



ANALYSIS OF RISK FACTORS FOR RECURRENT URINARY TRACT INFECTION IN WOMEN OF REPRODUCTIVE AGE : A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS AND PRIMARY OBSERVATIONAL STUDIES

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ABSTRACT

Introduction: Recurrent urinary tract infection is among the most common reasons for an otherwise healthy woman to consult a physician, and it is a principal driver of outpatient antimicrobial consumption worldwide. More than half of all adult women experience at least one urinary tract infection during their lifetime and approximately one quarter go on to experience recurrence. Although frequently framed as a disorder of the postmenopausal years, contemporary cohorts demonstrate a bimodal incidence with a distinct peak in the reproductive-age decades. The determinants operating in this younger stratum are behavioural, sexual, microbiological, and constitutional. This review aimed to identify, appraise, and quantitatively pool the risk factors for recurrent urinary tract infection in women of reproductive age.

Methods: A systematic review and meta-analysis was conducted in accordance with PRISMA 2020. Eligible designs included randomised controlled trials, cohort studies, case-control studies, cross-sectional studies, and other analytical observational designs. The population was premenopausal women aged 15–49 years. The outcome was recurrent urinary tract infection (≥ 2 episodes within 6 months or ≥ 3 within 12 months). Two reviewers independently screened, extracted data, and assessed risk of bias using the Newcastle-Ottawa Scale, RoB 2, and AXIS. Effect estimates were pooled on the logarithmic scale using DerSimonian-Laird random-effects models. Heterogeneity was quantified with Q , τ^2 , and I^2 ; small-study effects were examined with funnel plots and Egger's test. Certainty of evidence was rated with GRADE.

Results: Of 4,247 records, 32 studies met the criteria, with 18 contributing to at least one of six pooled outcome domains. Recent or frequent sexual intercourse was associated with a pooled odds ratio of 6.78 (95% CI 1.80–25.49; $P = 0.005$; $I^2 = 90.5\%$). Exposure to spermicide, diaphragm, or spermicide-coated condoms yielded a pooled odds ratio of 2.78 (95% CI 1.70–4.57; $P < 0.001$; $I^2 = 67.0\%$), with a clear exposure-response gradient. A prior history of urinary tract infection or a first infection at or before the age of 15 years gave a pooled odds ratio of 3.36 (95% CI 2.16–5.22; $P < 0.001$) with no detectable heterogeneity. A history of infection in first-degree female relatives yielded a pooled odds ratio of 3.26 (95% CI 2.14–4.97; $P < 0.001$; $I^2 = 62.9\%$). Randomised modification of candidate risk factors (increased water intake, intravaginal lactobacillus repletion, cranberry proanthocyanidins, and D-mannose) produced a pooled risk ratio of 0.61 (95% CI 0.43–0.87; $P = 0.006$). The association between diabetes mellitus and recurrence differed markedly by

stratum: the adjusted risk ratio was 1.07 (95% CI 1.04–1.10) in a reproductive-age-inclusive cohort of 374,171 women but 2.04 (95% CI 1.59–2.62) in pooled postmenopausal data, a ratio of ratios of 1.91 (95% CI 1.49–2.45; $P = 4.2 \times 10^{-7}$). Vaginal colonisation with *Escherichia coli* was present in 35% of cases versus 11% of controls.

Conclusion: In women of reproductive age, recurrent urinary tract infection is driven by a small number of strong, consistently replicated determinants. Spermicide-containing contraception, coital frequency, a personal or familial history of infection, vaginal lactobacillus depletion, low fluid intake, and recent antimicrobial exposure together account for most of the identifiable risk, and several of these are directly modifiable. Diabetes mellitus and other factors that dominate guidance written for older women should not be allowed to displace these determinants in the consultation with a younger woman. Clinicians should routinely elicit a contraceptive and sexual history and a structured family history, should advise an additional 1.5 litres of water daily where baseline intake is low, should consider intravaginal lactobacillus or cranberry preparations as antibiotic-sparing options, and should apply rigorous antimicrobial stewardship.

Keywords: recurrent urinary tract infection; reproductive-age women; risk factors; spermicide; vaginal microbiota; meta-analysis

INTRODUCTION

Background

Urinary tract infection is one of the most frequently encountered bacterial infections in clinical medicine and is overwhelmingly a disease of women. More than half of all adult women will experience at least one episode during their lifetime, and almost one quarter of those women will subsequently meet the conventional definition of recurrence, namely at least two culture-confirmed episodes within a six-month period or at least three episodes within twelve months, with at least one episode confirmed by culture in order to establish an infectious aetiology. The condition imposes a burden that is disproportionate to its reputation as a minor complaint: it generates symptom days, restricted-activity days, repeated consultations, laboratory investigation and, above all, repeated courses of antimicrobial therapy.^{1,2}

The public health significance of that last consequence is difficult to overstate. Urinary tract infection is among the commonest indications for antibiotic prescription worldwide, and analyses of primary-care prescribing demonstrate that the great majority of episodes receive same-day empirical therapy with limited microbiological confirmation. In a national English primary-care dataset of 494,675 infections, same-day antibiotics were issued for 85.7% of episodes and urine sampling was undertaken in only a quarter. Each such prescription exerts selection pressure both on the infecting organism and on the wider intestinal and urogenital reservoir of the host, and contemporary cohort data show that this pressure is not merely theoretical but translates into measurably increased subsequent infection risk.^{11,61,78}

Much of the authoritative guidance on recurrent urinary tract infection has been written with the older woman principally in view. Guideline syntheses, narrative reviews and clinical updates consistently emphasise hypo-oestrogenism, vaginal atrophy, pelvic organ prolapse, elevated post-void residual volume, incontinence and functional dependence, and they position vaginal oestrogen as a cornerstone of prevention. These emphases are entirely appropriate for the population they address. They are, however, largely inapplicable to a twenty-five-year-old woman presenting with

her fourth episode of cystitis in a year, for whom oestrogen deficiency is not a plausible explanation and for whom vaginal oestrogen is not an available intervention.^{5–8,20}

