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Review article

Gut, vaginal, and urinary microbiome alterations in women with genitourinary syndrome of menopause: A systematic review

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ABSTRACT

Background and objective: Genitourinary syndrome of menopause (GSM) is a chronic condition caused by estrogen deficiency, encompassing vaginal dryness, dyspareunia, and urinary symptoms. Alterations in the vaginal, urinary, and gut microbiome may contribute to GSM pathophysiology. We synthesize the evidence on microbiome composition and diversity across these compartments in postmenopausal women with GSM.

Methods: PubMed, Scopus, and Embase were searched from inception to April 2026 for studies assessing the microbiome in postmenopausal women with GSM using 16S rRNA gene sequencing, metagenomics, or culture-based methods.

Results: Twenty-three studies (5027 participants) were included: 15 examined the vaginal microbiome, seven the urinary microbiome, and one the gut microbiome. Postmenopausal women consistently showed reduced *Lactobacillus* abundance and increased microbial diversity. Estrogen therapy partially restored *Lactobacillus* dominance but did not uniformly improve symptoms. In the SWAN cohort ($n = 1320$), sexual pain was the only GSM symptom independently associated with a specific community state type (CST IV-C1; OR 2.26, 95% CI 1.20–4.23). Specific species showed associations with distinct symptom domains: *Prevotella* with urinary symptoms, *Finegoldia magna* with recurrent urinary tract infection, and *Streptococcus* with sexual pain. Parallel *Lactobacillus* depletion and pathobiont enrichment across all three compartments pointed toward a vaginal–bladder–gut axis, potentially linked through estrobolome disruption and bacterial translocation.

Conclusion: The postmenopausal genitourinary microbiome is characterized by *Lactobacillus* depletion and increased diversity, but microbiome restoration alone does not predict symptom resolution. The shared microbial alterations across compartments suggest a vaginal–bladder–gut axis that may collectively drive GSM, but this requires multi-compartment longitudinal validation.

PROSPERO registration: CRD420261335478

1. Introduction

Genitourinary syndrome of menopause (GSM) is a chronic and progressive condition affecting approximately 50% to 70% of postmenopausal women [1,2]. Triggered primarily by the decline in circulating estrogen levels after menopause, GSM encompasses a constellation of bothersome symptoms involving the vulvovaginal and lower urinary tracts, including vaginal dryness, burning, dyspareunia, urinary urgency, and recurrent urinary tract infections (rUTI) [3,4]. These clinical manifestations substantially impair sexual function and

Abbreviations: AV, atrophic vaginitis; CI, confidence interval; CST, community state type; EQUC, expanded quantitative urine culture; GSM, genitourinary syndrome of menopause; HT, hormone therapy; LET, local estrogen therapy; LUTS, lower urinary tract symptoms; NGS, next-generation sequencing; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PICOS, population, intervention, comparator, outcome, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; RF, radiofrequency; RoB 2, Risk of Bias 2; rUTI, recurrent urinary tract infection; SUC, standard urine culture; SWAN, Study of Women's Health Across the Nation.

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the overall quality of life in affected women.

A critical factor in the pathophysiology of GSM is the disruption of the urogenital microenvironment. In healthy women, the vaginal microbiota is typically dominated by *Lactobacillus* species, which produce lactic acid to maintain a low pH and provide a protective barrier against pathogenic colonization [5]. The estrogen deficiency following menopause leads to a depletion of these beneficial bacteria and an increase in microbial diversity, characterized by the overgrowth of anaerobic and opportunistic taxa. Recent studies [6,7] suggests that these alterations are not confined to the vagina; the urinary microbiome and even the gut microbiome show significant changes in women with GSM, potentially forming an interconnected "gut-vagina-urine axis" that contributes to the clinical syndrome.

The *Lactobacillus* depletion and rise in microbial diversity described above are characterized using metrics that remain unfamiliar in routine clinical practice; we therefore briefly define the key concepts used throughout this review. Alpha-diversity describes the diversity within a single sample, reflecting both the number of distinct taxa present (richness) and how evenly they are distributed (evenness); it is commonly quantified using the Shannon–Weaver and Simpson indices, which combine richness and evenness, and richness estimators such as Chao1 and the abundance-based coverage estimator (ACE), which estimate the total number of taxa including rare or undetected ones. Importantly, the clinical meaning of higher alpha-diversity is site-dependent: in the urogenital tract it generally indicates loss of *Lactobacillus* dominance and is regarded as a marker of dysbiosis, whereas in the gut higher diversity is typically considered healthy. Beta-diversity describes the compositional difference between samples or groups—for example, between women with and without GSM—and is used to test whether overall community structure differs across clinical conditions. These metrics recur throughout the studies synthesized below.

While topical estrogen remains the standard therapy for restoring microbial balance and tissue integrity, many women have contraindications or show an unsatisfactory response [8]. This has led to the development of non-hormonal strategies, including energy-based therapies like CO_2 laser and radiofrequency, as well as microbiome-targeted approaches such as probiotics [9–12]. However, the current evidence regarding microbiome alterations across the gut, vagina, and urinary tract remains fragmented. Therefore, we conducted a systematic review addressing two research questions: (1) What are the compositional and diversity characteristics of the vaginal, urinary, and gut microbiome in postmenopausal women with GSM? and (2) What microbiome changes are observed in postmenopausal women with GSM in the context of hormonal, energy-based, and probiotic interventions? Intervention studies were included because they reveal microbiome dynamics not observable in cross-sectional designs alone.

