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SPECIAL CONTRIBUTION

Clinical epidemiological insights into urinary incontinence

Vatché A. Minassian[1,2] · **Tony Bazi**[3] · **Walter F. Stewart**[4]

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Abstract
Introduction and hypothesis Urinary incontinence (UI) is very common and heterogeneous among women with limited knowledge of progression or prognosis. Evidence based on clinical epidemiology can help to better understand the natural history of UI.
Methods We examine the challenges of UI definition and its subtypes, its impact on quality of life and health-seeking behavior. We review the proposed pathophysiology of UI subtypes and known risk factors as they relate to our current knowledge of the disease state. Finally, we emphasize the role of epidemiology in the process of acquiring new insight, improving knowledge, and translating this information into clinical practice.
Results Stress UI is most common overall, but mixed UI is most prevalent in older women. The three UI subtypes have some common risk factors, and others that are unique, but there remains a significant gap in our understanding of how they develop. Although the pathophysiology of stress UI is somewhat understood, urgency UI remains mostly idiopathic, whereas mixed UI is the least studied and most complex subtype. Moreover, there exists limited information on the progression of symptoms over time, and disproportionate UI health-seeking behavior. We identify areas of exploration (e.g., epigenetics, urinary microbiome), and offer new insights into a better understanding of the relationship among the UI subtypes and to develop an integrated construct of UI natural history.
Conclusion Future epidemiological strategies using longitudinal study designs could play a pivotal role in better elucidating the controversies in UI natural history and the pathophysiology of its subtypes leading to improved clinical care.

Keywords Stress · Urgency · Mixed urinary incontinence · Epidemiology

Introduction

Managing disease begins with an understanding of the healthy state followed by studying its transition to disease. The application of clinical epidemiology helps to identify disease phenotypes, recognize the population at risk, and understand its demographics and health characteristics. It is the discipline that enables us to study the natural history of disease as it transitions from a normal state to overt clinical disease [1]. Different epidemiological study methods are used to identify means of preventing disease onset, to slow or reverse its progression, and to validate treatment efficacy and intervention effectiveness [2].

Similar to other disease states, epidemiology is important in revealing the etiology of urinary incontinence (UI) and risk factors that mitigate or mediate onset and progression (Fig. 1). UI is highly prevalent in women and is a source of bother, with a significant impact on quality of life (QOL) and health care costs. It commonly presents as either stress UI, urgency UI, or mixed UI. Despite its high prevalence and socioeconomic impact, little is known about the natural history of its subtypes, and rates of health-seeking behavior are dismal.

