



Original Article – Editor's choice

Editorial by Juan F. Peñañiel, Alexandre Dubois, Marie de Tayrac, Benoit Peyronnet on pp. 182–183 of this issue

Association of Polygenic Risk Scores for Depression, Anxiety, and Neuroticism with Lower Urinary Tract Symptoms Among Women

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Abstract

Background and objective: Observational studies have found that depression, anxiety, and neuroticism are prospectively associated with lower urinary tract symptoms (LUTS) among women, but are limited by confounding and measurement errors. We examined whether genetic liability for these psychiatric traits is associated with LUTS among women.

Methods: Participants were from the mothers cohort of the Avon Longitudinal Study of Parents and Children (ALSPAC). Polygenic risk scores (PRSs) for depression, anxiety, and neuroticism were calculated using summary data from genome-wide association studies. LUTS were assessed using validated questionnaires at two time points: 2002–2004 ($n = 4758$; median age 40 yr, interquartile range [IQR] 37–43) and 2011–2012 ($n = 3026$; median age 50 yr, IQR 47–53). Separate logistic regression models, adjusted for age and population structure, were fitted to examine the association of each PRS with each LUTS.

Key findings and limitations: The neuroticism PRS was associated with nocturia at both time points [odds ratio and 95% confidence intervals=1.24 (1.10,1.40) and 1.21 (1.07,1.37)], and with any urinary incontinence (UI), any urgency, and mixed UI (2002–04) [1.14 (1.05,1.23), 1.12 (1.02,1.23), and 1.23 (1.07,1.43), respectively]. The depression PRS was associated with nocturia [OR 1.33, 95% CI 1.17–1.50] and 1.24 (1.09,1.40) and any UI [1.09 (1.01,1.18); 1.11 (1.02,1.20)] at both time points, and with any urgency (2011–12) [1.13 (1.03,1.24)]. The anxiety PRS was associated with mixed UI (2002–04) [1.20 (1.03,1.39)]. Limitations include PRS not capturing all genetic liability, potential pleiotropic effects, and restriction of the cohort to parous women of predominantly European ancestry.

Conclusions and clinical implications: Genetic liability for depression, anxiety, and neuroticism is associated with higher risk of LUTS among women. This finding indicates a

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potential shared aetiology or a possible contribution of mental health problems in the development of LUTS.

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ADVANCING PRACTICE

What does this study add?

Psychiatric traits are associated with higher risk of specific lower urinary tract symptoms (LUTS). Women with high genetic risk of neuroticism and depression are more likely to develop nocturia or urinary incontinence. Mental health is not routinely assessed in current clinical evaluations of LUTS, despite its potential influence.

Clinical Relevance

Urinary symptoms have long been associated with psychiatric traits, but interpretation of clinical data has been limited by confounding and potential reverse causation. This study introduces a novel approach by examining genetic susceptibility to depression, anxiety, and neuroticism in relation to LUTS among women. Using polygenic risk scores, the authors show that predisposition to depression and neuroticism, and to a lesser extent anxiety, is linked to a higher risk of nocturia and urinary incontinence. By relying on genetic rather than self-reported measures, the analysis reduces bias and suggests possible shared biological mechanisms between mental health and bladder function. Clinically, the study highlights that psychological vulnerability may not only arise because of LUTS but could also contribute to its development. Even more importantly, it reminds us that treating LUTS is not merely about improving urinary symptoms but about enhancing overall quality of life. Ultimately, effective care requires a holistic approach that considers the whole person, not just the disease. Associate Editor: Mikkel Fode, MD.

Patient Summary

Our study looked at whether mothers with high genetic risk for mental health problems and neuroticism (a personality trait associated with negative emotions) are more likely to experience urinary symptoms. We found that genetic risk for depression, anxiety, and neuroticism were associated with a higher risk of urinary symptoms. There was strong evidence that genetic risk for depression and neuroticism was associated with a higher risk of waking during the night to pass urine. Our findings suggest that mental health is important to consider in the development of urinary symptoms. More research is needed to find out if these associations apply to other patient groups.