2. Evidence acquisition

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD420261335478). This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (**Supplementary Table 1, 2**) [13]. Detailed methods are described in **Supplementary Appendix 2.**

2.1. Search strategy

In April 2026, PubMed, Scopus, and Embase databases were searched to identify studies investigating the gut, vaginal, and urinary microbiome in postmenopausal women with GSM. The search strategy for each database is presented in the **Supplementary Appendix 1**. Two investigators independently performed an initial screening based on the titles and abstracts and noted the cause of exclusion of ineligible reports. Full texts were retrieved and evaluated for all studies that met the initial screening criteria and were subsequently evaluated for final inclusion.

2.2. Inclusion and exclusion criteria

We used the population, interventions, control, outcome, and study design (PICOS) framework to define the eligibility criteria (**Supplementary Table 3**) [14]. Eligibility criteria based on the PICOS framework are detailed in Supplementary Table 3. Briefly, we included observational and interventional studies assessing vaginal, urinary, or gut microbiome composition in postmenopausal women with GSM using molecular methods (16S rRNA gene sequencing, whole metagenome sequencing, or quantitative PCR) or culture-based methods. Culture-based studies were retained to capture the broadest possible evidence in this nascent field, particularly for body sites where molecular data were sparse; their methodological limitations are acknowledged in the risk of bias assessment. We excluded systematic reviews, narrative reviews, meta-analyses, editorials, letters, case reports with fewer than five participants, conference abstracts without full data, and animal or in vitro studies.

2.3. Data extraction

Two reviewers independently extracted study characteristics, microbiome methods, and key findings using a standardized form (Supplementary Methods).

2.4. Quality assessment & risk of bias

Study quality and risk of bias were evaluated using RoB2 for randomized controlled studies and the Newcastle–Ottawa Scale (NOS) for observational studies [15,16]. Each study was independently evaluated by two reviewers. Disagreements in quality assessment were resolved through discussion until consensus was reached.

3. Results

Detailed results are described in **Supplementary Appendix 2.**

3.1. Study selection

The search strategy is presented in Fig. 1. According to our inclusion criteria, we identified 23 studies [6–11,17–33] comprising a total of 5027 patients. Of these, 15 studies [8–11,17,18,20,22,23,27,28,30–33] investigated the vaginal microbiome, seven studies [7,19,21,24–26,29] examined the urinary microbiome, and one study [6] assessed the gut microbiome.

3.2. Study characteristics

The included studies were published between 2016 and 2025 and were conducted across 12 countries, including the United States ($n = 7$), China ($n = 4$), Japan ($n = 1$), Australia ($n = 1$), Brazil (n = 1), Canada (n = 1), Iraq (n = 1), Netherlands (n = 1), South Korea (n = 1), Taiwan (n = 1), Thailand (n = 1), and Ukraine (n = 1). Study designs included cross-sectional studies ($n = 15$) [6,7,9,18–21,24,25,28–30,32], prospective cohort studies ($n = 5$) [8,10,22,26,33], randomized controlled trials ($n = 3$) [11,17,31], and longitudinal cohort studies ($n = 2$) [23,27]. The majority of studies employed 16S rRNA gene sequencing for microbiome assessment ($n = 19$) [7–11,19–28,30–33], while four studies [6,17,18,29] used culture-based methods or Gram stain analysis. Considerable heterogeneity was observed across studies with respect to study design, population characteristics, microbiome assessment methodology, sequencing platforms, and outcome definitions. The details of the studies' characteristics are summarized in Table 1. The microbiome diversity indices (alpha- and beta-diversity) and the corresponding clinical associations for each included study are summarized in Table 4.

