


Investigating Causal Links Between Uterine Prolapse, Urinary Tract Infections, and Lower Urinary Tract Symptoms: A Two-Sample Mendelian Randomization Study

Xiaoyue Zhu , Chunyan Hu, Anneng Hu, Yongbo Zheng, Junyang Li, Fuwen Luo, Lin Yang, Yuhang Lin, Xiaodong Yu

Department of Urology, Affiliated Hospital of North Sichuan Medical College, Nanchong, 637000, People's Republic of China

Correspondence: Xiaodong Yu, Department of Urology, Affiliated Hospital of North Sichuan Medical College, No. 1, Maoyuan South Road, Shunqing District, Nanchong, 637000, People's Republic of China, Tel +8613990856788, Email 21434379@qq.com

Background: Uterine prolapse (UP), a subtype of pelvic organ prolapse (POP), frequently coexists with urinary tract infections (UTIs) and lower urinary tract symptoms (LUTS), including urinary frequency (UF), urinary incontinence (UI), and urinary retention (UR), is a common pelvic floor dysfunction disorder in women. However, the causal relationship between these conditions remains controversial. This study aims to fill this gap by applying two-sample Mendelian randomization.

Methods: A two-sample Mendelian randomization (MR) study was conducted to genetically evaluate associations between UP and UTIs/LUTS. The inverse variance weighting (IVW) method served as the primary analysis, supplemented by sensitivity analyses to assess the validity and reliability of results.

Results: MR analysis suggested a potential causal link between UP and increased risk of UTIs ($p = 0.048$). No causal associations were observed between UP and UF, UI, or UR. Sensitivity analyses confirmed stability of results, with no evidence of heterogeneity or horizontal pleiotropy among instrumental variables (IVs).

Conclusion: UP may act as a risk factor for UTIs, though further validation is needed given the borderline statistical significance. No clear causal relationships were identified between UP and UF, UI, or UR.

Keywords: urinary tract infections, uterine prolapse, urinary frequency, urinary incontinence, urinary retention, Mendelian randomization

Introduction

Uterine prolapse (UP), a subtype of pelvic organ prolapse (POP), involves the descent of the uterus from its normal anatomical position into or beyond the vaginal opening, resulting from weakened pelvic floor muscles that fail to support pelvic organs.¹ This condition may be accompanied by various symptoms, including a feeling of heaviness, as well as non-specific symptoms such as sexual dysfunction, urinary dysfunction, and intestinal dysfunction.^{1–3} Pelvic floor physical therapy and pessaries have been shown to be effective in alleviating symptoms associated with UP.³ In the UK, UP accounts for 20% of women awaiting major gynecological surgery, with age-specific incidence increasing with older age and a lifetime surgical risk of 11–20%.^{4–7} UP is different from anterior (bladder) or posterior (rectal) vaginal wall prolapse, the uterus is a pivotal pelvic organ with distinct anatomical connections, such as the cardinal and uterosacral ligaments, and its positioning is affected by hormonal fluctuations, parity, and menopausal condition. UP specifically affects uterine positioning and may present distinct anatomical impacts on urinary function due to its proximity to the bladder neck and urethra. The distinctive anatomical foundation, risk factors, symptomatology, treatment strategies, and wider public health implications, which differ from other pelvic organ prolapse subtypes, require public

attention. Therefore, studying UP in isolation is critical, and its specific relationship with urinary outcomes remains understudied.⁸

One of the most prevalent bacterial diseases, UTIs impact about 150 million individuals worldwide annually.⁹ UTIs can be classified as uncomplicated or complicated, with uropathogenic *Escherichia coli* being the most prevalent pathogen in both categories.¹⁰ These bacteria typically reside around the urethra and colonize the bladder, but they are often flushed away during urination. The shorter distance from the urethra to the bladder in women, compared to men, facilitates the easier colonization of bacteria, resulting in a significantly higher incidence of UTIs among women.¹¹ Traditionally, UTIs have been considered a female disease, with about 50% of women experiencing at least one UTI in their lifetime.¹² Moreover, UTIs tend to recur, with frequency varying among different populations.¹³ They are the second leading cause of antibiotic prescriptions, following respiratory infections.¹⁴ Both afflicted men and women may experience severe health problems and a decline in quality of life as a result of these persistent illnesses.⁹ UTIs impose a substantial burden in the US, with an estimated 2–3 million annual emergency department visits and 10.5 million outpatient visits (0.9% of total outpatients), alongside annual societal costs of approximately \$3.5 billion, encompassing healthcare expenses and lost productivity. These figures underscore the significant economic and public health impact, as well as the impaired quality of life for affected individuals.^{10,15,16}

LUTS are very common in the broad populace.¹⁷ The International Continence Society (ICS) defines the term as a broad category of symptoms related to urine storage, voiding, and post-voiding.^{18,19} The most common and distressing symptoms among them are urgency, UF, UI, and UR.^{19,20} These lower urinary tract symptoms often occur simultaneously and share many common underlying causes. Each year, up to 25% of the female population seeks medical care due to lower urinary tract inflammation syndromes, resulting in over 5 million doctor visits and millions of dollars in diagnostic tests and medications.²¹ The presence of LUTS may be associated with a deficiency or reduction in pelvic floor muscle (PFM) strength. These muscles play a crucial role in supporting pelvic organs, aiding in sexual function, and maintaining urinary and fecal continence through strong, rapid, and reflexive contractions.^{22–24} The prevalence of this condition is particularly high among the elderly, and its negative impacts on the psychological, physical, and social well-being of affected individuals significantly affect their quality of life.^{25,26} Current treatment methods can alleviate but not completely eliminate most symptoms, leading to a potential lifelong burden of ongoing medication and economic costs.¹⁹