1. Introduction

Urinary incontinence (UI) is a lower urinary tract symptom (LUTS) experienced at least weekly by ~10% of women [1]. The most prevalent subtype is stress UI (prevalence 10–39%), which is urine leakage during exertion, such as when coughing or laughing [1]. Urgency UI, which is urine leakage following a strong and sudden need to urinate, is less common (prevalence 1–7%) [1]. Mixed UI (prevalence 7.5–25%) is a combination of stress UI and urgency UI [1]. Another common type of LUTS is nocturia, which is waking during the night to void (prevalence 11–14%) [2].

Comorbidity of UI with depression and anxiety is well established in cross-sectional studies [3]. A systematic review revealed cross-sectional associations of both depression and anxiety with nocturia [4]. An observational study among women with overactive bladder (OAB) found a positive correlation of daily urinary urgency scores with both depression and anxiety [5].

Cross-sectional studies cannot provide insights into the direction of associations between depression/anxiety and LUTS. Some prospective studies that examined associations

between LUTS and depression/anxiety have provided evidence of bidirectional associations [6,7]. A prospective cohort study among parous women (mean age 41.0 yr) found that depression was associated with subsequent LUTS (any UI, mixed UI, and urgency), while anxiety was only associated with subsequent nocturia [8]. The study found little evidence that LUTS were associated with subsequent depression or anxiety; only stress UI was associated with subsequent depression [8]. A cohort study involving older women (mean age 50.3 yr) found evidence that depressive symptoms were associated with subsequent LUTS [9]. Neuroticism, one of the “big five” domains of personality characterised by a disposition to experience negative affect including anxiety and depression [10], was prospectively associated with UI in a cohort of women (mean age 46.8 yr) [11]. Evidence that mental health problems are associated with subsequent LUTS warrants further investigation because this contradicts the common assumption that poor mental health is a consequence, not a potential cause, of LUTS.

Although prospective studies can provide evidence of the direction of the association between depression/anxiety and

LUTS, these studies are limited by unmeasured and residual confounding [12]. Measurement errors are another limitation of prospective studies that rely on self-reported questionnaires to assess psychiatric traits [13]. An alternative approach is the use of polygenic risk scores (PRSs) as estimates of genetic liability for complex traits including depression, anxiety, and neuroticism [14]. As genetic variants are randomly inherited at meiosis and fixed at conception, PRSs should not be associated with environmental confounders at a population level, and any associations with outcomes of interest identified should not be a result of reverse causation.

Using data from a population-based cohort of middle-aged parous women in the UK, we conducted a study to estimate the associations of genetic liability for depression, anxiety, and neuroticism according to PRSs with LUTS among women. We assessed LUTS using validated questionnaires at two time points, and we hypothesised that higher PRSs for depression, anxiety, and neuroticism are associated with higher odds of LUTS.

2. Patients and methods

2.1. Study population

The women included in this study are from the Avon Longitudinal Study of Parents and Children (ALSPAC) [15–17]. ALSPAC is a population-based, prospective cohort study that followed pregnant women (and their newborns) resident in Avon, with a total sample size of 15 447 pregnancies (Supplementary material).

Fig. 1 shows the analysis samples for the study. Differing sample sizes are a result of questionnaire completion rates and attrition between the two time points. Associations of depression, anxiety, and neuroticism PRSs with LUTS were examined in sample 3 for 2002–2004 and sample 4 for 2011–2012.

2.2. Discovery sample: genome-wide association studies

Summary data for genome-wide association studies (GWAS) were used to extract genetic variants associated with depression [18], anxiety [19], and neuroticism [20] (Supplementary material).

2.3. PRSs

A PRS allows estimation of an individual's genetic liability for a complex trait (Supplementary material). PRSs for depression, anxiety, and neuroticism were calculated for all participants with sufficient genotype data.

2.4. Target sample

ALSPAC mothers were genotyped using the Illumina human660W-quadrant array at Centre National de Genotypage. Genotypes were called with Illumina GenomeStudio. PLINK v1.07 was used to carry out quality control measures on an initial set of 10 015 participants and 557 124 directly genotyped single-nucleotide polymorphisms (SNPs).

