children. For example, Järvelin [39] found that the children of mothers who had suffered from toxaemia had RR of 8.5 (CI1.4-51.9) for day UI.

4. OTHER RISK FACTORS FOR DAY UI

Sometimes, functional day UI is difficult to distinguish from UI due to organic anomalies. The most prominent examples are the adolescent form of posterior urethral valves in boys and epispadias in girls.

In many papers, UTI is regarded as a risk factor for day UI. Järvelin [39] found RR of 8.6 (2.3-32.3) for UTI in day UI children. Neveus [33] was able to demonstrate similar connections; OR 2.3 (1.3-3.9) and similar results were seen in the Sureshkumar study [69]; OR 5.6 (2.0-15.6). However, these infections should probably be regarded as a consequence of the functional bladder disturbance with UI and not the other way round as a cause of the UI.

VI. SUMMARY POINTS

Nocturnal enuresis (NE)

- The prevalence of NE at age 7 seems to be around 10% for most countries, at age 11-12 years around 3% and at age 16 around 1.3%.

- The spontaneous resolution rate seems to be around 15% annually between 7 and 12 years, and between 12 and 17 years 11%.

- In an adult population the prevalence of NE seems to be 0.5%. The prevalence was 0.1% when including only those with a history of NE during childhood. Thus the risk for NE as adult if having the condition at 7 years of age can be calculated to 1%.

- Potential risk factors for NE in children include OAB, polyuria, family history, psychopathology, developmental delay, mental retardation, socio-cultural factors, sleep and arousal problems, sleep apnoea, constipation, sexual abuse and organic conditions such as infravesical obstruction.

- **Functional incontinence**

- Children who are and remain dry in the day seem to attain their diurnal continence between age 4 and 5 years.

- Diurnal UI, or combined diurnal and nocturnal UI, in children is caused by overactive bladder in the great majority of cases.

- Prevalence of functional UI decreases with age. At age 7 years prevalence figures vary between 3.2% and 9%, with the highest prevalence in recent studies. At age 15-17 years the corresponding prevalence is 1.2-3%.

- Variation in prevalence figures is mainly dependant on differences in frequency of incontinence episodes in the studies.

- Potential risk factors for diurnal UI in children include bowel problems such as constipation and functional faecal incontinence, family history, psychopathology, socio-cultural factors, minor neurological dysfunction, developmental delay, organic anomalies such as infravesical obstruction in boys and sexual abuse.

D. EPIDEMIOLOGY OF UI IN WOMEN

I. GENERAL COMMENTS AND DEFINITIONS

In this section we address the epidemiology of female UI, including its common subtypes, stress UI, urgency UI, and mixed UI. Current terminology for female UI is drawn from the 2010 IUGA/ICS joint terminology report [2] but in most instances is entirely compatible with current terminology for men [1] , and children [4] In considering the epidemiology of female UI, we mainly address the epidemiology of *the symptom of UI*, defined as complaint of involuntary loss of urine. There remains a paucity of work at a population level concerning either *the sign of UI*, defined as observation of involuntary loss of urine on examination, or on the formal diagnoses of urodynamic stress incontinence or detrusor overactivity.

A large majority of epidemiological studies have either not considered subtypes of UI, or only reported on *stress UI* (complaint of involuntary loss of urine on effort or physical exertion or on sneezing or coughing), *urgency UI* (complaint of involuntary loss of urine associated with urgency), and *mixed UI* (complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing). A small number of studies have reported prevalence and risk factors for adult *nocturnal enuresis* (complaint of involuntary urinary loss of urine which occurs during sleep). With a lack of validated questionnaire items for less common subtypes, the current literature is almost silent regarding the population prevalence and risks for *postural incontinence, continuous incontinence, insensible incontinence,* and *coital incontinence*, although they are sometimes grouped as "other incontinence".

The validity of urinary symptom questionnaires employed in epidemiological research is considered in detail in Chapter 5. Most questionnaires were initially developed using secondary care samples, with criterion validity demonstrated in comparison to bladder diaries, pad tests, or urodynamic diagnoses. Quite widely varying terminology is used in the items assessing stress incontinence and urgency incontinence in different questionnaires and some items do not capture all aspects of the standardised definitions. Even the surrounding context for the items is known to strongly affect prevalence estimates [74], and small variations in terminology from different questionnaires may have similar effects.

The optimal assessment of incontinence subtype remains controversial [75-76], but it is clear that self-report of symptoms differs systematically from detailed clinical evaluation. In particular, for women mixed incontinence is more common than would be expected by chance using questionnaire evaluation [77], and is reproduced less frequently using urodynamics [78-79]. Stress and urgency incontinence have different treatment options, and are presumed to have different underlying pathophysiology. Caution is therefore needed when comparing epidemiological studies that either do or do not report a separate mixed incontinence subgroup, and when generalising from population level data on mixed incontinence to clinical practice.

Self-report of incontinence symptoms should reflect the woman's own experience of incontinence, but may bear little relationship to expressed need for treatment. Across multiple measures, incontinence severity is shown to be only a moderate predictor of incontinence specific quality of life impairment [80-81]. It is important therefore to characterise both the severity of symptoms, through frequency of leakage and/or quantity of loss, and the perceived bother or impact on activities. Most questionnaires in contemporary use, including the ICIQ-SF, ICIQ-FLUTS and DAN-PSS, therefore ask patients to report both the frequency of UI, and its perceived bother. Cautious interpretation should be made of high prevalence rates obtained with case definitions that do not incorporate a measure of symptom bother.

Incontinence is a stigmatising condition in many populations [82], which creates a high risk for respondent bias in incontinence epidemiology [83-84]. Perhaps because of stigma, incontinence is also associated with low rates of presentation for care. Surveys assessing incontinence may therefore also be highly prone to both medical surveillance bias and Berksonian bias. In this section we therefore focus on community or population based samples with high response rate. To further minimise differential effects of such biases, where possible we report outcomes stratified by age, by type of incontinence, and by major subgroups of interest.

The majority of work reviewed in previous editions of this chapter, originated from developed countries. There have been many recent studies from both developing and developed countries [85], which are now reviewed. Subsequent discussion excludes however the epidemiology of obstetric vesico-vaginal fistula, which is covered in a later chapter.

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II. PREVALENCE

Among general population studies included in previous ICI editions, crude prevalence estimates for the most inclusive definitions of UI ('ever' 'any' or 'at least once in the past 12 months') have ranged from 5% to 69%, with most studies reporting a prevalence of any UI in the range of 25% to 45% (**Table 6**). This enormous variation between studies is seen both within and between countries, with few studies reporting age standardised rates, largely precludes meaningful comparison between countries. If there is variation in true prevalence rates between countries, it is obscured by cultural differences in the perception of UI and willingness to report UI, as well as methodological differences [86], including in the wording of questionnaire items, in the method of administration of questionnaires, and perhaps most importantly, with differences in case definitions employed [87-88].

Only four studies have used the same survey tools and methods to report female UI general population prevalence in more than one country (**Table 7**). Three studies have attempted to assess the relative prevalence in western nations [89-91]. Across all countries surveyed, all these three studies find that SUI is the most common subtype, followed by MUI, and then UUI. Hunskaar and colleagues surveyed 29,500 women in France, Germany, the UK and Spain [89]. By demonstration of similar age trends across all countries, they suggested both lower overall prevalence of incontinence in Spain, and a relative excess of urgency incontinence in France. The EPIC and EpiLUTS studies [90-91], used similar questionnaire items explicitly based on standard definitions. However, there was inconsistency between studies. The EpiLUTS study found similar prevalence of each UI subtype in the US, UK, and Sweden, while the EPIC study reported a more than 3-fold variation in prevalence between countries, with Sweden having a prevalence of 29.5% and Italy only 9.3%. The disparity in results could be explained by differences in sampling methods, or different response rates (58%, 33% and 59% respectively). A further recent study set in Senegal, Mauritania, and Chad, reports substantial variation in prevalence across countries, even after age stratification [92] The lack of consistency in between country comparisons, even for large surveys set in western nations, makes it impossible to assess the extent of true variation between countries. It remains difficult to establish stable, meaningful prevalence rates for female UI, when there is no consensus about what constitutes significant UI. Again, extreme caution is needed in making direct comparison of crude prevalence rates.

Although between study comparisons of female UI prevalence are largely unrewarding, we can meaningfully compare within study distributions of UI by age and UI subtype. **Table 8** summarises prevalence estimates by age for female UI from community or population based studies with response rate >60%, over the period January 2008 through December 2011. Again a 10 fold variation in crude prevalence is evident between studies, so where available, overall prevalence rates are given by UI subtype, while age trends are depicted with sparklines.

As in the studies comparing prevalence between countries, although absolute prevalence rates vary widely in recent cross-sectional work, the distribution of UI subtypes is consistent. Isolated stress incontinence accounts for approximately half of all incontinence, with most studies reporting 10-39% prevalence. With few exceptions mixed incontinence is found to be next most common, with most studies report 7.5-25% prevalence. Isolated urgency incontinence is uncommon, with 1-7% prevalence, and where recorded at all, other causes of incontinence occur with approximately 0.5-1% prevalence.

In summary, current data provide very disparate estimates of population prevalence for UI in women. Approximately 10% of all adult women report leakage at least weekly. Occasional leakage is much more common, affecting 25%-45% of all adult women. Prevalence rates from cross-sectional studies uniformly demonstrate an association with age, which is explored in more detail in the section on risk factors.

III. INCIDENCE AND REMISSION

Many prospective longitudinal studies have examined UI in women, either in the general population, or focused on pregnancy, menopause or old age. However, interpretation and comparison of incidence and remission rates is fraught with difficulties. Incontinence is not intuitively a condition, with fluctuating severity, indeed the popular perception in both the medical community and the laity, is of a chronic condition. However misclassification due to the unreliability of symptom assessment tools may cause the appearance of symptom fluctuation. Measuring the short term test re-test reliability for the BFLUTS questionnaire [116], the DAN-PSS [117], the IIQ[118], or any of the other commonly used questionnaires suggests that only 80-85% of item responses are stable over even a brief retest period. Thus even when a longitudinal study is able to use the exact same item for assessment across even relatively long periods of follow up, the effect of misclassification due to questionnaire unreliability may obscure a true effect of incidence or

Table 6. Population prevalence rates for female UI from studies assessing more than one country.

Reference	Method	Age	Country	Sample		Overall Prevalence %		
Hunskaa (89)	Postal	18+	France	3,881	All UI	44		
					SUI	13.6		
					UUI	11.9		
					MUI	15.0		
					Other UI	4.0		
			Germany	3,824	All UI	41		
					SUI	16.4		
					UUI	6.6		
					MUI	15.6		
					Other UI	2.9		
			Spain	6,444	All UI	23		
					SUI	9.0		
					UUI	4.8		
					MUI	6.0		
					Other UI	3.5		
			UK	2,931	All UI	42		
					SUI	17.2		
					UUI	6.7		
					MUI	14.3		
					Other UI	3.8		
Niang (92)	Postal	16+			Age Groups	<30	30-59	60+
			Senegal	682	All UI	31.4	30.9	25.0
			Mauritania	740	All UI	8.0	13.2	22.7
			Chad	648	All UI	8.0	17.5	95.0
Irwin (90)	Direct or telephone interview	18+	Sweden	19,165	All UI	29.5		
			Italy		All UI	9.3		
			Canada		All UI	13.0		
			Germany		All UI	11.4		
			UK		All UI	14.9		
Coyne (93)	Web Based	40+	US	10,584	All UI	67.0		
					SUI	23.1		
					UUI	6.7		
					MUI	21.1		
					Other UI	5.3		
			UK	3,983	All UI	69.0		
					SUI	28.6		
					UUI	7.1		
					MUI	19.6		
					Other UI	4.9		
			Sweden	1,293	All UI	67.1		
					SUI	26.9		
					UUI	7.9		
					MUI	16.9		
					Other UI	5.0		

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Table 7. Population based studies with response rate >60%, reporting prevalence of female UI by age.

Reference	Country	Sample Size	Survey Method	Age Range	Overall Prevalence (%)		Age Trend
Espuna-Pons(94)	Spain	9,063	Postal	15+	All UI	12.2	
Herschorn (95)	Canada	518	Telephone	18-90	SUI	25.5	
					UUI	9.3	
Tahtinen (96)	Finland	2,002	Postal	18-79	SUI	11.2	
					UUI	3.1	
Tennstedt (97)	US	3,205	Direct Interview	30-79	All UI	10.4	
					SUI	2.8	
					UUI	1.1	
					MUI	5.9	
					Other UI	0.7	
Lee (98)	South Korea	13,484	Direct Interview	19+	All UI	24.4	
					SUI	11.9	
					UUI	1.9	
					MUI	10.2	
					Other UI	0.5	
Zhu (99)	China	5,300	Direct Interview	20+	All UI	38.5	
					SUI	22.9	
					UUI	2.8	
					MUI	12.4	
Nygaard (100)	US	1,961	Direct Interview	20+	All UI	15.7	
Martinez-Agullo (101)	Spain	3,090	Direct Interview	25-64	All UI	4.0	
Bodhare (102)	India	552	Direct Interview	35+	All UI	9.6	
Ojengbede (103)	Nigeria	5,001	Direct Interview	15+	All UI	2.8	
					SUI	2.3	
					UUI	1.0	
					MUI	0.6	
Ahmadi (104)	Iran	800	Direct Interview	40-95	All UI	38.4	
Liapis (105)	Greece	2,000	Direct Interview	20-80	All UI	27.0	
					SUI	11.9	
					UUI	3.0	
					MUI	11.1	
					Other UI	1.1	
Amaro (106)	Brazil	685	Postal	22-96	All UI	27.0	
Lopez (107)	Puerto Rico	276	Direct Interview	21-64	All UI	34.8	
					SUI	16.7	
					UUI	4.0	
					MUI	14.1	
Correia (108)	Portugal	1,483	Telephone	40+	All UI	21.4	
Slieker-ten Hove (109)	Netherlands	1,397	Postal	45-84	All UI	58.8	
					SUI	30.6	
					UUI	6.1	
					MUI	23.2	
Ge (110)	China	3,058	Direct Interview	20-96	All UI	22.1	
					SUI	12.9	
					UUI	1.7	
					MUI	7.5	
Botlero (86)	Aus	504	Postal	24-80	All	6.8	
					SUI	4.8	
					UUI	0.7	
					MUI	1.3	
Wennberg (111)	Sweden	1,023	Postal	20+	1991 All	14.7	
					2007 All	27.8	
Franzen (112)	Sweden	4,609	Postal	18-79	All	28.9	
Zhu (113)	China	19,024	Direct Interview	20-99	All	30.9	
					SUI	18.9	
					UUI	2.6	
					MUI	9.4	
Lasserre (114)	France	2,183	Direct Interview	18+	All	26.8	
					SUI	12.1	
					UUI	2.9	
					MUI	11.2	
Onur (115)	Turkey	2,275	Direct Interview	17-80	All	46.3	
					SUI	21.3	
					UUI	19.9	
					MUI	16.7	

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Table 8. Studies reporting incidence and/or remission for UI in women.

Study	Country	Period (yr)	♀Sample Size	Loss to Follow Up (%)	Baseline Age	Case Definition	Prevalence at baseline (%)	Prevalence at follow up (%)	Annual Incidence (%)	Annual Remission (%)
Samuelsson (121)	Sweden	5	457	16.4	20-59	Any UI	23.5	27.5	2.9	5.9
Hagglund (122)	Sweden	4	338	26.6	20-50	Any UI	45.6	47.5	4.2	4.0
Wehrberger (123)	Austria	6.5	925	52.3	20+	Any UI Weekly UI	32.0 n/a	43.3 n/a	3.9 2.1	2.9 n/a
Townsend (124)	US	2	64,650	18.4	36-55	Monthly UI Weekly UI	52.5 n/a	48.3 n/a	6.9 1.9	7.0 n/a
Dallosso (125)	UK	1	6,424	48.9	40+	Monthly SUI	17.3	n/a	8.3	n/a
McGrother (126)	UK	1	12,036	20.2	40+	Any UI	34.2	n/a	8.8	25.2
Donaldson (127)	UK	3	12,750	33.0	40+	Any SUI	16.9	n/a	6.1-7.3	33.7-34.9
Waetjen (128)	US	5	3,301	18.1	40-55	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI Other UI	46.7 15.3 32.2 9.2 13.8 2.7	n/a	11.1 1.2 5.0 3.2 2.4 0.5	n/a
Liu (129)	Australia	2	2,272 (♂&♀)	13.9	65+	Any SUI Any UUI	12.1 38.4	15.4 37.4	15.4 18.8	n/a n/a
Goode (130)	US	3	490	5.0	65+	Monthly UI	0.41	n/a	9.7	13.0
Ostbye (131)	Canada	10	5,332	60.2	65+	Any UI	19.5	28.8	1.8	n/a
Wennberg (120)	Sweden	16	2,911	51.6	20+	Any UI	14.6	27.8	1.3	2.1
Moller (132)	Denmark	1	2,860	20.1	40-60	Weekly SUI Weekly UUI	13.1 7.3	11.0 6.7	4.0 2.7	41.4 42.0
Hotledahl (133)	Norway	1	507	3.6	50-74	Monthly UI	30.6	29.8	0.9	1.4
Byles (134)	Australia	9	12,432	42.4	70-75	Sometimes UI	20.7	27.3	1.62	n/a
Lifford (135)	US	2	58,703	10.4	54-79	Monthly UI Weekly UI	45.2 n/a	51.6 n/a	4.6 1.8	6.6 4.4
Jackson (136)	US	2	1,017	19.0	55-75	Any UI	66.0	63.1	9.6	7.1
Nygaard (137)	US	6	2,025	n/a	65+	Any SUI Any UUI	40.3 36.3	n/a n/a	4.77 4.75	5.02 3.68
Gavira Iglesias (138)	Spain	5	486	34.9	65+	Any UI	41.0	54.0	7.2	2.8
Herzog (139)	US	2	1,154	30.2	60+	Any UI	37.7	52.7	15.8	7.5
Burgio (140)	US	3	541	61.9	42-50	Monthly UI	30.7	n/a	2.7	n/a
Melville (141)	US	6	5,820	18.1	57-67	Monthly UI	13.5	n/a	3.5	n/a
Jahanlu (142)	Norway	10	2331	13.0	40-44	Any UI	38.9	43.9	4.9	n/a
Botlero (143)	Australia	2	506	12.6	26-82	Any UI	41.6	44.6	8.5	8.4

remission. Even non-differential misclassification bias, can have devastating consequences both for estimates of absolute cumulative incidence, and relative incidence risk, and such effects are largest for conditions such as UI, with high prevalence and low incidence [119].

Other methodological differences may also cause wide variation. Questionnaires that use different recall periods (e.g. any leakage in last week, any leakage in last year, any leakage ever), will produce different estimates of incidence and remission. Due to changes in standard definitions, many studies also use different case definitions

at baseline and follow-up. Finally, although loss to follow up itself is very variable between studies, differential loss to follow-up is observed in almost all studies, and must substantially decrease generalisability.

Annual incidence rates for broad definitions of UI ("monthly" or "any") range from 0.9% to 18.8%, while rates for weekly UI show less variation at 1.2-4.0% (**Table 8**). There is a significant negative correlation between the length of a study and its reported annualised incidence rate, suggesting that short studies of 1-2 years overestimate incidence due to a dominating effect of misclassification.

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Limiting comparisons to studies with >5yr follow up suggests incidence of 1.3-4.9% even for inclusive definitions of UI. Fewer studies have reported remission rates, and again estimates vary widely between 1.2 and 42%. Again limiting comparisons to longer studies of >5yrs suggests rates of 2.1 to 5.0%. Overall these results are compatible with findings from cross-sectional studies, with modest increases in UI prevalence across the whole female population of 0.5-1% per year. Although the extent of cohort effects has rarely been reported, current data suggests that earlier cohorts are less likely to report incontinence, consistent with evidence of increased care seeking among later cohorts[111,120],

IV. RISK FACTORS

In this section we summarise the most important reported demographic, social, environmental, and lifestyle correlates of urinary incontinence in women. Genetic risk factors for incontinence and prolapse are considered together in a later section. While a majority of previously cited studies have reported associations with incontinence, some caution is again needed in judging whether these may be causal risk factors.

As already seen, a large majority of studies are cross-sectional in design, providing limited evidence of causation, since the temporal association of the putative risk factor and the onset of incontinence cannot be assessed. Where possible we therefore try to focus on risk factors for incident UI, from longitudinal studies. Again though, with the exceptions of mode of delivery, menopause hormone therapy, and weight loss, there remains a dearth of interventional studies. Even the highest quality observational studies may suffer from residual or unmeasured confounding.

1. AGE

The age distribution for incontinence of all causes reported in the widely cited EPINCONT study[144], depicts a steady increase in moderate and severe incontinence throughout the adult lifespan, but with a distinct peak in slight incontinence around the time of the menopause. Other large studies have however, reported a steady increase in prevalence for both slight and severe UI, without a distinct menopausal peak[145]. The timing and causes of a fifth and sixth decade peak have been explored in a number of high quality longitudinal studies of menopausal transition, discussed subsequently. Where such a peak is identified from cross-sectional studies, it is most pronounced for stress incontinence[89,146]. Across most cross-sectional studies isolated stress incontinence declines into old age, as mixed incontinence becomes relatively more common[144,147]. Besides methodological differences, disparity in age ranges, severity thresholds, and proportion of each subtype of incontinence probably therefore explains the differences in age trends seen in **Table 3**. These age trends from cross-sectional studies may in any case be biased by cohort or period effects.