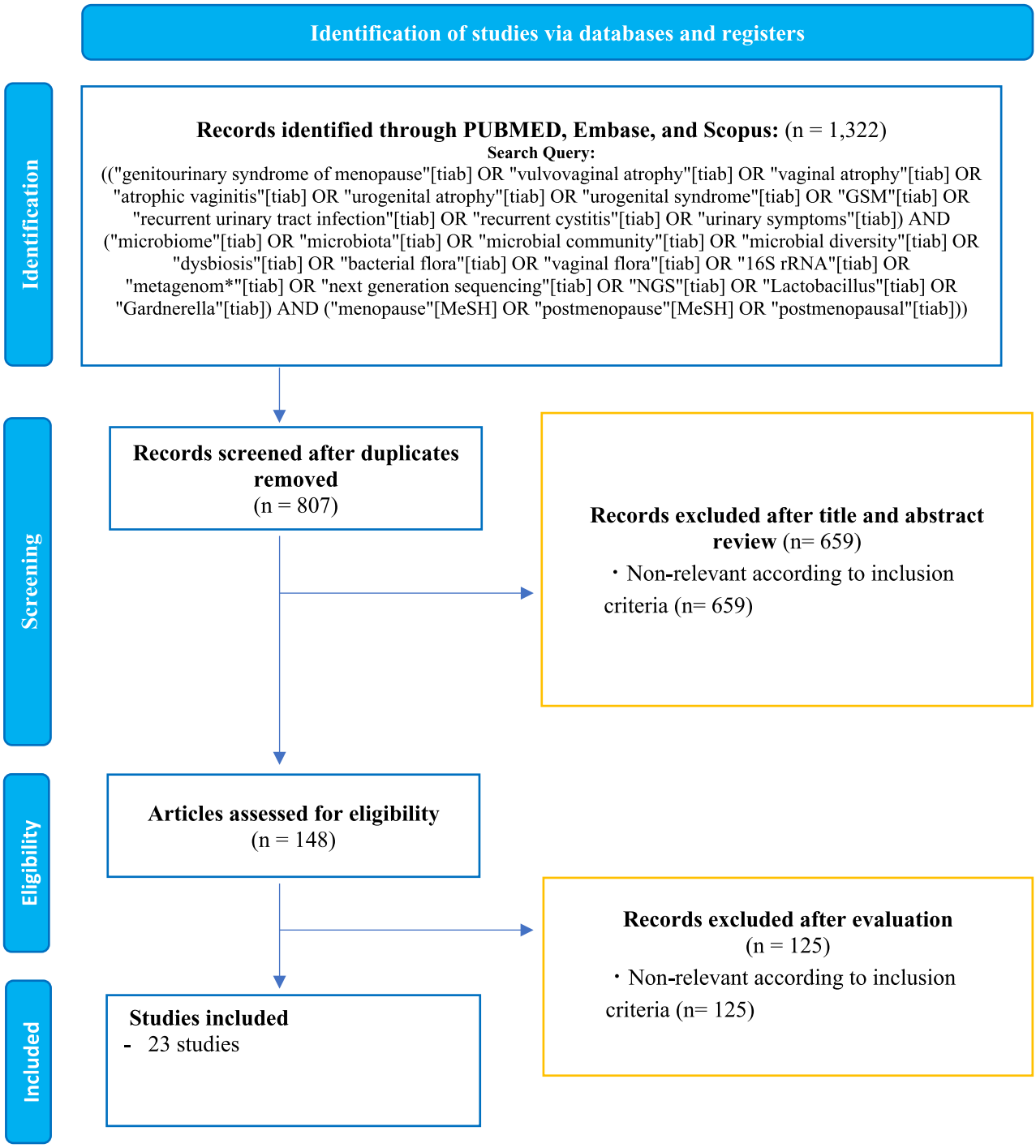

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, detailing the article selection process.

3.3. Risk of bias assessment

Authors' judgments about each domain for each included study are presented in Supplementary Table 5 and 6. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the Newcastle–Ottawa Scale (NOS) for observational studies. Of the four studies assessed with RoB 2, Qi et al. was judged to be at high risk of bias, primarily due to the lack of blinding (open-label design without sham laser) and a very small microbiome subsample (n = 16). The remaining three RCTs [17,28,31] were judged to have some concerns, mainly related to secondary analyses of parent trials designed for non-microbiome outcomes or the use of culture-based methods without molecular confirmation. Of the 19 observational studies assessed with the NOS, four were rated as good quality (7–9/9) and the remaining eight were rated as moderate quality (5–6/9). Common limitations included small sample sizes, lack of control for important confounders (diet, sexual activity, antibiotic use), culture-based methods without molecular validation, and single-arm pre–post designs without concurrent control groups. No study was judged to be at critical risk of bias. Overall, the certainty of the evidence is limited by the predominance of small, often underpowered, cross-sectional studies with heterogeneous methodologies; this caveat is particularly relevant to the urinary microbiome, where high inter-individual variability and sparsity demand larger sample sizes than the vaginal or gut niches to detect true

Table 1
Characteristics of the 23 included studies.