UP patients often present with various complaints, including urinary, gastrointestinal, and sexual dysfunction symptoms. Due to anatomical and physiological changes, many clinicians typically associate prolapse with UTIs, both symptomatic and asymptomatic.^{8,27} Prolapse often causes a sensation of vaginal fullness or visible or palpable masses at the vaginal opening. UI can occur in women who have prolapse, particularly if the urethra is not adequately maintained. Additionally, urethral kinking may cause them to experience urinary difficulties. Hesitancy, weak urinary stream, and UF (resulting from inadequate bladder emptying) can all be caused by urinary dysfunction. This results in urine stagnation in the urethra, which provides a breeding ground for bacterial growth. Incomplete bladder emptying can lead to recurrent UTIs, often accompanied by UF, urgency, and UI. Most asymptomatic bacteriuria is considered subclinical UTIs. This condition can be aggravated by surgery and other stress factors.²⁷ Observational studies indicate that urinary complaints such as UI, UF, and UR are common in women with prolapse, often coexisting with UP. Based on their pathogenic processes, LUTS, UTIs, and UP may all share a similar pathophysiological phenotype. However, the relationship between prolapse, UTIs, and LUTS remains unclear.⁸

The challenge of drawing causal conclusions from observational studies primarily lies in their susceptibility to bias, encompassing the existence of confounding variables and reverse causality.²⁸ MR addresses a critical knowledge gap: while UP is associated with UTIs and LUTS in observational data, it remains unknown whether these relationships are causal or driven by shared risk factors. MR is a genetic instrumental variable method that infers a causal relationship between two traits using single nucleotide polymorphisms (SNPs) as IVs. As a statistical technique to evaluate causal links in genome-wide association studies (GWAS) summary data, two-sample MR analysis relies on the natural random allocation of genetic variation. Its advantage is that it can minimize errors brought on by reverse causation and confounding variables. This method has been successfully applied in urogynecology to clarify causal relationships. By extending this method to UP and pay attention to the above-mentioned pathophysiological mechanisms, we seek to

determine whether UP directly contributes to urinary morbidity, with implications for targeted prevention and treatment strategies.

Methods

Study Design

To examine the causal relationships between UP, UTIs, and three LUTS (UF, UI, and UR), we performed a two-sample MR analysis. Figure 1 shows the flowchart for the study design. In the forward MR analysis, UP is regarded as the exposure, while UTIs, UF, UI, and UR are treated as outcome variables. When performing MR analysis, the following three basic presumptions must be met: 1. The variant must be associated with the exposure; 2. The variant must be independent of confounders; 3. The variant can only have an impact on the result through the exposure. The assumptions of MR analysis are illustrated in Figure 2.

Data Sources

The UP (ebi-a-GCST90018937) summary statistics in this article are from a large-scale GWAS meta-analysis, with 10,647 cases and 224,175 controls. A total of 24,102,530 SNPs were included. The GWAS data for UTIs (ebi-a-GCST90013890) consists of 397,867 people of European ancestry from a large-scale GWAS meta-analysis, encompassing 11,037,343 SNPs. The summary statistics for UF (finn-b-R18_POLYURIA) include 3,340 cases and 202,910 controls from a large-scale GWAS meta-analysis, with a total of 16,380,442 SNPs. The summary statistics for UI (finn-b-R18_UNspe_URINARY_INCONTINENCE) include 1,357 cases and 202,910 controls from a large-scale GWAS meta-analysis, comprising 16,380,434 SNPs. The summary statistics for UR (finn-b-R18_RETEN_URINE) include 4,999 cases and 202,910 controls from a large-scale GWAS meta-analysis, with a total of 16,380,442 SNPs. Among these, the data for UTIs underwent Firth correction, which effectively reduces bias due to small sample sizes or rare events, enhancing the reliability and precision of statistical analyses and improving the association accuracy between

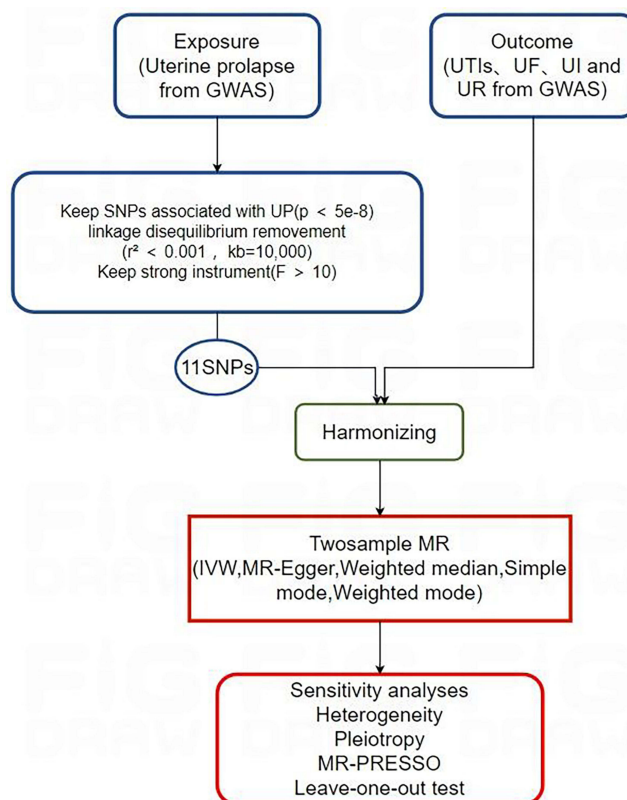


Figure 1 The flowchart of study design.

