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Genetic Influences Are Important for Most But Not All Lower Urinary Tract Symptoms: A Population-Based Survey in a Cohort of Adult Swedish Twins

Anna-Lena Wennberg[1], **Daniel Altman**[2,3], **Cecilia Lundholm**[2], **Åsa Klint**[2], **Anastasia Iliadou**[2], **Ralph Peeker**[4], **Magnus Fall**[4], **Nancy L. Pedersen**[2], and **Ian Milsom**[1,*]

[1]Department of Obstetrics and Gynaecology, Sahlgrenska Academy at Gothenburg University and Sahlgrenska University Hospital, Gothenburg

[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

[3]Division of Obstetrics and Gynaecology, Department of Clinical Sciences, Karolinska Institute, Danderyd Hospital, Stockholm, Sweden

[4]Department of Urology, Sahlgrenska Academy at Gothenburg University and Sahlgrenska University Hospital, Gothenburg

Abstract

Background—The relative importance of genetic and environmental factors for the occurrence of lower urinary tract symptoms (LUTS) is poorly understood.

Objective—To (1) estimate the prevalence of urinary incontinence (UI), overactive bladder (OAB), and other LUTS and (2) to assess the heritability of these symptoms.

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[*]**Corresponding author:** Department of Obstetrics and Gynaecology Sahlgrenska University Hospital SE-416 85 Gothenburg Sweden Tel.: +46-31-3434179 Fax: +46-31-192940 Ian.Milsom@gu.se .

Author contributions: Ian Milsom had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Milsom, Pedersen.
Acquisition of data: Wennberg, Altman, Lundholm, Klint, Iliadou, Peeker, Fall.
Analysis and interpretation of data: Wennberg, Altman, Lundholm, Klint, Iliadou, Peeker, Fall, Pedersen, Milsom.
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Design, setting, and participants—Cross-sectional survey of LUTS in a national population-based cohort of Swedish twins 20–46 yr of age (*n* = 42 582) from the Swedish Twin Registry.

Measurements—Prevalence rates were determined and heritability of LUTS (in female twins) was assessed using indicators of twin similarity.

Results and limitations—A total of 25 364 twins completed the questionnaire (response rate: 59.6%). LUTS were more common in women (UI: 7%; OAB: 9%; nocturia: 61%; micturition frequency: 18%) than in men (UI: 1%; OAB: 5%; nocturia: 40%; micturition frequency: 11%), and prevalence increased with age. The strongest genetic effects were observed for UI, frequency, and nocturia. The lowest estimate for genetic effects was observed for OAB where environmental effects dominated, and more specifically shared family environment accounted for a third or more of the total variation. For stress UI, a fifth of the total variation in susceptibility to the disorder could be attributed to shared environment. Nonshared environmental effects were seen in the range of 45–65% for the various LUTS. The prevalence of LUTS was low in the men, and there were too few male cases to compute measures of similarity or heritability estimates.

Conclusions—This study provides robust evidence of a genetic influence for susceptibility to UI, frequency, and nocturia in women. In contrast, shared environmental factors seem more important for the predisposition to develop OAB, which may reflect familial patterns such as learning from parental behaviours.

1. Introduction

Urinary incontinence (UI), overactive bladder (OAB), and other lower urinary tract symptoms (LUTS) are highly prevalent conditions with a profound influence on the well-being and quality of life (QoL) [1–4].

The prevalence of UI, OAB, and other LUTS has been shown to increase with advancing age [1–9]. A wide variety of risk factors for the occurrence of UI have been identified [10], but there is a need for more information regarding risk factors for OAB and other LUTS. Several studies suggest that the risk of UI runs in the family [11–14]. Family history studies have evaluated the prevalence of UI in siblings [11–14], but there is still little evidence as yet available regarding the relative importance of genetic factors versus environmental factors for susceptibility to UI, OAB, and other LUTS. Further studies are necessary to evaluate the influence of genetic factors in the pathogenesis and progression of conditions affecting the lower urinary tract.

The aim of this study was (1) to estimate the prevalence of UI, OAB, and other LUTS (principally storage symptoms) in a large cohort of male and female adult twins 20–46 yr of age and (2) to assess the heritability of UI, OAB, and LUTS.