While most cross-sectional studies find an increase in crude prevalence into old age, some recent studies identify a peak in all causes of incontinence, with a decline in the eighth and ninth decade. Such a large disparity might be explained by sampling strategies that include or exclude institutionalised adults. The epidemiology of UI in this vulnerable group deserves special attention. Only one study provides data from more than one country, allowing cross-border comparisons. From a population of 279,191 elderly people in care homes, from Denmark, France, Iceland, Italy, Japan, Sweden, and the US, the prevalence of female urinary incontinence was relatively stable at 42.0-72.5%[148], with much of that variation accounted for by differences in age structure, and proportion of residents with functional or cognitive impairment. Indeed variability in prevalence estimates for female care home residents across the entire literature is much less than for the general population[149], ranging from 42.0% in Japan [78] through to 78.4% in the US (using a much more inclusive definition) [150]. Urinary incontinence is associated with nursing home admission from the community [151]. This may in part explain the apparent steeper increase in prevalence with age in nursing homes compared to community dwelling samples [150]. Loss to follow up certainly limits our ability to accurately assess age trends in the elderly from cross-sectional studies.

Given the difficulties in establishing robust incidence estimates, most longitudinal studies do not provide good evidence of age trends in incidence. Many studies have either reported no change in incidence with age, or a stable incidence in middle age, with a sharp increase in old age. However, the large Nurse's Health Study cohort [145], provided good evidence of a decrease in incidence of stress UI following the menopause, which has more recently been explored in analyses of the SWAN study[152], the 1946 British Birth Cohort[146], and the Hordaland Women's Cohort [142,153]. All these studies provide consistent evidence of a peak in incontinence at the time of the menopause, with pre and peri-menopausal status being associated with increased incidence of UI and decreased remission of UI compared to post-menopause. As will be discussed in the section on menopausal replacement therapy, part of this peak may be iatrogenic. Consistent with evidence from cross-sectional studies [89,144], the peak is attributable mainly to slight stress incontinence.

While the association between age and female UI is clearly important for planning healthcare resource allocation, in many studies this is not an independent association. Other risk factors associated with age, including parity, co-morbidities, and BMI attenuate the association with UI [145], and additional adjustment for relevant co-morbidities typically eliminates the association [97]. Confounding factors adequately explain the association between age and UI, and therefore UI in women should not be considered as an intrinsic consequence of the aging process itself.

2. OBESITY AND ADIPOSITY

Perhaps even more than age, obesity is the most clearly established risk factor for UI in women. There is a wealth of cross-sectional, longitudinal, and interventional data demonstrating a positive association between BMI and UI, which has recently been subject to two systematic reviews [154-155]. Across a wide range of studies obese women have approximately double the risk of UI. A typical pattern of association, taken from the large Nurses' Health Study II [156]. (n=83,355) is demonstrated in **figure 5**. The ORs for UI by severity are plotted against BMI, from underweight through to obese. Although the Nurses' Health Study II is limited to middle aged women, such findings are consistent across all age groups, both within studies[157], and between studies[154]. This association is quite minimally attenuated by adjustment for other risks for UI.

Data from the EPINCONT survey also demonstrate the same positive association between BMI and more severe incontinence. Additionally they indicate that such associations hold for the major subtypes of incontinence (**Figure 6**), but are most pronounced for mixed UI, and relatively modest for UUI. Similar findings were reported for data from HERS [158]. and the 1946 British Birth Cohort[159]. with the associations with BMI being greater for stress or mixed UI compared with urgency UI.

The temporal association between BMI and UI is also established with data from the 1946 British Birth Cohort [161]., SWAN [128]., MRC Incontinence [125]. and the Nurses' Health II studies [162]. demonstrating that earlier onset of obesity is associated with increased risk for UI in middle age[161], and that both higher BMI and greater weight gain are associated with increased risk of incident UI [125,128,162]. Although again it is hard to compare between studies, it appears that BMI may be a greater risk factor for incident UI than for prevalent UI adding credence to its causal association [128]. As for cross-sectional studies, the association is stronger for incident stress UI and mixed UI, compared with incident urgency UI [125, 128].

There is adequate evidence [163-164], that obesity increases intraabdominal pressure, predisposing to stress incontinence, while coexisting
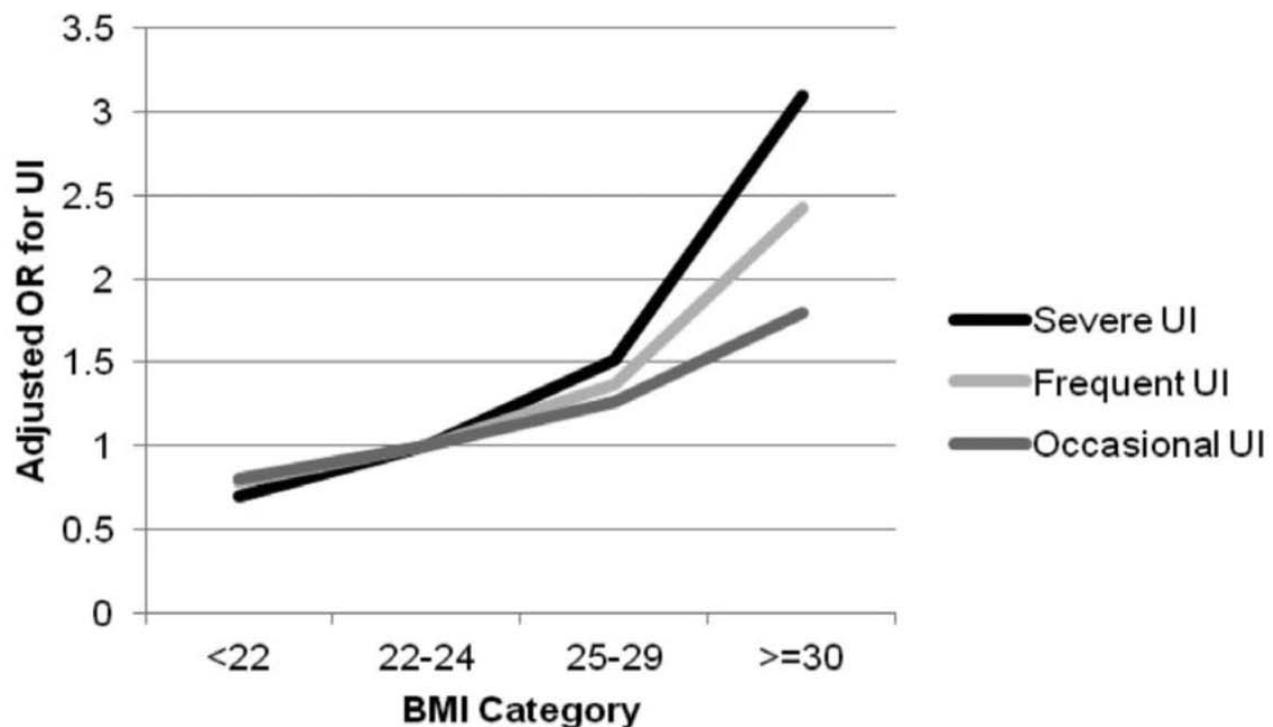
Figure 5. Associations between BMI and UI severity from [156].

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metabolic syndrome predisposes to urgency incontinence [165-168]. Consistent with this hypothesis waist circumference and waist to hip ratio appeared to be associated only with stress UI, and not with urgency UI in the SWAN [128] and HERS studies[158]. More recent data from BACH [159] and KNHNES [170]. indicate that measures of central adiposity are also correlated with urgency UI.

Finally, intervention studies for weight reduction have reported that even modest weight loss is associated with improvement or resolution of both stress and urgency UI, with the probability of resolution correlated to the degree of weight loss [163,171-174]. Despite the complex interplay between weight and other risk factors for UI, we therefore have very robust evidence to support a causal role of BMI in the development of UI.

3. PARITY, PREGNANCY AND MODE OF DELIVERY

Parity is considered by the laity as among the most important risk factors for UI. This is reflected in almost all large cross-sectional surveys (**Figure 7**). Some early studies reported a threshold effect at one delivery and little or no additional risk with increasing parity [175-177], but in most subsequent work, increasing parity is associated with increased risk of UI. A single delivery is typically associated with adjusted OR of around 1.3-1.6 for UI, and further deliveries linearly increasing the risk up to an adjusted OR of 1.5-2.0 [128,145,156,178]. As expected these effects are strongest in the third and fourth decades, with substantial attenuation through middle age, and in many studies no persistent effect in old age [157,178-180], as other risk factors come to dominate. Although the EPINCONT[178] and SWAN [128] studies reported only association between parity and stress or mixed UI, other studies have suggested, a reduced but significant association with urge UI also [181-182].

There is a substantial difference in effect between vaginal delivery and caesarean delivery, that has also been subject of a systematic review [183]. Meta-analysing data from four large cross-sectional studies [184-187], suggested a significant protective effect of caesarean on stress UI (OR 0.56) and mixed UI (OR 0.70), consistent with data both from more recent cross-sectional [179,181], and longitudinal studies [188-191]. While the existing interventional studies remain significantly underpowered, even in aggregate, a trend towards protective effect of caesarean is still seen [192].
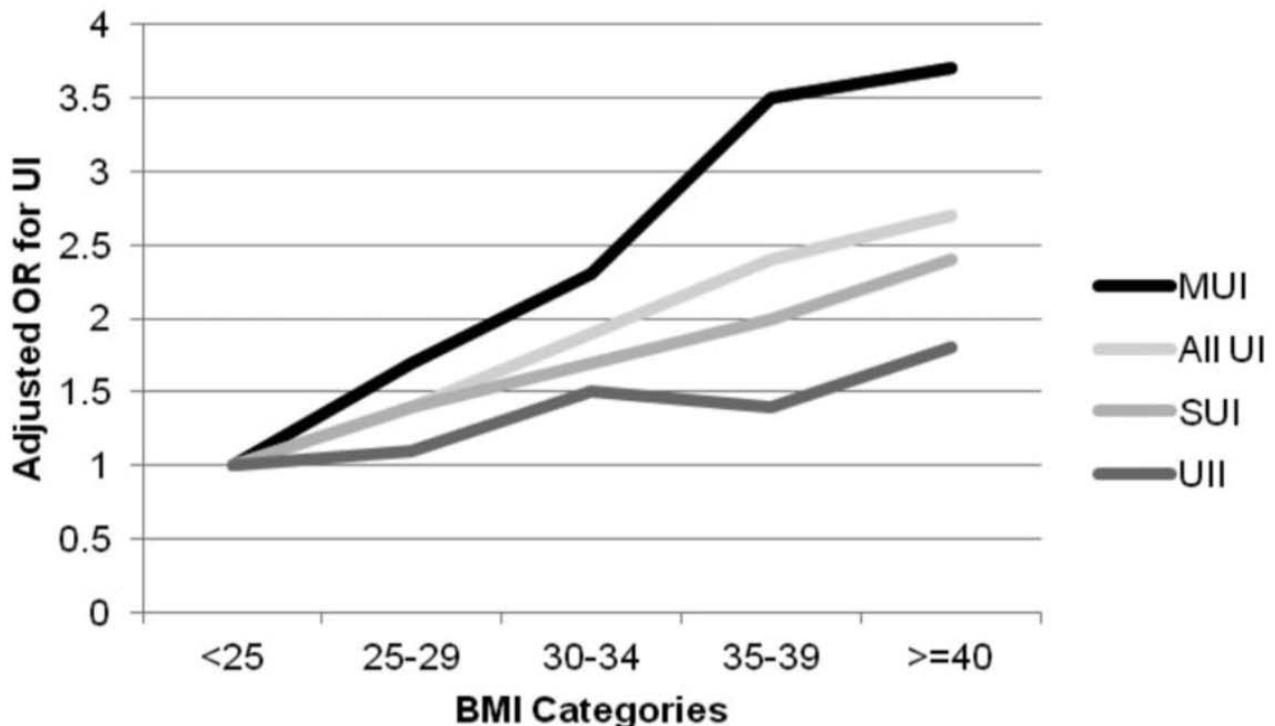

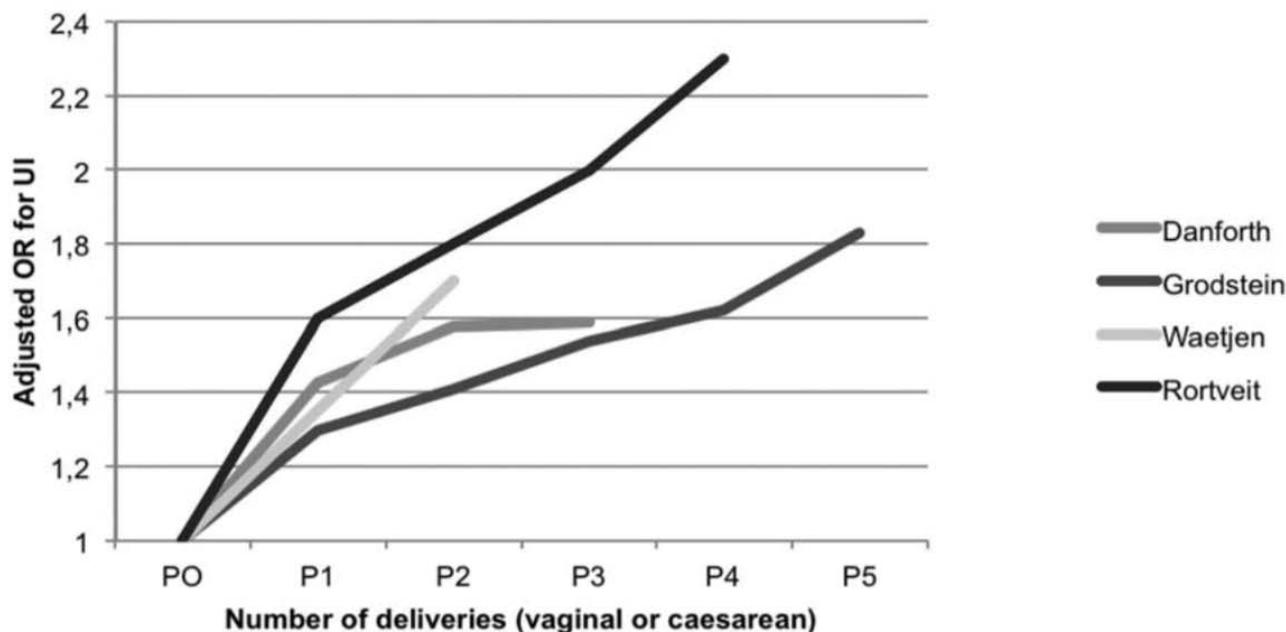Figure 6. Associations between BMI and UI subtype from [160].

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Figure 7. Adjusted OR for UI from large cross-sectional surveys grouped according to number of deliveries(128,145,156,178)

Pregnant women, and those in the early post-partum period are typically excluded from population-based studies of UI, but a large body of work considers the specific epidemiology of UI in and around pregnancy. A recent systematic review including 33 population based studies, each with response rate over 50% [193], concluded that the prevalence of UI in the first three months post-delivery was 30%, and with infrequent stress UI being most common. As demonstrated in **Table 9**, there is a gradual decrease in prevalence during the first post-partum year. The difference in UI rates between women delivering vaginally and those delivering by caesarean is evident immediately after delivery.

Despite the protective effect of caesarean, for many women the onset of incontinence is during pregnancy itself. Point prevalence of UI is low in the first trimester, rising rapidly in the second trimester and increasing slightly in the 3rd trimester [204-205]. In the population based Norwegian Mother and Child Cohort Study, (n=43,279), the prevalence of stress incontinence from before to during pregnancy, rose from 9% to 31% in nulliparous women, and from 24% to 42% in parous women. In contrast, mixed incontinence showed a similar rise in both groups (from 6% to 16% and from 8% to 20%, respectively). Urge incontinence remained virtually unchanged in both groups at less than 5%. In follow up of these women, onset of incontinence during pregnancy was strongly predictive of post-partum UI, with little modification by mode of delivery. Such an effect seems to persist even into long term follow up [189-190, 206-

207], even for women who return to full continence in the immediate post-partum period. It seems that the temporary physiological changes during pregnancy may reveal women with a predisposition to incontinence in later life, in a manner analogous to gestational diabetes.

There are other suggested potentially modifiable obstetric risk factors, including induction of labour, forceps delivery, and use of episiotomy. Regardless of conflicting observational evidence of an effect of episiotomy (for example [195,203,208-209]), there are a large number of interventional studies that have not shown either harm or benefit [210]. Similarly while forceps delivery has conflicting evidence from observational studies (for example [199,209,211-212]), within the context of the second stage of labour, maternal urinary incontinence is of secondary importance in decision making regarding choice of delivery instrument [213]. In a similar vein, while induction and augmentation of labour, and use of epidural anaesthesia have each been identified as being associated with both early postpartum and persistent UI [198,214-216], it is doubtful whether this should have any effect on current obstetric practice.

Many other suggested obstetric risk factors, including age at first delivery, and birth weight, are perhaps not meaningfully modifiable. Several studies have suggested that older age at either first or last birth is associated with UI [159,217-219], although more recent data from the RRISK study suggested a U shaped distribution [216], with very young mothers also at increased risk. Inadequate adjustment for

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Table 9. Prevalence of urinary incontinence in the first post-partum year among primiparous women by type of delivery

| Reference | Country | Type of delivey | N | Type of UI | Freq. of UI | Prevalence (%) by months post partum | | |
						1 to 3 months	4 to 6 months	7 to 12 months
Chaliha (194)	UK	VD	289	All Stress	Any	15 13		
		CS	131	All Stress	Any	9 8		
Eason (195)	Canada	VD	467	All	Any >weekly Daily	31 10 3		
		CS	104	All	Any >weekly Daily	12 2 1		
Eftekhar(196)	Iran	VD	357	Stress	Any		16*	
		CS ECS CSL	345	Stress	Any		12* 11* 25*	
Ekstrom (197)	Sweden	VD	197	Stress Urge	Any	20 4		15 6
		CS	192	Stress Urge	Any	4 3		5 5
Pregazzi (198)	Italy	VD	379	Stress Urge	Any	8 6		
		SVD	218	Stress Urge	Any	16 1		
Farrell (199)	Canada	SVD	313	All	Any	23*	22*	
		CS ECS CSL	125 27 98	All	Any	8* 4* 9*	10* 5* 12*	
Groutz (200)	Israel	SVD	145	Stress	2+/mo.			10*
		ECS CSL	118 100	Stress	2+/mo.			3* 12*
Glazener(201)	New Zealand, UK	VD SVD IVD	2805 1954 851	All	Any	32, 29* 31, 28* 33, 30*		
		CS	569	All	Any	16, 12*		
Schytt (202)	Sweden	VD SVD IVD	750 617 133	SUI	Any			20 19 22
		CS ECS CSL	165 43 122	Stress	Any			9 0 11
Borello-France (203)	USA	VD	356	All Stress Urge Mixed	Any	35 17 4 15	31 14 3 14	
		ECS	116	All Stress Urge Mixed	Any	25 11 4 10	23 14 1 8	

* Restricted to women with no UI prior to pregnancy
VD=all vaginal deliveries; SVD=spontaneous vaginal delivery; IVD=instrumental vaginal delivery (forceps and/or vacuum); CS=all Cesarean sections; ECS=elective Cesarean section (prior to labour); CSL=Cesarean section after onset of labour

socio-economic class may explain all these effects. Numerous studies have suggested that greater birth weight at a single delivery, or maximum weight of infant across all deliveries may also be associated with UI [177,179,201,216,220], but again randomized interventional trials of elective caesarean are needed before making clinical recommendations.

4. ETHNICITY AND RACE

With wide variations in UI prevalence between studies, comparison by race and ethnicity can be made only where such data have been reported within one study. Almost all population-based studies comparing the prevalence of UI among women from one or more racial or ethnic groups originate from the US, which may limit generalisability of conclusions. Results are summarised in Table 10. In general, across all studies, white women have a higher prevalence of UI, and in particular stress UI than all other groups.

The starkest and most consistent contrast is in rates of stress UI for black and white women. In most studies, black women have half the prevalence of stress UI compared to white women, with differences persisting after adjustment for age, parity and BMI. In comparing prevalence of mixed and urge UI for white and black women, there is less consistency. Most studies suggest similar prevalence of urge UI and mixed UI, however, the recent BACH survey found very high rates of mixed UI [27] among black women, while the EPI study reported very high rates of pure urgency UI [221].(**Table 10**) These cross-sectional data are supplemented by longitudinal studies. In SWAN [128], black women were at half the risk of incident stress UI, but nearly double the risk of incident urgency UI. In the Nurses Health Studies [222], black women had lower risk of both overall UI, and stress UI after adjustment. The consistency of this difference across both cross-sectional and longitudinal studies, employing different case definitions suggests a real difference in prevalence rather than simply reporting bias.

Typically smaller groups of east Asian or Hispanic women have been included in these studies, which precludes clear conclusions. Broadly though, Asian women report lower prevalence of both stress and urgency UI. There is less consistency in comparisons of Hispanic and non-Hispanic white women, with some studies reporting higher, and others lower overall prevalence. This heterogeneity may be explained, at least in part, by differences in prevalence among sub-populations, with Mexican-American women being at higher risk than other Hispanic women [226], or differences in extent of adjustment for covariates.