✉ Vatché A. Minassian
vminassian@partners.org

[1] Brigham and Women's Hospital, Boston, MA, USA

[2] Department of OB/GYN, 75 Francis Street, Boston, MA 02115, USA

[3] American University of Beirut, Beirut, Lebanon

[4] Sutter Health System, Walnut Creek, CA, USA

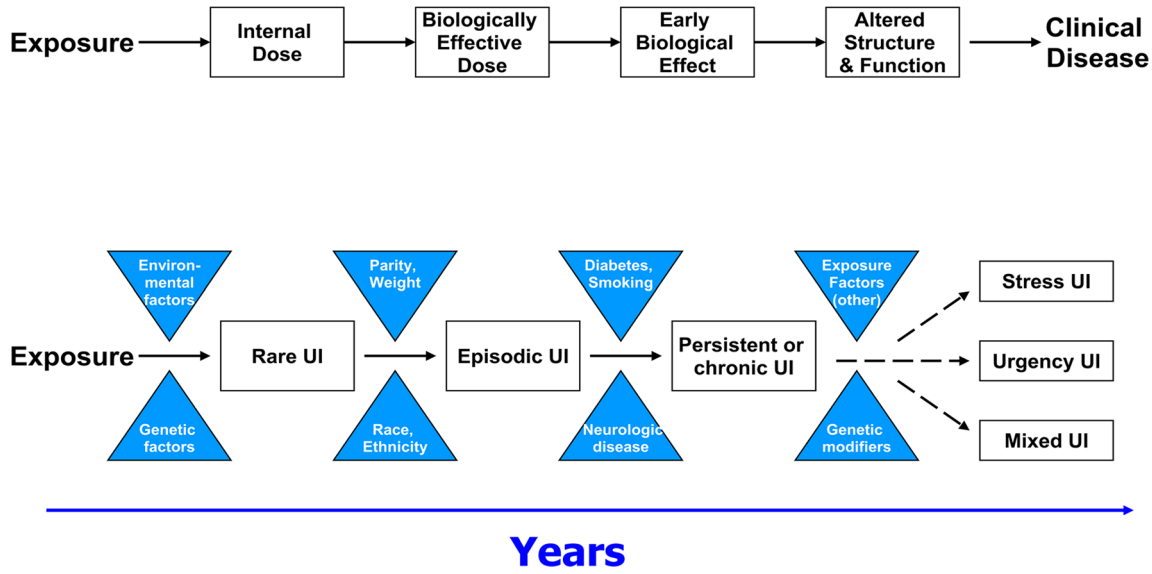

Fig. 1 Natural history of urinary incontinence. Exposure represents the interaction of the individual with a risk factor; internal dose is the amount of injury sustained with few to no sequelae; a biologically effective dose of an exposure represents the threshold needed to be crossed to produce an effect (i.e., UI); early biological effect is the untoward expression of symptoms of UI as a result of prolonged or sustained exposure, but which may still be reversible; the altered structure and function represent advanced disease (stress, urgency or mixed UI) that is not spontaneously reversible without an intervention

Consequently, limited funding is available for studying and managing this condition.

Our objective is to define UI and its subtypes, describe its natural history, and review the proposed pathophysiology of UI subtypes and known risk factors. We also present evidence from the evolving scientific fields of epigenetics and microbiomes, and propose future epidemiological strategies that could play a role in better elucidating the controversies in the natural history of UI. To achieve this objective, an English-language literature search was performed using MEDLINE (through 31 May 2016). Pertinent articles were reviewed using relevant key words—urinary incontinence, stress incontinence, urgency incontinence, mixed incontinence—combined with the terms definition, etiology, pathophysiology, risk factors, prevalence, incidence, remission, QOL, genetics, and microbiome.

Defining UI and its subtypes

There are two challenges involved in defining UI and its subtypes. One is being able to distinguish normal from abnormal lower urinary tract function. The second is to establish valid disease subtypes that differ by etiology, pathophysiology, expression, and treatment options.

Although much of the focus of clinical research is on individuals with frank UI, the ultimate challenge is to understand when preclinical UI starts, along with the time at which the transition to a persistent abnormal state has occurred. This, in turn, relies on understanding the epidemiology of normal adult urinary function. Historically, UI was defined as the involuntary loss of urine represented as an objectively demonstrable event, and described to be a social or hygienic problem [3]. Although this definition was highly specific, it was clinically impractical. Women who presented with subjective UI to their clinicians received little or no attention if UI was not observed during an examination, or if UI was not reported by patients to be a "hygienic" problem. Currently, UI is defined as the complaint of any involuntary leakage of urine [4]. Paradoxically, this new definition includes a substantial spectrum of women who have experienced rare incidental UI events. Consequently, some report UI prevalence estimates of up to 60% [5]. Clearly, such estimates of epic proportions, where disease is more prevalent than the normal state, are difficult to justify.