That younger woman is not a rare presentation. In the largest contemporary analysis of recurrence, drawn from the electronic health records of 374,171 women with an index uncomplicated urinary tract infection in an integrated health system, 14.5% developed recurrence, and women aged eighteen to twenty-seven years were over-represented among recurrent cases relative to those without recurrence. Relative to that youngest stratum, women aged forty-eight to fifty-seven years had a significantly lower adjusted risk ratio of 0.83. National claims data from the United States similarly identify a bimodal incidence distribution with peaks at eighteen to thirty-four and at fifty-five to sixty-four years. In a Welsh primary-care population of more than 1.5 million women, 6.0% carried a recurrence diagnosis. Recurrence in the reproductive years is therefore common, and it is demographically distinct from recurrence after the menopause.^{4,13,14}

The determinants operating in this younger stratum have been investigated for four decades, beginning with the classical epidemiological case-control studies of diaphragm use and coital frequency in North American college populations and progressing through prospective diary-based cohorts, population-based case-control studies with genotyping, and, most recently, longitudinal multi-omic characterisation of the gut-bladder axis. Individually these studies are informative. Collectively they have never been subjected to a quantitative synthesis restricted to the reproductive-age population, and the risk-factor hierarchy that a clinician might reasonably apply at the bedside has accordingly remained a matter of expert impression rather than pooled estimation.^{18,19,23,34,40}

Research gap

Three specific deficiencies in the existing literature motivated this review. First, no systematic review has confined its population to women of reproductive age. Existing syntheses either address the entire adult female population, in which the numerically dominant postmenopausal stratum inevitably drives pooled estimates, or address prevention rather than aetiology. The consequence is that the relative weight of any given determinant in a premenopausal woman cannot be read off from the available literature. Second, the evidence on risk factors and the

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evidence from randomised prevention trials have been synthesised in parallel rather than in combination, despite the fact that several randomised trials have experimentally modified precisely the exposures identified by the observational literature and therefore constitute an unusually direct form of corroboration. Third, the certainty of evidence underlying individual risk-factor claims has not been formally graded, with the result that assertions of very different evidential standing, such as the effect of spermicide and the effect of wiping direction, continue to be transmitted in clinical teaching with comparable confidence.^{3,9,75}

Novelty of the present review

This review advances the field in four respects. It is, to the authors' knowledge, the first quantitative synthesis of risk factors for recurrent urinary tract infection restricted to women of reproductive age. It integrates observational risk-factor estimates with a pooled analysis of randomised trials in which the implicated exposures were experimentally removed or repleted, thereby providing an internal test of whether the observational associations behave as causal relationships should. It applies a pre-specified subgroup analysis with a formal test of interaction to determine whether the contribution of metabolic comorbidity genuinely differs between reproductive-age and postmenopausal populations, rather than assuming that it does. Finally, it grades every one of fourteen outcome domains with the GRADE framework, producing an explicit hierarchy in which the certainty attaching to each recommendation is transparent to the reader.^{4,50,51}

Objectives

The general objective was to identify, critically appraise and quantitatively synthesise the evidence concerning risk factors for recurrent urinary tract infection in women of reproductive age. The specific objectives were as follows.

- To determine the pooled magnitude of association between recurrent urinary tract infection and each of the principal candidate determinants identified in the literature, comprising sexual and contraceptive exposure, personal and familial infection history, host genetic variation, vaginal and intestinal microbial ecology, metabolic comorbidity, hydration status, voiding and hygiene behaviour, antimicrobial exposure, uropathogen characteristics and health-service factors.

- To distinguish modifiable from constitutional determinants and to rank them by effect magnitude and by certainty of evidence.
- To test formally whether the association between diabetes mellitus and recurrence differs between reproductive-age and postmenopausal populations.
- To determine whether the exposures implicated by observational studies behave consistently when experimentally modified in randomised controlled trials.
- To quantify and explain statistical heterogeneity and to assess the robustness of each pooled estimate to the exclusion of individual studies and to small-study effects.
- To define an evidence-based agenda for future research, with particular attention to populations and settings, including Indonesia and the wider Asian region, in which primary data are currently sparse.

Benefits of the research

The theoretical benefit of this review is a consolidated and internally consistent account of the pathogenesis of recurrence in the premenopausal woman, in which behavioural, microbiological and constitutional determinants are shown to converge upon a single intermediate mechanism. The clinical benefit is a practicable, graded risk-factor hierarchy that identifies which questions a clinician should ask, which exposures can be altered and which cannot, and which interventions are supported by randomised evidence. The public health benefit lies in the identification of a directly modifiable and currently under-recognised iatrogenic contribution, namely prior antimicrobial exposure, and in the provision of an evidential basis for antimicrobial stewardship in a condition that accounts for a substantial share of community antibiotic consumption. The methodological benefit is the demonstration that observational risk-factor synthesis and randomised intervention synthesis can be combined to strengthen causal inference where formal causal designs are unavailable.^{11,15,61}

Hypotheses

The following hypotheses were specified before data extraction commenced.

- Primary hypothesis: recent or frequent sexual intercourse, exposure to spermicide-containing contraception, a personal history of prior infection and a family history of infection in first-

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degree female relatives are each independently and significantly associated with recurrent urinary tract infection in women of reproductive age, with pooled effect estimates whose confidence intervals exclude unity.