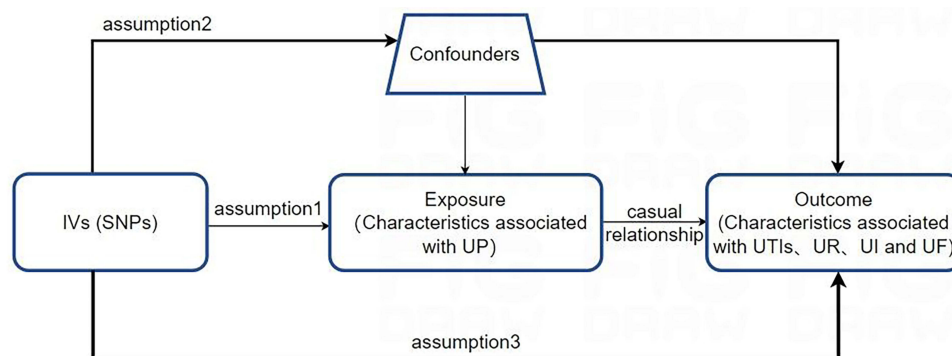


Figure 2 Mendelian randomization assumptions.

SNPs and outcome variables, thereby increasing the accuracy of MR analysis. All summary statistics for UP, UTIs, UF, UI, and UR are available for download from the Integrative Epidemiology Unit (IEU) open GWAS database, [Table 1](#) shows the data source of study variables. In order to mitigate potential bias caused by population heterogeneity, all SNPs are derived from GWAS conducted on individuals of European descent.

Selection of IVs

In accordance with the majority of MR investigations, SNPs linked to UP were chosen according on a significance threshold of $p < 5 \times 10^{-8}$. In order to ascertain genetic linkage among SNPs, linkage disequilibrium (LD) was evaluated, with a threshold of $r^2 < 0.001$ and a window size of 10,000 kb. The formula $F = (R^2 / (1 - R^2)) \cdot ((n - k - 1) / k)$ was employed to compute the F-statistic for each SNP. SNPs with an F-statistic of less than 10 were excluded.²⁹ Before analysis, exposure (UP) and outcome (UTIs, UF, UI, UR) datasets were harmonized using the TwoSampleMR package in R to ensure allele alignment and exclude palindromic SNPs with ambiguous alleles. SNPs with mismatched effect alleles or ambiguous strand information were removed to avoid flip errors. Additionally, SNPs associated with potential confounders related to UTIs, UF, UI, and UR (such as Endometrial cancer, irregular menstruation, Age at menopause, Endometriosis, Female infertility, Sex hormone-binding globulin levels, Preterm delivery, Inguinal hernia, Metabolic syndrome, diabetes, Depression, etc) were removed from the final MR analysis using data from LD trait.

MR Analysis

We used the IVW method as the main technique in a two-sample MR analysis to examine the causative associations between UP and UTIs, UF, UI, and UR, with $p < 0.05$ being considered statistically significant. The MR-Egger regression, weighted model, weighted median, and simple model approaches were used for complementary analyses. IVW is the most widely used technique among these for variance-specific causal estimation in two-sample MR analyses;

Table 1 Summary of Datasets Used in the Study

Variables	Phenotype	IEU Open GWAS ID	Sample Size		Population	PMID	Author
			Case	Controls			
Exposure	UP	ebi-a-GCST90018937	10,647	224,175	European	34,594,039	Sakaue S
Outcomes	UTIs	ebi-a-GCST90013890	397,867		European	34,017,140	Mbatchou J
	UR	finn-b-R18_RETEN_URINE	4,999	202,910	European	-	-
	UI	finn-b-R18_UNSP_E_URINARY_INCONTINENCE	1,357	202,910	European	-	-
	UF	finn-b-R18_POLYURIA	3,340	202,910	European	-	-

Abbreviations: UP, uterine prolapse; UTIs, urinary tract infections; UF, urinary frequency; UR, urinary retention; UI, urinary incontinence.

as a result, it was selected as the primary and most efficient analysis method for this study, offering more dependable evidence of causal relationships, especially when all included IVs exhibit robust validity. Every outcome is shown as an odds ratio (OR) with a 95% confidence interval (CI). For calculating the statistical power of the MR estimates, the online tool (<https://sb452.shinyapps.io/power/>) was utilized.³⁰ In order to determine the statistical power of the MR analysis, the effect sizes of the causal estimate outcomes were selected as the effect sizes of the causal effect using the IVW approach. Furthermore, we applied a rigorous Bonferroni correction, using a significance level of $\alpha = 0.05/n$, where n is the number of comparisons, to account for the increased risk of false positives due to multiple testing and significantly enhance the credibility of the study conclusions. When the p -value is more than the Bonferroni-corrected threshold but less than 0.05, it is considered evidence of a potential association.