5. MENOPAUSAL REPLACEMENT THERAPY

Menopausal oestrogen replacement therapy was widely prescribed as a treatment for urinary incontinence during or after menopause, on the basis of rather heterogenous data from clinical trials [231] and inconsistent associations in cross-sectional studies [215,232]. While current evidence overall continues to support prescribing of topical oestrogen [233], the Nurse's Health Study[234], the Heart Estrogen/Progestin Replacement Study (HERS) [235], and Womens' Health Initiative (WHI) Hormone Replacement Trial [165] all provided strong evidence that oral oestrogens, with or without combined progestogens were associated with increased incident UI. In the placebo controlled HERS trial, women randomized to conjugated oral oestrogen plus medroxyprogesterone were more likely to experience worsening of their incontinence over 4 years (39% vs 27%, p<.001)[164]. In the randomized WHI trial, continent women receiving oestrogen, with or without progestogen, were approximately twice as likely to have developed stress incontinence at 1 year (16% vs 9%, p<.0001) [236]. The risks of mixed and urge incontinence were also significantly increased, though more modestly. Further trials including oestrogen arms have subsequently been reported during development of selective oestrogen receptor modulators (SERMs), confirming these findings [237]. Some SERMs, have themselves been associated with an increased risk of UI [238] although raloxifene appears safe.

6. HYSTERECTOMY

Hysterectomy is among the most common major procedures performed for women in Western nations. Many women date the onset of incontinence to a hysterectomy, but uncontrolled case series and small randomised trials produced conflicting results. Evidence from large population based observational studies has increasingly suggested a causal link, although the underlying pathophysiological mechanism is poorly understood.

Among a sample of 1,517 Taiwanese women aged 65+, hysterectomy was associated with OR 1.8 for UI, with no difference by hysterectomy route [239]. Earlier trials had however suggested either no effect [121,135] or rather more modest effects [240]. Where an association is found, it is strongest with case defintions consistent with "severe UI" [136,156,185], perhaps reflecting high rates of mild UI in controls. Using a sample of more than 900,000 women from the Swedish Population Register, abdominal hysterectomy for benign disease was associated with hazard ratio 2.1 for subsequent stress UI surgery, while vaginal hysterectomy for prolapse was associated with hazard ratio 6.3 [241]. Similar results were observed comparing hysterectomy and endometrial ablation in the Scottish Morbidity Returns database [242]. Recent data from a randomised trial of levonorgestrel-IUS versus hysterectomy [243] does confirm this effect. In follow up of 236 women, increased incidence of both stress UI (OR 1.83) and urgency UI (OR 1.48) was first noticed only at 10 years, with corresponding higher rates of treatment.

Table 10. Prevalence of UI by Race/Ethnicity in Population-based Studies.

Reference	Age	Sample	Case Definition	White	Hispanic	Black	Asian
Fultz (223)	70+	3,991	Any UI	23	-	16	-
Nygaard (224)	50-69	5,701	Any UI	17	10	10	-
Nygaard (100)	20+	1,961	Monthly UI	16	16	14	-
Burgio (140)	42-50	541	Monthly UI	32	-	18	-
Grodstein (145)	50-75	82,936	Monthly UI Weekly UI	35 18	28 16	21 10	26 13
Danforth (156)	37-54	85,670	Monthly UI Weekly UI	18 26	19 26	14 22	14 18
Sampselle (225)	42-52	3,258	Any UI	66	42	50	52
Waetjen (128)	42-52	3,002	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI	57 20 32 8 16	28 11 21 1 5	39 13 13 12 13	39 9 27 4 7
Anger (226)	60+	23,477,726	Any UI Monthly UI Weekly UI Daily UI	41 35 25 15	31 27 25 8	20 17 15 11	-
Jackson (227)	70-79	1,558	Weekly UI Weekly SUI Weekly UUI	27 12 11	- 	14 5 7	-
Dooley (228)	20+	4,229	Any UI Any SUI Any UUI Any MUI	53 27 8 19	50 26 8 17	38 12 11 15	-
Fenner (221)	35-64	2,814	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI	33 21 13 4 7	- 	15 9 4 4 4	-
Thom (83)	40-69	2109	Monthly UI Weekly UI Daily UI Weekly SUI Weekly UUI Weekly MUI	45 30 12 15 9 3	51 36 17 18 10 5	37 25 12 8 14 2	34 19 9 8 7 3
Markland (229)	65+	421	Any UI	45	29	-	-
Markland (230)	65+	490	Monthly UI	41		25	
Tennstedt (97)	30-79	3,205	Weekly SUI Weekly UUI Weekly MUI Weekly Other UI	35 13 44 7	14 11 69 6	9 3 82 5	-

Overall hysterectomy by any route appears to be associated with development of subsequent incontinence symptoms, and particularly with need for stress UI surgery. The data from observational studies should still be considered cautiously, as findings may be influenced by both healthy responder bias and medical surveillance bias, the latter of which may also affect unblinded interventional studies.

7. DIET

Studying diet as a risk factor for UI remains challenging. While some dietary constituents such as coffee, alcohol or carbonated beverages have been suspected as worsening UI, there is little theoretical reason to suspect other dietary constituents as causing, or protecting from, UI. Dietary data are difficult to obtain reliably. Studies of dietary factors must adjust for confounders, notably age and body mass, and should consider the trade-offs made with other constituents. Finally, women may change dietary intake in response to UI, making cross- sectional studies of diet and UI difficult to interpret.

Several studies have examined the consumption of coffee as a risk factor for UI. While some studies report a positive association with an increased risk of UI [131,244-245], others have either reported no association [246], or a protective effect [125,247]. Even within the large EPINCONT study there appeared to be conflicting findings with a positive association with mixed UI, but a negative association with stress UI [160]. The WHI study demonstrates a dose-dependent positive association between caffeinated coffee and urgency UI, but not for decaffeinated coffee or other UI subtypes [248]. The overall picture is therefore unclear.

The EPINCONT study suggested a positive association between tea drinking and stress UI or mixed UI [160], while analysis of the Swedish Twin Registry Cohort showed an association only with overactive bladder [247]. The Leicester MRC Incontinence study is one of two studies to have used food frequency questionnaires, and found no association with tea [125]. It is unclear whether tea consumption contributed significantly to the overall association between UI and dietary caffeine in the WHI study [248]. A positive association between alcohol consumption and UI has been reported by some studies [249], but is found to be either protective [125,250], or of no significance [160] in other studies.

The most comprehensive assessment of diet as a risk factor for UI comes from the Leicester MRC study [125]. Besides effects reported above, this study also found an increased incidence of stress UI with carbonated drinks, and reduced incidence of overactive bladder with bread, potato and vegetable consumption. While these effects certainly provide interesting avenues for further research, there is a concern that they may be surrogates for other unidentified socioeconomic risks, rather than truly causal. Overall there is a lack of consistency in reports of dietary associations with UI that most likely reflects methodological limitations rather than differences between populations.

8. SOCIOECONOMIC STATUS

Socio-economic status (SES) is strongly correlated with many of the other risk factors for UI including parity, BMI, diabetes, depression, smoking and timing of menopause. Higher SES is consistently associated with increased care seeking for UI, but there is conflicting evidence of association between SES and UI prevalence, or bother. While many studies do include some measure of SES as a potential confounder, its effect is frequently not reported. **Table 11** summarises some of the major studies that have reported associations, to highlight inconsistencies both by SES definition and UI definition. In the table a positive association is cited where women of higher SES, i.e. higher income, more education, report a greater prevalence of UI.

9. SMOKING

Data from observational studies on smoking are again quite inconsistent. It has been reported to be an independent risk factor for UI in women in some cross-sectional studies [108,156,160,225,256] but not in many others [96-97,110]. Within studies that do find an association, former smokers have a risk intermediate between never smokers and current smokers, and some dose response effect is evident, adding plausibility.

However, with one exception longitudinal studies have consistently failed to find a significant association between either past or current smoking and incident UI in multivariate analysis [121,128,131,135,257]. Only in the Leicester MRC study [125] was current smoking associated with increased risk for incident stress UI. The conflicting data from cross-sectional studies and lack of association between smoking and incident UI in most prospective studies suggests that smoking is probably not a causal risk factor for UI.

10. PHYSICAL ACTIVITY

Evaluating associations between physical activity and incontinence remains complex. It is clear that high impact exercise such as gymnastics [258-259] or trampolining [260-261]. is a direct cause of stress UI, with a dose dependent deleterious effect. However, women who suffer from UI, and particularly stress UI, may feel less able to engage in such sports [262]. Furthermore with increasing interest in core training as a treatment for UI [263], there are theoretical reasons to believe that low impact exercise might have a direct therapeutic effect. With these competing mechanisms at play, unsurprisingly cross-sectional studies have again

Table 11. Selected studies reporting associations between socioeconomic status and UI in women.

Reference	Country	♀Sample	SES Measure	Incontinence Definition	Association
Huang (251)	US	2,109	Educational level	Bothersome UI	Negative
Sampselle (225)	US	3,302	Educational level Financial strain	Any UI Bothersome UI	Positive Negative
Waetjen (128)	US	2,702	Educational level Social Support	Monthly UI Monthly UUI	Negative Positive
Kraus (252)	US	654	Occupation	Bothersome UI	Negative
Tennstedt (97)	US	3,205	Composite Index	Weekly UI	Nil
Melville (185)	US	3,506	Educational level Income	Monthly UI Monthly UI	Negative Negative
Saadoun (253)	France	2,640	Educational level Occupation	Monthly UI Monthly UI	Nil Nil
Roe (254)	UK	2,699	Occupation	Monthly UI	Nil
Kuh (159)	UK	1,333	Educational level Educational level	Monthly SUI Monthly UUI	Positive Nil
Coyne (255)	US/UK/ Sweden	15,861	Educational level Occupation	Monthly UI Monthly UI	Negative Negative
Ge (110)	China	3,058	Educational level Occupation	Monthly UI Monthly UI	Negative Negative

produced conflicting evidence (see for example [97,264-265]). However, among cross-sectional studies, comparison of low impact and high impact exercise is suggestive that, as hypothesised, high impact sports might be harmful, while low impact sports might be protective [160,266].

Evidence from longitudinal studies overall suggests that exercise does have a protective effect against incident UI, but perhaps only mediated via an effect on weight. In the Leicester MRC study, women who reported that they exercised less frequently were at increased risk for both incident stress UI and OAB in a model that adjusted for physical functioning, although notably this association was eliminated in a full model, adjusting for obesity[125]. In a study of 4,291 older women exercise at baseline was not associated with incident UI at 10 year follow up after multivariate adjustment [131]. Perhaps the strongest evidence comes from the Nurses' Health Study [267]. In this population of US nurses aged 54-79, a higher level of physical activity across 14 years of follow-up, was associated with a reduced risk of UI overall, and specifically stress UI, although after adjustment for BMI and other factors, the overall effect was small.

11. COMORBIDITIES: DIABETES, UTI, COGNITIVE IMPAIRMENT, ISCHAEMIC HEART DISEASE, PHYSICAL IMPAIRMENT AND DEPRESSION

In cross-sectional studies many different comorbidities have been associated with UI in univariate analysis [232,255,268]. However, in most cases these have no explicatory power, being neither a cause nor consequence of UI, but only associated with other known or unknown mediators of UI, or differentially diagnosed due to medical surveillance bias. In this section, we therefore concentrate on studies that are able to adjust for a wide range of confounders, and give priority to associations of incident UI.

Many, though not all, cross sectional studies have reported urinary incontinence to be more common in women with either type 1 or type 2 diabetes than among women with normal glucose levels even after extensive adjustment for known risk factors [128,135,185,258,269-271]. There are conflicting data regarding a dose dependent association [270,272]. Longitudinal evidence is also conflicting. In the Nurses' Health Study cohort, diabetes was a slight but significant predictor of incident UI

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(RR=1.21), and the strength of the association was seen to increase both with duration of diabetes and with severity of incontinence. Despite strong associations with prevalent UI in the SWAN study, no association with either incident UI[128], or worsening UI was found [128]. Despite a host of plausible pathophysiological mechanisms by which diabetes might induce incontinence, it remains unclear whether it truly has a causal role.

Acute urinary tract infection (UTI) is a direct cause of transient UI [273], but caution is required regarding a causal association with chronic UI. UTIs are often diagnosed and treated based on symptoms alone, and there may therefore be a risk of misclassification between exposure and outcome. Many cross-sectional studies have found that women with UI are more likely to report having had one or more lifetime UTIs [221,246,274-275], and longitudinal data suggest both that UI can cause UTI, and that UTI can lead to UI. Two recent prospective studies found that baseline UI was a risk for incident UTI [273,276], among middle aged and elderly women, and in the Leicester MRC study, a history of cystitis was associated with both incident stress UI (OR 1.9) and incident OAB (OR 2.1) in women aged >40.

Prevalent UI has a clear dose dependent association with dementia [277-278], but until recently longitudinal studies did not identify an association with incident UI. One longitudinal study of 6,349 community dwelling women found that a decrease in mental functioning as measured by the modified mini mental status exam (MMSE) was not associated with increased frequency of UI over 6 years, but did predict a greater impact [279]. Despite strong associations with baseline UI in the Canadian Study of Health and Aging, moderate or severe cognitive impairment, again defined by the modified MMSE, was not associated with incident UI over 10 years [131]. However, in a sample of 12,432 women aged 70-75, followed up for 9 years, the Australian Longitudinal Survey of Women's Health did demonstrate a strong longitudinal association with diagnosed dementia (OR 2.34) [134]. In 9 year follow up of 1,453 women aged 65+ enrolled in a US HMO diagnosed dementia was strongly associated with incident diagnosis of UI (RR 3.0) [280]. Given the strength and consistency of associations with prevalent and incident UI, and given that treatment for reversible dementias can improve UI [210,211], a causal role seems certain.

Ischaemic heart disease is associated with many risk factors for UI, but perhaps because of Neyman's bias, cross-sectional studies have often failed to identify an association with UI itself even in univariate analysis [227,232]. The BACH study reported a strong association only among Black participants (OR 2.52) in multivariate analysis [97]. In the Leicester MRC study [268], a history of ischaemic heart disease was associated with baseline stress UI and OAB only in univariate analysis, and with no association with incident symptoms. In contrast, the Nurses' Health Study found that coronary heart disease was associated with incident weekly UI (OR 1.46), and incident severe UI (OR 1.79) [135]. If ischaemic heart disease is a risk factor for incident UI, its effects might be mediated by cardiac failure [280], or polypharmacy [283-284].

Several cross-sectional studies have documented an association between depression and incontinence [128,185,224,229,240,285]. It seems plausible both that the stigma of UI leads to depression (for example by reducing a woman's social network), and depression is likely to increase the bother of UI symptoms. In the SWAN study, depression was not associated with incident UI, but in the UAB Study of Aging, in a sample of 490 women aged 65+, baseline depression was weakly associated with incident UI (OR 1.2) over 3 years of follow-up [130]. Similarly in the Health and Retirement Study confounders (n=5,820), major depression was a modest predictor of incident UI (OR 1.46) over six years of follow-up, and including extensive adjustment for confounder. Baseline incontinence did not predict incident depression in the same study. Follow up of women aged 65+ enrolled in an HMO, diagnosed depression was also associated with incident diagnosed UI over 9 years (OR 1.6) [280].

Functional impairments, particularly mobility limitations, a history of falls, arthritis, dizziness, need to use walking aids, and poor lower extremity strength, have been correlated with UI in many community-based and nursing home studies [97,224,229.230,278]. In the Nurse's Health Study osteoarthritis and functional limitations were plausibly associated only with incident urgency UI (RR 1.86 and 2.10), not with incident stress UI or mixed UI [135]. In a study of 2,025 older women improvement in ADLs was associated with remission of urge UI at 3 year follow up [224]. Other longitudinal studies have shown similar findings [130,279]. It remains unclear whether UI is a direct consequence of difficulties in getting to the bathroom and/or removing clothing, or whether mobility limitations and UI may both be consequences of general frailty in older age or of an underlying systemic illness.

V. SUMMARY POINTS

1. The estimated prevalence of UI in middle-aged and older women in the general population appears to be in the range of 30% to 60% (increasing with age); while the prevalence of daily UI ranges from 5% to 15%, rising to over 15% in women over age 70 who are institutionalised. Some studies have found prevalences outside theses ranges, demonstrating that there remains a large variation in the estimated prevalence of

urinary incontinence in women, even after taking into account differences in definitions, ascertainment, and demographic characteristics. At least part of this variation is likely to be due to the sensitivity of the subject and subtle differences in the conduct of studies. (LE 1)

2. Multiple observational studies have confirmed that White, non-Hispanic women have a substantially higher prevalence of stress UI than Black or Asian women that is not explained by differences in known risk factors for UI. (LE 1)

3. Pregnancy, labour and vaginal delivery (vs Caesarean section) are significant risk factors for later UI, but the strength of this association diminishes substantially with age. (LE 1)

4. While several specific parturition factors such as instrumental delivery and birth weight are risk factors for UI in the post-partum period, their association with UI in later life is weak or non-existent, suggesting that changes in birthing practices in developed countries are unlikely to affect UI in older age. (LE 2)

5. Additional evidence has now established body mass as an important, modifiable risk factors for UI. (LE 1)

6. Physical function also appears to be an independent risk factor for UI in older women. Whether improvement in physical function leads to a reduction in UI remains to be established. (LE 2)

7. Evidence from 2 blinded, randomised controlled trials indicate that oral oestrogen, with or without progestogen, is a significant risk factor for UI in women age 55 and older (LE 1).

8. Diabetes is a risk factor for UI in most studies. While diabetic neuropathy and/or vasculopathy are possible mechanisms by which diabetes could lead to UI, no mechanism has been established, nor is it clear whether prevention or treatment of diabetes, separate from weight reduction, will reduce the risk of UI. (LE 2)

9. Menopause, as generally defined, does not appear to be an independent risk factor for stress UI. (LE 2)

10. Hysterectomy remains a possible risk factor for later UI, but the evidence is inconsistent. (LE 2)

11. Moderate to severe dementia in older women is a moderate to strong independent risk factor for UI (LE 2). Whether interventions to maintain or improve cognitive functioning also reduce UI has not been evaluated.

12. Mild loss of cognitive function in community-dwelling women, separated from physical function and other factors, increases the risk of UI slightly if at all, but may increase the impact of UI. (LE 2)

13. Data from twin studies suggests that there is a substantial genetic component to UI. (LE 1)

14. Other potential risk factors, including smoking, diet, depression, constipation, UTIs, and exercise, while associated with UI, have not been established as aetiological risk factors and are in fact difficult to study with observational data because of the potential for unmeasured confounding and questions of direction of the association. (LE 3).

VI. FUTURE DIRECTIONS

Since the 4th ICI in 2009, the quantity and quality of epidemiological studies of UI has continued to increase. Most notable are the availability of prospective data from several studies that can examine risk factors for incident incontinence and a growing number of studies comparing the prevalence and incidence of UI among Caucasian, Black, Asian and Hispanic women using population-based samples and multivariate analysis. Below are several suggestions for research over the next 5 years.

• Obesity is now an established, modifiable risk factor for UI. Investigation and dissemination of strategies to reduce the risk of UI through weight control or reduction should be a priority.

• Poor physical function is a consistent risk factor for incontinence, particularly in the elderly. Whether or not it is modifiable is not clear. Intervention studies are needed to assess the impact of improvement of physical function on prevention or reduction of UI in frail elderly.

• Moderate to severe dementia is also a consistent risk factor for incontinence. Studies aimed to maintain or improve cognitive functioning should assess change in UI as an outcome variable.

• The higher prevalence and incidence of UI, particularly stress UI, among Caucasian women, compared to Black or Asian women remains unexplained. Further studies are needed to identify additional exposures or biological factors that could explain these differences.

• Determining the role of genes and identifying specific genes that increase the risk of UI is a daunting challenge. Nonetheless, laboratory and epidemiological studies are needed to investigate this area.

• While the role of oestrogen in the aetiology of UI has been rendered largely moot due to the move away from estrogen use because of concerns about increased risk of breast cancer and cardiovascular disease, the use of other medications for control of menopausal symptoms and the introduction of selective oestrogen receptor modulators (SERMs) is growing. Their impact on UI

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needs to be studied. Add something about the role of vaginal oestrogens.

• More is now understood about the prevalence of and factors affecting treatment seeking among women with UI. However, more work needs to be done to identify women who would benefit from treatment, but who do not seek, or who do not receive, treatment and to develop interventions to help these women.

E. EPIDEMIOLOGY OF UI IN MEN

I. GENERAL COMMENTS

The epidemiology of UI in men has not been investigated to the same extent as women. However, progress has been made during recent years, particularly in the reporting of population-based studies of urinary incontinence among men and more specifically, of urinary incontinence associated with prostatectomy. In addition, more reports have been published on the risk factors for the development of UI in men.

In almost all community based studies, the prevalence rates of UI continue to be reported to be less in men than in women by a 1:2 ratio. The type and age distribution of UI appear to be different between the sexes, and risk factors, although less investigated in men, seem to be different from women. It is also important not to consider UI as an isolated problem in men, but rather as a component of a multifactorial problem. Often other urogenital symptoms (LUTS) such as weak stream, hesitancy, and dribbling, or erectile dysfunction, coexist.

Post-prostatectomy incontinence has been studied and reported with increasing regularity in the last few years. Since radical prostatectomy is being performed with increased frequency, and incontinence is one of the main complications of the procedure, a specific review of UI in the postprostatectomy patient population is presented in this section. In addition to epidemiological studies, we included clinical trial data on postprostectomy incontinence.

II. PREVALENCE

Several surveys from the general population have been conducted to determine the prevalence of UI in men (**Table 12**). Prevalences ranging from 1 – 39% have been published. The wide span of results may be explained by the variation in the population studied, the definition of incontinence used and the methods used in the surveys. A systematic review of 21 studies reported a prevalence of UI in older

men ranging from 11-34% (median = 17, pooled mean = 22%), while that among middle-aged and younger men was from 3% to 5% (median = 4% , pooled mean = 5%). In the same review, the prevalence of daily UI in men ranged from 2-11% (median = 4%, pooled mean = 5%) [286]. A more recent systematic review of 69 prevalence studies on UI in community-dwelling men showed pooled overall prevalence rates from 4.81% to 32.17%, with prevalence increasing with age. [333]. A wide definition of UI, older age, inclusion of institutionalised men, and the use of self-reporting methods tend to result in higher prevalence rates [286-287].