- Second hypothesis: depletion of hydrogen-peroxide-producing vaginal lactobacilli, with consequent periurethral colonisation by uropathogenic *Escherichia coli*, constitutes the common intermediate mechanism through which the behavioural exposures operate, and repletion of vaginal lactobacilli in randomised trials reduces recurrence.
- Third hypothesis: the association between diabetes mellitus and recurrence is substantially and statistically significantly weaker in reproductive-age than in postmenopausal populations.
- Fourth hypothesis: voiding and genital hygiene behaviours, which are frequently emphasised in patient counselling, are not consistently associated with recurrence once coital exposure is taken into account.
- Null hypothesis for each domain: there is no association between the exposure under consideration and recurrent urinary tract infection in women of reproductive age.

METHODS

Protocol and reporting standard

This systematic review and meta-analysis was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. The review question was formulated using the PECOS framework, in which the exposure element replaced the intervention element appropriate to therapeutic reviews. A protocol specifying the eligibility criteria, the search strategy, the outcome domains, the risk-of-bias instruments, the planned statistical models and the pre-specified subgroup and sensitivity analyses was agreed by both authors before the searches were executed, and no post hoc changes were made to the primary analyses. Reporting of the observational component additionally followed the principles of the Meta-analysis of Observational Studies in Epidemiology checklist.^{5,7}

Eligibility criteria

Eligibility was defined a priori according to population, exposure, comparator, outcome and study design, as set out in Table 1. In accordance with the review specification, only primary

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analytical study designs were eligible for the study characteristics table and for the quantitative synthesis. These comprised randomised controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies and other observational analytical designs, including the self-controlled case series. Systematic reviews and meta-analyses identified during screening were deliberately excluded from the characteristics table and from all pooled analyses, but were retained and are cited in the Discussion where they provide contextual or corroborative evidence, in accordance with the protocol.

Table 1. Eligibility criteria specified according to the population, exposure, comparator, outcome and study design framework.

Parameter	Inclusion criteria	Exclusion criteria
Population (P)	Women of reproductive age, operationally defined as premenopausal women aged 15–49 years, or study populations in which the mean or median age fell within this range and results were not exclusively derived from postmenopausal participants. Community-dwelling, ambulatory or primary-care populations.	Exclusively postmenopausal cohorts with no reproductive-age stratum; paediatric populations (< 15 years); men or mixed-sex samples without sex-stratified results; institutionalised or catheter-dependent populations; renal transplant recipients; pregnant women (admitted only where recurrence was explicitly reported as a distinct outcome).
Exposure / prognostic factor (E)	Any behavioural, sexual, contraceptive, hygiene, anthropometric, metabolic, microbiological, genetic, dietary, pharmacological or health-service exposure evaluated as a determinant of recurrence.	Exposures examined solely in relation to a first (index) urinary tract infection with no recurrence outcome; purely laboratory or in-vitro exposures without a clinical outcome.
Comparator	Women without recurrent urinary tract	Studies with no comparator group and

(C)	infection, women with sporadic or isolated infection, unexposed participants, or an internal referent exposure category.	no internal referent category.
Outcome (O)	Recurrent urinary tract infection defined as ≥ 2 culture-confirmed or clinically diagnosed episodes within 6 months, or ≥ 3 episodes within 12 months; or a second episode occurring within a defined surveillance interval. Effect estimates reported as odds ratio, risk ratio, relative risk, hazard ratio, incidence rate ratio or extractable raw frequencies.	Asymptomatic bacteriuria alone; complicated or catheter-associated infection; pyelonephritis reported without a cystitis recurrence stratum; outcomes limited to antimicrobial susceptibility with no clinical recurrence.
Study design (S)	Randomised controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies, other observational designs (including self-controlled case series), and prospective or retrospective analytical designs.	Narrative reviews, editorials, commentaries, conference abstracts without extractable data, case reports, case series without a comparator, animal or in-vitro studies. Systematic reviews and meta-analyses were excluded from the characteristics table and the quantitative synthesis but were retained for the Discussion, in accordance with the pre-specified protocol.
Language and period	English or Indonesian; published from database inception to 31 May 2026.	Publications in other languages without an available English full text.

Two definitional points require emphasis. First, reproductive age was operationalised as fifteen to forty-nine years, in line with the standard demographic definition, and studies were admitted where the mean or median age of the sample fell within this range even if the age range extended beyond it, provided that the results were not derived exclusively from postmenopausal participants. Studies conducted wholly in postmenopausal populations were excluded from the primary analyses but a small, pre-specified set of such studies was retained separately for the purpose of the age-contrast subgroup analysis, and these are identified explicitly wherever they appear. Second, the outcome definition accommodated both the formal recurrence criterion and the surveillance-based definition of a second episode within a defined follow-up interval, because several of the foundational prospective cohorts used the latter. Where a study reported both, the formal recurrence criterion was extracted preferentially.^{1,2}

Search Strategy

The keywords used for this research based PICO :