On the other hand, revealing UI subtypes raises etiological questions of common pathways to onset, transition, and convergence to the end stage. Stress UI is defined as a loss of urine associated with activities such as coughing, sneezing, lifting, or laughing; urgency UI is defined as a loss of urine associated with a strong desire to urinate; finally, mixed UI is defined as urine loss associated with activity *and* with a strong desire to urinate [4]. Although stress and urgency UI are generally regarded as different disease entities, epidemiological evidence shows that women move among and between these different subtypes. In one study of over 10,000 women, significant changes in UI status were reported over a 2-year period: women with baseline urgency UI, 34–38% remitted, 4–9% transitioned to stress UI and 16–20% to mixed UI; women with baseline stress UI, 32–41% remitted, 4% transitioned to

urgency UI, and 16–23% to mixed UI; women with baseline mixed UI, 22–27% remitted, 10–11% transitioned to urgency UI, and 11–15% to stress UI [6]. Therefore, consistent UI subtype prevalence estimates across studies have been difficult to reproduce. The joint IUGA/ICS nomenclature does recommend gathering further information on the duration of time with symptoms, frequency, severity, and volume of urine loss [4]; however, it is not possible to generate accurate estimates without a clear understanding of the clinical epidemiology of UI and its subtypes [7].

Natural history of UI

Psychological and socioeconomic impact

The impact of UI on QOL is substantial and includes impaired social and physical relationships [8]. There is a downward cycle of impairment resulting in worsening psychological function. For instance, depression and anxiety occur at a high rate in women with UI [9, 10]; women with UI have low SF-36 QOL, high CES-D depression scores, and a poor quality of sleep [11]. Finally, managing UI is a substantial burden and cost for caregivers and the community. The presence of UI increases the risk of nursing home admissions [12], and in community-dwelling women, total UI costs (direct and indirect) are about $11.2 billion/year [13].

Prevalence

Urinary incontinence is a highly prevalent condition that afflicts more than 1 in 3 women in their lifetime [14]. More than 20 million women in the USA have UI, and, given the current demographics, this is projected to increase by more than 50% in the coming decades [15]. Prevalence estimates of UI among community-dwelling women range from 2 to 58% [5]. Although UI prevalence increases with age [16–19], prevalence patterns differ by UI subtype. Stress UI prevalence (average = 13%) peaks during the 50s, and then declines thereafter. The prevalence of urgency UI and mixed UI is low between 20 and 30 years of age, but gradually increases with age, with an average prevalence of 5 and 11% respectively. Although stress UI is most common overall, mixed UI becomes the most dominant subtype in late adulthood (Fig. 2) [18–21].

Although little is known about the relationship between stress and urgency UI, epidemiological studies show that mixed UI is far more common than expected if pure stress (13%) and pure urgency (5%) UI are assumed to be independent [22]. The observed prevalence of mixed UI (11%) is several times higher than the expected co-occurrence of stress and urgency UI [22]. Potential explanations include the *liability model*, which posits that the presence of one subtype

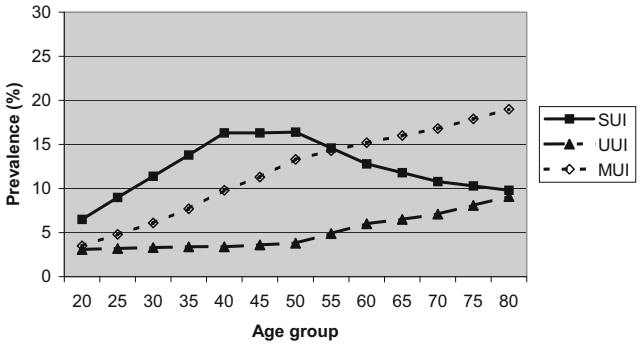

Fig. 2 Prevalence of stress, urgency, and mixed urinary incontinence by age group. *SUI* stress urinary incontinence, *UUI* urgency urinary incontinence, *MUI* mixed urinary incontinence. Prevalence estimates of stress, urgency, and mixed incontinence represent pooled estimates of several population-based studies, including Hannestad et al., Hunskaar et al., Melville et al., and Minassian et al. [18–21]

(i.e., stress UI) leads to the increased risk of developing the other subtype (i.e., urgency UI) [23]. Another explanation is offered by the *severity model*, which suggests that women with mixed UI might have more severe symptoms and hence might be less likely to experience remission when compared with pure stress or pure urgency UI [6].