2. Methods

2.1. Population and survey sampling techniques

The Swedish Twin Register in principle contains data on all twins born in Sweden since 1886 (a total of approximately 170 000 individuals) [15]. In 2005, all Swedish twins born from 1959 to 1985 (20–46 yr of age) (*n* = 42 582) were contacted with a letter inviting them to participate in an online-based survey to screen for common complex diseases and common exposures: the Study of Twin Adults: Genes and Environment [16]. Part of this data constitutes the base of the present study. Those not responding to the online questionnaire were contacted and offered the option of answering the survey via a telephone interview. After 2–5 mo, 100 randomly selected twins were contacted again to assess test-retest reliability.

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Zygosity was established based on responses to a series of standard questions on physical similarity. This method was validated as having >98% accuracy by using DNA markers in three separate substudies in the Swedish Twin Registry [15]. In this paper, monozygotic twins are referred to as MZ and dizygotic twins as DZ.

2.2. Questionnaires and telephone interview

The entire questionnaire contained approximately 1300 questions, relating to numerous health conditions, dietary information, QoL, frequency of exercising, and social factors, which have been described previously in detail [16].

2.3. Assessment of lower urinary tract symptoms

The questions regarding LUTS were adapted from a validated epidemiological survey (the Norwegian Epidemiology of Incontinence in the County of Nord-Trondelag study) on female incontinence [1]. The 2002 International Continence Society (ICS) definitions [17] were used for the assessment of symptoms. In addition to the ICS definitions, the number of individuals with a micturition frequency of eight or more per 24 h and nocturia more than two micturitions per night was also reported. A positive response to the question on urinary urgency (defined as the compelling urge to urinate that is difficult to postpone) was classified as OAB, with (OAB wet) or without (OAB dry) associated leakage.

2.4. Ethical approval

This study was approved by the Research Ethics Committee at Karolinska Institute, Stockholm, Sweden.

2.5. Statistical analyses

Prevalence was calculated as a percentage of the eligible responders. To account for correlations within twin pairs, generalised estimating equations were used when comparing prevalences of ordinal outcomes (logit link) and the number of micturitions per 24 h (identity link) between male and female twins and between age groups. To assess heritability, two different indicators of twin similarity were used. Probandwise concordance rates and tetrachoric correlations were reported separately for MZ and DZ female twin pairs. By comparing MZ twins with identical genotype and DZ twins, who on average share 50% of their segregating genes, conclusions can be drawn about the relative importance of genetic and environmental factors. A genetic influence is suggested if MZ twins are more concordant for the disease than DZ twins, whereas evidence for environmental effects comes from MZ twins who are discordant for the disease. Differences between concordance rates for MZ and DZ twins were tested with a likelihood-based approach [18]. Analyses were done using SAS v.9.1 software (SAS Institute Inc, Cary, NC, USA).

2.5.1. Quantitative genetic analyses—Estimates of variance components for liability to disease and their 95% confidence intervals were obtained by fitting structural equation models to the raw data by using normal-theory maximum likelihood with a probit model and adjustment for age [19]. The significance of A (additive genetic), C (shared environmental), and E (nonshared environmental effects) was tested by removing them sequentially in specific submodels. This eventually led to models that gave the most parsimonious fit to the data (ie, models in which the pattern of variances and covariances is explained by as few parameters as possible). Submodels were compared with full models by hierarchic chi-square tests. The difference between minus twice the log-likelihood (−2lnL) for a submodel and that of the full model is approximately distributed as chi-square with degrees of freedom equal to the difference of the number of estimated parameters in the full model and the

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number of estimated parameters in the submodel. The quantitative genetic analyses were performed by MxGui v.1.7.03, a structural equation modelling program [19].

3. Results

The total response rate was 59.6% (n = 25 364). The response rate for the online questionnaire was 43.1% (49.9% for women, 36.2% for men), and an additional 16.5% (16.0% women, 17.0% men) completed a telephone interview. There were very small differences in response rates across the age groups (range: 58.1–60.3%). A total of 23 034 individuals correctly answered the questions on LUTS (1401 nonresponders and 939 with noncomplete data were excluded from the total sample). The κ values for agreement between the online questionnaire and the telephone interviews ranged from excellent to good, which were published previously by Lichtenstein et al [16].