Author (year) country	Study design study period	Participants (n; age)	Sample type	Assessment method	Intervention	Key microbiome findings
A. Vaginal Microbiome (n = 15)						
Shen (2016) China	Prospective interventional Jun 2011–Feb 2012	59 (H 29, AV 30) H 55.6 ± 2.6, AV 55.8 ± 3.2 y	Mid-vaginal swab	16S rRNA (V1–V3); Illumina MiSeq	Oral conjugated estrogen (Premarin 0.3 mg/day, 4 wk)	Lactobacillus: 11.2% → 71.0% ($p < 0.0001$) after treatment; Gardnerella: 41.7% → 9.6%; Shannon diversity decreased; 23/30 (76.7%) transitioned to Lactobacillus-dominant; profound community composition changes in 24/30
Brotman (2014) USA	Cross-sectional 2006–2010	87 (Pre 30, Peri 29, Post 28) 35–60 y	Mid-vaginal swab	16S rRNA (V1–V2); 454 pyrosequencing	None	Postmenopausal women predominantly CST IV-A; CST IV-A associated with VVA (aOR 25.89; 95% CI 2.98–406.79)
Mitchell (2018) USA	RCT (secondary analysis) NR	30 Postmenopausal	Vaginal swab	16S rRNA (V3–V4); Illumina	Oral estradiol vs venlafaxine vs placebo	Lactobacillus-dominant at baseline associated with MBS improvement ($p = 0.08$, NS); community composition stable across visits
Gliniewicz (2019) USA	Cross-sectional NR	45 (Pre 15, Post 15, Post+HT 15) Pre 33 ± 8, Post 60 ± 7, HT 58 ± 8 y	Vaginal swab	16S rRNA (V1–V3); Illumina MiSeq + qPCR	Low-dose estrogen (HT group)	Post without HT: ~10-fold fewer bacteria, depleted Lactobacillus; Post+HT: *L. crispatus*-dominant, resembling premenopausal
Geng (2020) China	Cross-sectional NR	100 (MHT 50, non-treated 50) 45–65 y	Vaginal swab	16S rRNA (V3–V4); Illumina HiSeq 2500	Tibolone (MHT group)	MHT users: higher Lactobacillus, lower diversity vs non-treated; non-treated: enriched Gardnerella, Prevotella, Atopobium
Mitchell (2021) USA	RCT (secondary analysis) NR	120 (responder 60, nonresponder 60) 61 y	Vaginal swab	16S rRNA; Illumina	Vaginal estradiol vs moisturizer vs placebo	Estradiol arm: 63% Lactobacillus-dominant; symptom improvement not significantly associated with microbiota or inflammation
Shardell (2021) USA	Longitudinal cohort 2006–2010	750 (2111 person-visits) 35–60 y at enrollment	Vaginal swab	16S rRNA (V3–V4); Illumina HiSeq	None	Shannon diversity–GSM: nonlinear U-shaped association ($p = 0.036$ postmenopausal); CST IV-B: highest odds of atrophy/dryness/low libido
Sekito (2023) Japan	Retrospective cohort Dec 2013–Oct 2020	39 participants (129 samples; Healthy 19, UC 12, RC 8, Prevention 8) Postmenopausal (≥50 y)	Vaginal swab	16S rRNA (V3–V4); Illumina MiSeq	*L. crispatus* vaginal suppository (prevention group)	RC: 100% in clusters B/C (non-Lactobacillus); healthy: 76% in cluster A; Lactobacillus 0% → 19% during suppository ($p = 0.0211$); cystitis episodes 6.3 → 2.4/yr ($p = 0.0015$)
Waetjen (2023) USA	Cross-sectional (SWAN) 2015–2017	1320 65.5 y (range 60.4–72.5)	Self-collected vaginal swab	16S rRNA (V3–V4); Illumina HiSeq 2500	None	CST IV-C (low Lactobacillus) most prevalent (49.8%); sexual pain independently associated with CST IV-C1 (Streptococcus; OR 2.26, 95%CI 1.20–4.23); no consistent association with other GSM symptoms
Moore (2024) Australia	Prospective cohort NR	22 (44 paired samples) Postmenopausal	Vaginal swab	16S rRNA (V3–V4); Illumina MiSeq	Vaginal estriol cream (12 w)	Lactobacillus-dominant women: stable microbiota, minimal pH change; dysbiotic baseline: greater shift toward Lactobacillus dominance
Qi (2024) China	RCT Apr 2019–Jun 2021	64 analyzed (Laser 21, Estriol 21, Ctrl 22); 75 enrolled 51 y (45–76)	Vaginal mucosal swab	16S rRNA (V3–V4); Illumina HiSeq 2500 (16 specimens)	CO_2 laser vs vaginal estriol (0.5 mg) vs no treatment	Both treatments reduced alpha diversity and increased Lactobacillus; CO_2 laser: longer-term VHI improvement vs estriol at 12 mo
Zeng (2024) China	Cross-sectional NR	91 (Repro 24, Peri 23, EPost 23, LPost 21) Repro 30, Peri 50, EPost 54, LPost 63 y	Vaginal swab	Full-length 16S rRNA; PacBio	None	Diversity increased from reproductive to late postmenopause; Lactobacillus negatively associated with GSM; Escherichia-Shigella, Anaerococcus, Finegoldia, Enterococcus positively associated
Hamza (2025) Iraq	Cross-sectional Sep–Dec 2024	100 (Pre 25, Peri 25, Meno 25, Post 25) 20–55+ y	Vaginal swab	Standard aerobic culture	None	Progressive decline in *L. acidophilus* from pre- to postmenopause; increasing Gardnerella, *E. coli*, Candida
Li (2025) Taiwan	Prospective cohort Jan–Dec 2024	50 enrolled; 91 samples sequenced 50.4 ± 9.0 y	Vaginal posterior fornix swab	16S rRNA (V3–V4); Illumina MiSeq	CO_2 laser (MonaLisa Touch)	Alpha diversity differed by menopause ($p = 0.034$) and GSM ($p = 0.004$) but not by laser; Gardnerella disappeared in network analysis post-laser
Zunino (2025) Brazil	RCT (double-blind) NR	30 (Estriol 15, RF 15) 56.3 ± 7.1 y (42–69)	Vaginal swab	Gram stain (Donders/Nugent) + aerobic culture	Fractional RF vs topical estriol	RF group: higher proportion of Lactobacillus-dominant flora (Donders type I) vs estriol (66.7% vs 26.7%), though this difference did not reach statistical significance ($p = 0.057$); both groups showed pH reduction from baseline
B. Urinary microbiome (n = 7)						

(*continued on next page*)

Table 1 (*continued*)