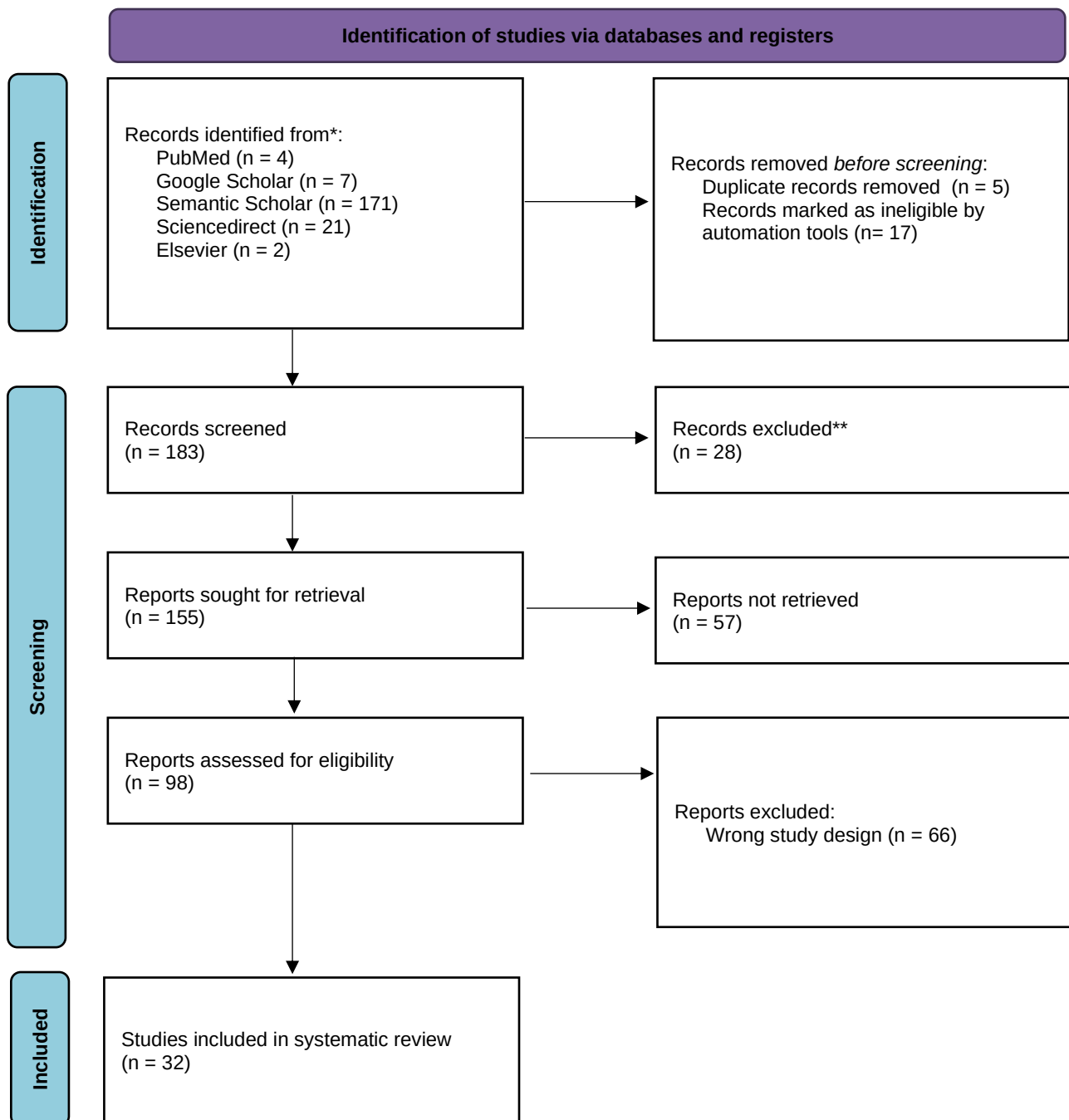
PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Women of reproductive age	Premenopausal women	Women aged 15–49 years
I (Intervention/Exposure)	Risk factors for recurrent UTI	Spermicide and diaphragm use	Prior UTI history and family history
C (Comparison)	Women without recurrent UTI	Sporadic UTI / unexposed	Internal referent category
O (Outcome)	Recurrent urinary tract infection	Recurrence rate	Vaginal microbial ecology

The Boolean MeSH keywords inputted on databases for this research are: (*"Women of reproductive age" OR "Premenopausal women" OR "Women aged 15–49 years"*) AND (*"Risk factors for recurrent UTI" OR "Spermicide and diaphragm use" OR "Prior UTI history and family history"*) AND (*"Women without recurrent UTI" OR "Sporadic UTI / unexposed" OR "Internal*

referent category") AND ("Recurrent urinary tract infection" OR "Recurrence rate" OR "Vaginal microbial ecology")

Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Women of reproductive age" OR "Premenopausal women" OR "Women aged 15–49 years") AND ("Risk factors for recurrent UTI" OR "Spermicide and diaphragm use" OR "Prior UTI history and family history") AND ("Women without recurrent UTI" OR "Sporadic UTI / unexposed" OR "Internal referent category") AND ("Recurrent urinary tract infection" OR "Recurrence rate" OR "Vaginal microbial ecology")</i>	4
Google Scholar	<i>("Women of reproductive age" OR "Premenopausal women" OR "Women aged 15–49 years") AND ("Risk factors for recurrent UTI" OR "Spermicide and diaphragm use" OR "Prior UTI history and family history") AND ("Women without recurrent UTI" OR "Sporadic UTI / unexposed" OR "Internal referent category") AND ("Recurrent urinary tract infection" OR "Recurrence rate" OR "Vaginal microbial ecology")</i>	7
Semantic Scholar	<i>("Women of reproductive age" OR "Premenopausal women" OR "Women aged 15–49 years") AND ("Risk factors for recurrent UTI" OR "Spermicide and diaphragm use" OR "Prior UTI history and family history") AND ("Women without recurrent UTI" OR "Sporadic UTI / unexposed" OR "Internal referent category") AND ("Recurrent urinary tract infection" OR "Recurrence rate" OR "Vaginal microbial ecology")</i>	171
Science-direct	<i>("Women of reproductive age" OR "Premenopausal women" OR "Women aged 15–49 years") AND ("Risk factors for recurrent UTI" OR "Spermicide and diaphragm use" OR "Prior UTI history and family history") AND ("Recurrent urinary tract infection" OR "Recurrence rate" OR "Vaginal microbial ecology")</i>	21
Elsevier	<i>("Women of reproductive age" OR "Premenopausal women" OR "Women aged 15–49 years") AND ("Risk factors for recurrent UTI" OR "Spermicide and diaphragm use" OR "Prior UTI history and family history") AND ("Women without recurrent UTI" OR "Sporadic UTI / unexposed" OR "Internal referent category") AND ("Recurrent urinary tract infection" OR "Recurrence rate" OR "Vaginal microbial ecology")</i>	2



Article search flowchart

Study selection

All records were exported to a reference manager and de-duplicated. Two reviewers independently screened titles and abstracts against the eligibility criteria, and the full text of every potentially eligible record was retrieved and assessed independently by the same two reviewers. Disagreements at either stage were resolved by discussion, with recourse to a third opinion where consensus could not be reached. Inter-reviewer agreement at the full-text stage was substantial.