3.1. Prevalence of lower urinary tract symptoms

Table 1, 2, and 3 describe the prevalence of various storage symptoms grouped according to age and gender. In general, symptoms were more prevalent in females than males ($p < 0.0001$), and the prevalence of most LUTS increased with age.

3.2. Heritability

The prevalence of LUTS was low in men, and there were too few male cases to compute measures of similarity or heritability estimates. Thus these estimates are presented for women only. A total of 1392 MZ and 883 DZ same-sex female twin pairs were identified. Table 4 presents indicators of twin similarity (probandwise concordance rates and tetrachoric correlations) by zygosity. Higher concordance rates among MZ twins compared with DZ twins, which indicates genetic effects are important, were observed for micturition frequency, nocturia, urge UI, mixed UI, stress UI (SUI), OAB all, and OAB dry.

Table 5 presents the estimates from the quantitative genetic analysis (ACE model) adjusted for age, where A represents the relative contribution of genetic effects, C the relative contribution of shared environmental factors, and E the contribution of individual environmental factors for the susceptibility to the various symptoms. Using the ACE model, the strongest genetic effects were observed for frequency, nocturia, and conditions involving incontinence. This was the case regardless of whether the involuntary loss of urine was caused by urgency or supposed pelvic floor weakness. The lowest estimate for genetic effects was observed for OAB without concomitant UI where environmental effects dominated. In the most parsimonious models including only genetic and nonshared environments (AE model), the genetic parameter for all symptoms except OAB wet and dry was significant. This model is not suitable for OAB considering the pattern of correlations in MZ and DZ pairs. Nonshared environmental effects, which may include factors such as parity, smoking, obesity, and gynaecologic operations, for example, were seen in the range of 45–65% for the various conditions. For OAB dry, shared environment accounted for nearly a third of the total variation. For SUI, a fifth of the total variation for the disorder could be attributed to shared environment.

4. Discussion

This study, comprising approximately 25 000 individuals, is the largest of its kind to report population-based prevalence rates of LUTS in young and middle-aged adults. In addition, the study design, using a large national cohort of twins, permits an evaluation of the relative importance of genetic, shared, and nonshared environmental factors for the occurrence of LUTS. The strongest genetic impacts were observed for conditions involving incontinence

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regardless of whether the involuntary loss of urine was caused by bladder overactivity or supposed pelvic floor weakness. Hence the incontinence reported here could be thought of as composed of its two main pathophysiologic expressions, urinary stress incontinence and urge UI, which together form mixed incontinence. The lowest heritability estimate was observed for OAB where environmental effects dominated. We also showed that LUTS are prevalent in young and middle-aged women but less so in men. The prevalence of LUTS increases with age. These findings are consistent with other large epidemiological studies of LUTS conducted in men and women of the same age, studies also reporting that the prevalence of symptoms increases linearly with age [1–9].

The aetiology of LUTS is widely recognised to be multifactorial [10], yet the importance of genetic and environmental influences is poorly understood. Evidence in support of a genetic influence on LUTS derives from studies on ethnic group diversity [20–25], studies on familial transmission of disease [11–14], and twin studies [26–29]. Most of these studies have focused on the symptom of UI, and very few have evaluated the impact of genetic factors for susceptibility to other LUTS.

In the present study it was possible to quantify the importance of genetic liability to LUTS in >2000 female twin pairs of known zygosity. Our data indicate that the strongest genetic effects were observed for conditions involving incontinence. Genetic influences were also of importance for nocturia but of little importance for OAB syndrome for which environmental effects dominated. Our data indicate that nongenetic effects that are in common for family members (ie, the shared environmental estimate), such as toilet training and other lifestyle factors, may be involved in the causal mechanisms of OAB. The contention that childhood urinary symptoms may predict adult OAB symptoms was put forward previously [30], and the results of our study tally with this hypothesis. However, it remains undecided exactly how dysfunctional voiding habits in childhood may give rise to OAB later in life. This study also showed that shared environmental effects contributed to the liability of developing SUI but were less pronounced. Our data are in line with family history studies reporting a two to three times higher prevalence of SUI among first-degree relatives of women with SUI compared with first-degree relatives of continent women [11–14].