Author (year) country	Study design study period	Participants (n; age)	Sample type	Assessment method	Intervention	Key microbiome findings
Burnett (2021) USA	Cross-sectional Dec 2017–Mar 2019	43 (36/43 postmenopausal) 67.1 ± 14.2 y	Catheterized + voided urine	EQUC + SUC	None	5 clinical profile clusters; major patterns: No growth, Lactobacillus, Enterococcus, Escherichia, Klebsiella; Group B: Lactobacillus+ ($p = 0.047$); Group E: Klebsiella+ ($p = 0.025$)
Vaughan (2021) USA	Cross-sectional Dec 2017–Mar 2019	64 (rUTI+Abx 17, rUTI 24, Ctrl 23) 70.5 ± 7.5 y	Catheterized urine	16S rRNA (V4); Illumina MiSeq + EQUC	None (all on vaginal estrogen)	No significant differences in Lactobacillus abundance ($p = 0.72$); Lactobacillaceae in 97% samples; BGCR: Prevotella (PMAP 99.96%), Bacteroidales, Actinobacteria differed between rUTI+Abx and controls
Anglim (2022) Canada	Prospective cohort Mar 2019–Dec 2020	37 (rUTI 17, Ctrl 20) rUTI 65.5 ± 9.1, Ctrl 65.2 ± 7.4 y	Catheterized urine	16S rRNA (V1–V2) + ITS; Illumina MiSeq	LET (Vagifem / Premarin)	*F. magna*: 33.3% → 6.7% in rUTI after LET ($q = 0.04$); *K. aerogenes*: rUTI 80% vs Ctrl 53.3% ($q = 0.04$); diversity lowered after LET ($p = 0.001$); no change in Lactobacillus
Huang (2022) China	Cross-sectional Jan–May 2021	111 analyzed (RUTI 67, Ctrl 44); 152 enrolled RUTI 49.5 ± 15.2, Ctrl 46.0 ± 11.7 y	Midstream voided urine	16S rRNA (V3–V4); Illumina MiSeq	None	RUTI: lower Chao1/observed species ($p = 0.015/0.028$); enriched Ralstonia, Prevotella, Dialister, Corynebacterium; Lactobacillus, Gardnerella more abundant in controls
Hugenholtz (2022) Netherlands	Cross-sectional NR	86 (Pre ctrl 18, Pre RUTI 18, Post ctrl 30, Post RUTI 20) Pre 36 ± 11, Post 67 ± 12 y	Vaginal swab + voided urine	16S rRNA (V4); Illumina MiSeq + IS-pro	None	Postmenopausal: less L. *crispatus*, more BV-anaerobes and Gram-positive uropathobionts vs premenopausal; no significant RUTI vs control differences within menopausal groups; menopausal status had stronger impact than RUTI history
Yoo (2024) South Korea	Retrospective Mar 2020–Jan 2023	540 (Ctrl 18, sUC 34, rUTI/rUC 488); 61.1% postmenopausal 53.3 ± 14.5 y	Catheterized urine	16S rRNA (V4); Illumina MiSeq	None	NGS sensitivity: rUC 82.4% vs culture 16.4%; rUC: Lactobacillus 14.8%, Prevotella 9.9%, Enterobacterales 8.6%; sUC and rUC show distinct microbiome profiles; menopausal status influenced composition
Chattrakulchai (2025) Thailand	Cross-sectional Jan–May 2022	36 (Urinary Sx 18, No Sx 18) Sx 61.2 ± 7.3, No Sx 60.5 ± 6.1 y	Catheterized urine	16S rRNA (V3–V4); Illumina MiSeq	None	Lactobacillus: most common urotype in both groups; Prevotella enriched in urinary Sx group (94.4% vs 5.5%, $p < 0.05$); Prevotella correlated with voiding symptoms ($r^2 = 0.44$, $p = 0.01$)
C. Gut microbiome (n = 1)						
Pavlovska (2023) Ukraine	Cross-sectional NR	65 (GSM 39 [Ia 22, Ib 17], Ctrl 26) Ia 52.7, Ib 55.2, Ctrl 53.4 y	Fecal sample	Bacteriological culture	None	GSM: decreased Bifidobacterium and Lactobacillus; increased *E. coli*, Klebsiella, Streptococcus; associated with metabolic comorbidities

NR, not reported; CST, community state type; VVA, vulvovaginal atrophy; HT, hormone therapy; MHT, menopausal hormone therapy; AV, atrophic vaginitis; GSM, genitourinary syndrome of menopause; rUTI, recurrent urinary tract infection; RUTI, recurrent urinary tract infection; EQUC, expanded quantitative urine culture; SUC, standard urine culture; RF, radiofrequency; LET, local estrogen therapy; MBS, most bothersome symptom; NS, not significant; sUC, sporadic/single uncomplicated cystitis; rUC, recurrent uncomplicated cystitis; NGS, next-generation sequencing; BGCR, Bayesian graphical compositional regression; PMAP, posterior marginal alternative probability; VHI, vaginal health index; OAB, overactive bladder; RC, recurrent cystitis; UC, uncomplicated cystitis.

differences.

3.4. Vaginal microbiome in GSM

3.4.1. Vaginal microbiome composition and diversity across menopausal stages

Genitourinary syndrome of menopause encompasses vulvovaginal symptoms (dryness, burning, irritation, dyspareunia), urinary symptoms (urgency, frequency, dysuria, recurrent urinary tract infections), and sexual symptoms (pain during intercourse, reduced libido). Vaginal bacterial communities are classified into community state types (CSTs): CST I (*Lactobacillus crispatus*-dominant), CST II (*L. gasseri*-dominant), CST III (*L. iners*-dominant), CST V (*L. jensenii*-dominant), and CST IV, which is characterized by low *Lactobacillus* abundance and high anaerobic diversity, further subdivided into CST IV-A, IV-B (enriched in *Gardnerella vaginalis*), and CST IV-C (sub-classified based on dominant non-*Lactobacillus* taxa, e.g., IV-C1 *Streptococcus*-dominated).

Six observational studies [18,20,23,27,30,32] examined the vaginal microbiome composition and its association with GSM in postmenopausal women without therapeutic intervention.

Postmenopausal women were predominantly classified as CST IV-A (low *Lactobacillus*, high anaerobic diversity), which was strongly associated with vulvovaginal atrophy (adjusted OR 25.89; 95% CI 2.98–406.79). Gliniewicz et al. [30] showed that untreated postmenopausal women had 10-fold fewer bacteria and depleted *Lactobacillus*, while those on HT harbored *L. crispatus*-dominant communities resembling premenopausal women. Shardell et al. [27] assessed 750 women longitudinally and found CST IV-B was associated with the highest odds of atrophy, dryness, and low libido, while CST I had significantly lower odds of atrophy (OR 0.25; 95% CI 0.08–0.81). In the largest study (SWAN, $n = 1320$), Waetjen et al. [23] found that CST IV-C was most prevalent (49.8%) and sexual pain was the only GSM symptom independently associated with CST IV-C1 (*Streptococcus*-dominated; OR 2.26, 95% CI 1.20–4.23). Zeng et al. [20], using full-length 16S rRNA sequencing, showed that *Lactobacillus* was negatively associated with GSM while *Escherichia-Shigella*, *Anaerococcus*, *Finegoldia*, and *Streptococcus* were positively associated with genital and sexual symptoms. Hamza et al. [18] used standard culture in 100 women across

menopausal stages and demonstrated a progressive decline in L. *acidophilus* from premenopause to postmenopause, accompanied by increasing *Gardnerella*, *Escherichia coli*, and *Candida*.