Sensitivity Analysis

To offer a more credible evaluation, we conducted sensitivity analyses to evaluate heterogeneity and pleiotropy in the MR studies along with any possible genetic outliers. Using the Cochran Q-test, the heterogeneity between the IVs utilized in the IVW approach was evaluated; $p > 0.05$ indicated no heterogeneity in causation. MR-PRESSO outlier analysis was used to detect outlier SNPs, thereby reducing bias due to horizontal pleiotropy, and Horizontal pleiotropy was evaluated by MR-Egger intercept estimation. Through the use of leave-one-out analysis, single SNPs were eliminated from the survey in order to evaluate the impact of each SNP on the final results. The quantitative consistency and directionality of the remaining results following SNP removal demonstrated the dependability and stability of the causal associations.

R (version 4.4.1) was the program used for all statistical studies. The MR analysis was conducted using the R-based software “TwosampleMR”.

Results

Instruments Selection

Using UP as the exposure factor, we included 11 SNPs also associated with outcomes as IVs after filtering for high LD. After calculation, the F-statistic of each SNP is greater than 10. Four viable SNPs with F-values more than 10 were included in the final MR analysis after SNPs linked to confounding variables were excluded. This suggests that weak instrumental factors need not be taken into account when interpreting the causal link results from our study. Comprehensive details on the chosen SNPs are available in [Supplementary Table 1](#).

Effect of UP on UTIs and UF, UI, and UR

Based on the IVW method, the MR analysis indicates a causal relationship between genetically predicted UP and UTIs (IVW: OR = 1.103, 95% CI: 1.001–1.215, $P = 0.048$). Additionally, the weighted median method, basic model, and weighted model demonstrate comparable patterns in the influence of UP on UTIs, while their results fail to reach statistical significance. [Figure 3](#) illustrates these results. The main and overall most effective analytical technique in this investigation, the IVW method, as previously indicated, allowed for the conclusion that genetically predicted UP is linked to a higher risk of UTIs. However, it is considered that there is a potential association between UP and UTIs when the P value is less than 0.05 but greater than the Bonferroni correction threshold ($\alpha=0.0125$).

After that, in order to assess the stability of the causal association between UP and UTIs, we performed a sensitivity analysis. The MR-Egger analysis results' Egger intercept (intercept = 0.018, $p = 0.696$) revealed no indication of possible horizontal pleiotropy. Both IVW and MR-Egger regression methods were used to evaluate the IVs' heterogeneity; the results indicated no significant heterogeneity (IVW: $Q = 2.931$, $Q\text{-}df = 3$, $P = 0.402$; MR-Egger: $Q = 2.660$, $Q\text{-}df = 2$, $P = 0.264$). Furthermore, according to the MR-PRESSO analysis, there were no outliers or horizontal pleiotropy among the IVs ($p\text{-global test} = 0.423$). The above detailed results are shown in [Table 2](#). The effects of the four SNPs that were chosen were graphically represented by scatter plots on exposure and outcomes ([Supplementary Figure 1](#)), and the distribution of the effects of each individual SNP was shown by funnel plots ([Supplementary Figure 2](#)). To show how each SNP affected outcome estimates, forest plots were used ([Supplementary Figure 3](#)). The MR study's robustness and

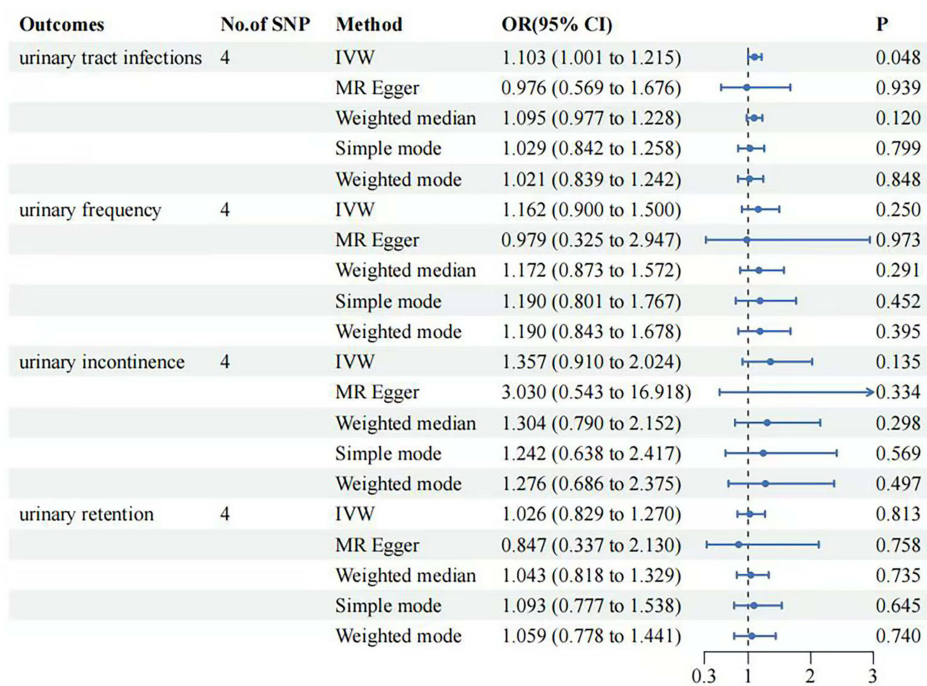


Figure 3 Forest plot of the causal effects of uterine prolapse on urinary tract infections and urinary frequency, urinary incontinence and urinary retention.

dependability were further shown by the leave-one-out analysis, which showed that no one SNP substantially affected the results (see [Supplementary Figure 4](#)). According to these results, there may be a link between UP and a higher chance of UTIs.