After quality control and excluding participants who had withdrawn consent, sufficient genetic data for PRS derivation were available for 7728 participants (Supplementary material).

2.5. PRS estimation

PRSs were calculated using PLINK v1.9 according to the method described by the Psychiatric Genomics Consortium [21]. We removed SNPs with mismatching alleles between the discovery and target data sets. The major histocompatibility complex region was removed (25–34 Mb), except for one SNP representing the strongest signal within the region. Using ALSPAC data as the reference panel, SNPs were LD clumped with an r^2 of 0.25 and a physical distance threshold of 500 kb. PRSs for each participant were calculated across 13 p -value thresholds (<0.5 to $<5 \times 10^{-8}$) and were

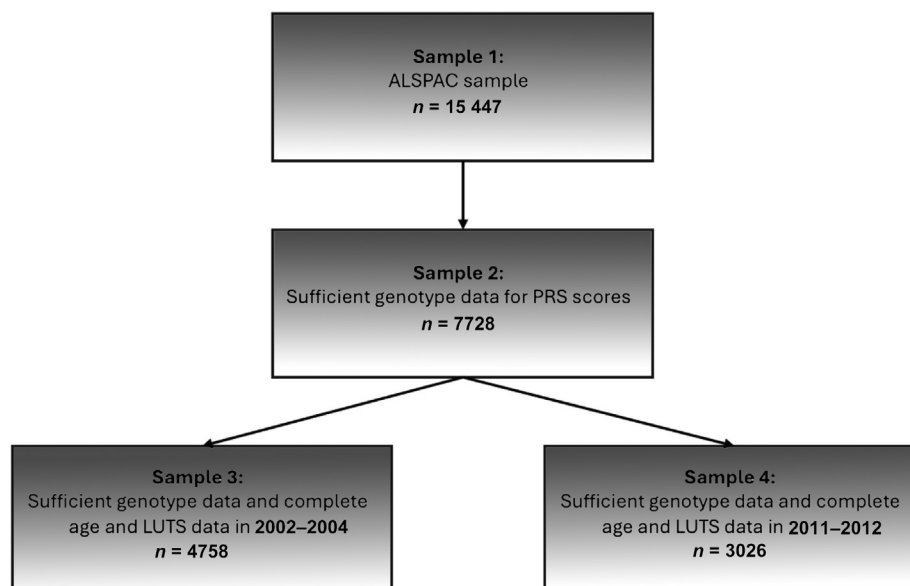


Fig. 1 – Flow diagram of the analysis samples. LUTS = lower urinary tract symptoms; PRS = polygenic risk score.

standardised by subtracting the mean and dividing by the standard deviation.

We assessed the performance of depression and anxiety PRSs by testing their associations with validated questionnaire-based measures of depression and anxiety, respectively, which were administered to mothers from the ALSPAC birth cohort at 18 wk of gestation ([Supplementary material](#)).

2.6. LUTS measures

Participants completed the Bristol Female LUTS (BFLUTS) questionnaire in 2002–2004 and the International Consultation on Incontinence Questionnaire on Female LUTS (ICIQ-FLUTS) in 2011–2012 [22].

Stress UI was defined by the question “Does urine leak when you are physically active, exert yourself, cough or sneeze?” Urgency UI was defined by the questions “Does urine leak before you can get to the toilet?” and “Do you have a sudden need to rush to the toilet to urinate?” Participants who met the criteria for both stress UI and urgency UI were defined as mixed UI cases. Participants who were defined in any of the three UI categories (stress, urgency, or mixed) were classified as having any UI. Any urgency was defined by the question “Do you have a sudden need to rush to the toilet to urinate?” Responses to the questions were recorded using a 5-point Likert scale with the following options: never; occasionally; sometimes; most of the time; all of the time. Participants who responded with at least “sometimes” were defined as cases.

Nocturia was assessed by the question “What is the number of times you urinate throughout the night?” Cases were defined as those waking to urinate two or more times.