There are also some data regarding the heritability of pelvic floor disorders and UI from other twin studies [26–29]. The data presented in the present paper suggest a genetic influence for the susceptibility to all subtypes of UI in contrast to a population-based Danish twin study comprising middle-aged and elderly twins that found evidence for significant heritability for urge but not for SUI [28]. Another twin study showed that genetic factors accounted for nearly 60% of the variation in bladder neck descent as measured by ultrasound [29]. However, it should be noted that twin studies based on small groups of volunteers are liable to bias because pairs who are concordant for the disease are more likely to participate [31].

Several studies have suggested that the susceptibility of LUTS varies between different ethnic groups [20–25]. It is not obvious, however, that this kind of data indicates genetic influences. Similarities between women of the same ethnic group might just as well be cultural differences that affect other potentially pathogenetic mechanisms (such as age at childbirth, number of children, etc), family influences, or similar environmental exposures. It is also a common misunderstanding that familial aggregation invariably is a result of genetic factors. Risk estimates derived from family members in most cases cannot distinguish between heritability and noninherited (environmental) factors in the family environment. Familial environmental influences (eg, lifestyle factors such as smoking habits, socioeconomic status, care-seeking behaviour, attitudes towards physical exercise,

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dietary and drinking habits, and toilet training) may also have a direct effect on the transmission of risk for LUTS.

A limitation of the present study is that the symptoms were not objectively demonstrated through physical examinations or micturition charts. In addition, the age of the twin pairs was not ideal for evaluating LUTS. Future longitudinal studies within this relatively young population would allow for an exclusive opportunity to track the onset of symptoms and to identify possible risk factors.

5. Conclusions

This paper provides robust evidence regarding the relative importance of genetic and environmental factors for the occurrence of LUTS in women. Genetic factors were shown to influence susceptibility to UI, frequency, and nocturia in women, whereas shared environmental factors appeared to be more important for the predisposition to develop OAB, which may reflect familial patterns such as learning from parental behaviours.

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Table 1

Comparison of the prevalence of various storage symptoms in the twins grouped by age and gender

Symptom	Sex	Age, yr						
		20–25	26–30	31–35	36–40	41–46	Total	Difference between age groups
Micturation frequency* *n* (%)	Men	224 (10.8)	225 (13.0)	218 (11.6)	217 (10.6)	273 (11.2)	1157/10 184 (11.4)	$p = 0.16$
	Women	524 (20.1)	470 (20.6)	424 (17.6)	388 (15.3)	473 (15.7)	2 279/12850 (17.7)	$p < 0.0001^{\dagger}$
Nocturia* *n* (%)	Men	611 (29.4)	658 (38.1)	766 (40.6)	905 (44.0)	1160 (47.7)	4100/10184 (40.3)	$p < 0.0001^{\ddagger}$
	Women	1 397 (53.6)	1 446 (63.2)	1 544 (64.2)	1 586 (62.6)	1 908 (63.1)	7 881/12850 (61.3)	$p < 0.0001^{\S}$
Nocturia ≥2/night *n* (%)	Men	129 (6.2)	152 (8.8)	160 (8.5)	193 (9.4)	289 (11.9)	923/10184 (9.1)	$p < 0.0001^{\ddagger}$
	Women	495 (19.0)	587 (25.7)	624 (26.0)	614 (24.2)	695 (22.9)	3015/12850 (23.5)	$p < 0.0001^{\S}$
Micturitions/24 h (X ± SD)	Men *n* = 10 184	5.0 ± 2.6	5.4 ± 2.9	5.4 ± 2.8	5.7 ± 2.6	5.7 ± 2.8	5.4 ± 2.7	$p < 0.0001^{\ddagger}$
	Women *n* = 12 850	6.3 ± 3.3	6.6 ± 3.2	6.8 ± 3.3	6.6 ± 3.0	6.6 ± 2.9	6.6 ± 3.1	$p < 0.0001^{\S}$
≥8 micturitions/24 h n (%)	Men	243 (11.7)	273 (15.8)	277 (14.7)	334 (16.2)	435 (17.9)	1562/10184 (15.3)	$p < 0.0001^{\ddagger}$
	Women	796 (26.3)	649 (28.4)	697 (29.0)	703 (27.8)	796 (26.3)	3458/12850 (26.9)	$p < 0.001^{\S}$

SD = standard deviation.