However, there were no correlations found between UP and UF, UI, or UR by the MR analysis. [Figure 3](#) presents these findings. Sensitivity analyses also showed no significant heterogeneity or evidence of horizontal pleiotropy ([Table 2](#)). Overall, with all p-values >0.05, the findings of the fixed-effect IVW, MR-Egger, weighted median, simple mode, and weighted mode analyses show that there is no obvious causal association between genetically predicted UP and the risks of UF, UR, or UI. ([Figure 3](#)) The following were the post hoc power calculations for the MR analysis: P_{UTIs}

Table 2 Sensitivity Analysis of the Causal Effect Between Uterine Prolapse and Urinary Tract Infections, Urinary Frequency, Urinary Incontinence, and Urinary Retention

Exposure	Outcome	Heterogeneity Test				Pleiotropy Test			MRPRESSO
		MR Methods	Q Statistic	Q-df	p-value	Egger Intercept	se	pval	Global Test Pvalue
Uterine prolapse	Urinary tract infection	IVW	2.931	3	0.402	0.018	0.040	0.696	0.434
		MR Egger	2.660	2	0.264				
	Urinary frequency	IVW	0.247	3	0.970	0.025	0.079	0.784	0.974
		MR Egger	0.149	2	0.928				
	Urinary incontinence	IVW	2.617	3	0.454	-0.116	0.123	0.446	0.545
		MR Egger	1.730	2	0.420				
	Urinary retention	IVW	0.664	3	0.882	0.028	0.066	0.716	0.895
		MR Egger	0.489	2	0.783				

= 99.3%, P_{UF} = 23.3%, P_{UR} = 4.4%, P_{UI} = 36.1% (Supplementary Table 2). It is worth noting that only the power of UTIs is high, while the other outcomes' statistical power of MR Estimates may be insufficient.

Discussion

There is relatively strong evidence, according to the study's findings, that there is a potential association between UP and UTIs. These findings are verified by an array of sensitivity studies, suggesting that the causal link is consistent and stable. However, no causal relationship was found between UP and UF, UR, or UI, which may be related to the insufficient power of UF, UR, and UI, and the results may be false-negative due to the insufficient power, which needs to be verified by subsequent large samples. Unfortunately, no usable SNPs were found in the genomic databases for UTIs, UF, UR, or UI using the rigorous Bonferroni correction and a "gold standard" criterion of $5e-8$. As a result, it was not possible to conduct a reverse MR test.

Numerous prior investigations have documented the frequent coexistence of POP with UTIs and LUTS, including UF, UI, and UR.^{3,31} L J Romanzi's prospective study of 60 women, whose mean age was 52 years, utilizing pressure-flow video urodynamics and cotton swab testing revealed that LUTS was widespread in women with genital prolapse. Dyspareunia, bladder outlet blockage, and concealed stress incontinence are associated with prolapse and may coexist.³² According to Serge P. Marinkovic, prolapse and UI can frequently coexist. Other possible outcomes include Bladder prolapse, rectal prolapse, small bowel prolapse, and UP may also occur.³³ Genital prolapse is increasingly being blamed for UTIs in middle-aged and older women.^{34,35} However, there is disagreement regarding the relationship between UP and UTIs as well as LUTS like UF, UI, and UR. Some research indicates that there is only a weak correlation between prolapse and UTIs and symptoms, and they interpret their frequent co-occurrence as a shared etiology rather than a direct causal relationship.^{36,37} OAB symptoms are somewhat relieved by all POP therapies (surgery, uterine rest).³⁸ No conclusive evidence has been found to link prolapse to UTIs or symptoms related to the urinary tract.

Herniation of the anterior, posterior, and vaginal apex (apical prolapse) into the vagina is known as POP, and it can occur in one or more of these structures. Of the three types, anterior compartment prolapse is the most common.³⁹ The fundamental mechanisms driving UP and LUTS such as UF, UI, and UR, have not been clearly demonstrated by current studies. Three explanations are put out by De Boer et al to explain the association between POP and symptoms related to the lower urinary tract, including UI, UF, and UR: 1. Obstruction of the bladder outflow tract; 2. Dilation of the bladder wall and irritation of the detrusor receptor; and 3. Urethral traction and opening, which initiates the voiding reflex.^{38,40} That is, UP not only causes physical obstruction, but also activates sensory receptors in the detrusor muscle, leading to urgency and frequency of urination, even with a low bladder capacity. The type of prolapse most frequently linked to UTIs is usually thought to be anterior prolapse, or bladder bulging. On the other hand, posterior prolapse, also known as anterior rectal protrusion, can exert a great deal of pressure on the urethra, which can cause difficulty voiding and raise the risk of UTIs.^{41,42} Prior studies have often classified UP within the wider category of POP, often neglecting its unique anatomical and physiological ramifications. In a large number of relevant studies, the processes by which it leads to UTIs are less frequently discussed. According to Eberhard, conditions such as hormone-related atrophy, neurogenic disorders, metabolic disorders, and the direct mechanical effects of prolapse on urethral function are common etiologic factors for defective pelvic support, which in turn is linked to UTIs, UF, and UI.⁴³ The pathophysiology of UI involves the co-contraction of pelvic floor muscles and abdominal muscles. Zeynep Sahiner discovered that UI was independently linked to abdominal muscle mass, specifically the rectus abdominis, irrespective of age, frailty, malnutrition, and polypharmacy. The bulk and function of the pelvic floor muscles may be reflected in the abdominal muscles, particularly the rectus abdominis.⁴⁴ UI and UF symptoms are more common in POP patients than in non-POP patients, according to research conducted in hospitals and the community. 1,140 women undergoing standard urogynecologic assessment for complaints of pelvic floor dysfunction participated in a prospective study by Haylen et al regarding UTIs. Every patient had urodynamic investigations performed, and nulliparity and a PVR more than 30 mL were found to be significant positive correlations of recurrent UTIs.⁴⁵ Instead, by looking through hospital databases for women with pelvic floor disorders and going over all medical records for recurrent UTIs—which were identified by two or more positive urine cultures taken consecutively over a 12-month period—Emrah Töz had created a prolapse group and a control group. The control