2.7. Statistical analysis

Associations of the depression, anxiety, and neuroticism PRSs with LUTS were examined using logistic regression. All models were adjusted for age (at the time of LUTS questionnaire completion) and the first ten genetic principal components in ALSPAC ([Supplementary material](#)).

Associations were separately examined between three psychiatric traits and six LUTS phenotypes at two time points, resulting in 36 tests. False discovery rate (FDR)-adjusted p values were used to control type 1 errors across the tests (<5%) [23].

The primary analysis was based on PRSs constructed using SNPs associated with the trait at a threshold of $p < 0.05$, consistent with previous ALSPAC studies [24]. We appraised our findings in terms of the consistency of the estimates and the respective confidence intervals (CIs) across multiple PRS p -value thresholds (<0.5 to $<5 \times 10^{-8}$) for SNP inclusion [25].

A sensitivity analysis excluded participants with organic causes of LUTS ([Supplementary material](#)).

3. Results

[Table 1](#) presents the demographic data and LUTS prevalence rates for each analysis sample. The proportions of women categorised in the manual social class and those with the

lowest level of educational attainment were lower in the more restricted samples. LUTS prevalence was similar across the different samples and was higher at the later (2011–2012) than at the earlier (2002–2004) time point.

[Fig. 2](#) shows odds ratios, 95% CIs, and p values for the associations of anxiety, depression, and neuroticism PRSs with LUTS at the SNP inclusion threshold of $p < 0.05$. The results are also presented in [Supplementary Table 4.1](#).

Odds ratios for associations between the PRSs and LUTS were all >1, except for neuroticism and mixed UI in 2011–2012. The greatest numbers of associations were found for the neuroticism and depression PRSs, which were strongly associated with nocturia at both time points. The neuroticism PRS was also associated with any UI, any urgency, and mixed UI (2002–2004 only). The depression PRS was also associated with any UI at both time points and any urgency at the second time point (there was weak evidence of an association at the first time point). The anxiety PRS was only associated with mixed UI (2002–2004 only). It is notable that many of these associations survived FDR adjustment, specifically, neuroticism and depression PRSs with nocturia (both time points), depression PRS with any urgency (second time point), and neuroticism PRS with any UI and mixed UI (first time point).

Weak evidence was found for associations of the anxiety PRS with any UI (both time points), nocturia (first time point), and any urgency (second time point). The depression PRS was weakly associated with stress UI (first time point) and urgency UI (second time point).

The sensitivity analysis excluded participants with organic causes of LUTS, including diabetes, pregnancy, kidney disease, and pelvic inflammatory disease ([Supplementary Tables 5.1 and 5.2](#)). In this restricted sample, the associations between PRSs and LUTS remained consistent with the primary analysis ([Supplementary Fig. 5.1](#)).

A similar pattern of associations was seen across the other p -value thresholds for SNP inclusion ([Supplementary Figs. 6.1–6.12](#)).

4. Discussion

We found evidence that genetic liability for depression, anxiety, and neuroticism is associated with LUTS among middle-aged women. Our study took a novel approach by using PRSs as opposed to questionnaire-based measures of depression, anxiety, and neuroticism. We found the strongest evidence for association of depression and neuroticism PRSs with nocturia.

A key strength of our study is the use of data from a large, prospective, community-based cohort and of validated questionnaires to assess LUTS, including UI subtypes. While voiding diaries are the ideal diagnostic tool for evaluating LUTS [26], this was not feasible in a large cohort study.