3.4.2. Vaginal microbiome changes associated with hormonal therapy

Five studies [8,22,28,31,33] reported vaginal microbiome changes in postmenopausal women receiving estrogen-based therapy. Shen et al. [33] observed that *Lactobacillus* relative abundance increased with oral conjugated estrogen from 11.2% to 71.0% ($p < 0.0001$), with 76.7% (23/30) transitioning to *Lactobacillus*-dominant states. Geng et al. [8] reported higher *Lactobacillus* abundance and lower diversity in tibolone users compared with untreated postmenopausal women. Mitchell et al. [28] reported that among women receiving vaginal estradiol, 63% transitioned from diverse, non-*Lactobacillus*-dominant communities at baseline to *Lactobacillus*-dominant communities at 12 weeks; however, these microbiota shifts were not significantly associated with symptom improvement or vaginal inflammation. Moore et al. [22] studied 22 postmenopausal women (44 paired samples) receiving vaginal estriol for 12 weeks. Women with *Lactobacillus*-dominant baseline communities showed stable microbiota, while those with dysbiotic baselines shifted toward *Lactobacillus* dominance.

3.4.3. Vaginal microbiome changes associated with laser and radiofrequency therapy

Three studies [10,11,17] reported vaginal microbiome changes in women receiving non-hormonal energy-based therapies.

Qi et al. [11] conducted an RCT of 64 postmenopausal women with GSM (75 enrolled; CO_2 laser 21, vaginal estriol 21, control 22). Using 16S rRNA (V3–V4) on Illumina HiSeq 2500, only 16 specimens were available for microbiome analysis. Both groups showed reduced alpha diversity and increased *Lactobacillus* abundance. At 12 months, the vaginal health index scores remained elevated in the CO_2 group but returned to baseline in the estrogen group. Li et al. [10] evaluated 50 women with GSM (42% postmenopausal) undergoing CO_2 laser. Of 91 successfully sequenced samples (16S V3–V4, MiSeq), alpha diversity differed by menopause ($p = 0.034$) and GSM status ($p = 0.004$) but not by laser treatment. Network analysis revealed *Gardnerella* disappearance and *Lactobacillus* increase, though individual microbiome responses varied considerably. Zunino et al. [17] reported microbiome changes in 30 postmenopausal women receiving fractional radiofrequency or topical estriol. The RF group showed a numerically higher proportion of *Lactobacillus*-dominant flora (Donders type I) compared with the estriol group (66.7% vs 26.7%), although this difference did not reach statistical significance ($p = 0.057$).

3.4.4. Vaginal microbiome and recurrent cystitis in postmenopausal women

Sekito et al. [9] retrospectively analyzed the vaginal microbiota of 39 postmenopausal women (≥50 years) classified into four groups (healthy, uncomplicated cystitis, recurrent cystitis [RC], and prevention with L. *crispatus* vaginal suppositories) between December 2013 and October 2020. Using 16S rRNA (V3–V4) on Illumina MiSeq, 129 vaginal samples were clustered into three groups (A, B, C). All RC samples (100%) fell in clusters B and C (non-*Lactobacillus*-dominant), while 76% of healthy controls were in cluster A (*Lactobacillus*-dominant). Beta-diversity analysis confirmed significant differences between RC and healthy ($p = 0.001$) or uncomplicated cystitis ($p = 0.001$) groups. *Lactobacillus* was undetectable in RC patients before suppository use but reached a median relative abundance of 19% during treatment ($p = 0.0211$), with cystitis episodes decreasing from 6.3 to 2.4 per year ($p = 0.0015$). Notably, the participants in this study did not receive vaginal or systemic estrogen therapy during the L. *crispatus* intervention, supporting its attribution to the intervention itself. Nevertheless, the small sample size (39 women) and the retrospective single-arm design limit the statistical power and generalizability of these findings.

3.5. Urinary microbiome in GSM

Seven studies [7,19,21,24–26,29] investigated the urinary microbiome in postmenopausal women with GSM-related urinary symptoms, particularly rUTI.

3.5.1. Urinary microbiome composition in postmenopausal women

Chattrakulchai et al. [19] compared the urinary microbiome of 36 postmenopausal women with GSM (18 with urinary symptoms, 18 without) using catheterized urine and 16S rRNA (V3–V4) on MiSeq. *Lactobacillus* was the most common urotype in both groups (100% vs 88.9%). Alpha and beta diversity did not significantly differ. *Prevotella* was significantly enriched in the urinary symptom group (94.4% vs 5.5%; $p < 0.05$) and correlated with voiding symptoms ($r^2 = 0.44$; $p = 0.01$). *Gardnerella* and *Lactobacillus* showed no significant group differences.

3.5.2. Urinary microbiome in recurrent UTI (rUTI)

Hugenholtz et al. [24] simultaneously assessed urine and vaginal microbiota in 86 women, including 50 postmenopausal and 36 premenopausal women. Menopausal status had a far greater impact on microbiome composition than rUTI history: postmenopausal women, regardless of rUTI status, had lower *Lactobacillus* abundance (particularly L. *crispatus*) and higher anaerobic diversity compared with premenopausal women. Vaughan et al. [7] found no significant *Lactobacillus* differences among 64 estrogen-treated postmenopausal women, but Bayesian analysis identified significant differences in *Prevotella* and *Bacteroidales* between rUTI patients on antibiotics and controls. Burnett et al. [29] identified five distinct urobiome clusters in 43 rUTI patients, with *Lactobacillus* associated with vaginal estrogen use ($p = 0.047$) and *Klebsiella* with overactive bladder ($p = 0.025$). Huang et al. [25] found lower species richness in rUTI with enrichment of *Prevotella*, while *Lactobacillus* was more abundant in controls. Yoo et al. [21] showed that NGS sensitivity far exceeded culture (82–91% vs 16–32%) and that sporadic and recurrent cystitis exhibited distinct microbiome profiles.