group was made using a one-to-one match for age and menopausal status. POP patients were not more likely to be diagnosed with recurrent UTIs than patients without prolapse, according to a study with 210 participants and a mean age of 54.64±5.15 years, although Emrah Töz proposed that elevated PVR is the most important risk factor for POP associated with recurrent UTIs because women with POP are more likely to have a high PVR volume due to the lower urinary tract deformity in patients with POP.⁴⁶ Storme O concluded that prolapse does not increase the chance of getting UTIs when it does not result in urinary problems. The majority of these studies concluded that urinary problems, such as UR and UI, trigger UTIs due to POP, which is contrary to the MR results that we have.⁴² Even though our MR data did not reveal a possible causative link between UP and LUTS, such as UF, UR, or UI, UP was nevertheless identified as a risk factor for an increased risk of UTIs. In fact, a study by Ekwedigwe KC showed that the prevalence of asymptomatic bacteriuria in women with POP was 79.2%.²⁷ Most of the previous studies that have addressed such issues have rarely looked at anterior, apical or posterior ventricular prolapse separately, and there are rare studies that refer to UTIs and LUTS in UP alone. This result provides a new perspective on the potential mechanisms of UP causing UTIs and helps to address controversial issues in observational studies.

This study distinctly separates UP to investigate its independent correlation with UTIs and LUTS, so providing a more refined comprehension of how this particular subtype of POP may uniquely influence urinary dysfunction. By concentrating on UP exclusively, we seek to guide specific clinical strategies for the screening and management of urine symptoms in women experiencing uterine descent. We assessed the causal connection between UP and UTIs, UF, UI, and UR using the most recent GWAS summary data, with no sample overlap between exposures and outcomes. Our results contrast with several prior studies and provides more support for the assessment of the causal link between exposures and outcomes. The primary strengths of this study include the first-ever application of a MR analysis, the confirmation of a potential causal relationship between UP and UTIs, and the lack of a definitive causal relationship between UP and LUTS like UF, UI, and UR. When compared to previous studies, the application of MR assisted in reducing residual confounders and reverse causality bias in observational research. Furthermore, heterogeneity and horizontal pleiotropy were not found to have an impact on the outcomes of UTIs and UP, which appropriately blocks the influence of negative outcomes and validates the accuracy of our discoveries. Our study does have several limitations, though. First off, our exposure criterion exclusively included individuals of European descent, thus the results might not apply to people of different racial or cultural backgrounds. Second, although UP and UTIs are causally related, the exact process has to be investigated further. Moreover, the lack of a clear causal relationship between UP and LUTS such as UF, UI, and UR may also lead to false negatives due to insufficient power. Additionally, while the results from all methods were reliable, potential biases may still arise from factors such as the genetic instrument pools, small sample sizes, or possible overlap between the samples used for exposures and outcomes.

Conclusions

In summary, our MR study indicated that UTIs were more likely to occur in people with UP. However, this was not linked to LUTS such as UF, UI, or UR. To increase women's UTIs prevention, it is advised that greater attention be given to the clinical manifestations of UP. Furthermore, more investigation is required to uncover the pathophysiological processes underlying the connection between UTIs and UP.

Abbreviations

POP, pelvic organ prolapse; UP, uterine prolapse; UTIs, urinary tract infections; LUTS, lower urinary tract symptoms; UF, urinary frequency; UI, urinary incontinence; UR, urinary retention; MR, Mendelian randomization; GWAS, genome-wide association studies; IVW, inverse variance weighting; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; POPQ, Pelvic Organ Prolapse Quantification; ICS, International Continence Society; PFM, pelvic floor muscle; IEU, Integrative Epidemiology Unit; LD, linkage disequilibrium; OR, odds ratio; CI, confidence interval.

Data Sharing Statement

The data sources are provided in both the main text and supplementary material, which can be accessed at <https://gwas.mrcieu.ac.uk/>. If required, the data and materials in the current study are available from the corresponding author on reasonable request.

Acknowledgments

The authors remain honored to thank the researchers involved in the GWAS utilized in this study for their efforts in making the aggregated statistical data accessible to the public.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Declarations

Since the GWAS data used in this study are derived entirely from publicly available summary-level statistics, ethical approval is not required. According to Article 32 of China's Measures for the Ethical Review of Biomedical Research Involving Humans, which took effect on February 18, 2023, biomedical research involving human participants may be exempt from ethical review under the following conditions: 1. Item 1: Research based on public databases that does not involve the identification or use of personal information. 2. Item 2: Analysis of collected data that does not involve the collection of new data or direct intervention in participants. Based on these provisions, this study qualifies for an exemption from ethical review, as it exclusively utilizes publicly accessible data and involves no direct interaction with human subjects or collection of new personal information.