Another strength is our use of PRSs to capture genetic liability for complex traits. Genetic variants cannot be influenced by environmental factors after conception that could confound associations between psychiatric traits and LUTS. This approach addresses key limitations of questionnaire-

Table 1 – Demographics and LUTS prevalence rates across the analysis samples^a

	Sample 1 (n = 15 447)	Sample 2 (n = 7728)	Sample 3 (n = 4758)	Sample 4 (n = 3026)
Median age, yr (IQR) {range}				
2002–2004	40.0 (37–43){27–56}	40.0 (37–43){27–56}	40.0 (37–43){27–56}	41.0 (38–44){27–54}
2011–2012	49.0 (47–53){36–64}	50.0 (47–53){36–64}	50.0 (47–53){36–64}	50.0 (47–53){36–64}
Maternal social class, n (%)				
Manual	1983 (20)	1013 (17)	578 (15)	316 (12)
Maternal education, n (%)				
CSE/vocational	3706 (30)	1751 (25)	869 (19)	440 (15)
O level	4262 (35)	2400 (35)	1549 (34)	986 (33)
LUTS prevalence, n (%)				
2002–2004				
Stress UI	771 (10)	501 (10)	495 (10)	283 (10)
Urgency UI	107 (1.4)	70 (1.5)	70 (1.5)	46 (1.6)
Mixed UI	327 (4.4)	188 (3.9)	187 (3.9)	101 (3.6)
Nocturia	469 (6.3)	282 (5.9)	278 (5.8)	139 (5.0)
Any UI	1,205 (16)	759 (16)	752 (16)	430 (15)
Any urgency	858 (12)	508 (11)	504 (11)	267 (9.6)
2011–2012				
Stress UI	614 (14)	409 (14)	371 (13)	409 (14)
Urgency UI	117 (2.6)	87 (2.9)	80 (2.9)	87 (2.9)
Mixed UI	392 (8.9)	256 (8.5)	234 (8.4)	256 (8.5)
Nocturia	399 (9.0)	273 (9.0)	245 (8.8)	273 (9.0)
Any UI	1,123 (25)	752 (25)	685 (25)	752 (25)
Any urgency	791 (18)	542 (18)	490 (18)	542 (18)

CSE = certificate of secondary education; IQR = interquartile range; LUTS = lower urinary tract symptoms; UI = urinary incontinence

^a Question completion rates may differ within the same sample. Sample 1: ALSPAC sample. Sample 2: genotype data. Sample 3: genotype data and complete age and LUTS for 2002–2004. Sample 4: genotype data and complete age and LUTS data for 2011–2012.

based measures of mental health, which are prone to confounding and measurement errors.

As we tested 36 associations, we reported FDR-adjusted *p* values to control the rate of false positives; this approach is less conservative than Bonferroni correction, and thus maintains statistical power for detection of true associations. We interpreted results on the basis of effect estimates, *p* values, and CIs rather than relying solely on significance thresholds [27]. We also examined consistency across multiple SNP inclusion thresholds (Supplementary Figs. 6.1–6.12) to ensure that findings were not artefacts of any single threshold.

Despite these strengths, several limitations warrant consideration. PRSs may not capture all of the genetic influence related to psychiatric traits, particularly contributions from rare genetic variants [28]. Furthermore, PRSs do not incorporate environmental factors, which can influence psychiatric traits independently or via gene-environment interactions. Consequently, an elevated PRS does not guarantee phenotype development. It is notable, however, that the depression and anxiety PRSs demonstrated robust associations with their respective questionnaire-based measures (Supplementary Figs. 3.1 and 3.2).

A further limitation is that PRSs cannot account for horizontal pleiotropy, whereby genetic variants independently influence both psychiatric traits and LUTS, leading to non-causal associations [29]. However, the alignment of our findings with those from observational studies, which have different sources of bias, supports the possibility that our results reflect underlying biological relationships [30].

The use of PRSs also raises important ethical considerations. Disclosure of scores to patients could lead to psycho-

logical harms: low scores may create false reassurance about disease risk, while high scores could provoke anxiety or overtreatment [31]. Additional concerns include potential genetic discrimination and the exacerbation of health inequalities because of the use of Eurocentric GWAS data [31].

Differences between the underlying GWAS studies may have also influenced our findings. The depression GWAS and anxiety GWAS used binary case definitions [32], which may limit statistical power and fail to capture the full spectrum of these psychiatric traits. By contrast, the neuroticism GWAS used a continuous phenotype score, which potentially provides greater statistical power and more comprehensive trait measurement. This may partly explain why we observed stronger associations for neuroticism.