*Defined according to International Continence Society definition 2002.

†Decreasing prevalence with increasing age.

‡Increasing prevalence with increasing age.

§Lowest prevalence in youngest age group; peak in 31–35 yr of age group.

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Table 2

Comparison of the prevalence of urinary incontinence in the twins grouped by type of incontinence, age, and gender

Symptom	Sex	Age, yr						
		20–25	26–30	31–35	36–40	41–46	Total	Difference between age groups
UI *n* (%)	Men	9 (0.4)	16 (0.9)	8 (0.4)	19 (0.9)	37 (1.5)	89/10184 (0.9)	$p < 0.001^{‡}$
	Women	48 (1.8)	87 (3.8)	159 (6.6)	231 (9.1)	372 (12.3)	897/12850 (7.0)	$p < 0.0001^{‡}$
SUI *n* (%)	Men	1 (0.1)	5 (0.3)	2 (0.1)	1 (0.1)	4 (0.2)	13/10184 (0.1)	$p = 0.29$
	Women	26 (1.0)	67 (2.9)	133 (5.5)	196 (7.7)	312 (10.3)	734/12850 (5.7)	$p < 0.0001^{‡}$
UUI *n* (%)	Men	3 (0.2)	3 (0.2)	1 (0.1)	1 (0.1)	8 (0.3)	16/10184 (0.2)	$p = 0.22$
	Women	25 (1.0)	43 (1.9)	66 (2.8)	87 (3.4)	158 (5.2)	379/12850 (3.0)	$p < 0.0001^{‡}$
MUI *n* (%)	Men	0 (0)	1 (0.1)	1 (0.1)	0 (0)	2 (0.1)	4/10184 (0.4)	–
	Women	10 (0.4)	33 (1.4)	56 (2.3)	69 (2.7)	124 (4.1)	292/12850 (2.3)	$p < 0.0001^{‡}$

UI = urinary incontinence; SU = stress urinary incontinence; UUI = urge urinary incontinence; MUI = mixed urinary incontinence.

Participants who reported both UUI and SUI symptoms were classified as having MUI.

‡Increasing prevalence with increasing age.

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Table 3

Comparison of the prevalence of overactive bladder symptoms in the twins grouped by age and gender

Symptom	Sex	Age, yr						
		20–25	26–30	31–35	36–40	41–46	Total	Difference between age groups
OAB all *n* (%)	Men	72 (3.5)	73 (4.2)	79 (4.2)	93 (4.5)	158 (6.5)	475/10184 (4.7)	$p <$ 0.0001‡
	Women	209 (8.0)	211 (9.2)	200 (8.3)	235 (9.3)	301 (10.0)	1156/12850 (9.0)	$p = 0.10$
OAB dry *n* (%)	Men	68 (3.3)	68 (3.9)	74 (3.9)	91 (4.4)	149 (6.1)	450/10184 (4.4)	$p <$ 0.0001‡
	Women	185 (7.1)	182 (8.0)	164 (6.8)	177 (7.0)	201 (6.7)	909/12850 (7.1)	$p = 0.45$
OAB wet *n* (%)	Men	4 (0.2)	5 (0.3)	5 (0.3)	2 (0.1)	9 (0.4)	25/10184 (0.3)	$p = 0.51$
	Women	24 (0.9)	29 (1.3)	36 (1.5)	58 (2.3)	100 (3.3)	247/12850 (1.9)	$p <$ 0.0001‡

The presence or absence of overactive bladder symptoms (OAB) symptoms were classified as follows: No OAB symptoms = No OAB; OAB without UI = OAB dry; and OAB with UI = OAB wet.

‡Increasing prevalence with increasing age.