Incidence and remission

Data from longitudinal studies suggest that women with UI might cycle in and out of active and inactive symptom phases [24]. UI is associated with high incidence rates of 5–20% with equally significant remission rates of 3–12% [25–31]. In one meta-analysis, age-specific incidence was less than 2/1,000 person-years before age 40, increased to 5/1,000 person-years at age 50, decreased to 3/1,000 person-years at 60–65, only to increase again in the later decades of life [32]. Incidence rates varied as much as six-fold across studies, a finding largely explained by case definition. Conversely, remission of UI is also quite common, especially during the early stages of the disease. Most UI studies describe remission as the absence of symptoms following a period of active symptoms [25–27, 31]. Yet, little to no attention is given to transient remission, where women may go from an active to a dormant stage with no symptoms, followed by re-emergence of symptoms.

Longitudinal UI research relies on two time points to estimate onset and progression of UI spread by one or more years [32]. These studies have certain limitations. First, there is a lack of specificity in short-term UI variability. As UI is highly dynamic (i.e., women move in and out of disease or transition from one subtype to another), these studies do not offer an accurate estimate of change in UI symptoms. Second, the ideal time interval to distinguish between complete (permanent) versus transient (moving in and out of disease) remission is not known. The same is true for the new onset of symptoms.

Previous studies have used intervals of 1 [31], 2 [25, 26], 3 [27, 33], 4 [29] or 5+ years [28, 30]. Our research with 6-monthly questionnaires representing longitudinal UI data over a period of 4 years, and involving over 8,000 women over the age of 40 in a general population [23, 24], suggests that it might be only after the third follow-up survey (i.e., 18 months) that a more accurate predictor of the true long-term status of UI can be obtained (data not yet published).

Disease severity and progression

Previous studies have examined outcomes such as bother and impact on QOL in relation to UI subtypes, including stress, urgency, and mixed UI. Most have shown that mixed UI, versus stress and urgency UI, is more severe and has a greater impact on QOL [34–36]. However, very little research exists on the relationship between UI severity and disease progression (resulting in increased bother and worsening QOL), which is the fundamental marker of treatment management. As discussed elsewhere, UI subtypes transition amongst each other, where the general trend is toward increased progression into mixed UI [6]. However, as most women with early stages of UI (i.e., mild UI to moderate UI) do not seek care [5], when they finally present with advanced symptoms (severe UI), there is lost opportunity to develop and implement mitigating interventions that postpone or revert disease progression.

Pathophysiology

Of the three UI subtypes, the underlying mechanisms of onset and progression of stress UI are the most understood [37]. Traditionally, the key urethral support responsible for continence was considered to be at the bladder neck and proximal urethra, namely the pubo-urethral ligaments [38]. In subsequent years, DeLancey in the USA formulated the *Hammock Theory*, demonstrating the primary support of the bladder neck to be an intact vaginal wall at the base of the bladder [39]. Through its fibrous and muscular attachments to the pelvic side wall, the vagina was shown to act as a hammock to support the bladder neck, and hence maintain continence [39].

Concurrently, research conducted in Sweden and Australia produced the *Integral Theory* of continence [40]. It posited that stress UI is mainly the result of connective tissue laxity in the vagina and its supporting ligaments, namely the pubo-urethral, cardinal/uterosacral, and the tendinous arch of the pelvic fascia. It emphasized the role of the suspensory ligaments in supporting the proximal vagina and mid-urethra to maintain continence [41].

More recently, based on urodynamics, imaging, and clinical observations, Delancey demonstrated that the integrity of the urethra, as measured by the maximum urethral closure pressure, is more important in maintaining continence than the underlying support structures. These structures include the urethral mucosa with its neurovasculature, smooth muscles, and the striated sphincter muscles [42].