The limited evidence for associations with stress or urgency UI subtypes may reflect statistical power issues, particularly given the low prevalence of urgency UI (1.4%) in our sample, which aligns with prevalence rates in other studies (1–7%) [1].

In addition, our cohort included only parous women who were predominantly affluent and of European ancestry, limiting generalisability to nulliparous women, other ethnicities, and socioeconomically deprived groups. Since the GWAS samples were also European ancestry-based and PRS performance is population-specific [33], applicability to other backgrounds remains uncertain.

Our findings for the depression PRS broadly align with another study in the same cohort, which linked self-reported depression to subsequent LUTS [8]. However, unlike that study, we did not find associations between anxiety and nocturia. The smaller sample size for the anxiety

Primary analysis: odds ratios (95% CI)

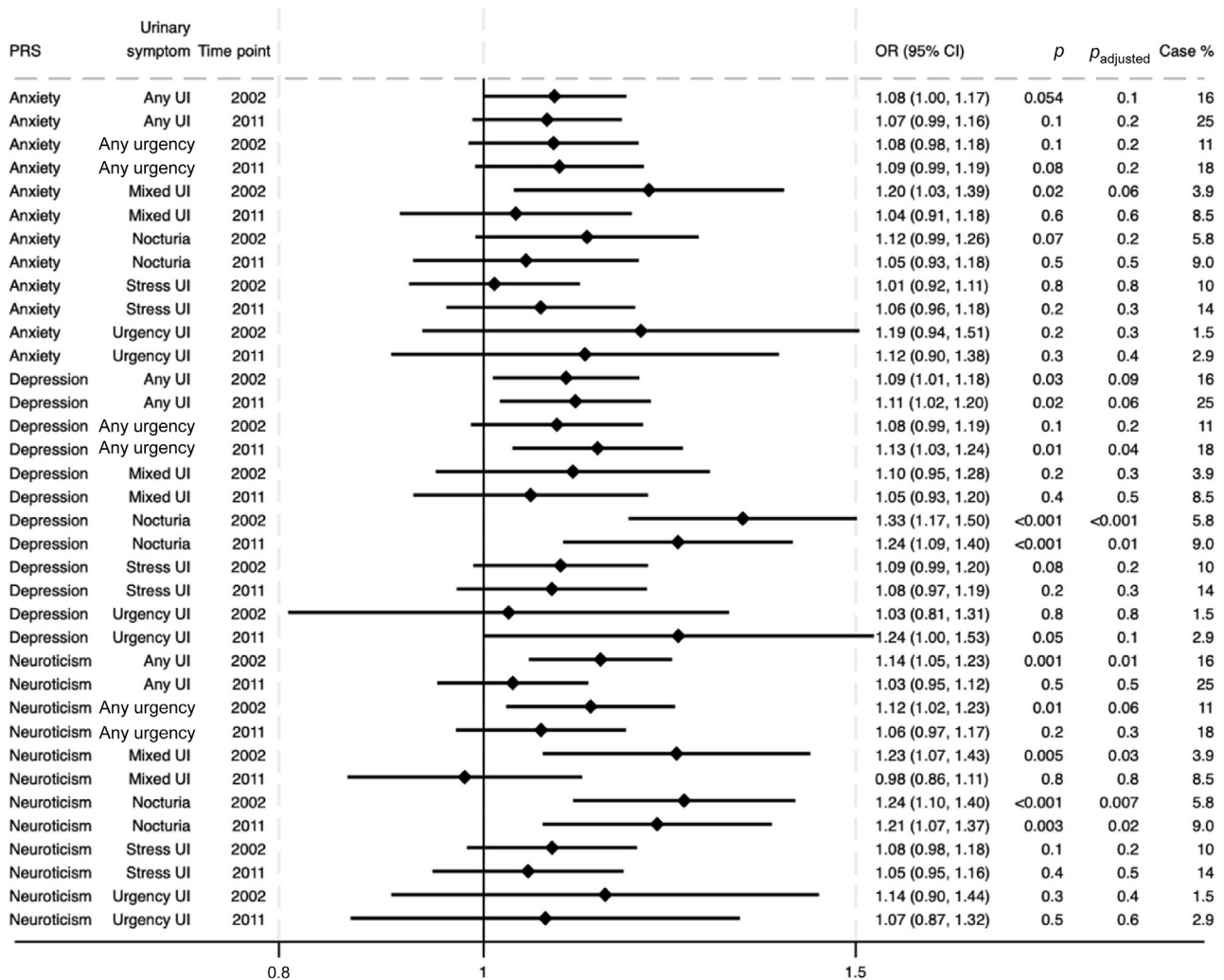


Fig. 2 – Association of polygenic risk scores (PRSs) for depression, anxiety, and neuroticism (at a significance level of $p < 0.05$ for inclusion of single-nucleotide polymorphisms) with lower urinary tract symptoms. All models are adjusted for age and the first ten principal components in ALSPAC. The figure shows the odds ratio (OR) and 95% confidence interval (CI), unadjusted and adjusted p values controlled for the false discovery rate, and the percentage of participants who reported the urinary symptom. UI = urinary incontinence.

GWAS ($n = 83\,566$) in comparison to the depression GWAS ($n = 1\,349\,887$) and neuroticism GWAS ($n = 32\,821$), may explain the weaker anxiety associations in our study.

Associations with the neuroticism PRS (and, to a lesser extent, the anxiety PRS) were stronger at the earlier time point (median age 40 yr) than the later one (median age 50 yr). This pattern may reflect lower statistical power at the later time point but could also suggest that psychological factors play a greater role earlier in life, while age-related factors—including medication use and menopausal physiological changes such as lower bladder capacity—may dominate later [34]. Similarly, the depression PRS showed stronger associations with nocturia at the earlier time point but stronger associations with urgency at the later time point, possibly reflecting the higher prevalence of urgency at the later time point (18% vs 11%). A Swedish study found that genetic overlap between depressive disorders and urgency or mixed UI was entirely mediated by