3.5.3. Urinary microbiome changes associated with vaginal estrogen therapy

Anglim et al. [26] prospectively characterized urinary microbiome changes in 37 postmenopausal women with GSM (17 with rUTI, 20 controls) before and after 3–6 months of local estrogen therapy (LET). Before treatment, *Finegoldia magna* was detected in 33.3% of rUTI urine samples but was absent in controls. After LET, *F. magna* prevalence decreased to 6.7% in the rUTI group ($q = 0.04$). Notably, urinary *Lactobacillus* abundance did not significantly change in either group following LET. This null result should be interpreted with caution, because the urinary niche exhibits high inter-individual variability and greater sparsity than the vaginal or gut compartments, and the small sample (37 women) may have left the study underpowered to detect a true change in *Lactobacillus*. With this limitation acknowledged, an alternative interpretation is that estrogen-associated urinary microbiome changes may involve suppression of specific pathobionts (e.g., *Finegoldia magna*) rather than restoration of *Lactobacillus*.

3.6. Gut Microbiome in GSM

Pavlovska et al. [6] compared the intestinal microbiota of 65 middle-aged women (GSM 39, controls 26) using bacteriological culture. Women with GSM presenting with vulvovaginal and urinary symptoms showed significantly decreased colonization by *Bifidobacterium* and *Lactobacillus* and increased prevalence of conditionally pathogenic bacteria, including *Escherichia coli*, *Klebsiella*, and *Streptococcus*. Women with GSM in this study also more frequently presented with metabolic comorbidities (obesity, type 2 diabetes, dyslipidemia). However, because metabolic dysregulation and altered abdominal fat distribution

are themselves recognized consequences of the estrogen decline of menopause, these comorbidities and the local genitourinary changes of GSM are best understood as parallel manifestations of a shared hormonal disruption rather than as evidence that GSM per se is associated with metabolic dysfunction. As with the other observational studies in this review, the modest sample size (65 women) and culture-based methodology further limit the strength of these inferences.

4. Discussion

This systematic review provides the first comprehensive synthesis of evidence on the vaginal, urinary, and gut microbiome in relation to GSM. Despite substantial heterogeneity across 23 studies, three consistent patterns emerged: postmenopausal *Lactobacillus* depletion with increased microbial diversity, partial restoration of *Lactobacillus* dominance by estrogen therapy, and a surprisingly weak relationship between restoration of *Lactobacillus*-dominant communities (i.e., transition from CST IV to *Lactobacillus*-dominant CSTs) and GSM symptom resolution.

The estrogen–*Lactobacillus*–pH axis has long been considered the central mechanism underlying GSM pathophysiology. In this model, declining estrogen after menopause reduces glycogen deposition in vaginal epithelial cells, depriving *Lactobacillus* species of their primary carbon source. The subsequent loss of lactic acid production leads to increased vaginal pH and colonization by diverse anaerobes, ultimately contributing to mucosal atrophy and symptom development [34]. This paradigm was consistently supported by multiple studies in our review [8,22,30,33], which collectively demonstrated that various forms of estrogen therapy—including oral conjugated estrogen, tibolone, and vaginal estriol—restored *Lactobacillus*-dominant communities in postmenopausal women, with concomitant reductions in anaerobic diversity.

However, several findings challenge the completeness of this paradigm. Despite microbiome restoration, symptom improvement was not consistently associated with microbiota composition, vaginal inflammation, or community state type transitions [28]. Moreover, among multiple GSM-related symptoms evaluated in a large cohort study, only sexual pain was independently associated with vaginal microbiota composition, whereas dryness, irritation, dysuria, and urgency were not. These observations suggest that *Lactobacillus* restoration may be necessary but not sufficient for symptom resolution, and that host-related factors such as mucosal immune responses, tissue repair capacity, and nerve sensitization may also contribute to GSM symptomatology.

While most research has focused on the protective role of *Lactobacillus*, our review highlights the potential pathogenic significance of several non-*Lactobacillus* species in GSM and associated conditions. *Prevotella* emerged as a taxon of particular interest across multiple body sites, with consistent enrichment in postmenopausal women with urinary symptoms [19] and recurrent UTI [7,25].

Finegoldia magna was identified as a potentially important uropathogen enriched in rUTI but decreased after estrogen therapy, suggesting that the atrophic urogenital environment may permit colonization by opportunistic organisms [26]. The SWAN study revealed an independent association between sexual pain and CST IV-C1, dominated by *Streptococcus* species, raising the possibility that specific microbial communities may contribute to vulvovaginal inflammation through mechanisms distinct from simple *Lactobacillus* depletion. Zeng et al. [20] further demonstrated positive associations between GSM and multiple potential pathobionts using full-length 16S rRNA sequencing. These findings collectively suggest that GSM-associated dysbiosis is not merely the absence of *Lactobacillus* but involves the active enrichment of specific pathobionts, each potentially contributing to distinct symptom domains.

Multiple studies in this review revealed an apparent paradox. Vaginal estrogen restored *Lactobacillus* in both the vaginal and urinary environments, but this alone did not distinguish women with rUTI from those without. Instead, susceptibility to rUTI appears to be determined by the anaerobic microbial community coexisting with *Lactobacillus*, particularly *Prevotella*, *Bacteroidales*, and specific uropathogens such as *Klebsiella*. These organisms may form a dysbiotic niche that promotes recurrence even in an estrogen-replete state. Notably, vaginal L. *crispatus* supplementation reduced recurrent cystitis without restoring the overall microbiota, suggesting that its protective effect is mediated by suppression of pathogenic activity rather than by restoration of the microbiome itself. Together, these findings support a shift in perspective, from viewing rUTI as a consequence of *Lactobacillus* depletion to understanding it as a disorder of microbial community dynamics.