For any definition of UI, there is a steady increase in prevalence with increasing age (**Table 13**).

1. TYPES OF INCONTINENCE

Due to differences in anatomy and pathophysiology of UI in men and women, there is a different distribution in incontinence subtypes. Recent studies confirmed our previous reports of the predominance of urgency incontinence (40-80%), followed by mixed forms of UI (10-30%), and stress incontinence (<10%) [322]. The pooled prevalence rates in a systematic review confirmed that such distribution pattern across the different types of UI is consistent across the different age groups [333]. (**Table 14**).

The higher percentages of urgency and mixed types of incontinence are more significant in studies involving older people. In fact, the increasing prevalence of any UI by age in men is largely due to the contribution of urgency incontinence rather than stress incontinence. One study demonstrated an increasing rate of urge UI from 0.7% between age 50-59, 2.7% between 60-69 and 3.4% for 70 years and older respondents. Stress UI was steady at 0.5%, 0.5% and 0.1% for the above groups respectively [295]. A similar trend of increasing proportions of urgency and UI with increasing age is demonstrated in a large population-based study in the US [313], and a smaller population-based Canadian study [336]. On the other hand, Maral and coworkers [292] reported increasing prevalence also of SUI with age, from 0.9% between age 35-44, to 1.2% between 45-54, 3.8% between 55-64, and 4.9% at age 65 and older [292].

Most studies report a significant fraction of other/unclassified types of urinary incontinence. One study reported that a majority of men with UI had overflow and functional types of incontinence [293], while another found constant dribbling in 7% of their respondents [319]. Terminal dribbling or postvoid dribbling is another type of leakage in men that is difficult to assign to the conventional subtypes of UI. In an Australian survey, 12% of respondents reported frequent terminal dribbling [337].

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Table 12. Examples of prevalence studies of UI among men
A. General Population Sampling, all adult age groups

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Boyle 2003 [288]	4 979	28-72%	France, Netherlands, UK, Korea	40-79	Lack of control over bladder function which caused urine leakage at times	Self-administered questionnaire	7 (France), 16 (The Netherlands), 14 (UK), 4 (Korea)
Engstrom 2003 [289]	?	86		40-80		Self-administered questionnaire	2 (SUI)
Van Oyen 2002 [290]	7 266	-		> =15			1.4
Schmidbauer 2001 [291]	1 236	-		Mean 49			5
Maral 2001 [292]	1 000	90		> = 15			1 (SUI), 3 (UUI)
Bortolotti 2000 [293]	2 721	-		≥ 50	Any urine loss in the last year	Telephone interview	32 (last year), 14 (weekly)
Smoger 2000 [294]	840	85		293, VA clinic	Incontinence in the past 12 months	Self administered questionnaire	32.3
Ueda 2000 [295]	3 500	52.5	Japan	> 40		Mailed self-administered questionnaire	10.5 (UUI)
Roberts 1999 [296]	778	-		≥ 50			25.6 (95CI 22.5-28.8)
Roberts 1998 [297]	2 150	-		≥ 40	Urinary leakage in the previous 12 months	self	18
Schulman 1997 [298]	2 499	-		≥ 30			5.2
Malmsten 1997 [299]	10 458	74		≥ 45			9
Brocklehurst 2003 [300]	1883	-		>=30	Ever suffered from bladder problems such as leaking, wet pants, damp pants	Interview	6.6% overall, 3.8% incontinent in the previous year, 2.8% in the previous 2 months
Irwin 2006 [301]	19165	33%		>=18	ICS 2002 definition	Telephone interview	5.4 (1.9-5.9)
Legace 1993 [302]	2830	86%		>-20	Any urine loss in the past 12 months	Self-administered questionnaire	11 (9-13)
McGrother 2004 [303]	92491	60.2		>=40	In the last year, did you ever leak urine when you don't mean to?	Postal questionnaire	14.2
Obrien 1991 [304]	2496	79				Self administered questionnaire	7.4 (95CI 6.4 – 8.4)
Parrazzini 2002 [305]	9613	97.5		>=50	Involuntarily leaked in the past 3 months		8.3 (7.7-8.9)
Roe 1999 [306]	12529	53	US				5.3
Markland 2011 [307]	9071	-	US	>=20	Positive response to SUI/UUI/Other	Personal interview	13.9% SUI = UUI = 8.3% (7.6-9.0)
Markland 2010 [308]	5297	-	US	>=20	Score of 3 or greater on a validated incontinence severity index (moderate to severe leakage)	interview	4.5 (3.8-5.4)
De Souza 2010 [309]	?		Brazil	>=18			6.2%
Malmsten 2010 [344]	4072	80	Sweden	45-103			
Finkelstei2002 [310]	25400	88.7	Canada	>=30	urinary incontinence diagnosed by a health professional	interview	1.4 (per 100 population)
Diokno 2007 [311]	21,590	66.5	US	>=18	Involuntary leakage or loss of urine in the past 30 days	Postal questionnaire	12.7%
Lee 2011 [312]	888	22.%	Korea	>=18	Involuntary urinary leakage	Telephone interview using a questionnaire	2.9% (other UI = 1.3, SUI = 0,9)
Espuna-Pons 2009 [313]	15,929		Spain	>=15		questionnaire	3.6%

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Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Dios-Diz 2003 [315]	350	-		> 64	-	-	? (95CI: 15-28)
Stoddart 2001 [316]	1 000	79		> 65	Incontinence in the previous month		23
Aggazzotti 2000 [317]	893	90		> 65, Community and residential homes	Involuntary loss of urine at least 2x/month	Questionnaire, review of clinical record	39.2
Gavira-Iglesias 2000 [318]	827	-		≥ 65	-	-	29 (25-38 95CI)
Smoger 2000 [294]	840	85		25-93, VA clinic	Incontinence in the past 12 months	Self administered questionnaire	32.3
Damian 1998 [319]	589 (iincluding women)	78		> 65	Current experience of difficulty in controlling urine or urine escaping involuntarily	Interview	15
Umlauf 1996 [320]	1 490	53		Elderly	Uncontrolled urinary leakage of any amount the month before	Mailed self administered questionnaire	29
Nuotio 2003 [321]	171	-		≥ 70			24 (UUI)
Herzog 1990 (MESA study) [322]		66% - 72%		>=60	In the past 12 months about on how many days have you lost any urine, even a small amount beyond control	Interview	18.9%
Janssen 2007 [323]		57%		>= 65	Leaked or lost control of urine in the past year	Interview	13.1%
Landi 2003 [324]	5372			>= 85	MDS urinary incontinence scale of >=1	Health care professional assessment	49%
Thom 1997 [325]	1420	NA		>=65		Review of database	5.3
Diokno 1986 [314]	805	65.1	US	60 older			
Kwong 2010 [326]	1705	47	Australia	>=70	Urinary leakage at least 2x/week over the past 4 weeks	Self administered questionnaire	14.8%
Smith 2010 [327]	572		US (Latino)	older			26.9%
Yu 2009 [328]	743		China (rural)	>=60		Face to face interview	33.38%

2. SEVERITY OF INCONTINENCE

When it comes to severity, the distribution in men follows that of the women. Estimates for severe UI in older women tend to be about twice as high as for older men [322].

3. RACE/ETHNICITY

Very few studies have included the impact of race or ethnicity on the prevalence of UI among men. A four-country study presented lower prevalences of reported UI among men from Korea (4%) and France (7%) than in men from Britain (14%) and Denmark (16%) [288]. On the other hand, unpublished data from the MESA study did not indicate differences in prevalence among white male respondents compared to African American respondents. Similarly, the National Health and Nutrition Examination Survey did not find any difference in prevalence of UI by racial/ethnic group [308].

4. INCIDENCE AND REMISSION

Literature on the incidence of male UI is very scarce. The MESA study [322] found a one-year incidence rate for men older than 60 years of 9-10%. In a population-based survey in the UK among men over 40 years of age, the one-year incidence of UI was noted to be 3.8% [303]. A review of a health organisation database of males at least 65 years old revealed an UI incidence of 23.8 per 1000 person years. Malmsten [299] analysed the age of onset of UI for each age cohort. Mean debut age for all men was 63 years. The mean duration was about 8-10 years in the cohorts. A longitudinal population based study in Sweden showed that 8.6% [212/2471] of those without UI at the initial survey were found to have UI at the survey done 11 years later [344].

Substantial remission rates for UI in males were noted by the MESA study, higher among men (27-32%) than women (11-13%) [322]. A similarly high one-year remission rate of 39.6% was noted among British males [303]. In the Swedish longitudinal study, 47.8% (55/115) of those found to have UI at the initial survey did not present with the problem at the time of the follow up survey 11 years later [344].

One possible explanation for the difference in the published incidence and remission rates in men compared to women, is the predominance of urgency type incontinence among men, and its close relation to overactive bladder with and without incontinence. Another factor is the close association between urgency UI and prostate gland disease, infections, or bowel dysfunction, all of which are relatively amenable to treatment or may improve even without treatment.

III. POTENTIAL RISK FACTORS FOR UI

There is relatively little research concerning conditions and factors that may be associated with UI in men, and clear risk factors are more seldom scientifically documented. However, a few available studies have identified potential risk factors, which are described below.

1. AGE

As in women, increasing age is correlated with increasing prevalence of UI. Multivariate analysis in several studies has shown that age

Table 13. Examples of prevalence of UI across age spectrum in men

Author and year [ref]	N	Distribution by age	Prevalence [1] (%) (95%CI)
Yarnell, 1979 [329]	169	65 70 – 80 80+	9 8 22
Thomas, 1980 [330]	?	45 – 54 55 – 64 65 – 74 75+	5 9 15 18
Diokno,1986 [314]	805	60+	19
Malmsten, 1997 [299]	10458	45 50 55 60 65 70 75 80 85 90+	3.6 4.1 3.3 5.1 6.1 7.3 9.6 19.7 21.8 28.2
Schulman, 1997 [298]	2499	50 – 54 60 – 64 70+	5 6 14
Bortolotti, 2000 [293]	2721	51 – 60 61 – 70 70+	2 3 7
Ueda, 2000 [295]	3500	40 – 59 60 – 69 70+	2 4 4
Aggazzotti, 2000 [317]	839	<65 65 – 74 75 – 84 85+ >= 95	19 23 52 53 57
Temml, 2000 [331]	1236	20 – 39 40 – 59 60 – 69 70+	2 4 8 12
Smoger, 2000 [294]	840	≤40 41 – 50 51 – 60 61 – 70 71 – 80 >80	25.4 30.9 31.4 36.3 33.2 20.0
Mariappan 2006 [332]	353	40-49 50-59 60-69 >=70	6.6 7.9 10.6 10.3
McGrother 2004 [303]	92491	40-49 50-59 60-69 70-79 >=80	7.4 11.1 16.8 23.2 30.5
O Brien 1991 [304]	2496	35-44 45-54 55-64 65-74 >=75	2.4 5.5 5.7 12.1 15.4
Thom 1997 [325]	1420	65-74 75-79 >=80	2.8 5.6 7.6
Shamliyan 2009 [333]		19-44 45-64 65+ 80+	4.81 (3.69-5.94) 11.2 (10.14-12.26) 21.13 (19.9-22.35) 32.17 (29.62-34.73)
Finkelstein 2002 [310]	25400	30-39 40-49 50-59 60-69 70-79 80+	0.2 0.4 1.1 2.7 5.7 6.4
Diokno 2007 [311]	21590	18-34 35-44 45-54 55-64 65-74 75+	7.25 7.17 10.98 15.58 23.82 30.19
Kwong 2010 [326]	1,705	70-74 >=90	12.0 16.3
Espuna-Pons 2009 [313]	15929 (men and women)	45-64 65-74 >=75	2.8% [2] 10.2% [2] 22.7% [2]

1 – Crude prevalence, unless otherwise specified
2 – prevalence estimated using survey sampling weights

Table 14. Relative proportion of types of urinary incontinence in men.

CITATION	Population	Age group	UUI	SUI	MUI	Others
Diokno 1986 [314]		>= 60 y	34.9	7.9	28.9	28.3
Damian 1998 [319]	589	>=65 y	52.2	10.6	16.1	21.1
Chaojie 2002 [334]	2087 (total)	>=70 y	17.4	11.9		
			30.4	20.7		
Nuotio 2003 [285]	171	>70	70.8	8.3	25.0	
Irwin 2006 [301]	19,165	>=18 y	22.2	11.1	11.1	53.7
Herschorn 2007 [336]	482	>=18 y	58	27	15	-
Shamliyan 2009 [333]	*	19-44 y 45-64 65+ 80+	68.2 59.3 54.2 65.9	16.3 28.9 8.0 0	15.5 11.7 17.9 34.1	-
Diokno 2007 [311]	21,590	>=18 18-34 35-44 45-54 55-64 65-74 75+	44.6 30.0 35.4 38.9 46.8 53.8 56.3	24.5 38.1 35.8 30.8 19.3 16.7 13.2	18.8 14.8 12.6 16.5 21.0 22.6 22.4	12.1 17.1 16.2 13.8 13.0 6.9 8.1

is an independent risk factor for incontinence [288,311,324,338-339] Compared to women, however, there seems to be a more steady increase in prevalence in men with increasing age. The National Health and Nutrition Examination Survey in the US reported an odds ratio for moderate to severe UI of 1.8 (95%CI 1.6-2.0) for every 10-year increase in age in a cohort of 5,297 men 20 years or older [308].

2. LOWER URINARY TRACT SYMPTOMS (LUTS) AND INFECTIONS

In postal and telephone surveys of community-living incontinent men, a majority had experienced a variety of other medical conditions, many of which may cause or aggravate UI. LUTS like urgency, nocturia, feeling of incomplete voiding and reduced flow are typically associated with UI [291,314,320, 343]. In one study, UI was reported by 15% of men without voiding symptoms, frequency or urgency and by 34% of those with such symptoms [314].

Studies have also reported that urinary tract infections and cystitis are strongly associated with male UI [295,319], with an odds ratio of 3.7 for UI in men reporting cystitis [295] and an odds ratio of 12.5 among men with recurrent infections [293]. The metaanalysis of 5 studies including the previously mentioned studies showed a significantly higher risk of UI among men with UTI, with a pooled odds ratio of 3.6 (95% CI 2.17-6.00) [333]. It should be noted that most reports indicating a positive association between UTI and incontinence involved men aged older than 60 years.

3. FUNCTIONAL AND COGNITIVE IMPAIRMENT, PHYSICAL ACTIVITY

Mobility problems such as use of a wheelchair or aids to walking, as well as diagnosed arthritis or rheumatism or having a fall the last year, were

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significantly greater among incontinent than continent men [319,345]. The Canadian National Population Health Study involving 25,400 men found that those afflicted with arthritis were more likely to have UI with an odds ratio of 1.59 (95% CI 1.07-2.38) [310]. The same study demonstrated that men with back problems were 2x more likely to have UI (OR 2.1, 95%CI 1.50-2.93). A Japanese study on community dwelling men noted that UI is more likely among men whose activities of daily living (ADL) are impaired, specifically those who are unable to change clothes and unable to walk outside, with odds ratio of 17.4 and 4.36 respectively [295]. A Canadian study found odds ratios of 1.8 and 6.4 for partially and totally immobile men aged 65+, respectively, for daily UI compared to those with normal ambulatory function [343]. Similarly, the Silver Network Home Care project among the frail older persons in Italy showed that those with higher ADL scores (i.e., greater functional impairment) had 2-4x higher odds of having UI. A survey of nursing home residents in Wisconsin identified dementia and poor ADL as risk factors for the occurrence of UI [339]. In general, most studies find similarities between men and women (see subsection on women) for functional and cognitive impairment as risk factors for UI.

Corollary to this, the association between physical activity and UI has been studied by Kikuchi and co workers among the elderly, community-based population in Japan [340]. They found that middle level physical activity in men was associated with a lower UI prevalence compared to those with low level physical activity, with as odds ratio of 0.38 (0.17-0.78). High level physical activity showed similar relations but was not statistically significant.

4. NEUROLOGICAL DISORDERS

Many specific neurological diseases may lead to UI [341]. Detrusor hyper-reflexia is seen commonly in mengingo-myelocele patients and in spinal injuries, Parkinson's disease and multiple sclerosis. Areflexic bladder dysfunction due to a cauda equina lesion or diabetes might cause overflow or a paralysed pelvic floor and hence stress incontinence. A meta-analysis of 5 studies showed that men who suffered stroke were at an increased risk for UI with a pooled odds ratio of 2.68 (95% CI 1.31-5.45) [333]. Men who had suffered a stroke were at increased risk for incontinence with an odds ratio of 7.1 [295]. The Canadian National Population Health Survey showed that stroke in men increased their odds of having UI by 8x (OR = 8.26, 95%CI 3.63-18.8) [310]. In a study of 235 stroke patients, the occurrence of UI correlated with motor weakness (OR 5.4), visual defects (OR 4.8, and dysphagia (OR 4.0) [342].

5. DIABETES

Several reports have not found diabetes to be a factor significantly associated with UI in men.

This includes the Canadian population-based study involving more than 25,000 men showing no increased risk for UI among men with diabetes [310]. However the pooled analysis of 6 studies showed that diabetic men were significantly more likely to have UI with an odds ratio of 1.36 (95%CI 1.14-1.61) [333].

IV. FACTORS OF UNCLEAR ASSOCIATION WITH UI IN MEN

A 9 year study of Janssen [323] showed increasing rates of UI with increasing BMI among the older men and women. However, multivariate analysis failed to show increased BMI (overweight and obese levels) as an independent risk factor for the development of UI.

In a study including a younger population in Australia, obesity was noted to be associated with UI with an odds ratio of 3.2 (1.2-9.0) [338]. In this study, however, being merely overweight was not associated with UI.

Several studies in older persons have shown an association between physical activity and UI among women that is not seen among men [288,340].

V. SUMMARY POINTS:

• The epidemiology of UI in men has not been investigated to the same extent as for women. But it appears that UI is at least twice as prevalent in women as compared to men. There seems to be a more steady increase in prevalence with increasing age than for women.

• Most studies find a predominance of urgency incontinence, followed by mixed forms of UI and stress incontinence the least. Most studies have a large fraction of other/unclassified types.

• Literature on incidence and remission of male UI is still very scarce.

• Clear risk factors are more seldom scientifically documented, but several medical correlates have been reported. Established risk factors predisposing men to UI include increasing age, presence of lower urinary tract symptoms (LUTS), urinary tract infections, functional and cognitive impairment, diabetes, neurological disorders, and prostatectomy.

• Substantial gains have been achieved on the study of the epidemiology of UI in men compared to the previous years. The conduct of more population-based prevalence studies permitted a better understanding of the problem of UI among men.

F. EPIDEMIOLOGY OF OVERACTIVE BLADDER AND NOCTURIA

I. OVERACTIVE BLADDER

1. GENERAL COMMENTS AND DEFINITIONS

Overactive bladder (OAB) and nocturia have been neglected topics in the medical literature [392-394], with early epidemiological research on urinary symptoms focused either on lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men or on urinary incontinence in women [4]. However, there has been increased research interest in OAB and nocturia during the last decade [393-396].

OAB can be bothersome [397-399], and is associated with increased comorbidity [400], impaired quality of life [8], and reduced emotional well-being and work productivity [401]. Nocturia is a common cause of sleep maintenance insomnia [402-404]. Nocturia can be bothersome [405-412] and is associated with impaired mental and physical health [413] and impaired quality of life [412, 414]. Both OAB and nocturia have been reported to be associated with increased risk of falls and fractures [415-422] and nocturia also with mortality [421,423-425].

Generally, the definition of any condition is a critical factor in evaluating its epidemiology, and OAB and nocturia are no exception to this rule [394, 426]. To facilitate discussion and research related to LUTS, the International Continence Society (ICS) has produced standardisation reports The ICS revised and re-revised its Standardisation Report of lower urinary tract function terminology in 2002 [427] and 2009 [428]. We will use the ICS definitions as basis of this chapter. However, we acknowledge that these definitions are not perfect and we encourage further discussion [396,428-431].

OAB is a term to describe the clinical problem of urgency and urgency incontinence from a symptomatic rather than from a urodynamic perspective. Previously various terms, such as 'irritable bladder' or 'unstable bladder' have been used. According to the ICS, OAB is a symptom-defined condition characterised by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia [427,428]. The ICS defines *urinary urgency* as sudden compelling desire to pass urine, and the term OAB is appropriate if there is no proven infection or other obvious pathology [427].

For a long time, it has been known that among healthy people urine production is lower during the night than during the day [432]. Urologists have traditionally defined nocturia as frequency of urination at night without reference to urine amount, while internists have assumed that nocturia results from an increased amount of urine produced with less focus on other urinary symptoms [433]. By the ICS definitions, *nocturia* refers to waking at night one or more times to void, and nocturnal polyuria (NP) to the production of an abnormally large volume of urine during sleep [434]. *Nocturnal urinary* incontinence or nighttime bed wetting (enuresis) differs from nocturia.

According to the ICS, as stated earlier, nocturia is also a component of OAB. However, there is an ongoing debate on the definitions, especially regarding urinary urgency and OAB [396, 430-431, 435-445].

Sometimes OAB has been divided into 'OAB wet' (OAB with urgency urinary incontinence) and 'OAB dry' (OAB without urgency urinary incontinence). In this part of the chapter we focus on the epidemiology of OAB – without distinction between OAB 'wet' and 'dry' – and nocturia. 'OAB wet' (i.e., urgency urinary incontinence) is covered separately in urinary incontinence sections (Epidemiology of UI in Women and Epidemiology of UI in men).