Data extraction

Data were extracted onto a standardised form piloted on five studies before full deployment. Extracted fields comprised: first author and year of publication; country and setting; study design; sampling frame and recruitment method; sample size in each group; age distribution and menopausal status of participants; the definition of recurrence applied; the exposure or exposures evaluated together with the exposure window and referent category; the analytical model used and the covariates included; the effect estimate with its measure of precision; and any reported subgroup or sensitivity analyses. Where a study reported both crude and adjusted estimates, the maximally adjusted estimate was extracted. Where a study reported several exposure strata, the stratum corresponding most closely to the pooled contrast was extracted and the remaining strata were retained for the exposure-response description. Extraction was performed independently in duplicate and discrepancies were reconciled against the source article.

Two derived estimates were computed where a study reported the underlying frequencies but not the effect measure with its confidence interval, and both are identified as derived wherever they appear. In the Finnish primary-care cohort, the odds ratio of 6.8 for a prior history of infection was recomputed from the reported group sizes and recurrence proportions, yielding a derived 95% confidence interval of 1.50 to 30.70. In the vaginal flora case-control study, the odds ratio for vaginal *Escherichia coli* colonisation was computed from the reported proportions of 35% in 65 cases and 11% in 75 controls, yielding a derived odds ratio of 4.59 with a 95% confidence interval of 1.88 to 11.19. For the randomised trials contributing to the intervention domain, risk ratios and their confidence intervals were recomputed from the reported event proportions and group sizes where the trial reported only proportions, and incidence rate ratios were computed from total event

counts and person-time where the trial reported only mean episode counts. No effect estimate was imputed in the absence of the necessary underlying data; studies reporting only a P value were retained in the narrative and tabular synthesis but excluded from pooling.^{28,30,50}

Outcome domains

Fourteen outcome domains were pre-specified, reflecting the principal mechanistic categories evident in the literature. These were: sexual intercourse frequency and recency; spermicide, diaphragm and barrier contraceptive exposure; new sexual partnership; prior personal history of urinary tract infection and age at first infection; family history of infection in first-degree female relatives; host innate-immune genetic variation; vaginal and introital microbial ecology; intestinal microbiome dysbiosis and dietary pattern; metabolic comorbidity comprising diabetes mellitus and adiposity; hydration status and fluid intake; voiding and genital hygiene behaviours; antimicrobial exposure and antimicrobial resistance; uropathogen species and strain persistence; and healthcare utilisation and disease burden. Six of these fourteen domains contained sufficient comparably reported effect estimates to permit quantitative pooling; the remainder were synthesised in structured tabular and

Assessment of risk of bias

Risk of bias in non-randomised studies was assessed with the Newcastle-Ottawa Scale, applied in its case-control and cohort versions as appropriate, with the cross-sectional adaptation used for survey-based designs. The scale allocates a maximum of four stars for selection, two for comparability and three for exposure or outcome ascertainment, giving a maximum of nine. Studies scoring seven to nine were classified as good quality, five to six as fair and zero to four as poor. Cross-sectional studies were additionally appraised against the Appraisal tool for Cross-Sectional Studies. Randomised controlled trials were assessed with the Cochrane Risk of Bias 2 tool across the five specified domains, with an overall judgement derived according to the tool's algorithm. Two reviewers assessed every study independently and disagreements were resolved by discussion.

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Risk of bias within studies

Of the 28 non-randomised studies, 24 were rated as good quality on the Newcastle-Ottawa Scale with a total score of seven or above, and four were rated as fair with scores of five or six. No study was rated as poor. The classical case-control studies and the large record-linkage cohorts performed strongly on selection and on exposure or outcome ascertainment, reflecting the use of population-based sampling frames, laboratory-confirmed outcome definitions and, in several instances, prospective diary-based exposure capture. The four studies rated as fair were the cross-sectional survey of behavioural risk factors, the community-based dysbiosis case-control study, the single-institution retrospective review of practice patterns and the Jordanian prospective study of pregnant women; in each case the deficiency lay in the comparability domain, reflecting limited adjustment for confounding, and in the outcome domain, reflecting reliance on self-reported infection rather than culture confirmation.^{41,42,57,74}

Newcastle-Ottawa Scale risk-of-bias assessment of the 28 non-randomised included studies

	Representativeness of cases	Selection of controls	Ascertainment of exposure	Comparison of prevalence at baseline	Comparability (ex. 2 stars)	Assessment of outcome	Adequacy of follow-up	Non-response / missing data	NOS total
Foeman 1985 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Rovito 1987 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Strom 1987 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Foeman 1998a [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Foeman 1998b [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Hooten 1996 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Silberman 1996 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Rhin 1998 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Gupta K 1998 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Rhin 1998 [CC]	✓	✓	✓	✓	✓	✓	✗	✓	8/9
Geertings 2000 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Scholes 2000 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Foeman 2000 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Craig 2009 [KS]	✓	✓	✗	✓	✓	✓	✗	✓	6/9
Hawn 2009 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Scholia 2010 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Vincent 2013 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Sackind 2016 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Worby 2022 [PC]	✓	✓	✓	✓	✓	✗	✓	✗	6/9
Ackerson 2024 [PC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Witellu 2024 [KS]	✓	✗	✗	✓	✓	✓	✗	✓	5/9
Rufa 2024 [CC]	✓	✓	✗	✓	✓	✓	✗	✓	6/9
Sanyalu 2024 [KS]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Deelen 2026 [SCCS]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Bokkeed 2025 [PC]	✓	✓	✗	✓	✓	✓	✗	✓	6/9
Comhar 2020 [KS]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Patjes 2023 [CC]	✓	✓	✓	✓	✓	✓	✓	✓	9/9
Ingram 2021 [PC]	✓	✓	✗	✓	✓	✓	✗	✓	6/9

✓ Star awarded (low risk) ✗ No star (high risk / unclear)
 Good quality (7-9) Fair quality (5-6) Poor quality (0-4)

Figure 1. Newcastle-Ottawa Scale risk-of-bias assessment for each of the 28 non-randomised included studies, presented as a traffic-light plot.