neuroticism [35], which suggests that neuroticism variants may drive depression-UI associations and supports our observation of robust neuroticism-LUTS associations.

Several biological mechanisms may underlie the associations observed. The bladder-gut-brain axis provides a conceptual framework for understanding the co-occurrence of urological and psychiatric conditions, with chronic stress affecting both emotional regulation and organ function [36]. Neuroticism, characterised by higher sensitivity to stress, may contribute to LUTS via this pathway. Elevated inflammation could be a potential aetiological factor for both mood disorders and LUTS [37]. Depressed patients may lack the typical nocturnal elevation in levels of antidiuretic hormone levels, resting in an increase in nighttime urine volume [38]. The reduction in monoamines linked to depression, such as serotonin and noradrenaline, has been associated with bladder symptoms including urinary frequency in animal models [39].

5. Conclusions

Our findings suggest that genetic liability for neuroticism and depression, and to a lesser extent anxiety, is associated with a higher risk of LUTS among women. This could indicate a potential shared aetiology or that mental health problems possibly contribute to the development of LUTS. However, further research is needed to assess causality, clarify the underlying mechanisms, and determine generalisability beyond a population of parous women of predominantly white European ancestry. Assessment of the potential treatment effect of mental health interventions on LUTS is another important area of focus for future studies. Poor adherence to OAB treatments [40] may be partly explained by coexisting mental health issues; thus, screening for these conditions may improve treatment adherence and outcomes.

Author contributions: Zayn Rajan 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: Rajan, Dardani, Burrows, Joinson.

Acquisition of data: Rajan, Dardani, Burrows, Joinson.

Analysis and interpretation of data: Rajan, Dardani, Burrows, Joinson, Drake, Bastiani.

Drafting of the manuscript: Rajan, Dardani, Burrows, Joinson, Drake, Bastiani.

Critical revision of the manuscript for important intellectual content: Rajan, Dardani, Burrows, Joinson, Drake, Bastiani.

Statistical analysis: Rajan, Dardani, Burrows, Joinson.

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Supervision: Dardani, Burrows, Joinson.

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Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eururo.2025.09.4154>.

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