2. PREVALENCE OF OVERACTIVE BLADDER

Prevalence estimates from as low as 2% [446] up to 53%[447] have been reported. Most studies on OAB have reported prevalence estimates between 10% and 20% [448-455], and the most cited articles estimate a prevalence of between 12% and 17% %,[448,450, 455].

In **Table 15**, we have reviewed all population-based studies assessing prevalence of OAB in adults of both sexes. To identify these studies [398, 448, 450, 452, 455-465], a Medline search [English-language articles published before January 2012] was carried out on with the search strategy (((Overactive bladder.mp) or (OAB$.mp)) and ((prevalence.mp). Non-population-based (i.e. based on doctor attendances or similar) studies or studies not conducted among both sexes are not included in **Table 15**.

Among these population-based studies identified, different populations, different sample selection and different data collection methods were often used (**Table 15**). Sample size varied between 913 and 162,906, median being 2,005 individuals. Three (20%) out of 15 studies did not report any response proportion. Among those which reported, as many as seven (58%) studies had response proportion less than 50%. There was significant heterogeneity in symptom assessment, exclusion criteria, case definitions (some studies used grading of symptom severity whereas others did not), and in the time period during which the occurrence of symptoms was asked (**Table 15**). Hence, dissimilarities in study

Table 15. Overview of published population-based studies assessing prevalence of OAB in both sexes (PubMed indexed English-language articles before January 2012 in chronological order).

Origin	Data collection method	Sample source	Respondents (response proportion, %)	Age range (years)	2002 ICS Consensus Definition of OAB	Definition of normal - abnormal occurrence	Time period	Prevalence, %: Men/women
European [448]	Telephone interview / in person interview	Telephone registry / electoral census	16,776 (unreported)	40 – 75+	N/A	N/A	Undefined	16 / 17
USA [450]	Telephone interview	Telephone registry	5,204 (44.5)	18 – 75+	N/A	N/A	Past 4 weeks	16 / 17
Canada [456]	Telephone interview	Telephone registry	3,249 (43.4)	35 – 75+	N/A	N/A	Past month	15 / 21
Japan [452]	Mailed questionnaire	Not reported	4,570 (45.3)	40 – 100	N/A	N/A	Past month	14 / 11
Brazil [457]	Unreported	Not reported	913 (unreported)	15 – 55	Yes	Unreported	Undefined	14 / 23
Taiwan [458]	Questionnaire administered by nurse	Population registry	1,921 (67.0)	30 – 79	No	N/A	Past 4 weeks	16 / 18
International [455]	Telephone interview	Telephone registry	19,165 (33.0)	18 – 70+	Yes	No – Yes	Undefined	11 / 13
Finland [459]	Mailed questionnaire	Population registry	3,727 (62.4)	18 – 79	Yes	Rarely – often	Past 2 weeks	7 / 9
Korea [460]	Telephone interview	Telephone registry	2,005 (13.8)	40 – 89	No	N/A	Past 4 weeks	21 / 31
Canada [461]	Telephone interview	Telephone registry	1,000 (unreported)	18 – 90	No	N/A	Undefined	13 / 15
USA [462]	Mailed questionnaire / Telephone interview	Consumer panel	162,906 (62.7)	18 – 85+	No	N/A	Undefined	24 / 29
Portugal [463]	Telephone interview	Telephone registry	1,934 (59.6)	40 – 80+	No	N/A	Past 4 weeks	35 / 29
International [398]	Web-based interview	Consumer/ voter panel	30,000 (49.5)	40 – 99	Yes	Rarely – sometimes (Sometimes – often)	Past 4 weeks	22 / 36 (5 / 11)
Korea [464]	Telephone interview	Telephone registry	2,000 (22.1)	18 – 96	Yes	Unreported	Undefined	10 / 14
China [465]	Interviewer assisted	Unreported	14,844 (69.0)	18 – 70+	Yes	<1 a week – ≥1 a week	Past week	6 / 6

a In the European study, in five out of six countries, telephone interview was used (excluding Spain, where direct interviews were conducted due to lower proportion of households with telephone). Study sample was obtained from telephone number listings (except Spain, where electoral census data was used).
b Out of 11,740 participants (of 17,231 households contacted), 5,539 were considered ineligible. To calculate response rate, the number of respondents was divided by eligible participants (the former response rate). If same proportion of non-participants, as there were ineligible among participants (47%), were also considered ineligible, response rate was greater (the latter response rate).
c Out of 7487 individuals, 3239 completed the questionnaire (response proportion 43.4%).
d Invitation to complete email survey was sent to 88,150 members of the Internet-based panel. Of the members, 51,546 responded but 7,947 were excluded due to high rates of missing or inconsistent data, or discontinuation of the survey. Finally, 30,000 participants were randomly selected from the pool of respondents with completed surveys.
e ICS, International Continence Society; OAB, overactive bladder; UTI, urinary tract infection.
f Cut-off point (threshold) used for normal vs. abnormal symptom occurrence. Reviewed only for studies using current ICS definition of OAB.1
g Time period during which the occurrence of symptoms was asked.

procedures likely explain the differences in prevalence estimates. Overall, prevalence rates varied between 6% and 32% (Table 15). However, estimates of the prevalence of OAB have actually been smaller in many recent studies compared to earlier estimates (**Table 15**).

Only very few population-based studies have evaluated OAB prevalence using the ICS definition *and* reported bother. Assessing perceived bother associated with OAB drastically decreases the prevalence estimates. In the FINNO Study (conducted in Finland among people aged 18-79) [399], as many as 54% of men and 57% reported *any* (at least rarely) urinary urgency. However, prevalence of at least moderate bother from urgency was 7% for men and 9% for women. Overall, more than 96% of individuals with rare urgency reported no or small bother from it whereas 65% of individuals with urgency *often* and more than 70% with urgency *always* reported moderate or major bother (scale: none-small-moderate-major) [399]. These results are in concordance with two international studies

[397-398]. In the EpiLUTS study (conducted in the US, UK and Sweden among people aged 40–99) [398], 22.4% of men and 35.7% of women reported urinary urgency at least sometimes (in scale: never - rarely - sometimes - often - almost - always). However, prevalence estimates were substantially lower when bother was taken into account. Only 6% of men and 12% of women reported "quite a bit" or more bother from urgency (in scale: not at all-a little bit-somewhat-quite a bit-a great deal) [398]. Bother analysis from the EPIC Study [397] showed also that infrequent urinary urgency is not considered as very bothersome by most individuals. Out of OAB cases, 46% did not report symptom bother from it [397]. All these results suggest that bother measurement is essential in estimating the clinically relevant prevalence of OAB [396-398].

3. INCIDENCE OF OVERACTIVE BLADDER

The natural history of OAB has been systematically reviewed quite recently [English articles published between January 1, 1990, and September 20, 2009] [466]. Authors identified 7 longitudinal studies

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of OAB. OAB incidence varied between 3.7% and 8.8%; and included studies provided evidence for dynamic nature of OAB [466]. The authors also noted that the variations in symptom definitions and methods used across studies prevent statistical determinations of overall incidence rates. Overall, longitudinal studies have confirmed that OAB prevalence increases with age but also that OAB is a dynamic condition [467-471]. In a population-based study (conducted between 1991 and 2007 in Gothenburg, Sweden) [469], the number of women with OAB with urgency incontinence ("OAB wet") increased from 6% to 16%, however, the proportion of women with OAB without UUI (OAB dry) did not differ significantly (11% vs. 10%). Among women with OAB dry in 1991, 23% remained OAB dry, 28% reported symptom progression to OAB wet and approximately half reported remission of OAB by 2007, supporting the concept of the dynamic nature of OAB. The rate of remission OAB symptoms was greater for women who were OAB dry (49%) compared with those who were OAB wet (26%). Similar findings were recently reported in an Austrian study. The authors concluded that "OAB is a dynamic disease with long-lasting stable disease courses as well as remissions and progressions" [471].

4. RISK FACTORS FOR OVERACTIVE BLADDER

The causes and risk factors of urinary urgency and/or OAB are not well studied. Available studies, that have identified potential risk factors, are summarised below.

a) Age

In numerous cross-sectional studies older individuals reported more OAB than younger ones [448, 450, 452, 455-456, 458-462, 464]. Furthermore, longitudinal studies have confirmed that OAB increases with age [466]. However, while OAB is age-related, it may not be age-dependent. In some studies, OAB was not associated with age after adjustment for other factors/ confounders [400, 472-473]. Besides increasing age, also having urgency in childhood predicts having urgency in later life [474-475].

b) Gender

In **Table 15**, we summarised population-based studies assessing prevalence of OAB among both sexes. In most studies OAB was more common among women [398, 448, 450,455-462, 464-465]. In only two (13%) out of 15 studies, men reported more OAB than women. However, these two studies [452, 463] did not include younger age groups, and typically OAB is more common among women especially in younger ages [448, 455-456, 458-462, 464].

c) Obesity

In a British, prospective study, obesity was a risk factor for the onset of OAB (OR 1.5, 1.0-2.1) in women [400] but not among men [468]). In a Kaiser Permanente study among women aged 25-84, obesity was associated with three-fold risk of OAB [476]. In a population-based study conducted among women in Southern Sweden [477] and in a Japanese study among elderly people [478], OAB was associated obesity. Similarly, among obese women, increasing obesity was associated with OAB after adjustment for age, mode of delivery, and parity [479]. Furthermore, among type 2 diabetic patients, increased waist circumference was associated with prevalence of OAB [480]. Among non-care seeking women (enrolled at one site in a randomised trial) [481], obesity was associated with increased OAB in univariate analysis, but the association did not remain significant after adjustment for confounders. Although OAB seems obesity-related, in many studies, incomplete adjustment for all relevant confounders was possible.

d) Life style

In a prospective study among British women, neither alcohol, coffee nor tea consumption were risk factors for the onset of OAB (defined as having either urgency, UUI, or a combination of these) but drinking carbonated drinks was [400]. Among men, neither tea, coffee nor wine consumption were associated with onset of OAB onset, but a negative association between beer intake at baseline and subsequent OAB onset was found [468]. However, this may be explained by a *systematic misclassification error* (individuals decrease or cease alcohol consumption due to ill health) [482-483], *residual confounding* (moderate drinkers have many other favouring lifestyle factors) [484-485], or direct biological effects. In a Swedish population-based study in young female twins [486], tea (but not coffee) drinking was associated with an increased risk for both OAB and nocturia. However, after controlling for confounders (including zygosity of twins) these associations did not remain significant. Concurring with these studies, among non-care seeking women [481], coffee or alcohol consumption was not associated with OAB. In a population-based study among women in Southern Sweden [477], OAB was not associated with alcohol consumption.

In a prospective British study, smoking was a risk factor for the onset of OAB (defined as having either urgency, UUI, or a combination of these) in women [468] but not in men [468]. In a population-based study among Finnish women aged 18-79 [487], urgency was approximately three times more common among current and twice as common among former than never smokers. Parallel associations for urgency with smoking intensity suggested a dose–response relationship [487]. Other supporting findings have also been reported [473, 488-490]. However, some other studies did not find smoking to be a risk factor for urgency [463, 478, 486].

A prospective study among British men did not provide evidence of any specific dietary patterns as

a risk factor for onset of OAB [468]. Furthermore, physical activity was not significantly associated with OAB onset in men [468]. Contradictory results were found among non-care seeking women [481] where physical activity was associated with decreased OAB.

e) Race/ethnicity and socioeconomic status

Evidence regarding the role of race/ethnicity on OAB prevalence is limited. In a small Taiwanese study [491], higher prevalence of urgency (7.7% vs. 4.3%, p=0.02), was found in indigenous woman than in non-indigenous women. In the US part of the EpiLUTS study [473], OAB was reported by 26% of White, 33% of Black, 27% of Asian and 28% of Hispanic men. In the multivariate analysis, OAB was significantly more common among African-American (OR 2.0, p<.001) and Hispanic (OR 1.7, p<.001) male participants. The authors reported no statistically significant differences among women after multivariate analysis, despite wide variation in crude prevalence (27% for Asian women, 43% for White, 46% for African-American and 42% for Hispanic) [473]. Hospital-based studies have reported no difference in the prevalence of OAB by race/ethnicity [492-493].

f) Reproductive factors and pelvic surgery

Urinary urgency is a common symptom during pregnancy [494]. In a Taiwanese study [495], only 1% of women reported having urgency before pregnancy, whereas corresponding estimates were 16% in the first, 25% in the second, and 31% in the third trimester. Other studies have also found increasing prevalence of urgency with advanced gestational age [496-497]. However, in a Nigerian study, women in 3rd trimester did not report more urgency than women in 2nd trimester [498]. Although one quarter of pregnant women reported urgency, it was associated with moderate or severe bother for only 5% of symptomatic women [498].

The association between parity and urinary urgency is controversial. Some studies reported no association for parity with urgency or OAB [400, 481, 499-500], whereas others found increased prevalence of urgency among parous women [472, 491, 501-503]. However, there were substantial differences in methods between these studies. Regarding delivery mode, most studies demonstrated no effect on prevalence of urgency, urgency incontinence or OAB [463, 499 502-505]. On the other hand, contrary findings have also been reported [506-507]. In a Swedish prospective study, weekly urgency was reported in late pregnancy by 2.6% of women in the elected vaginal delivery and by 2.7% of the women in the elected cesarean section group [506]. Corresponding figures were 7.9% for vaginal delivery and 2.7% for cesarean section groups at 9 months postpartum [506] concurring with the results of a cross-sectional US study [507]. In a recent US study [99],

for women with a history of at least one operative vaginal birth, the adjusted odds of OAB was more than quadrupled (OR 4.9, 95% CI 2.2-11; women who had delivered all their children by pre-labor cesarean as reference).

The association of the postmenopausal years with increased urgency or OAB has been reported in several studies [465, 472, 502-503, 508-509]. The impact of hormone therapy on OAB is unclear. The Cochrane Incontinence Group review of urinary incontinence and oestrogens (urgency or nocturia not as the primary objective of the study) found that there were less nocturnal voids and urgency episodes among women treated with local (but not systemic) oestrogen [510]. There were no significant differences in OAB prevalence among women using either oral contraceptives or a levonorgestrel-releasing intrauterine device, in comparison to non-contraceptive users in a population-based study among young, Swedish women [511].

Radical hysterectomy is related to increased prevalence of pelvic floor problems [512]. For instance, patients treated for cervical cancer reported urgency 2-3 times more commonly than the matched controls: 36% of those with history of radical hysterectomy and pelvic lymph node dissection, 49% of those with surgery and adjuvant radiotherapy, and 48% of those with primary radiotherapy reported experiencing urgency [513]. However, the relationship between urgency and hysterectomy for benign indications is less clear. Many studies did not find a significant association between hysterectomy and urgency [499-500, 514-519] . However, some studies reported less [509, 520-523] and some more [463, 472, 501, 524] urinary urgency after hysterectomy. No differences according to the route of hysterectomy on urgency have been found [509, 523, 525-526]. Both prolapse surgery and stress incontinence surgery are associated with a risk of (de novo) urgency or urgency incontinence in both hospital based, and population based studies [489, 500, 527-528].

g) Specific conditions

There is a paucity of studies concerning conditions and co-morbidities that may be associated with OAB, and clear causal risk factors are even more seldom documented. Few available studies have identified potential risk factors, which are described below.

1. *Benign prostatic hyperplasia.* Instead of OAB/ urgency, observational, clinic-based studies have assessed the relationship between detrusor overactivity and benign prostatic hyperplasia/obstruction. Although patients with detrusor overactivity are less likely to get symptom improvement after BPH surgery than those without detrusor overactivity, many patients report less urgency after BPH surgery [529]. Similar findings were reported following a prostatectomy study among men aged 47-85,

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32% (n=49) reported urgency pre-operatively and 13% post-operatively (n=20) [530]. In another study, detrusor overactivity was present in 68% of patients (n=21) at baseline and in 31% (n=10) at follow-up (mean 2 years) in the prostatectomy group [531]. However, many patients remain symptomatic after prostate surgery, and prognostic factors for success remain largely unknown [532].

2. Pelvic organ prolapse. In community-based studies [476, 533-535], pelvic organ prolapse was associated with 2-6 times higher risk of having urgency incontinence. Concurrent with this finding, hospital based studies have also found pelvic organ prolapse to be a risk factor for urgency incontinence, and in interventional studies urgency incontinence is often (but not always) relieved [536].

3. Mental health. In the BACH survey [537], urinary frequency, urgency, and nocturia were associated with previously experienced sexual, physical, and emotional abuse for both genders and for all ethnic groups in the study (White, Black, Hispanic). Concurring results were found in a German, clinic-based study where 31% of women with OAB reported almost twice as often earlier physical or sexual abuse as did the women with stress urinary incontinence (18%) or women without urinary symptoms (18%) [538]. In an Iranian study, individuals with OAB had a higher prevalence of anxiety (28.2 vs. 8.8%; p=0.001) and depression (38.2 vs. 18.2%; P = 0.02) [453] concurring with finding from multinational EpiLUTS study where increased depression and anxiety scores were found among individuals with OAB [148]. Furthermore, postpartum depression has also been reported to be associated with urgency incontinence [540].

4. Other conditions. In the BACH survey [541], urgency was associated with almost double the risk of hypertension and heart disease in women and with more than double the risk of diabetes in men. However, In a Japanese study among the elderly, OAB was not associated with diabetes or kidney disease but was associated with depression, alcohol use, and increasing BMI [478]. In a UK prospective cohort study within a random sample of 19,241 women aged 40 or more identified from Health Authority lists of 108 general practices [400], predictors of OAB included faecal urgency, imbalance, osteoporosis, ankle swelling, diabetes, DVT and cystitis [9]. Urgency/OAB has also been reported to be common among patients with diabetes [542], stroke [543] and asthma [463].

II. NOCTURIA

1. PREVALENCE OF NOCTURIA

Most earlier studies assessing the prevalence of nocturia have been conducted among elderly men [544-552]. They consistently found that nocturia 1) is a very common symptom and 2) increases with age. These finding have recently been confirmed in comparative studies conducted in both sexes [405-406, 411, 424, 455, 461, 553-558] (**Figure 8**).

We have reviewed all population-based studies assessing prevalence of nocturia in adults of both sexes. To identify these studies, a Medline search [English-language articles published before January 2012] was carried out on with the strategy ((nocturia.mp) and ((prevalence.mp)). Non-population-based (i.e. not based on doctor attendances or similar) studies, studies not conducted among both sexes of adults, studies with narrow age range (less than 40 years), or studies with percentage data unavailable are not shown in **Figure 8**.

In the FINNO Study (individuals aged 18 to 79), approximately one out of eight men and women reported at least two voids per night, in addition one third reported one void per night [557]. Young women reported more nocturia than young men, prevalence of nocturia in men and women equalized only in the sixth to seventh decade of life, and in older age groups men had more nocturia than women. Many other recent studies have supported these findings: higher prevalence of nocturia among young women than young men, and an equalisation of prevalence in middle age [411, 414, 455, 461, 561-562]. As the gender difference has been found across different continents (Europe, Asia, Australia and North America) it probably is not due to the specific country, lifestyle or cultural factors (**Figure 1**) [394, 411, 414, 455, 461, 557,559-562]. The reasons for the excess of nocturia among older men remain unknown, but prostatic enlargement is likely to be the predominant factor.

The Krimpen study (conducted in the Netherlands among elderly men) [563] is one of the few studies where nocturia was assessed by frequency-volume charts). One and a half or more voids/night (average of information on two to three nights) was present in 60% of men aged 70-78 years, whereas at least 2.5 voids per night was present in 20%, respectively. These estimations are comparable to questionnaire studies: most elderly people void at least once per night [564] (**Figure 8**).

2. INCIDENCE OF NOCTURIA

There remains a paucity of studies on the incidence and natural history of nocturia [565]. This is not only due to the fact that longitudinal studies are more difficult to perform than cross-sectional studies but also due to the youth of "nocturia research" [434], uncertainty not only about "incidental nocturia" definition [566-569] but also about the appropriate time interval for repeated sampling [570].