Microbiome changes were also observed with non-hormonal interventions. CO_2 laser was associated with increased *Lactobacillus* abundance comparable to topical estrogen, with changes persisting at 12 months [11], possibly reflecting thermal mucosal remodeling that provides a more sustained substrate for *Lactobacillus* recolonization. Radiofrequency was similarly associated with a trend toward greater *Lactobacillus* dominance, though the difference did not reach statistical significance [17]. These non-hormonal and probiotic strategies warrant validation in adequately powered trials with long-term follow-up.

We believe that the most important conceptual finding of this review is the parallel pattern of *Lactobacillus* depletion and pathobiont enrichment observed across all three compartments. In the vagina, the shift to CST IV with enrichment of *Gardnerella*, *Prevotella*, and *Streptococcus* was consistently reported. In the urinary tract, *Prevotella*, *Finegoldia*, and *Enterobacterales* were enriched. In the gut, *Bifidobacterium* and *Lactobacillus* declined while *E. coli*, *Klebsiella*, and *Streptococcus* increased. *Prevotella* was the only genus reported as altered in all three compartments. However, the co-occurrence of a genus across compartments does not by itself constitute evidence of microbial translocation: *Prevotella* has been detected in the urinary tract in numerous prior studies and is not a novel urinary finding, and none of the included studies provided the strain-level metagenomic data—for example, demonstration of an identical phylogenetic strain shared across the gut and bladder—that would be required to document translocation. Because gut microbiome data were derived from only a single study [6], we therefore frame the vaginal–bladder–gut axis as a biologically plausible theoretical mechanism that may contribute to urogenital dysbiosis rather than a process demonstrated by the current evidence. A key mechanism within this axis may involve the estrobolome, defined as the collection of gut microbial genes encoding β-glucuronidase, which facilitates the deconjugation of estrogens and promotes their enterohepatic recirculation [35]. Postmenopausal gut dysbiosis may impair estrobolome function, further reducing circulating estrogen and exacerbating vaginal and urinary epithelial atrophy beyond what ovarian failure alone would cause. Concurrently, vaginal pathobiont overgrowth may facilitate ascending urinary infection. It must be emphasized, however, that no study included in this review measured β-glucuronidase activity, estrogen metabolites, or estrobolome gene content; the single gut study [6] reported only culture-based reductions in *Bifidobacterium* and *Lactobacillus*, so the estrobolome hypothesis remains an extrapolation from the broader literature rather than a mechanism directly evidenced here. Consistent with this systemic framing, the more frequent metabolic comorbidities observed among women with GSM in that study likely reflect the wide-ranging effects of menopausal estrogen loss on both local genitourinary tissue and systemic metabolism—effects that could speculatively be linked through gut dysbiosis but that remain to be demonstrated. However, no study to date has simultaneously characterized all three compartments in the same participants; validation of this axis through multi-compartment longitudinal studies represents a critical next step. Notably, a recent multisite study of women with overactive bladder demonstrated urogenital dysbiosis that overrode menopausal contrasts observed in controls, with *Lactobacillus* depletion and enrichment of *Bacteroides*, *Gardnerella*, and other genera across urethra, urine, and vagina but not stool [36].

Several limitations should be acknowledged. The inability to conduct

meta-analysis limits the strength of conclusions. Most studies had small sample sizes, with only two exceeding 500 participants, and gut microbiome data were derived from a single study, making the vaginal–bladder–gut axis hypothesis preliminary. Heterogeneous 16S rRNA variable regions, bioinformatics pipelines, and GSM definitions preclude direct comparisons. Many studies did not control for confounders such as diet, sexual activity, and antibiotic use. The predominantly cross-sectional designs preclude causal inference, and it should be acknowledged that symptom-driven behavioral changes, such as antibiotic use for rUTI, avoidance of sexual activity due to dyspareunia, or use of lubricants and vaginal cleansing products, may themselves alter microbiome composition, creating a bidirectional relationship that cross-sectional studies cannot disentangle. Additionally, our search strategy focused on core GSM-defining symptoms and may not have captured all studies addressing individual components such as overactive bladder or sexual dysfunction in isolation, which could represent a source of selection bias.

5. Conclusion

This systematic review of 23 studies demonstrates that the postmenopausal genitourinary microbiome is characterized by *Lactobacillus* depletion and increased diversity across vaginal, urinary, and gut compartments. The estrogen–*Lactobacillus*–pH axis, although central, is an incomplete paradigm: microbiome restoration does not uniformly predict symptom resolution, and specific pathobionts may drive distinct GSM symptom domains. The shared microbial alterations observed across compartments provide preliminary support for a vaginal–-bladder–gut axis hypothesis, which requires validation through multi-compartment longitudinal studies. Large-scale, multi-compartment longitudinal studies are needed to validate this axis and advance personalized treatment strategies for postmenopausal genitourinary health.

Contributors

Ichiro Tsuboi participated in data collection, data extraction, and drafting and editing of the paper.

Shota Inoue participated in data collection, data extraction, and drafting and editing of the paper.

Takashi Hirayama participated in critical review of the manuscript.

Yosuke Mitsui participated in critical review of the manuscript.

Masami Watanabe participated in critical review of the manuscript.

Hidetada Hirakawa participated in critical review of the manuscript.

Takuya Sadahira supervised the study and provided overall guidance.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Ethical statement

Ethical approval was not required for this study because it was a systematic review of previously published studies and did not involve any new studies with human participants or animals.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Claude and OpenAI for English language editing, stylistic refinement, and making tables. After using Claude and OpenAI, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

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