In contrast, our understanding of urgency UI and OAB is not well developed [43]. Most women with this condition have idiopathic urgency UI or OAB [44]. Several etiological theories have been suggested, including neurogenic, epithelial, myogenic, and others [45]. A commonly accepted theory is the loss of inhibitory control by the central nervous system (CNS). In the normal state, the micturition center in the brain maintains continence in response to a full bladder by suppressing the urge to urinate [46]. Disruption of this communication results in urgency UI [47]. Neurogenic bladder (e.g., in multiple sclerosis) represents a small subset of women who experience urgency UI or OAB [48]. Most women, though, have idiopathic OAB.

The epithelial hypersensitivity theory proposes the presence of chemosensitizing agents leading to bladder instability. An increased risk of OAB exists in adult women with a history of childhood voiding dysfunction [49], which with time can lead to overdistention, and hyperexcitability of the detrusor muscle [50]. The myogenic theory suggests that the pelvic floor might sustain a physical strain during developmental years. Initially, the bladder may adapt. However, over time, the pelvic floor fails due to exhaustion, birth injury, genetic and/or environmental factors, resulting in loss of ability to support the urethral continence mechanism during an urgency episode [51]. These and other proposed theories are likely influenced by psychosocial disturbances, genetic predisposition, inflammatory, and drug-induced conditions [44].

Last, mixed UI, defined as co-occurring stress UI (somewhat understood) and urgency UI (poorly understood), has the most ambiguous pathophysiology. As the key feature in most bladder control conditions is urine loss, it is often difficult to accurately distinguish between different subtypes, especially when UI is severe [52]. When a woman presents with the chief complaint of UI, but her symptoms are neither purely stress UI nor purely urgency UI, a mixed UI label is typically assigned. However, women with mixed UI may have a combination of bladder control conditions of different etiologies. It is likely that mixed UI comprises different pathophysiological subtypes [53–55]. Theories explaining the etiological features of the different mixed UI phenotypes are discussed further below.

Despite its high prevalence, the burden on QOL, and the high cost to society, UI research has not received significant public awareness or funding to better understand its pathophysiology and basic science [56]. Moreover, interest in UI translational research has not equaled that of other chronic health conditions with similar prevalence estimates (e.g., diabetes, arthritis, COPD, and others) [57]. Consequently, the science needed to decipher the pathophysiology of UI and

its subtypes is not well established, and there remains a significant knowledge gap that needs to be uncovered to explain the various pathways leading to UI [56].

Risk factors

Establishing the etiology of UI requires a clear understanding of the mediators and modifiers of disease onset and progression. Risk factors include: age, race, parity, obesity, diabetes, chronic cough, COPD and smoking, previous pelvic surgery, medications, functional and motor impairment (Table 1). Many known UI risk factors are non-modifiable. These include age, race, and parity. *Advancing age*, a strong predictor of urgency UI and mixed UI, is inevitable. After the fifth decade of life, age is not a risk factor for pure stress UI [22]. This is likely due to the strong impact of vaginal birth on stress UI in the first two decades after childbirth, and not thereafter. The further away a woman gets from the delivery of her children (a strong corollary for advancing age), the lower is the impact of childbirth on the development of stress UI [58, 59].

Race is another risk factor. White women have a higher prevalence and incidence of UI compared with Hispanic, Asian, and black women [31, 60]. More specifically, white women are at a higher risk for developing stress UI, whereas black women are at a higher risk for developing urgency UI [31, 60, 61]. *Parity*, a key determinant of stress UI, is another irreversible risk factor. In one meta-analysis, vaginal, versus cesarean, delivery had a two-fold increased risk of long-term stress UI [58]. Some, but not all, epidemiological data suggest that cesarean sections (versus vaginal births), might mitigate this risk [58, 62–64]. It is noteworthy that parity is not a risk factor for urgency UI alone, except in the context of mixed UI, where stress and urgency UI co-exist [65].