Disclosure

The authors report no conflicts of interest in this work.

References

- Shah P. Uterine prolapse and maternal morbidity in nepal: a human rights imperative. *Drexel L Rev.* 2009;2:491.
- Onwude JL. Genital prolapse in women. *BMJ Clin Evid.* 2009;2009.
- Tunn R, Baessler K, Knüpfers S, Hampel C. Urinary incontinence and pelvic organ prolapse in women. *Dtsch Arztebl Int.* 2023;120(5):71–80. doi:10.3238/arztebl.m2022.0406
- Doshani A, Teo REC, Mayne CJ, Tincello DG. Uterine prolapse. *BMJ.* 2007;335(7624):819–823. doi:10.1136/bmj.39356.604074.BE
- Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstetrics Gynecol.* 1997;89(4):501–506. doi:10.1016/S0029-7844(97)00058-6
- Schulten SFM, Detollenaere RJ, Stekelenburg J, IntHout J, Kluijvers KB, van Eijndhoven HWF. Sacrospinous hysteropexy versus vaginal hysterectomy with uterosacral ligament suspension in women with uterine prolapse stage 2 or higher: observational follow-up of a multicentre randomised trial. *BMJ.* 2019;366:l5149. doi:10.1136/bmj.l5149
- Smith FJ, Holman CD, Moorin RE, Tsokos N. Lifetime risk of undergoing surgery for pelvic organ prolapse. *Obstetrics Gynecol.* 2010;116(5):1096–1100. doi:10.1097/AOG.0b013e3181f73729
- Lowder JL, Frankman EA, Ghetti C, et al. Lower urinary tract symptoms in women with pelvic organ prolapse. *Inter Urogynecol J.* 2010;21(6):665–672. doi:10.1007/s00192-009-1088-2
- McLellan LK, Hunstad DA. Urinary tract infection: pathogenesis and outlook. *Trends Mol Med.* 2016;22(11):946–957. doi:10.1016/j.molmed.2016.09.003
- Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol.* 2015;13(5):269–284. doi:10.1038/nrmicro3432
- Geerlings SE. *Clinical Presentations and Epidemiology of Urinary Tract Infections.* John Wiley & Sons Ltd; 2016.
- Gaitonde S, Malik RD, Zimmern PE. Financial burden of recurrent urinary tract infections in women: a time-driven activity-based cost analysis. *Urology.* 2019;128:47–54. doi:10.1016/j.urology.2019.01.031
- Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin NA.* 2014;28(1):1–13. doi:10.1016/j.idc.2013.09.003
- Schmiemann G, Kranz J, Mandraka F, Schubert S, Wagenlehner F, Gágyor I. The diagnosis, treatment, and prevention of recurrent urinary tract infection. *Dtsch Arztebl Int.* 2024;121(11):373–382. doi:10.3238/arztebl.m2024.0068