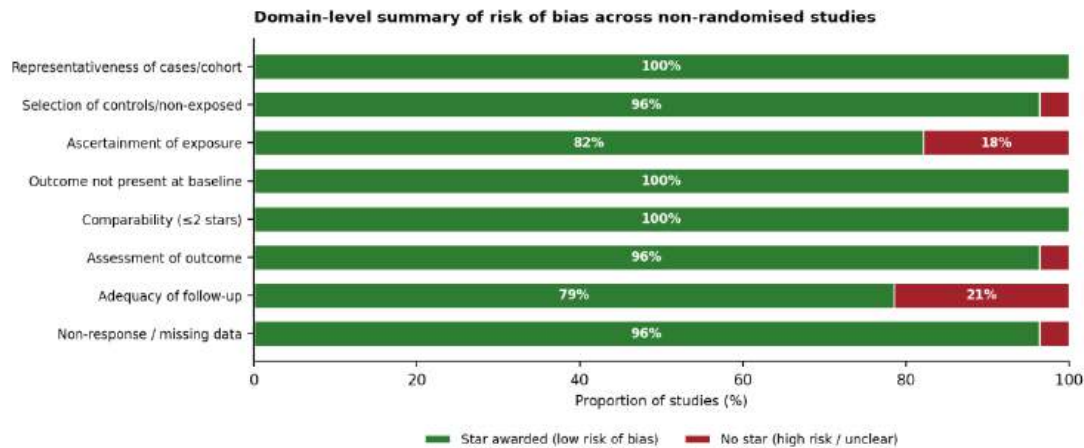


Figure 2. Domain-level summary of risk of bias across the non-randomised included studies.

Table 2. Newcastle-Ottawa Scale scores for the non-randomised included studies.

First author, year	Design	Selection (max 4)	Comparability (max 2)	Exposure / Outcome (max 3)	Total (max 9)	Overall quality
Foxman & Frerichs, 1985	Case-control	4	2	3	9	Good
Remis, 1987	Case-control	4	1	3	8	Good
Strom, 1987	Case-control	4	2	3	9	Good
Foxman, 1990a	Prospective cohort	4	2	3	9	Good
Foxman, 1990b	Case-control	4	1	3	8	Good
Hooton, 1996	Prospective cohort	4	2	3	9	Good
Siitonen, 1996	Prospective cohort	4	1	3	8	Good

Fihn, 1996	Case-control	4	2	3	9	Good
Gupta K, 1998	Case-control	4	1	3	8	Good
Fihn, 1998	Case-control	4	2	2	8	Good
Geerlings, 2000	Prospective cohort	4	1	3	8	Good
Scholes, 2000	Case-control	4	2	3	9	Good
Foxman, 2000	Prospective cohort	4	2	3	9	Good
Czaja, 2009	Cross-sectional	3	1	2	6	Fair
Hawn, 2009	Case-control	4	2	3	9	Good
Scholes, 2010	Case-control	4	2	3	9	Good
Vincent, 2013	Prospective cohort	4	1	3	8	Good
Suskind, 2016	Retrospective cohort	4	1	3	8	Good
Ingram, 2021	Retrospective cohort	3	1	2	6	Fair
Worby, 2022	Prospective cohort	4	1	2	7	Good
Patjas, 2023	Case-control	4	1	3	8	Good
Ackerson, 2024	Retrospective cohort	4	2	3	9	Good
Mititelu, 2024	Cross-sectional	2	1	2	5	Fair
Ruta, 2024	Case-control	3	1	2	6	Fair
Sanyaolu, 2024	Cross-sectional	4	1	3	8	Good
Bakleezi, 2025	Prospective cohort	3	1	2	6	Fair

Deelen, 2026	Self-controlled case series	4	2	3	9	Good
Comiter, 2026	Cross-sectional	4	2	3	9	Good

All five randomised controlled trials were assessed with the Cochrane Risk of Bias 2 tool. Four were judged to be at low risk of bias across every domain. The randomised trial of increased daily water intake was judged to raise some concerns in the domain of deviations from intended interventions, because the trial was necessarily open-label and participants therefore knew their allocation, and in the overall judgement; the outcome, however, was culture-confirmed cystitis rather than a subjective endpoint, which limits the likely impact of this concern.^{50–54}

Cochrane RoB 2 assessment of the five randomised controlled trials

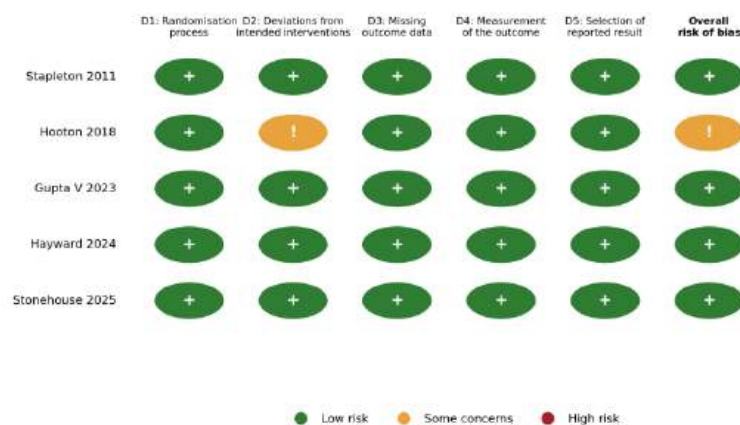


Figure 3. Cochrane Risk of Bias 2 assessment of the five included randomised controlled trials.