Table 1 Effect of common risk factors on urinary incontinence subtypes

Risk factor	Urinary incontinence subtype		
	Stress UI	Urgency UI	Mixed UI
Age			
<50	++	+	+
> = 50	No effect	++	++
Race (white = referent)			
Black	--	++	-
Hispanic	-	-	--
Parity	++	No effect	+
Obesity	++	++	++
Diabetes	++	++	+
COPD/smoking	++	+	++
Surgery for stress UI	--	+	-

Obesity is a potent risk factor for prevalent and incident UI across all UI subtypes [66, 67]. Similar to vaginal birth, persistent obesity weakens the pelvic floor urethral support structures leading to pelvic floor dysfunction [37], although the exact pathophysiology of weight-induced UI is still not well established [68]. The impact of BMI and increased weight circumference may lead to stress UI owing to the loss of support of the urethrovesical junction and to a lesser extent to urgency UI from detrusor muscle overactivity [68, 69]. *Diabetes* is strongly associated with obesity, which may explain, in part, the relation between obesity and urgency UI [70]. Diabetes also appears to be associated with all UI subtypes, with the strongest association for urgency UI [71]. Elevated blood sugar can act as a diuretic, with an increased risk for frequency and urgency UI [70]. Additionally, diabetic microvascular injury can result in neuropathic bladder dysfunction, affecting the stability of the detrusor muscle and the integrity of the urethral sphincter [69]. For instance, OAB is more commonly found in diabetics with a history of silent cerebrovascular accidents on brain MRI [72].

Cough, COPD, and smoking likely have similar disruptive mechanisms of action on the pelvic floor resulting in UI. For instance, in the EPINCONT study, past and current smoking history was associated with all UI subtypes [67]. Other potential UI risk factors include previous pelvic surgery (e.g., new onset urgency UI resulting from stress UI surgery), certain medications (e.g., psychotropic medications), and functional and motor impairment [5, 60, 67, 73–75]. Unlike age, race, and parity, some risk factors are modifiable. Blood sugar control improve urgency UI symptoms. A 10% weight loss in obese women results in 50% or more improvement in stress UI symptoms [76]. However, when one considers all known risk factors, a significant proportion of the attributable risk for UI remains unexplained [42, 75]. More importantly, little is known about the interaction of the mediators of disease and their impact on the incident and progression into the different UI subtypes [75].

New frontiers of UI research

Epidemiology has advanced our understanding of the natural history of UI, and the differentiation of subtype, etiology, and treatment modalities. However, many questions remain unanswered. In this section, we discuss new epidemiological research in the nascent fields of epigenetics and urinary microbiomes (and proteomics) that could potentially contribute to deciphering what remains unknown in UI, and help in answering the complex etiological questions on UI subtypes. Finally, we conclude this section by proposing the needed future epidemiological UI research that may lead to the development of better clinical identification, prevention, and treatment modalities.

Epigenetics

Most women who get a specific health problem, including UI, can be tied to familial aggregation where the dominant explanations are genetics and shared environments. For instance, specialty care female UI patients are more likely to have a family history of UI [77]. Epidemiological studies have validated these findings in nulliparous Catholic nuns and their parous sisters [78], and in the EPINCONT study of Norway female residents for stress UI and mixed UI, but not for urgency UI [79]. Studies of twins yield estimates of the relative proportion of phenotypic variance resulting from genetic and environmental factors. Evidence from such studies is mixed. In a survey of women attending a twin festival (i.e., 765 identical and 117 non-identical sisters), stress UI co-occurrence did not differ by twin type, suggesting the dominance of environmental risk factors [80]. In a Danish population-based twin registry study, urgency UI and mixed UI (but not stress UI) were found to have a significant genetic component [81]. Conversely, a Swedish population study from another twin registry suggested a strong genetic risk for stress UI [82].