In a US community-based study among adults over 60 [571], nocturia was ascertained during the baseline and
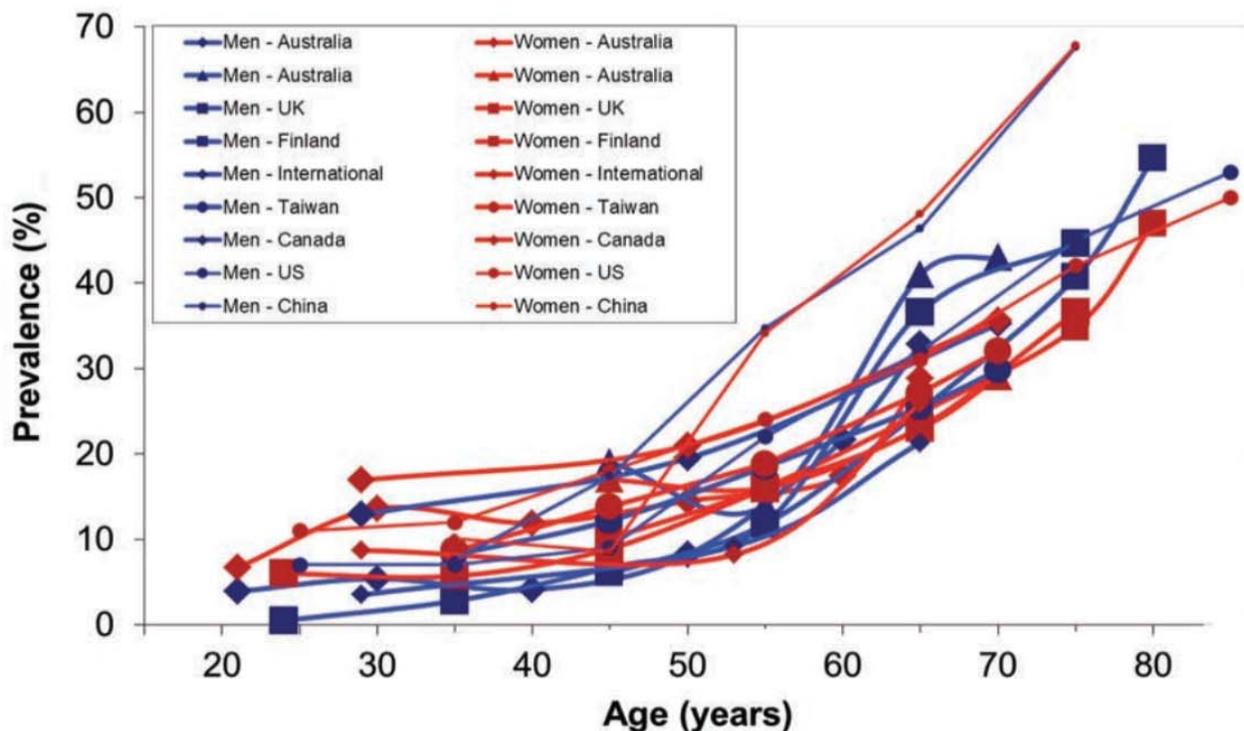
Figure 8. Prevalence of at least two voids per night across age groups by sex in population-based studies conducted among both sexes with wide age-range [411, 414, 455, 461, 557-561].

first and second year follow-ups. Of the 738 individuals with no nocturia at baseline, 34.6% reported having nocturia (2 or more) at follow-up, or an incidence rate of 213/1,000 person-years. Of the 357 individuals who had 2 or more episodes at baseline, 66.3% reported 1 or fewer at follow-up, for a remittance rate of 497/1,000 person years. These estimates were not calculated with adjustment for age- or gender, and the exact number of days between date at baseline and date at follow-up were not determined [568].

In a study conducted among elderly men in a Finnish county, questionnaires were mailed in 1994, 1999 and 2004 [572]. The crude incidence of nocturia for men from zero to one or more was 75 new cases per 1000 person-years during the first 5-year period and 126 during the second period. The younger cohort had a lower incidence than the two older cohorts (50-, 60-, 70-year old: 61, 91, 93 cases/1000 person-years, respectively). Interestingly, for all age cohorts the rate of incidence during the second five year period (102, 168, and 167 per 1000 person-years) was higher than during the first. The incidence of nocturia to 3 or more times (from 0 or 1-2 times) was less across all age groups (3, 12 and 16/1000 person-years, respectively for the age cohorts). However, this study is difficult to compare to other studies as no information on incidence of nocturia from <1 episode to >2 or more is available [572].

In a study conducted in the city of Gothenburg, Sweden questionnaires were mailed in 1992 to 10,456

men (aged 45-99) [470]. Follow-up was performed in 2003 when 3,257 men replied (3,000 men had died and 691 had emigrated or were no longer available in the register). The authors presented prevalence data at two time points. Nocturia prevalence increased from 12.8% to 50.1% (2 or more voids/night) among this study [470].

In the Krimpen study [563]. The overall incidence and remission rates (nocturia defined as ≥2 voids/night) were 23.9% and 36.7% after 2.1 years [563]. The incidence was highest among the oldest and lowest among the youngest men. As the absolute number of men with incident nocturia was higher, the prevalence rate increased over time. The authors concluded that "due to this fluctuation it is almost impossible to provide reliable incidence rates for nocturia in community dwelling older men" [563]. Overall, these longitudinal studies have shown that although nocturia increases with age it also has fluctuating character. However, the extent to which lack of reliability of the questionnaires has obscured true incidence or remission estimates remains unknown.

3. RISK FACTORS FOR NOCTURIA

The causes and risk factors of nocturia are not well understood [426, 565]. Available studies, that aimed to identify potential risk factors, are summarised below.

a) Age

There have been numerous studies showing that elderly subjects have more nocturia than younger

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people (**Figure 8**) - age is one, if not the most important correlates of nocturia. For instance, in a community-based US study, less than 5% of those aged 18-24 reported two voids per night while the corresponding figures were approximately 15% and 25% for those aged 45-54 and 65-74 respectively [406]. Besides increasing age, also childhood nocturia predicts nocturia in later life [474]

b) Gender

Although there is no remarkable difference in overall prevalence of nocturia between genders, in more detailed age specific analyses differences have emerged between the genders (**Figure 1**). Many studies found higher prevalence of nocturia among young women than young men, and an equalisation of prevalence in middle age [411, 426, 455, 461, 557, 561-562]. Prostatic enlargement has been suggested as a predominant factor for potential excess of nocturia among elderly men [564].

c) Obesity

Several studies have shown the relation between overweight/obesity and nocturia. Obesity was associated with more than three-fold risk of nocturia in a Swedish study among middle-aged women [573], and with more than two fold-risk in the FINNO Study [557]. Confirmatory findings have been reported in numerous studies [574-577]. In the longitudinal TAMUS study among men aged 50 or more [578], obese men had double the risk for nocturia compared with normal weight men. The frequency of nocturia at baseline did not increase the incidence of obesity at follow-up [578].

d) Life-style

Most studies have not found an association between nocturia and either alcohol [405, 556, 568, 576, 579-580] or coffee/caffeine [552, 573, 578, 580-581] consumption. In some studies moderate alcohol consumers had less nocturia than abstainers [578, 582, 583]. However (as discussed earlier in 'Risk factors of overactive bladder'), these findings may be due to systematic misclassification error or residual confounding [482-485].

Most studies have not found an association between nocturia and smoking [424, 552, 576, 578-581, 584]. Some conflicting results have also been reported: in a Swedish study [573] smoking was associated with increased nocturia but in Austrian [405] and Japanese [556] studies, with decreased nocturia.

Physical activity has been reported as being protective against LUTS in men [585-587], and against nocturia in women [573]. In an Austrian study [405], no relation was found between nocturia and physical activity. However, exercise programme has been shown to improve nocturia in a non-randomised trial [588].

e) Race/Ethnicity and socioeconomic status

In several US studies, African Americans were approximately twice as likely to report nocturia as other groups [574, 577, 589-591]. This effect was attenuated, although remained significant [577, 590], with adjustment for socioeconomic status and comorbidity. Furthermore, care-seeking black women also reported nocturia more commonly than other groups [592-593]. Conflicting results were found in a Kaiser Permanente study [594]. Less is known about the relationship between ethnicity and nocturia outside the US. In small studies in Taiwan [491, 595] and Scotland [596], associations between nocturia and ethnicity have been found. In the Scottish study, nocturnal polyuria was more common in Caucasian men compared to Asian men.

f) Reproductive factors and pelvic surgery

Nocturia is a very common symptom during pregnancy. In all studies most pregnant women report nocturia at least weekly, in many studies most women report having nocturia every night [494-498, 503, 597-598]. Typically the occurrence of nocturia increases during pregnancy. In an Indian study [598], nocturia (defined as more than one void per week) was reported by 50.6% of women before pregnancy (retrospective information), by 58.6% of those in the first, 71.9% in the second and 77.0% in the third trimester. In a Finnish study among women aged 18-79 [500], parous women reported slightly more nocturia than nulliparous women, contradicting earlier reports (conducted among perimenopausal women) of no association [501, 599]. The relationship of nocturia between parity has been suggested to be more likely to be due to pregnancy itself than trauma to the urinary tract during delivery [600] supported by the finding of no difference in nocturia between primi- and multiparous women in the same Finnish study [500] and by a finding of no difference between vaginal delivery and caesarean section in a Swedish prospective study [506]. In these studies, the postpartum period was also associated with increased nocturia [500, 506].

In a population-based Swedish study among young women, no difference in nocturia was found among oral contraceptive users and non-users, however, levonorgestrel-releasing intrauterine device (compared with non-contraceptive users), reported less nocturia (OR 0.53, 95% CI 0.32-0.89) [511].

Danish and Finnish population-based studies have reported more than double the risk of nocturia after the menopause [500, 501], consistent with other studies [508, 599]. One study attributed this to aging rather than to menopausal transition [601]. In these Finnish and Swedish studies, there were indications of increased nocturia among women using menopausal hormone therapy, but the findings were statistically insignificant [500, 599]. In a small randomised trial [602], there was

no difference in nocturia among those with menopausal hormone therapy or placebo. Similar findings were reported in a randomised trial of vaginal oestradiol and placebo after sling surgery [603].

The relationship between nocturia and hysterectomy is unclear, with hysterectomy being protective factor [515, 520, 522], risk factor [501], or not associated with nocturia [500, 509, 516]. Surgery for stress urinary incontinence was not associated with nocturia in a population-based study [500].

g) Specific conditions

1. *Benign Prostatic Hyperplasia And Prostate Cancer.* Benign prostatic hyperplasia (BPH) constitutes a well-recognised risk factor for nocturia [563, 580, 604]. In the FINNO Study [580], half of the subjects with physician-diagnosed BPH reported at least two voids per night; however, only a third of the men with nocturia reported BPH. However, nocturia is the least specific LUTS associated with BPO and medical treatment to relieve BPO has less effect on nocturia than on other LUTS [605-606]. Furthermore, nocturia has been reported as one of the most persistent LUTS following prostate surgery [530, 607], and in a study of men with bothersome LUTS, those receiving finasteride had an effect indistinguishable from placebo [608]. Many men with LUTS express a fear of prostate cancer [609], however, whether LUTS (including nocturia) are suggestive of prostate cancer is not clearly established [610]. In the large HUNT-2 study [611], LUTS severity was positively associated with the subsequent diagnosis of localised prostate cancer but not with advanced or fatal disease. More than 70% of men with physician-diagnosed prostate cancer reported at least two voids/night, while 7% of men with nocturia reported prostate cancer in the FINNO Study [580]. Whether men with nocturia are more likely to be diagnosed with prostate cancer (due to use of prostate-specific antigen), prostate cancer causes nocturia, or nocturia is a side-effect of various prostate cancer treatments remains unclear [412, 612]. Impact of radical prostatectomy on nocturia has been neutral or negative (i.e. increased nocturia) [613-615].

2. *Nocturnal polyuria.* The ICS defines nocturnal polyuria as an increased proportion of the 24-hour output of urine volume occurring at night [427]. However, there is a paucity of studies providing reference values. The Krimpen study authors suggested that nocturnal urine production exceeding 90 ml/hr is abnormal [563, 584] but concluded that "nocturnal urine production as an explanatory variable for nocturnal voiding frequency is of little value." [584]. The fundamental pathogenesis of nocturnal polyuria remains largely unknown.

3. *Overactive bladder.* Urinary urgency was a clear risk factor for nocturia in the FINNO Study (OR 7.4, 95% CI 4.5-12 for men, and OR 4.9, 95% CI 3.2-7.7 for women) [580]. However, while half of subjects with urgency also reported at least two voids per night, only one in three with nocturia reported urgency [459]. The finding that most people with nocturia do not report frequent urinary urgency (**Figure 9**), has also been reported in the EPIC and EpiLUTS studies [398, 455].

4. *Diabetes.* An association between diabetes and nocturia has been noted in most [556, 574, 576, 580, 583, 604, 616-619], but not all reports [555, 563, 568]. In the BACH Survey [574] and in a Danish study at ages 60-80 years [576], nocturia was associated with double the risk of diabetes. In these surveys [574, 576], it remained unreported whether there were gender differences. In the FINNO Study [580], diabetes was associated with nocturia after adjustment for other factors only in women.

5. *Hypertension.* It has been suggested that essential hypertension and nocturnal polyuria are part of the same pathophysiological process [620]. In Japanese [556] and US [568, 577] studies, hypertension was associated with nocturia, although effect sizes were modest (ORs between 1.5 and 1.6). However, in studies conducted in Europe [555, 563, 580], neither nocturnal polyuria nor nocturia were associated with hypertension. In a secondary analysis from the BACH survey [621], monotherapy with calcium channel blockers in women, and combination therapy with loop diuretics in men was associated with nocturia but no other associations for nocturia with any other antihypertensive was found [621]. While the treatment for hypertension may cause [395, 621-622] or alleviate nocturia [623] in some cases, appropriate methods are of particular importance when trying to assess the relationship between hypertension and nocturia.

6. *Coronary disease.* Earlier (male) studies [164, 165, 172] did not find a relationship between nocturia and cardiac disease. However, in these studies [555-556, 563], an association between cardiac symptoms/disease and nocturia was found in the preliminary analyses before multivariate modelling. In more recent studies [424, 574, 580, 583] coronary disease has been shown to be associated with nocturia.

7. *Depression.* In Swedish and US population-based studies [414, 624], depression and antidepressant use were both associated with increased prevalence of nocturia whereas in a Finnish study a relationship was found only among men using antidepressants after adjustment for other factors [580]. In another Finnish study (among men aged 50 or more), those with depressive symptoms at study entry were at almost triple risk for moderate or severe nocturia than those without depressive symptoms but nocturia had no effect on depressive symptoms during 5-year follow-up [625].

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8. *Sleep apnoea and snoring.* In clinic-based studies [618, 626-628], nocturia was associated with sleep apnoea. In US studies conducted among community-dwelling older adults, subjects with increased apnoea-hypopnoea index had greater mean nocturia episodes, nighttime urine production and atrial natriutretic peptide excretion [629-630]. Snoring was one of the three most important nocturia population-level risk factors for both sexes in the FINNO Study [580] concurrent with a Swedish urology clinic study [631].

9. *Neurological diseases.* Most patients with multiple sclerosis have bladder dysfunction, which may also lead to nocturia [632-633]. Nocturia was also associated with stroke and cerebrovascular disease [583, 616]. Moreover, in a study among Parkinson´s patients, severity of disease was also associated with increased nocturia [634]. Furthermore, a relationship between nocturia with restless legs syndrome was recently reported [580].

4. SUMMARY POINTS

• Overactive bladder (syndrome) (OAB) has been defined as urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia (in the absence of infection or other obvious pathology).

• Prevalence of OAB has been estimated from as low as 2% up to 53%.

• Recent population-based studies have shown that less than 10% of people have OAB with at least moderate bother suggesting that bother measurement is essential in estimating the clinically relevant prevalence of OAB.

• Longitudinal studies have shown that OAB increases with age, and that OAB is a dynamic condition, with not only substantial progression but also remission rates.

• OAB has been suggested to be associated with an increased risk of falls, fractures, and impaired quality of life.

• While age is a clear risk factor for urinary urgency and/or OAB, other risk factors have not been that well studied.

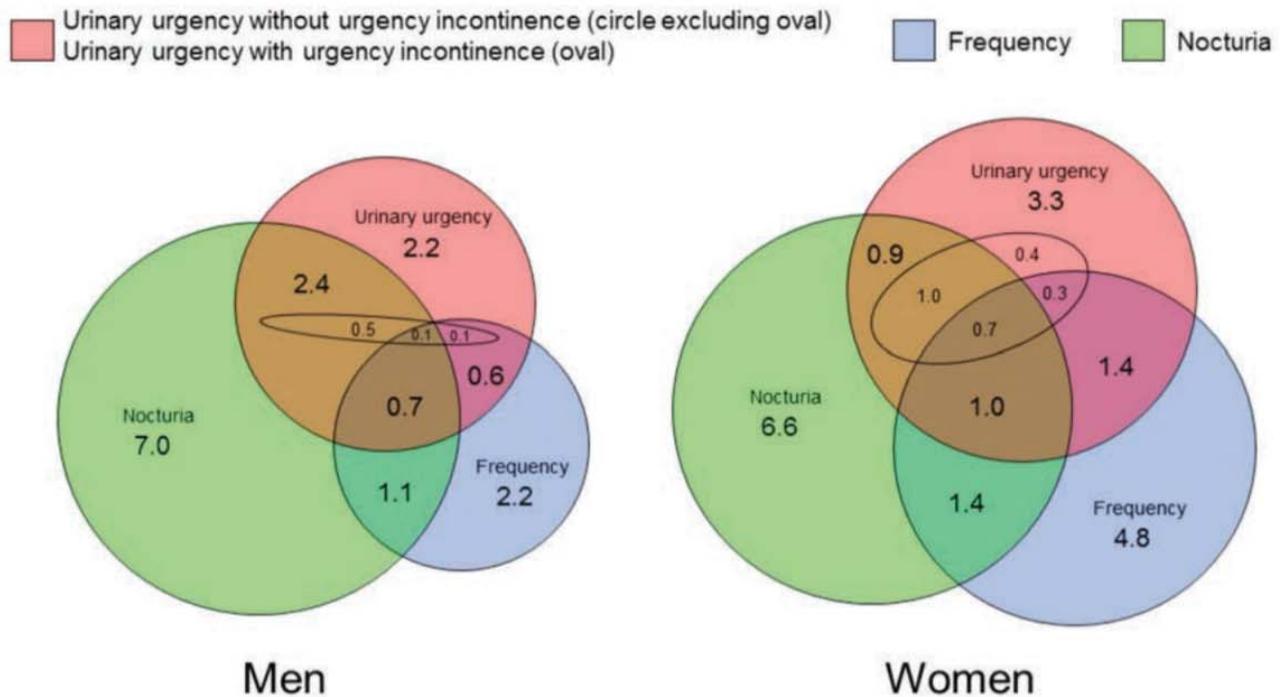• Individuals with benign prostatic hyperplasia, pelvic

Figure 9. Legend:
Urinary urgency without urgency incontinence (circle excluding oval)
Urinary urgency with urgency incontinence (oval)
Frequency
Nocturia

Men:
Urinary urgency 2.2
2.4
0.5 0.1 0.1
0.6
0.7
Nocturia 7.0
1.1
Frequency 2.2

Women:
Urinary urgency 3.3
0.9 0.4
1.0 0.3
0.7
1.4
Nocturia 6.6
1.0
1.4
Frequency 4.8

Figure 9. *Age-standardised prevalence of nocturia, urinary urgency (with or without urgency incontinence) and urinary frequency among Finnish people aged 18–79 years.*

The red circle represents individuals with urinary urgency (often or always in scale: never-rarely-often-always) without urgency incontinence (often or always in scale: never-rarely-often-always) excluding the area of the red oval representing individuals with urinary urgency with urgency incontinence. The blue circle represents individuals with urinary frequency (defined as more than eight voids/day) and the green circle nocturia (defined as at least two voids/night). Age-standardization performed using the age structure of Finland. Modified from 124 which is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

organ prolapse and mental health problems typically report urinary urgency more often than those without.

- Nocturia is one of – if not the - most common lower urinary tract symptom with similar overall prevalence in both genders.

- The prevalence of nocturia is higher among young women than young men, but prevalence increases more strongly with age in men.

- The literature on the incidence of nocturia remains relatively sparse. Incidence of nocturia has been shown to increase with age but also remarkable fluctuation has been identified.

- Two episodes of nocturia constitute meaningful nocturia, affecting quality of life and perceived health, while a single episode does not.

- Nocturia has been associated with an increased risk of falls, fractures, and death.

- Risk factors for nocturia include conditions of the lower urinary tract, but also a range of systemic conditions, including but not limited to prostatic hyperplasia, urinary urgency/overactive bladder, obesity, sleep apnoea, parity, and postmenopausal periods.

5. FUTURE NEEDS

- Due to the relative youth of research in OAB and nocturia, most data currently available are cross-sectional, hence, more prospective studies are needed.

- Natural history of OAB and nocturia needs more research – progression and remission of these symptoms is not yet well understood.

- Better understanding of relationship of different 'overactive bladder symptoms' would be beneficial.

- With prospective studies examining risk factors for incident OAB and nocturia will be possible, however, definition of incident OAB and nocturia may be challenging due to fluctuating character of these symptoms.

- Overall, further studies should be conducted with proper study designs and population-based samplings in order to decrease risk of bias.

G. EPIDEMIOLOGY OF POP

I. GENERAL COMMENTS AND DEFINITIONS

Pelvic organ prolapse (POP) refers to loss of support for the uterus, bladder, colon or rectum leading to prolapse of one or more of these organs into the vagina. Prolapse is thus a continuous condition when measured by visual inspection of the vaginal wall during valsalva. For clinical purposes, the de-

gree of POP is commonly described as above the introitus, at the introitus, or beyond the introitus with or without valsalva. The International Continence Society first developed a standardised definition for the condition of POP in 1996 [635]. The ICS Pelvic Organ Prolapse Quantification (POPQ) examination defines prolapse by measuring the descent of specific segments of the reproductive tract during valsalva strain relative to a fixed point, the hymen. The POPQ system describes the anatomic findings of pelvic organ prolapse without consideration for symptoms and bother perceived by the woman. Validation of this system has shown it to be highly reliable [636]. The stages of prolapse severity are arbitrarily defined, and there is no clear differentiation between normal anatomic variation and mild POP. For research purposes there is consensus for use of the POPQ system until further evidence might clarify the distinction between normal variation and mild prolapse [637].

Determining POP based on self-reported symptoms is difficult because of the lack of specificity and sensitivity of most symptoms attributed to pelvic organ prolapse [638] and the fact that prolapse above the level of the hymeneal ring is usually asymptomatic [639]. The only exception appears to be a sensation of bulging into the vagina [640], which is most strongly associated with prolapse at or below the hymeneal ring [641-642]. A recent study of 110 women found that a question asking about a feeling of something bulging in or dropping out of their vagina had a sensitivity of 84% and a specificity of 94% for POP at or beyond the hymeneal ring on examination [639]. Seeing prolapse would presumably be even more specific, but is too uncommon to be useful as a definition.