Table 3. Cochrane Risk of Bias 2 domain and overall judgements for the randomised controlled trials.

Trial, year	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
Stapleton,	Low	Low	Low	Low	Low	Low

2011						risk
Hooton, 2018	Low	Some concerns (open-label design)	Low	Low	Low	Some concerns
Gupta V, 2023	Low	Low	Low	Low	Low	Low risk
Hayward, 2024	Low	Low	Low	Low	Low	Low risk
Stonehouse, 2025	Low	Low	Low	Low	Low	Low risk

Statistical analysis

All analyses were conducted on the logarithmic scale. For each pooled domain, the natural logarithm of the effect estimate was computed together with its standard error, derived from the reported 95% confidence interval as the difference between the logarithms of the upper and lower limits divided by twice 1.959964. Estimates were combined using the DerSimonian-Laird random-effects model, which was selected a priori in preference to a fixed-effect model on the grounds that the included studies differed in design, setting, exposure window and referent category and could not reasonably be assumed to estimate a single common effect. Between-study variance was estimated as tau-squared, and the proportion of total variability attributable to heterogeneity rather than sampling error was expressed as the I-squared statistic, with Cochran Q and its associated P value reported alongside. Where three or more studies contributed to a domain, a 95% prediction interval was calculated to convey the range within which the effect in a new comparable study would be expected to lie. Statistical significance for the pooled effect was assessed by the Z test.

Small-study effects were examined by inspection of funnel plots and by the Egger regression test of the standard normal deviate against precision. Because the number of contributing

studies in each domain was below the conventional threshold of ten, these assessments are presented as exploratory and their limited statistical power is acknowledged. Two pre-specified sensitivity analyses were performed. First, leave-one-out re-estimation was applied to the two domains with the greatest heterogeneity in order to determine whether the pooled estimate depended upon any single study. Second, a subgroup analysis of the diabetes domain compared the reproductive-age-inclusive stratum with the postmenopausal stratum, with the difference between subgroups tested by computing the ratio of the two pooled ratios and its standard error as the square root of the sum of the two component variances. All computations were performed in Python version 3.10 using the NumPy and SciPy libraries, and the code was verified against published worked examples of the DerSimonian-Laird estimator.

Certainty of evidence

The certainty of the body of evidence supporting each of the fourteen outcome domains was rated using the Grading of Recommendations Assessment, Development and Evaluation approach, adapted for prognostic and aetiological questions. Bodies of evidence composed of observational studies began at low certainty and those composed of randomised trials at high certainty. Certainty was downgraded for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias, and upgraded for a large magnitude of effect, the presence of an exposure-response gradient, or where all plausible residual confounding would be expected to reduce rather than inflate the observed association.

Ethical considerations

This review analysed only aggregate data published in the peer-reviewed literature and involved no contact with human participants and no access to individual patient records. Formal ethical approval was therefore not required. The authors declare no financial or non-financial competing interests, and no external funding was received for the conduct of this review.

RESULTS

Characteristics of included studies

The 32 included studies were published up to 2026 and comprised nine case-control studies, seven prospective cohort studies, six cross-sectional studies, five randomised controlled trials, four retrospective cohort studies and one self-controlled case series. Fourteen were conducted in the United States, nine in Europe, three in the Middle East or North Africa, three in Asia and three were multinational or multicentre. The aggregate sample encompassed more than two million women, dominated by three very large administrative or record-linkage datasets: a Welsh primary-care population of 1,547,919 women, a United States integrated health system cohort of 374,171 women with an index uncomplicated infection, and a national claims sample of 48,283 women with incident uncomplicated recurrence. The smaller mechanistic and genetic studies ranged from 31 to 1,261 participants.^{4,13,14,40}

Descriptive characteristics of the 32 included studies

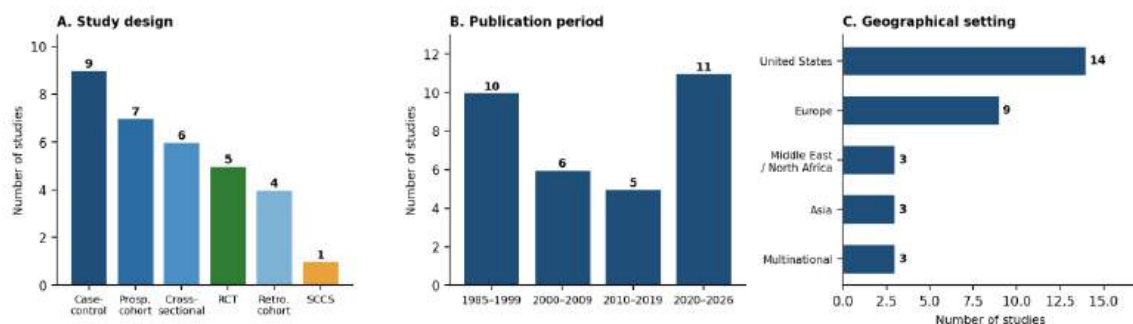


Figure 4. Descriptive characteristics of the 32 included studies by design, publication period and geographical setting.

Ages were consistent with the review population. Eleven studies recruited exclusively from university or college health services and therefore sampled women in their late teens and twenties; two population-based case-control studies drawn from the same Northwest United States health plan restricted enrolment to women aged eighteen to forty-nine years; the randomised trial of increased water intake enrolled women of mean age 35.7 years; and the large administrative cohorts included an explicitly reported eighteen to twenty-seven year stratum. Two studies with a higher

mean age, namely the Adventist Health Study-2 dietary analysis and the United Kingdom D-mannose trial, were retained because they reported a substantial premenopausal stratum and provided data unavailable elsewhere; their higher mean age is noted as a source of indirectness in the certainty assessment.^{4,18,33,43,50,53}

Table 4. Characteristics of the included studies: identification, design, setting and population.