An alternate approach to the evaluation of genetic factors for UI is to perform genome-wide association studies (GWAS) to discover regions in the genome that harbor disease susceptibility loci [83]. Genetic loci have been suggested for nocturnal enuresis, urgency UI, stress UI, and prolapse [84–86]. To date, only a few genetic epidemiological studies have been performed. Evidence suggests that genes involved in the extra-cellular matrix, smooth muscle, and wound healing process may also be associated with UI [87–89]. However, most of these studies have not been replicated in large datasets [90]. The Women's Health Initiative Genomics & Randomized Trials Network (GARNET) published 2,241 cases and 776 controls using GWAS that demonstrated the presence of as many as six loci that may be associated with urgency UI [90].

There are strong indications that UI is the product, in part, of a genetic predisposition, but there is no consistent or sufficiently detailed evidence to support this conclusion. Evidence regarding UI subtypes, and especially familial aggregation relations by stages of severity, is limited. More rigorous and comprehensive studies of familial aggregation would offer important clues about sub-groups who have a potential genetic predisposition and help to differentiate the influence of a shared environment. In addition, more GWAS using larger studies are needed to validate the urgency UI loci findings, and to study UI across all subtypes.

Urinary microbiome and proteome

The old teaching stating that the lower urinary tract is sterile has been shown to be no untrue [91]. With the development of new generation microbiological techniques, it has been possible to sequence and identify a plethora of micro-organisms and a diverse microbiota in the urinary system not previously identifiable through the standard culturing techniques [92]. The three most common microbial species isolated from the urinary flora are *Lactobacillus*, *Gardnerella*, and Enterobacteriaceae [93]. There appears to be some evidence linking the presence of an altered microbiome in women with bladder control conditions including urgency UI. The microbiome from women with urgency UI has increased *Gardnerella* species and decreased *Lactobacillus* species in addition to increased frequencies of other organisms [93].

Interestingly, the presence of an altered urinary microbiome has also been shown to be associated with a lower responsiveness to medical treatment with anticholinergics in women with urgency UI [94]. Conversely, the presence of a healthy (less diverse) microbiome was more common in controls without urgency UI [94]. However, it is still not clear what a "healthy" bladder really means with regard to the microbial flora. Other unknowns include variations by age, race, BMI, menopausal status, lifestyle, and other potential factors that confound the relationship between urgency UI and the microbiome. Finally, in a pilot study of women with stress UI, levels of 6 (out of 828) urinary proteins were shown to be significantly different from controls. Although urinary proteomics is an emerging field, there is early suggestion of an association between altered urinary protein with stress UI [95]. As a significant proportion of mixed UI remains unknown, we predict that improved understanding of the urinary microbiome (and possibly the proteome) may elucidate the true nature of the various mixed UI phenotypes.

Future epidemiological research and clinical medicine

Health-seeking behavior of UI patients

A primary question is how can UI be so prevalent, but receive little attention. Population research shows that only 25% of women with UI seek care, and less than half of those receive care [96]. UI can be a significant source of bother with a substantial impact on QOL, be it physical (mobility), psychological (depression and anxiety), social (sexual, friendships), and financial (expense of diapers and protective clothing) [8–11, 13, 60]. There clearly is a disconnect at two levels: first, patients with UI do not discuss their symptoms with their physicians; second, clinicians do not ask patients about their UI, nor do they readily offer them care. Studying the iceberg of health care delivery of UI (i.e., level 1: community-dwelling women with little to no UI; level 2: women with mild to moderate UI not seeking care; level 3: women with severe UI seeking primary care; level 4: women with UI receiving specialty care), and factors associated with care-seeking behavior can offer important clues to increasing awareness, promoting healthy bladder behavior, and treatment solutions.