II. PREVALENCE OF POP

Since the 4th ICI several additional studies have reported the prevalence of POP in a general population [643-648]. Reports from the Women's Health initiative (WHI) Oestrogen Plus Progestin Trial, and randomised controlled trial, have been included [643,645-646]. While not actually population-based, the women in the trial were recruited from the community rather then from women seeking gynaecological care, and provide important information on the prevalence of POP based on pelvic examination.

The prevalence of POP based on a sensation of a mass bulging into the vagina was remarkably consistent, ranging between 5 and 10 percent (**Table 16**). The study by Eva et al., which reported a substantially higher prevalence included in the definition of POP, pelvic heaviness or digital pressure on the perineum or in the vagina to aid with defaecation [649]. The prevalence of observed prolapse in women enrolled in the WHI trial is similar to the

Table 16. Prevalence of pelvic organ prolapse (POP) defined by symptoms or observed on pelvic examination in the general population .

First author	Country	Definition of POP	Ages (years)	N	Prevalence Subgroup: %
Kumari [651]	India	"a mass of flesh in the vagina" or equivalent using local terminology	15+	2990	15-24: 5 25-34: 10 35-44: 8 45-54: 6 55-64: 9 65+: 3
McLennan (652)	Australia	A feeling of something coming down in the vagina	15-97	1546	8
Tegerstedt (647)	Sweden	Validated 5 item quetionnaire	30-79	5489	8
Eva [649]	Sweden	Any symptom of pelvic heaviness, genital bulge, or use of fingers in vagina or on perineum for defecation	40 60	641 663	23 28
Samuelsson [650]	Sweden	Standardized pelvic examination	20-59 (mean=39)	487	Any prolapse: 31 To introitus: 2 Cystocele: 16 Rectocele: 14 Uterocele*: 5
Rortveit [648]	USA	Feeling of bulging, pressure or protrusion or visible bulge or protrusion	40-73 (mean=56)	2109	6
Lawrence [644]	USA	Sensation of bulge in vagina or something falling out of vagina with a degree of bother of at least 33 on a 1-100 visual analogue scale (validated)	25-84 (mean= 57)	4103	6
Hendrix [642]	USA	Standardized pelvic examination	50-79 (mean=63)	27,3 42	Any prolapse: 40 Cystocele: 34 Rectocele: 19 Uterocele*: 14
Handa [643]	USA	Standardized pelvic examination	50-79 (mean=63)	412	Any prolapse: 32 Cystocele any: 25 Cystocele grade 1: 14 Cystocele grade 2: 10 Rectocele any: 13 Rectocele grade 1: 8 Rectocele grade 2: 5 Uterocele any: 4 Uterocele grade 1: 3 Uterocele grade 2: 1
Nygaard [646]	USA	POP-Q**	50-79 (mean=68)	270	Stage 0: 2 Stage 1: 33 Stage 2: 63 Stage 3: 2 Stage 4: 0 ≥ hymeneal ring: 26
Bradley [645]	USA	POP-Q	50-79 (mean=68)	270	≥ hymeneal ring: 24

italic * Denominator is women with a uterus
** Stages defined as 0: no prolapse, 1: prolapse to 1 cm above hymen, 2: prolapse to between 1 cm above and 1 cm below hymen, 3: prolapse between 1 cm below hymen and 2 cm above introitus, 4: prolapse beyond 2 cm above introitus.
Note: Studies reported by Handa, Nygaard and Bradley are all subsets from study reported by Hendrix.

prevalence found in the one population-based study that also used pelvic examination [650], although the prevalence of each type of prolapse was higher in the WHI study [642]. In both studies, prolapse occurs most frequently in the anterior compartment, next most frequently in the posterior compartment, and least in the apical compartment.

Two studies that examined prolapse by race found the that Black women had the lowest prevalence and Hispanic women the highest after controlling for multiple other factors in multivariate analysis [642,648]. The study reported by Rortveit et al based on symptoms found adjusted odds ratios of 0.4 (95% CI=0.2-0.8) for Black and 1.3 (95% CI=0.8-2.2) for Hispanic women, with White women as the referent group [556].14 Hendrix et al reported adjusted odds ratios of 0.6 (95% CI=0.5-0.8) for Black and 1.2 (95% CI=1.0-1.5) for Hispanic women compared to White women for POP based on genital examination [643].

III. INCIDENCE

Only two studies could be located that reported the incidence of new POP. Both studies were done on sub-groups of women enrolled in the WHI Oestrogen Plus Progestin Trial. The first study of 412 women enrolled at the University of California, Davis site, used a standardised pelvic examination repeated every 2 years over 8 years [643]. The incidence of new cystocele, rectocele and uterine prolapse was 9%, 6% and 2%, respectively. Annual rates of remission from grade 1 (prolapse to above introitus) was relatively common for each type of POP (24%, 22% and 48%, respectively) but less common from grade 2 or 3 (prolapse to or beyond the introitus) (9%, 3% and 0%, respectively). In a second study of 259 postmenopausal women with a uterus who were examined using the POP-Q at baseline and annually for 3 years. POP was defined as prolapse to or beyond the hymeneal ring. The incidence of new POP was 26% at 1 year and 40% at 3 years, with remission rates of 21% at 1 year and 19% at 3 years [645].

Several studies have reported the annual incidence of surgery for POP in the US and at least one in the UK. A longitudinal study of over 17,000 women in the U K, age 25 to 39 at baseline, reported an annual rate of prolapse surgery of 0.16% [653]. This rate is consistent with the rate of approximately 0.2% per year reported in the US [654-655]. One US study reported an annual incidence rising with age from 0.05% in women age 30-39 to 0.5% in women age 70-79 with an estimated lifetime cumulative risk of surgery from prolapse of 7% to 11% [656]. A recent US study reported similar surgical rates: 0.07% for women 18-39, 0.24% for women age 40-59, and 0.31% for women age 60-79 [657]. Surgical rates drop substantially after age 80 [656-657]. Estimating rates of prolapse surgery has the advantage of

use of hospital discharge data on procedures, which is highly accurate for the procedure performed, but less accurate for the indications for the procedures, particularly when a procedure may have more then one indication.

IV. POTENTIAL RISK FACTORS

1. BOWEL DYSFUNCTION AND PELVIC ORGAN PROLAPSE

Women who seek urogynecological care report a high prevalence of bowel symptoms [658]. However, bowel dysfunction is highly prevalent among women in general and it has been estimated that up to 27% of the female population in industrialised countries is affected by constipation [659]. The overall prevalence of constipation and associated symptoms in women with pelvic organ prolapse ranges between 20-53% depending on the definition of disorders [660-662]. Although definitions of disease differ between studies it is widely acknowledged that bowel dysfunction is a complex condition with a multifactorial aethiology. Bowel dysfunction comprises a wide variety of symptoms including constipation, rectal emptying difficulties, incomplete defaecation, manually assisted defaecation, faecal urgency and irritable bowel syndrome (IBS). Neurophysiological assessments have shown that damage to the pelvic floor musculature and nerve supply can occur as a result of chronic constipation [663]. Other predisposing factors comprise low socio-economic status, pelvic floor surgery, depressive disorders, thyroid dysfunction, physical disability and inactivity, and food habits [664].

Current epidemiological evidence on the association between bowel dysfunction and pelvic organ prolapse are at odds. A number of studies suggest that women with pelvic organ prolapse are significantly more likely to experience constipation and other symptoms of bowel dysfunction, [662,665-668] whereas others show a weak or non-existent association [661,669-671]. In a case-control study, manually assisted defaecation was present in 19.7% of women with prolapse compared to 4.4% of control subjects (p<0.001) [662]. In a randomly selected population based study, irritable bowel syndrome and constipation were both strongly associated with pelvic organ prolapse (OR 2.8 95% CI 1.7-4.6, and OR 2.5 95% CI 1.7-3.7 respectively) [667]. Varma et al., [668] suggested that among randomly selected women, having symptomatic pelvic organ prolapse more than doubled the risk for obstructed defaecation (OR 2.3 95% CI 1.5-3.7). A retrospective questionnaire based survey of women with and without prolapse concluded that constipation as a young adult was an important factor in the development of uterovaginal prolapse[665]. In a case-control study, women with prolapse were at increased risk for constipation also after adjustment

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for dietary fibre intake (OR 2.9, 95% CI 1.1-13.5). when compared to women without prolapse[666].

In the cross-sectional Women's Health Initiative (WHI), cysto- and rectocele was only weakly associated with constipation (OR 1.1 95% CI 1.0-1.2) [669]. Similar weak associations between prolapse and bowel dysfunction have been observed in other large cross-sectional studies [661,670-671]. Overall severity and prevalence of bowel dysfunction has shown poor correlation with findings of pelvic organ prolapse at radiological imaging [672-674]. Also at clinical examination, increasing vaginal descent and prolapse severity, show a generally weak (or absent) association with symptoms related to bowel dysfunction [660,675-678]. In a substudy to the WHI, no specific bowel symptom was associated with increasing loss of pelvic organ support in any vaginal compartment [671]. When considering compartment-specific pelvic floor defects, most studies suggest that increasing posterior vaginal wall prolapse and perineal descent are correlated to more symptoms of obstructive defaecation [661,674,676]. In a cross-sectional study of 260 women with pelvic organ prolapse, women with posterior vaginal wall prolapse were more likely to incomplete emptying (41% vs 21%, P=0.003), straining at defaecation (39% vs 19%, P=0.002), and splinting with defecation (36% vs 14%, P<0.001) compared with women without posterior vaginal wall prolapse. But there was no significant association between bowel symptoms and increasing severity of prolapse [679].

The association between bowel dysfunction other than specifically obstructive symptoms and pelvic organ prolapse has been poorly investigated. In a random population-based study of 2109 racially diverse women women with IBS (prevalence =9.7%) had higher odds of reporting symptomatic pelvic organ prolapse (OR 2.4; 95% CI, 1.4-4.1) compared to those without IBS [680]. It has also between suggested that anal sphincter dysfunction such as paradoxical anal sphincter reaction is more common in patients with rectocele as compared to women without rectocele at defaecography [681].

2. PELVIC SURGERY AND POP

Even though the notion that hysterectomy increases the risk for pelvic organ prolapse has wide acceptance, longitudinal studies confirming a temporal association are few and previous studies do not often differentiate between various types of hysterectomy. A number of cross-sectional and retrospective studies implicate hysterectomy as an independent risk factor for pelvic organ prolapse. However, due to a delay of onset, large population samples and a sufficiently long duration of follow-up are required to determine an association with adequate certainty.

In a nationwide cohort study, Altman et al. [682]. reported that 3.2% of women with hysterectomy had pelvic organ prolapse surgery, compared with 2.0%

in non-hysterectomized controls, corresponding to a risk of 1.7 (95% CI, 1.6-1.7). In this Swedish study, vaginal hysterectomy had the highest risk for subsequent prolapse surgery (HR 3.8, 95% CI, 3.1 to 4.8) in comparison to non-hysterectomised controls. These results were corroborated by Cooper et al. in a large study from Scotland showing an increased risk for prolapse surgery among women after hysterectomy, compared to endometrial ablation [683]. These register-based data are largely in agreement with the longitudinal Oxford Family Planning Association study by Mant et al. [684] reporting increased overall incidence rates for prolapse surgery following hysterectomy. Although not separating various hysterectomy techniques, Mant el al. determined that the risk of prolapse following hysterectomy was 5.5 times higher (95% CI 3.1-9.7) in women whose hysterectomy was performed for prolapse as opposed to other benign conditions. A history of hysterectomy has also been identified to increase the risk for prolapse in several cross-sectional and retrospective studies [685-686].

Specific risk factors for posthysterectomy prolapse have been assessed in two case-control studies. Both Dällenbach et al. [687]. and Forsgren et al. [688]. reported that pelvic floor surgery before hysterectomy was the strongest risk factor for developing posthysterectomy pelvic organ prolapse (OR 7.9, 95% CI 1.3-48.2 and OR 2.8, 95% CI 1.0-7.7 respectively). The risk of prolapse repair was 4.7 times higher in women whose initial hysterectomy was indicated by prolapse [687]. Vaginal vault prolapse involves the loss of vaginal apical support and may per definition only occur after hysterectomy [689]. Marchionni et al. reported a 4.4% overall incidence of vaginal vault prolapse after hysterectomy but in women where uterine prolapse was the indication for hysterectomy the incidence was 11.6% [690]. In a register-based study Forsgren et al. showed that the greatest risks for prolapse surgery (HR 4.9, 95% CI 3.4-6.9) were observed subsequent to vaginal hysterectomy for pelvic organ prolapse but having a vaginal hysterectomy also for other indications significantly increased the risk for subsequent pelvic organ prolapse surgery compared to other modes of hysterectomy [691]. Similar observational results were shown by Cooper et al. [683].

It has also been suggested that pelvic surgery other than hysterectomy may predispose women to subsequent genital prolapse including: rectopexy for rectal prolapse (OR 3.1; 95% CI 1.4-6.9) [692].; gynaecological surgery in general (OR = 3.9, 95% CI 1.8-8.8) [693]; and retropubic colposuspension procedures are associated with a near 30% risk of subsequent vaginal vault and posterior vaginal prolapse at long-term evaluations [694-695]. In a prospective cohort study of 374 women, the 10-year re-operation rate was 17% after traditional prolapse or incontinence surgery[696]. Having undergone pelvic organ prolapse or incontinence surgery prior

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to the index operation increased the risk of re-operation to 17% compared with 12% for women who underwent a first procedure (p=.04) [696].

3. OBSTETRIC FACTORS AND POP

For ethical and practical reasons, randomised controlled trials to study the causal effects of vaginal and caesarean delivery on the pelvic floor will never be performed. Observational studies will therefore most likely remain the main source of knowledge on this subject. Nonetheless it is widely accepted that childbirth is a significant risk factor for pelvic organ prolapse, presumably due to overt or occult pelvic floor tissue trauma. Controversy does, however, remain with regard to the protective effect of caesarean section and if specific obstetric events should be considered as risk modifiers. Due to a delayed onset of pelvic organ prolapse in relation to giving birth, studies on the subject need a long duration of follow-up as well as large study populations to be able to elucidate the possible causative events. Therefore, the majority of studies on the subject are typically designed as cross-sectional surveys or retrospective cohort or case-control studies. It is, however, encouraging that long term longitudinal data are starting to emerge.

Pregnancy itself has been identified as a risk factor for stress urinary incontinence. With regard to pelvic organ prolapse, the association is less substantiated. In a clinical case-control study, all 21 nulliparous non-pregnant women had POP-Q stage 0 or 1, whereas 47.6% of 21 nulliparous pregnant women had pelvic organ descent corresponding to stage II (p<0.001) [697]. Overall POP-Q stage was higher in the third trimester than in the first (p=0.001). Also Sze et al.[698] found that in 94 nulliparous women evaluated at the 36 with antepartum visit and six weeks postpartum, POP-Q staging increased.

A large number of studies identify childbirth as one of the strongest predictors for developing pelvic organ prolapse later in life [667,669,684-685,699-704]. It is also a recurrent observation that the number of deliveries is associated with the risk of prolapse although there are data to suggest the contrary [705]. In the prospective Oxford Family Planning Association study, [684] childbirth was the single strongest risk factor for developing prolapse in women under 59 years of age and the risk increased by every delivery. Similar findings derived from the WHI, [669] where a parity of one conveyed an overall two-fold risk increase for prolapse compared to having no children, after which each additional childbirth added a 10-20% risk increase. In a case-control study, Tegerstedt et al. [703] found that the risk for symptomatic pelvic organ prolapse increased with the number of deliveries and were 3.3-times higher among mothers of four than among mothers of one. Similarly, Rortveit et al. [667] found that the risk of prolapse increased in women with one (OR 2.8 95% CI 1.1-7.2), two (OR 4.1, 95% CI

1.8-9.5), and three or more (OR 5.3, 95% CI 2.3-12.3) vaginal deliveries compared with nulliparous women. In a questionnaire based cross-sectional study among 2,640 middle-aged women the number of vaginal deliveries was a risk factor for past or present symptomatic prolapse [704].

Whether or not caesarean section provides sufficient protection to the pelvic floor, thereby preventing loss of pelvic organ support, is controversial. Several studies suggest that elective cesarean does indeed protect women from developing pelvic organ prolapse later in life [699,700-703]. In 4,458 randomly selected women, vaginal childbirth increased the risk of prolapse by 1.82 (95% CI 1.04-3.19) [701] In a nested case-control study, Uma et al. [702] found that caesarean section was associated with a significantly reduced risk of pelvic floor surgery compared with spontaneous vaginal delivery (OR 0.16, 95% CI 0.05-0.55). In a case-control study, Chiaffarino et al. [706] found that women who were delivered by caesarean section were at significantly lower risk of prolapse (OR 0.3 95% CI 0.1-1.0). Other investigators suggest that in the long term, caesarean delivery does not provide a significant risk reduction in pelvic floor morbidity compared with vaginal delivery [707-708]. In a cohort study of women having their first and all subsequent deliveries by cesarean (n = 33,167), and an age-matched sample of women only having vaginal deliveries (n = 63,229) between 1973 and 1983, Leijonhufvud et al. found that women only having vaginal deliveries had increased overall risk of subsequent prolapse surgery (hazard ratio, 9.2; 95% CI 7.0-12.1) compared with women only having cesarean deliveries [709] Among women with vaginal deliveries only the incidence rate for prolapse surgery increased steadily, reaching its peak close to three decades after first delivery. In women with cesarean deliveries only the incidence rate for POP surgery showed very little variation over time and being notably lower compared to the vaginal delivery cohort 10 years after first birth for the duration of the observational period. These observational data suggest that cesarean section conveys a long-term protective effect with regard to the development of pelvic organ prolapse (**Figure 10**).

A number of specific obstetric events and interventions have been implicated as risk factors for the development of pelvic organ prolapse. In one study, maternal age and use of epidural analgesia was associated with an increased need for pelvic organ prolapse surgery [700]. A case-control study found no significant association with maternal age, instrumental delivery (forceps or vacuum), or length of delivery when comparing women with prolapse to randomly selected controls [703] However, Handa et al. [710] found that operative vaginal birth significantly increased the risk for all pelvic floor disorders and pelvic organ prolapse in particular (OR 7.5, 95% CI 2.7-20.9). In a case-control study, Chiaffarino et al.
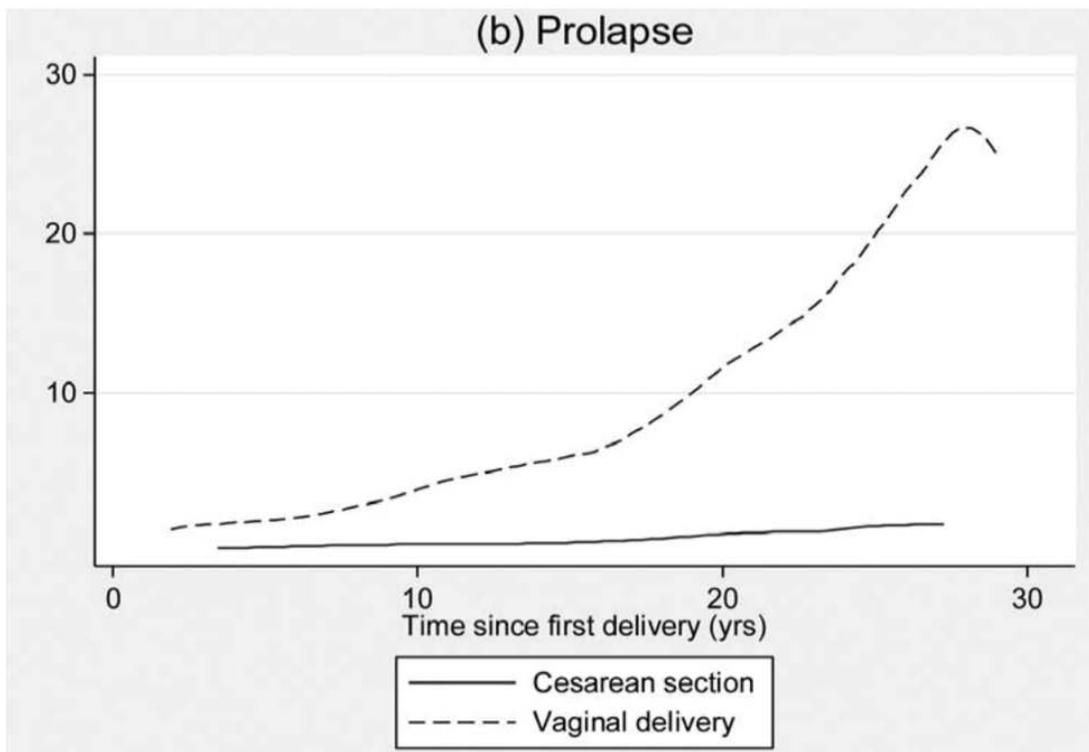
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(b) Prolapse

Figure 10. Rate of pelvic organ prolapse surgery in relation to mode of delivery and time from first childbirth[709].

[706] found that after forceps delivery women had an OR of 3.6 (95% CI 1.0-13.5) for developing pelvic organ prolapse, but after adjustment for vaginal delivery the odds were no longer significant (OR 1.3 95% CI 0.6-3.1). Also Moalli et al. [693] concluded that forceps delivery posed a risk for prolapse. On the othr hand, Uma et al. [702] found no significant association between pelvic organ prolapse and forceps delivery (OR 0.9, 95% CI 0.7-1.2); infant birthweight >4.0 kg (OR 0.9, 95% CI 0.5-1.7); episiotomy (OR 1.46, 95% CI 1.0-2.10); and labour prolonged >12 hours (OR 1.51, 95% CI 1.00, 2.27). The inconsistency and wide variety in the magnitude of the risk estimates suggest that most studies so far lack sufficient statistical power for valid conclusions.