15. Kostakioti M, Hultgren SJ, Hadjifrangskou M. Molecular blueprint of uropathogenic escherichia coli virulence provides clues toward the development of anti-virulence therapeutics. *Virulence*. 2012;3(7):592–594. doi:10.4161/viru.22364
16. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. *Vital and Health Statistics Series 13, Data From the National Health Survey*. 2011;(169):1–38.
17. Elia G, Dye TD, Schariati PD. Body mass index and urinary symptoms in women. *Inter Urogynecol J Pelvi Floor Dys Func*. 2001;12(6):366–369. doi:10.1007/PL00004043
18. Chapple CR, Wein AJ, Abrams P, et al. Lower urinary tract symptoms revisited: a broader clinical perspective. *Europ Urol*. 2008;54(3):563–569. doi:10.1016/j.eururo.2008.03.109
19. Abler LL, Vezina CM. Links between lower urinary tract symptoms, intermittent hypoxia and diabetes: causes or cures? *Respir Physiol Neurobiol*. 2018;256:87–96. doi:10.1016/j.resp.2017.09.009
20. Serdinšek T, Sobočan M, Š B, Špilak-gomboc M, But I. Lower urinary tract symptoms in adolescent girls: a questionnaire-based study. *Eur J Obstetrics Gynecol Reprod Biol*. 2021;258:452–456. doi:10.1016/j.ejogrb.2021.01.023
21. Walker HK, Hall WD, Hurst JW. *Dysuria, frequency, and urgency (clinical methods: the history, physical, and laboratory examinations)*. 1990.
22. Aoki Y, Brown HW, Brubaker L, Cornu JN, Daly JO, Cartwright R. Urinary incontinence in women. *Nat Rev Dis Primers*. 2017;3(1):17042. doi:10.1038/nrdp.2017.42
23. Shishido K, Peng Q, Jones R, Omata S, Constantinou CE. Influence of pelvic floor muscle contraction on the profile of vaginal closure pressure in continent and stress urinary incontinent women. *J Urol*. 2008;179(5):1917–1922. doi:10.1016/j.juro.2008.01.020
24. Deffieux X, Hubeaux K, Porcher R, Ismael SS, Raibaut P, Amarengo G. Abnormal pelvic response to cough in women with stress urinary incontinence. *Neurourol Urodyn*. 2008;27(4):291–296. doi:10.1002/nau.20506
25. Hunskaar S, Arnold EP, Burgio K, Diokno AC, Herzog AR, Mallett VT. Epidemiology and natural history of urinary incontinence. *Inter Urogynecol J Pelvi Floor Dys Func*. 2000;11(5):301–319. doi:10.1007/s001920070021
26. Gascón MRP, Mellão MA, Mello SH, Negrão RM, Casse J, Oliveira ACP. The impact of urinary incontinence on the quality of life and on the sexuality of patients with HAM/TSP. *Braz J Infect Dis*. 2018;22(4):288–293. doi:10.1016/j.bjid.2018.07.003
27. Ekwegigwe KC, Sunday-Adeoye I, Eliboh MO, et al. Prevalence and antimicrobial susceptibility of asymptomatic bacteriuria among women with pelvic organ prolapse in Abakaliki, South-East Nigeria. *BMC Women's Health*. 2018;18(1):53. doi:10.1186/s12905-018-0545-9
28. Evans DM, Davey Smith G. Mendelian randomization: new applications in the coming age of hypothesis-free causality. *Annu rev genom humg*. 2015;16(1):327–350. doi:10.1146/annurev-genom-090314-050016
29. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755–764. doi:10.1093/ije/dyr036
30. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol*. 2013;42(5):1497–1501. doi:10.1093/ije/dyt179
31. Schulz JA. Assessing and treating pelvic organ prolapse. *Ostomy Wound Manage*. 2001;47(5):54–59.
32. Romanzi LJ, Chaikin DC, Blaivas JG. The effect of genital prolapse on voiding. *J Urol*. 1999;161(2):581–586. doi:10.1016/S0022-5347(01)61957-8
33. Marinkovic SP, Stanton SL. Incontinence and voiding difficulties associated with prolapse. *J Urol*. 2004;171(3):1021–1028. doi:10.1097/01.ju.0000111782.37383.e2
34. Steensberg J, Bartels ED, Bay-Nielsen H, Fanoe E, Hede T. Epidemiology of urinary tract diseases in general practice. *Br Med J*. 1969;4(5680):390–394. doi:10.1136/bmj.4.5680.390
35. Bradley CS, Nygaard IE. Vaginal wall descensus and pelvic floor symptoms in older women. *Obstetrics Gynecol*. 2005;106(4):759–766. doi:10.1097/01.AOG.0000180183.03897.72
36. Groenendijk AG, Birnie E, Roovers JP, Bonsel GJ. Contribution of primary pelvic organ prolapse to micturition and defecation symptoms. *Obstet Gynecol Inter*. 2012;2012:798035. doi:10.1155/2012/798035
37. Teleman P, Laurikainen E, Kinne I, Pogosean R, Jakobsson U, Rudnicki M. Relationship between the pelvic organ prolapse quantification system (POP-Q), the pelvic floor impact questionnaire (PFIQ-7), and the pelvic floor distress inventory (PFDI-20) before and after anterior vaginal wall prolapse surgery. *Inter Urogynecol J*. 2015;26(2):195–200. doi:10.1007/s00192-014-2434-6
38. de Boer TA, Salvatore S, Cardozo L, et al. Pelvic organ prolapse and overactive bladder. *Neurourol Urodyn*. 2010;29(1):30–39. doi:10.1002/nau.20858
39. Iglesia CB, Smithling KR. Pelvic organ prolapse. *Am Family Phys*. 2017;96(3):179–185.
40. Karjalainen PK, Tolppanen AM, Mattsson NK, Wihersaari OAE, Jalkanen JT, Nieminen K. Pelvic organ prolapse surgery and overactive bladder symptoms—a population-based cohort (FINPOP). *Inter Urogynecol J*. 2022;33(1):95–105. doi:10.1007/s00192-021-04920-w
41. Weintraub AY, Gliner H, Marcus-Braun N. Narrative review of the epidemiology, diagnosis and pathophysiology of pelvic organ prolapse. *Int Braz J urol*. 2020;46(1):5–14. doi:10.1590/s1677-5538.ijbu.2018.0581
42. Storme O, Tirán Saucedo J, Garcia-Mora A, Dehesa-Dávila M, Naber KG. Risk factors and predisposing conditions for urinary tract infection. *Ther Adv Urol*. 2019;11:1756287218814382. doi:10.1177/1756287218814382
43. Eberhard J, Geissbühler V. Prolapse operation—also of help in urinary tract infections?. *Therapeutische Umschau Revue thérapeutique*. 2002;59(9):469–474. doi:10.1024/0040-5930.59.9.469
44. Sahiner Z, Mangır N, Güner M, et al. The relationship between urinary incontinence and abdominal muscle thickness in community-dwelling older women undergoing comprehensive geriatric assessment. *Eur Geriatric Med*. 2023;14(6):1319–1325. doi:10.1007/s41999-023-00874-y
45. Haylen BT, Lee J, Hussenbee S, Law M, Zhou J. Recurrent urinary tract infections in women with symptoms of pelvic floor dysfunction. *Inter Urogynecol J Pelvi Floor Dys Func*. 2009;20(7):837–842. doi:10.1007/s00192-009-0856-3
46. Töz E, Kurt S, Sahin Ç, Canda MT. Frequency of recurrent urinary tract infection in patients with pelvic organ prolapse. *Res Rep Urol*. 2015;7:9–12. doi:10.2147/RRU.S77061

International Journal of Women's Health

Publish your work in this journal

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of women's healthcare including gynecology, obstetrics, and breast cancer. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-womens-health-journal>

Dovepress
Taylor & Francis Group