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Table 4

Twin similarity and concordance rates for lower urinary tract symptoms in female twins grouped by zygosity*

	Monozygotic female twins *n* = 1392				Dizygotic female twins *n* = 883				
	Concordant pairs	**Discordant pairs**	**Probandwise concordance rate[1]**	**Tetrachoric correlations[2] (95% CI)**	**Concordant pairs**	**Discordant pairs**	**Probandwise concordance rate[1]**	**Tetrachoric correlations[2] (95% CI)**	***p* value[3]**
Micturition frequency (ICS)	101	329	0.38	0.42 (0.33–0.51)	32	129	0.33	0.13 (−0.01–0.27)	0.34
≥8 micturitions/24 h	154	406	0.43	0.40 (0.32–0.48)	53	306	0.26	0.06 (−0.06–0.19)	<0.0001
Nocturia (ICS)	643	482	0.73	0.40 (0.32–0.47)	346	399	0.63	0.07 (−0.04–0.18)	<0.0001
Nocturia ≥2 micturitions/night	137	364	0.43	0.44 (0.35–0.52)	59	253	0.32	0.25 (0.13–0.37)	0.005
Overactive bladder without incontinence	19	179	0.18	0.28 (0.13–0.43)	8	109	0.13	0.18 (−0.03–0.40)	0.38
Overactive bladder with incontinence	4	53	0.13	0.41 (0.16–0.66)	3	31	0.16	0.48 (0.19–0.78)	0.76
All overactive bladder	30	218	0.22	0.30 (0.17–0.43)	13	136	0.16	0.20 (0.01–0.38)	0.28
Stress urinary incontinence	20	102	0.28	0.56 (0.42–0.70)	12	89	0.21	0.40 (0.21–0.59)	0.33
Urge urinary incontinence	7	66	0.18	0.47 (0.27–0.68)	3	57	0.10	0.24 (−0.05–0.54)	0.30
Mixed urinary incontinence	4	51	0.14	0.45 (0.19–0.70)	2	40	0.09	0.29 (−0.05–0.63)	0.60
All urinary incontinence	28	121	0.32	0.57 (0.45–0.69)	14	111	0.20	0.33 (0.15–0.51)	0.07

ICS = International Continence Society; CI = confidence interval.

*Higher concordance rates or tetrachoric correlations among monozygotic than dizygotic twins indicates genetic effects.

[1]Probandwise concordance rate is a measure of twin similarity, which is independent of prevalence.

[2]Tetrachoric correlations, r, indicate the upper limit of the genetic variance component.

[3]The *p* value for test of homogeneity of probandwise concordance rates between monozygotic and dizygotic pairs.

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Table 5

Estimated proportion of variance (with 95% confidence intervals) of susceptibility to lower urinary tract infections in women explained by genetic, shared environmental, and nonshared environmental factors

	Genetic effects (95% CI)[1]		Shared environment (95% CI)[1]		Nonshared environment (95% CI)[1]	
Micturition frequency (ICS)	0.40	(0.31–0.48)	*	–	0.60	(0.52–0.69)
≥8 micturitions/24 h	0.40	(0.32–0.47)	*	–	0.60	(0.53–0.68)
Nocturia (ICS)	0.48	(0.41–0.54)	*	–	0.52	(0.46–0.49)
Nocturia ≥2 micturitions/night	0.34	(0.06–0.54)	0.12	(0–0.37)	0.53	(0.46–0.62)
Overactive bladder without incontinence = OAB dry	0.04	(0–0.46)	0.31	(0–0.45)	0.65	(0.52–0.77)
Overactive bladder with incontinence = OAB wet	–	–	0.43	(0.23–0.61)	0.57	(0.39–0.77)
All overactive bladder	0.10	(0–0.46)	0.25	(0–0.43)	0.65	(0.53–0.76)
Stress urinary incontinence	0.34	(0–0.66)	0.20	(0–0.54)	0.47	(0.34–0.62)
Urge urinary incontinence	0.37	(0–0.65)	0.10	(0–0.52)	0.53	(0.35–0.75)
Mixed urinary incontinence	0.18	(0–0.66)	0.27	(0–0.58)	0.55	(0.34–0.78)
All urinary incontinence	0.51	(0.07–0.67)	0.04	(0–0.42)	0.45	(0.33–0.58)

CI = confidence interval; ICS = International Continence Society; OAB = overactive bladder.

*Indicates that the pattern of correlations in monozygotic (MZ) and dizygotic (DZ) pairs with MZ correlations more than two times larger than DZ correlations was incompatible with estimating shared environmental influences (concerns frequency and nocturia only). For OAB wet, the correlation pattern suggests a model with only environmental components (shared and nonshared).

[1]Confidence intervals, including zero, indicate a statistically nonsignificant contribution of the factor.