Early detection of clinically significant UI

A second question is how to accurately identify women in the community with clinically significant UI within the continuum of the disease. Part of the complexity here stems from the wide variations in UI prevalence estimates across studies and over time. Survey questions administered at a specific time point within a population at risk do not represent a concrete picture of the natural history of UI. Such questions could only be answered by conducting longitudinal studies with sequential surveys performed at different time points and over a long time period [22]. It is also important to develop surveillance techniques in childhood and adolescence to gain a better understanding of mitigators and risk factors that may long predate the onset of UI in adulthood. This in turn will help develop strategies for prevention education and early detection. In early stages, women may go from periods of UI activity to inactivity, and may not present with any clinically significant symptoms. Over time, they may progress, remit, or transition from one subtype to another. As disease severity increases, UI may be less likely to remit, and more likely to persist within a specific UI subtype. Knowing how to distinguish early- versus late-stage disease states enables clinicians to better deploy appropriate preventive versus treatment strategies.

The enigma of mixed urinary incontinence

Classifying women into stress, urgency, and mixed UI understates the complexity of these bladder conditions. Many women with mixed UI may have features that overlap with stress and urgency UI because the bladder has a very limited set of ways of expressing loss of control [7]. For instance, one woman may have urgency (OAB-dry) with pure stress UI. Another woman may have co-existing stress and urgency UI with varying degrees of severity; she may have symptoms of stress and urgency UI occurring on the same day at different times or on different days. Some women with severe UI may be unable to distinguish between stress and urgency UI symptoms, and thus have mixed UI symptoms. Finally, it is plausible for a woman with mixed UI to have an as yet undefined UI condition, such as stress-induced urgency UI, whereby a stress event (with increased intra-abdominal pressure), may lead to an uninhibited detrusor contraction resulting in urine loss [23]. These phenotypes for mixed UI symptom expression are quite diverse. However, our current approach to defining UI does not adequately characterize these phenotypes.

It is imperative to clearly establish the pathophysiologies of the different mixed UI phenotypes. As described earlier, we propose the presence of various bladder control conditions with different pathways leading to mixed UI. Not all women with mixed UI present with similar symptoms nor do they respond to the same treatments [54, 97]. We hypothesize the presence of three treatment algorithms. The *traditionalists* recommend the least invasive intervention: for instance, pelvic floor exercises produce varying degrees of improvement in women with mixed UI. The *purists* favor treating the most bothersome UI subtype based on the patient's self report. Last, the *interventionalists* promote the most aggressive intervention: for example, anti-incontinence surgery not only treats stress UI symptoms, but it may also improve urgency symptoms in many women with mixed UI [98, 99]. Each approach has some merit and may play a role in a specific subset of women with mixed UI, but more research is needed to address the various treatment approaches [100].

Although some risk factors are similar to both UI subtypes (e.g., obesity), others are not (e.g., parity), suggesting that women who develop mixed UI might be influenced by a different set of mediators and their interaction with each other. Some women with mixed UI clearly have two co-existing, but mutually exclusive, disease subtypes: *pure* stress UI and *pure* urgency UI. However, the observed prevalence of mixed UI is much higher than its expected prevalence. This indicates that mixed UI cannot solely be explained by the co-occurrence of its stress UI and urgency UI components [22].

Conclusion

The *complexity* of the bladder lies in its *simplicity*. The key symptom in a woman with bladder control problems is urine loss. Yet, there are many underlying causes that can potentially lead to UI. Little is known about how mixed UI develops. It is likely that many women with mixed UI transition from pure stress UI or urgency UI to mixed UI; however, some women transition directly from continence to new onset mixed UI [6]. Daily bladder diary data demonstrate that many women with mixed UI symptoms have a stressful event immediately preceding their urgency UI symptoms [23]. These and other findings indicate that mixed UI is multifaceted. Exploring the various pathways that lead to mixed UI will result in a better understanding of pure stress UI, and more importantly pure urgency UI, which remains largely idiopathic. Equipped with this knowledge, future research should be aimed at developing algorithms with various targeted interventions appropriate for the different mixed UI phenotypes. The field of epidemiology plays a key role in this process of acquiring new insight, improving knowledge gaps, and translating this information into clinical practice for the betterment of UI health care in women.

Compliance with ethical standards

Conflicts of interest None.

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