4. MISCELLANEOUS RISK FACTORS AND POP

A wide variety of risk factors for pelvic organ prolapse, others than those addressed above, have been identified in the literature. Most of these have been investigated as part of larger multivariate analyses based on cross-sectional surveys or retrospective case-control studies. Overall, these associations are largely of level III-IV evidence and further research is needed to disentangle the effects and interactions of environmental risk factors for prolapse.

Several somatic risk factors for pelvic organ prolapse have been identified. Generalised connective tissue disorders such as Ehlers-Danhlos disease and Marfans syndrome [711-712] have been linked to an increased risk for pelvic organ prolapse. In a community-based study of prolapse in rural West Africa, chronic anaemia was the strongest risk fac-

tor for prolapse after parity and age (OR 2.1 95% CI 1.1-3.4). [713] and chronic obstructive pulmonary disorders. Skeletal abnormalities such as thoracic kyphosis, lumbar lordosis and pelvic dimension changes have been associated with an increased risk for prolapse [713-715]. Women with joint hypermobility have a significantly higher prevalence of genital (and rectal) prolapse in comparison to women with normal mobility[716-717] Weak associations have also been shown for osteoporosis and rheumatoid arthritis [707] Obesity may be associated with increased pelvic floor symptoms and more severe symptomatic prolapse [704,718-719] yet increasing body mass index and obesity have not consistently been identified as risk factors for prolapse as compared to stress urinary incontinence [720-721] Other factors that has not convincingly demonstrated any significant linkage to prolapse include the presence of chronic obstructive pulmonary disease and diabetes mellitus [685,721] Pulmonary impairment has been shown to more common in women with loss of pelvic organ support compared to those without [722].

A low educational level (OR 2.16, 95% CI 1.10-4.24) [723] and low annual income, [724] are socio-economic factors which have been associated with an increased risk for pelvic organ prolapse. In 21,449 non-hysterectomised Italian women, higher education was associated was a protective factor for uterine prolapse [708]. However, despite significant differences in educational level, smoking habits, alcohol consumption, and socio-economic indices, the prevalence of pelvic organ prolapse did not differ between

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Kroatian urban and rural women [725] Interestingly, risk factors for pelvic floor disorders including pelvic organ prolapse among women in developing countries were similar to those in industrialised countries (increased age and parity). In a review study across 16 low-income and lower middle-income countries the mean prevalence for pelvic organ prolapse was 19.7% (range 3.4-56.4%) but risk factors were similar to those described in studies from more affluent countries but additionally pelvic organ prolapse and other pelvic floor disorders were associated with other factors including poor nutrition and heavy physical work [726].

A physically strenuous occupation has also been shown to influence the risk for pelvic organ prolapse. In a register based study of 28,000 Danish assistant nurses exposed to repetitive heavy lifting, the risk for prolapse was higher among the nurses compared to controls (OR 1.6 95% CI 1.2-2.2) [727]. Women who were labourers/factory workers had significantly more severe prolapse than other job categories (p < 0.001) in a cross-sectional study of women presenting for routine gynecological care [724]. Also, hard physical training may increase the risk for prolapse as women attending paratrooper training, were more likely to present stage II prolapse compared to controls (RR=2.7 95% CI 1.4-5.4) [728].

V. SUMMARY POINTS

- Most studies have used a cross-sectional design and there are limited longitudinal data to suggest a causal relationship between symptoms of obstructed defaecation and pelvic organ prolapse or vice versa. Posterior vaginal wall prolapse and perineal descent are the specific pelvic defects most frequently associated with symptoms of obstructive defaecation.

- Current evidence suggest that hysterectomy increases the risk for subsequent pelvic organ prolapse in general.

- Vaginal hysterectomy and hysterectomy performed for pelvic organ prolapse are the strongest risk factors for having secondary pelvic floor surgery.

- Childbirth is associated with an increased risk for pelvic organ prolapse later in life and increasing number of deliveries is positively associated with the risk.

- Longitudinal long-term data suggest that caesarean section decreases the risk for surgically managed pelvic organ prolapse and most studies indicate that caesarean is associated with a decreased risk for subsequent pelvic floor morbidity in comparison to giving vaginal birth.

- There is a dearth in the understanding of how specific obstetric events and the process of labour and delivery affect the risk for pelvic organ pro-

lapse yet instrumental delivery may increase the risk for development of pelvic organ prolapse.

- Life style factors and socio-economic indices may be associated with the risk of pelvic organ prolapse in both industrialised and non-industrialised countries.

- A number of somatic diseases and conditions have been linked to the occurrence of prolapse but the cause-effect relationship is undetermined.

H. THE GENETIC EPIDEMIOLOGY OF UI AND POP IN ADULT WOMEN

The existence of both acquired and inherited risk factors for incontinence has been recognised for more than 150 years [729]. Although recent advances in formal genetics have quantified the relative contribution of environmental and genetic variation, we still have very limited understanding of the molecular genetics of these conditions. In this section we consider the evidence for genetic predisposition from family studies, twin studies and segregation analyses, and then consider in detail efforts to identify causal variants from linkage studies, candidate gene association studies, and the first reported genome wide association study for pelvic organ prolapse.

I. FAMILY STUDIES

Family studies have classically been considered the first step in establishing the genetic basis of any disease. However, familial aggregation provides limited evidence of heritability, since it fails to control for the effects of shared environmental factors. For pelvic floor disorders, exposures to all major lifestyle risk factors are likely to be at least partly determined by socio-cultural values that are shared within families. Such effects are at least plausible for family size, smoking, socio-economic status, care seeking behaviour, physical exercise, dietary and drinking habits, and toilet training. Both incontinence and prolapse are considered stigmatising in many populations, which places family studies at high risk of differential misclassification bias. This might be expected to have particular impact on the validity of estimates obtained from studies employing the family history method, and any study with non-random sampling of families, for example those relying on probands recruited in secondary care, or those recruiting volunteers via advertisement. Finally, while age correction of risks is possible to account for increasing disease prevalence with age, this has typically not been employed in family studies of pelvic floor disorders.

Although family studies may not provide robust evidence, there have been many studies that

examined prevalence of incontinence (**Table 17**) among relatives of women with incontinence [730-735]. Despite considerable variation in case ascertainment and sampling methods, all studies demonstrate increased risks for urinary incontinence among first degree relatives of probands. This appears to apply for all subtypes of urinary incontinence, and to have a plausible biological gradient, with higher risks among relatives of women with severe incontinence.

In the only study to attempt adjustment [732], it appears that these familial risks are attenuated but not eliminated by classic risk factors for incontinence including age, parity, and BMI. At least three studies have also assessed family history as a risk

factor for incident post-partum incontinence, with conflicting findings [737-739].

There is also a large body of evidence regarding familial transmission of pelvic organ prolapse. With wide variation in prolapse rates with different cases definitions?, uncontrolled studies have produced disparate estimates of the proportion of prolapse patients with a family history of prolapse [740-742]. Reports from controlled studies (**Table 18**) have however consistently demonstrated increased risks [743-746], with unadjusted OR of 2-3 for prolapse among first-degree relatives of prolapse sufferers. These risks are attenuated but not eliminated by adjustment for other risk factors [743-745]. As for

Table 17. Family studies investigating the prevalence of urinary incontinence amongst relatives of women with incontinence

Study	Setting	Design	Age range	n (♀ probands and controls)	Proband phenotype	Family member outcomes	OR or RR (95%CI)
Diokno 1990[730]	Population Based	Controlled – Family History Method	>60	1,154	Any UI	Either parent with UI as adult	2.04 (1.55-2.68)
						Any sibling with UI as adult	1.85 (1.32-2.60)
					Urge UI	Either parent with UI as adult	1.89 (0.93-3.82)
						Any sibling with UI as adult	0.68 (0.20-2.28)
					Stress UI	Either parent with UI as adult	1.74 (1.12-2.70)
						Any sibling with UI as adult	1.59 (0.92-2.75)
					Mixed UI	Either parent with UI as adult	2.63 (1.91-3.61)
						Any sibling with UI as adult	2.32 (1.58-3.40)
					Other UI	Either parent with UI as adult	0.23 (0.06-0.99)
						Any sibling with UI as adult	0.70 (0.21-2.34)
Mushkat 1995[731]	Secondary Care	Controlled – Direct ascertainment	>18	424	Urodynamic Stress UI	SUI among all first degree ♀ relatives	3.00 (2.06-4.38)
						SUI among mothers	3.68 (2.10-6.45)
						SUI among sisters	3.39 (1.89-6.08)
						SUI among daughters	2.43(0.68-8.65)
Hannestad 2004[732]	Population based	Controlled – Direct ascertainment	>18	8,771 (mothers) 2,866 (older sisters)	Any UI	Any UI among daughters	1.31(1.19-1.44)* 1.94(1.26 3.00)** -
						Any UI among younger sisters	1.59(1.34-1.89)*
					Stress UI	Stress UI among daughters	1.52(1.28-1.81)* 2.98(1.11-8.03)**
*RR adjusted for age, BMI, and parity						Stress UI among younger sisters	1.77(1.34-2.33)*
**RR adjusted for age, BMI, and parity and restricted to subgroup of daughters of mothers with severe UI					Urge UI	Urge UI among daughters	1.80(0.83-3.92)*
Note: unadjusted risks generally higher across all outcomes, indicative of substantial concordance/correlation in age, BMI, and parity between family pairs.					Mixed UI	Mixed UI among daughters	1.55(1.21-1.99)* 2.07(0.92-4.64)**
						Mixed UI among younger sisters	1.74(1.08-2.82)*
Elia et al 2002[733]	Secondary Care	Family history method	>18	667	Any UI	Any UI among any relatives	4.51(2.833-7.20)
Ertunc et al 2004[734]	Secondary Care	Direct ascertainment	>18	513	Surgically treated SUI	SUI among mothers	3.71(1.84-7.47)
						SUI among sisters	2.49(1.49-4.16)
Buchsbamet al 2005 [735]	Community Based	Direct ascertainment	Post menopause	143	Nulliparous with any UI	Any UI among parous sisters	2.89(1.46-5.70)
Lapitan et al, 2001[736]	Secondary Care	Family history	>18	5502	OAB	Any family history	1.62(1.42-1.83)

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Table 18. Familial transmission of pelvic organ prolapse.

Study	Setting	Design	Age range	n (♀ probands and controls)	Proband phenotype	Family member outcomes	Unadjusted OR (95%CI) (Unless specified)
Chiaffarino 1999 [743]	Secondary Care	Controlled – Family History Method	<75	208	Stage II-IV Baden-Walker	History of mother with prolapse	3.2 (1.1-7.6)*
						History of sister with prolapse	2.4 (1.0-5.6)*
McLennan 2008 [744]	Secondary Care	Controlled – Family History Method	>18	624	Stage I-IV Baden-Walker	Family history of any relative with hernia or prolapse	RR 1.81(1.41-2.32) RR 1.4 (1.2-1.8)** 2.71(1.83-4.01)
					Stage I-II Baden-Walker	Family history of any relative with hernia or prolapse	RR 1.69 (1.19-2.41) 2.37(1.27-4.39)
					Stage III-IV Baden-Walker	Family history of any relative with hernia or prolapse	RR 2.69 (2.13-3.41) 8.72 (5.26-14.42)
Sleiker-ten Hove 2009 [745]	Population based	Controlled - Family History Method	45-85	1397	Symptom of vaginal bulge	Mother with prolapse	1.99 (1.31-3.04) 1.67 (1.10-2.54)***
Mathlouthi 2011 [746]	Secondary Care	Controlled - Family History Method	<45	66	Surgically treated POP	Any family history POP	4.41 (0.47-41.8)

*Adjusted for age
**Adjusted for vaginal deliveries, incontinence status, and family history of incontinence
***Adjusted for age, current heavy physical work, and prolapse symptoms during pregnancy

incontinence, there again seems to be a plausible biological gradient [744], with anatomically more severe cases of prolapse being more likely to have a positive family history. This is consistent with the suggestion of an earlier onset of prolapse among familial cases [742].Only one study has used direct anatomic ascertainment, in a study based on sib-pairs discordant for parity [747].There familial concordance was observed not only for overall prolapse stage, but also by compartment. Where it has been tested, there also appears to be shared familial risk between prolapse and incontinence [744-745], although this overlapping propensity may be explained by known shared environmental risk factors, rather than common genetic predisposition.

In summary, family studies have consistently demonstrated familial aggregation of both incontinence and prolapse. A family history of incontinence or prolapse is associated with approximately double the risk of developing either condition. Such an effect appears to hold for all subtypes of incontinence, and prolapse in all compartments. There is plausible evidence that family history is associated with both earlier onset, and more severe phenotype. These effects are partly explained by known environmental risk factors, and family studies cannot exclude the risk of further unmeasured confounding from shared environmental risks. For this we should consider evidence from classical twin studies.

II. TWIN STUDIES

Twin studies compare the concordance in a trait or condition between monozygotic (MZ) twins and same-sex dizygotic (DZ) twins, to estimate heritability. For genetically determined traits higher concordance is observed in MZ twins compared to DZ twins, while for entirely environmentally determined traits, concordance should be the same in both types of twin pair. This simple idea is illustrated by consideration of a fully penetrant autosomal single gene disorder, which will display 100% concordance in MZ twins, while in DZ twins will have only 50% concordance for a gene with dominant mode of inheritance, or 25% concordance for a gene with recessive mode of inheritance. A fundamental assumption of these analyses is that both types of twin pair share equal environment. This assumption is clearly violated both pre-natally, and in later life. This bias can be partially compensated for either in studies of twins reared apart, or in adoption studies, but these designs have not been applied to the study of incontinence or prolapse.

Three major twin resources have been used to assess genetic influences on incontinence or prolapse: the US Twins Days festival, the Danish Twin Registry, and the Swedish Twin Registry. The Twins Days festival relies on volunteers, and the resulting recruitment bias is likely to overestimate concordance for many traits for both MZ and DZ twins. In the sample of 1,764, predominantly MZ, middle-aged twins from Twins Days, concordance of symptomatic stress urinary incontinence was 79.5% for MZ and 78.6% for DZ twins [748]. Such a result suggests no significant genetic contribution to stress urinary incontinence at all.

Among a sample of 2,336 twins surveyed as part of four surveys from the Danish Twin Register, concordances for both MZ and DZ twins were much lower

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not only for stress urinary incontinence, but also for urgency and mixed incontinence [749].With separate cohorts for middle-aged and elderly women, heritability was calculated separately in each age group. As in the Twins Day sample, genetic factors were not significant for stress incontinence in middle-aged women, but rose to a heritability of 39% in the elderly women. Similarly heritability increased with age for urgency incontinence (42% rising to 49%), and mixed incontinence (27% to 55%).

Women participating in the Swedish Twin Register have provided relevant data as part of two separate analyses [750-751].Treatment codes corresponding to stress incontinence and prolapse surgery from a nationwide surgical register were used to estimate heritability for a sample of 16,886 twins aged >50. As might be expected for such a strict phenotype definition, concordances for surgical treatment were low, but produced heritability estimates of 41% for stress incontinence surgery, and 43% for prolapse surgery. Similarly for female twins aged 20-46 from the same register (evaluable sample 4,550), using questionnaire based phenotyping, produced an estimate of 34% heritability for stress incontinence. From the same survey heritability was estimated for urgency incontinence (37%), mixed incontinence (18%), "any" incontinence (51%), nocturia (48%), and urinary frequency (40%). It should be noted that because of sample size limitations, an absence of genetic effects cannot be entirely precluded for stress, urgency, or mixed incontinence.

The mechanism of these probable genetic effects has been explored in analyses of joint hypermobility and pelvic floor mobility in twins [752-753].These data suggest heritability of 59% for oblique bladder neck descent on Valsalva in nulliparous twins aged 18-24, with a shared genetic component to both pelvic floor and elbow mobility.

In summary, twin studies to date have suggested significant heritability for stress incontinence, urgency incontinence, and pelvic organ prolapse, with genetic variation potentially contributing up to half of population phenotypic variation. Heritability appears to be highest for urgency incontinence, with apparent heritability increasing with age as environmental factors reduce in importance. This is consistent with our understanding of childbirth as a major environmental determinant of both incontinence and prolapse. Genetic predisposition to incontinence and prolapse may manifest at a preclinical stage in pelvic floor hypermobility. Together with data from family studies this provides strong evidence of genetic risk factors for incontinence and prolapse.

III. SEGREGATION ANALYSES

Despite the large number of family studies for incontinence and prolapse in adults, there have been few studies to examine segregation among extended pedigrees. Studies of families affected by nocturnal enuresis [754], have however included some adults affected by urgency incontinence. Analysis of different enuretic families has usually suggested autosomal dominant inheritance with high penetrance, but low penetrance and autosomal recessive modes have also been reported. In the only segregation analysis reported to date of 10 families affected by prolapse [742], a dominant mode of inheritance was again proposed. These findings could be a consequence of selection or ascertainment bias. In contrast results from more recent association studies strongly suggest that polygenic inheritance is most likely across the population as a whole.

IV. LINKAGE STUDIES

Again, many linkage studies have been conducted using families of children affected by nocturnal enuresis [754], but only two studies have considered uniquely adult symptoms. In a family including 6 women with early onset prolapse across three generations, 10 putative loci were suggested, but none approached genome wide significance [755]. Allen-Brady and colleagues [785] genotyped women from 32 families, including 70 patients needing surgical treatment for prolapse. There was strong overlap with other pelvic floor disorders including a high prevalence of treatment for both stress and urgency incontinence. Using a set of 27,157 markers from a larger Illumina array, they observed a genome wide significant peak at 9q21, and further suggestive peaks at 9q31 and 1q42.

V. GENE ASSOCIATED STUDIES

Currently reported candidate gene studies have assessed polymorphisms of 10 different genes for incontinence (**Table 19**), and 15 genes for prolapse (**Table 20**). To allow comparisons across all studies, we extracted all genotype counts, and recalculated the allelic test. As a check on study quality we also recalculated the power of the study for an OR of 2.0 between cases and controls based on observed minor allele frequencies, and finally rechecked Hardy-Weinberg Equilibrium for cases, controls, and the overall population. We assessed the credibility of associations using the interim Venice criteria [756].

Polymorphisms in COLIA1, ADRB3, HTR2A, LOX-L1, MMP1, MMP3, CYP17, CYP19, ESR, and AR, have been tested for an association with incontinence, or one of its subtypes. There is little uniformity in case definitions, with a mixture of urodynamic, clinical, and questionnaire based inclusion criteria used, and frequently inadequate matching between cases and controls for age, parity, or prolapse stage. In most cases we found significant

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Table 19. Candidate gene association studies for urinary incontinence

Gene	refSNP ID	Phenotyping	Authors	Population	n cases	n controls	Allelic Test OR(95% CI)	Power for OR>=2	Hardy-Weinberg	Notes
COLIA1	rs1800012	SUI confirmed using cough test and cystometry	Skorupski et al 2006 [757]	White Polish	50	50	2 (1.12-3.6)	38.8%	Deviation from HWE for controls p<0.01	Likely genotyping errors
COLIA1	rs1800012	SUI confirmed using cough test and cystometry	Sioutis et al 2011 [758]	White Greek	45	45	2.19 (1.15-4.17)	35.6%	In HWE	Inadequate matching for parity
ADRB3	rs4994	OAB (with and without UUI) determined using questionnaire and bladder diary	Ferreira et al 2011 [759]	Unselected Brazilian	49	169	2.41 (1.38-4.21)	68.2%	Deviation from HWE for cases p<0.05	High risk population stratification
ADRB3	rs4994	Idiopathic OAB (with and without UUI) confirmed with questionnaire	Honda et al 2006 [760]	Unselected Japanese	100	101	2.48 (1.47-4.20)	71.8%	In HWE	
HTR2A	rs6313	Self reported incontinence	Schwanke et al 2007 [761]	Unselected Brazilian	102	196	1.12 (0.69-1.82)	62.5%	Deviation from HWE for cases p<0.05	High risk population stratification
HTR2A	rs6313	Self reported incontinence confirmed with cystometry	Noronha et al 2010 [762]	Unselected Brazilian	68	162	1.61 (1.08-2.42)	54.4%	Deviation from HWE for controls p<0.05	Inadequate matching for ethnicity
LOX-L1	rs1048661	Self reported SUI	Ozbek et al 2011 [763]	Unselected Turkish	87	87	1.22(0.74-2.01)	<37.8% after correction for multiple comparisons	Massive deviation from HWE for cases p<0.0001	Low genotyping rate
	rs3825942						1.29(0.72-2.31)		In HWE	
	rs2165241						2.80(1.74-4.5))		Massive deviation from HWE for cases and controls p<0.0001	
MMP3	rs3025058	Self reported SUI	Skorupski et al 2010 [764]	Unselected Polish	149	109	1.01(0.72-1.44)	<53.8% after correction for multiple comparisons	Deviation from HWE for both controls (<0.05) and cases (<0.0001)	
MMP 1	rs1799750				155	111	0.83(0.59-1.18)		Deviation from HWE for cases (<0.05)	
MMP1	rs1799750	SUI confirmed by questionnaire	Vishwajit et al 2009 [765]	Unselected USA	12	8	1.66(0.46-6.00)	10.5%	Deviation from HWE for cases (<0.05)	
CYP17	rs743572	UUI or SUI confirmed by questionnaire and cough test	Cornu et al 2011[766]	Unselected French	121	66	ns	<41.2% after correction for multiple comparisons	Not calculable from published data	
CYP19	rs2414096									
ESR1	rs2234693									
AR	Exon1 CAG STR						Not calculable			

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