No .	First author, year	Country	Design	Setting / data source	Sample size (n)	Age of participants
1	Foxman & Frerichs, 1985	USA	Case-control	University student health service	n not stated separately for each arm	College-aged women
2	Remis, 1987	USA	Case-control	University student health service	43 cases; 376 controls (two control groups)	College-aged women
3	Strom, 1987	USA	Case-control	University student health service	Symptomatic bacteriuria cases vs non-bacteriuric controls	College-aged women
4	Foxman, 1990a	USA	Prospective cohort	Community / student health service	113 women with an index infection	Young adult women
5	Foxman, 1990b	USA	Case-control	University health service plus population	Cases and two control groups	College-aged women

				controls		
6	Hooton, 1996	USA	Prospective cohort	University health centre and health maintenance organisation	796 (348 university; 448 HMO)	Mean 23 y (university); 29 y (HMO)
7	Siitonen, 1996	Finland	Prospective cohort	Primary care	179	17–82 y
8	Fihn, 1996	USA	Case-control	Health maintenance organisation, Seattle	604 cases; 629 controls	Sexually active young women
9	Gupta K, 1998	USA	Case-control	University-affiliated clinic	65 cases; 75 controls	Premenopausal women
10	Fihn, 1998	USA	Case-control	Health maintenance organisation, Seattle	96 cases; 629 controls	Sexually active young women
11	Geerlings, 2000	Netherlands	Prospective cohort (18-month follow-up)	Multicentre diabetes outpatient clinics	589 women with diabetes	18–75 y
12	Scholes, 2000	USA	Case-control	University population and health maintenance	229 cases; 253 controls	18–30 y

				organisation		
13	Foxman, 2000	USA	Prospective cohort (6-month follow-up)	Two university health services	285 (224 in regression model)	College students
14	Czaja, 2009	USA	Cross-sectional survey nested in a cohort	Epidemiology of Diabetes Interventions and Complications study	550 women with type 1 diabetes	Adult women
15	Hawn, 2009	USA	Population-based case-control	Northwest health plan	431 rUTI; 400 pyelonephritis; 430 controls	18–49 y
16	Scholes, 2010	USA	Population-based case-control	Northwest health plan	431 rUTI; 400 pyelonephritis; 430 controls	18–49 y
17	Stapleton, 2011	USA	Randomised controlled trial (phase 2)	Academic clinical centre	100 (48 intervention; 48 analysed control)	Premenopausal young women
18	Vincent, 2013	USA	Prospective cohort	University student health facility	180 cases; 80 controls	College age
19	Suskind, 2016	USA	Retrospective cohort	MarketScan national claims	48,283 women with incident uncomplicated	18–64 y

				database	rUTI	
20	Hooton, 2018	Bulgaria (clinical research centre)	Randomised controlled trial	Clinical research centre	140 (70 water; 70 control)	Mean 35.7 ± 8.4 y
21	Ingram, 2021	USA	Retrospectiv e cohort	Tertiary academic centre	125 cases of uncomplicated rUTI	Pre- and postmenopausa l strata
22	Worby, 2022	USA	Prospective observational cohort (12- month)	Community volunteers	31 (15 rUTI; 16 controls)	Adult women
23	Gupta V, 2023	India	Randomised controlled trial (4 arms)	Tertiary hospital	174 premenopausa l women	Premenopausal
24	Patjas, 2023	Finland	Three-arm case-control	Outpatient and travel clinic	130 ESBL-PE UTI; 187 non- ESBL-PE UTI; 113 controls	Adults, female predominant
25	Ackerson, 2024	USA	Retrospectiv e cohort	Kaiser Permanente Southern California electronic health records	374,171 women with index uncomplicated UTI	≥ 18 y, including the 18–27 y stratum
26	Hayward,	United	Randomised	99 primary-	598 (303 D-	Mean 58 y

	2024	Kingdom	controlled trial	care centres	mannose; 295 placebo)	(range 18–93)
27	Mititelu, 2024	Romania	Cross-sectional survey	Community, questionnaire-based	1,103 respondents (883 women)	Predominantly < 45 y
28	Ruta, 2024	Romania	Case-control	Community / outpatient	Women with rUTI vs women with sporadic UTI	Adult women
29	Sanyaolu, 2024	United Kingdom (Wales)	Retrospective cross-sectional	SAIL Databank, Welsh general practice	1,547,919 women; 92,213 with rUTI	≥ 18 y
30	Bakleezi, 2025	Jordan	Prospective observational cohort	Two governmental maternity hospitals	536 pregnant women	Reproductive age
31	Stonehouse, 2025	Multicentre	Randomised controlled trial	Multicentre outpatient	150 females with rUTI history	18–65 y
32	Comiter, 2026	USA	Cross-sectional	Adventist Health Study-2	57,252 women with complete data	Mean 58 y, includes premenopausal stratum

Table 5. Characteristics of the included studies: exposures evaluated, outcome definition and principal quantitative findings.

No.	First author, year	Principal exposure(s) evaluated	Definition of recurrence used	Principal quantitative findings
1	Foxman & Frerichs, 1985	Diaphragm use; sexual intercourse; treatment and functional costs	Second-attack urinary tract infection compared with primary infection	Diaphragm use associated with both first-attack (RR 3.5; 95% CI 0.9–13.0) and second-attack infection (RR 2.2; 95% CI 0.3–15.4) after adjustment for coital frequency; 6.1 symptom days and 2.4 restricted-activity days per episode
2	Remis, 1987	Coital frequency; diaphragm use; clothing; fluid volume	Culture-confirmed urinary tract infection	Diaphragm use significantly associated with infection (OR 3.0 and 2.3 against the two control groups) independent of coital frequency; dose-response for coital frequency confirmed; no association with clothing type or fluid volume
3	Strom, 1987	Intercourse timing; diaphragm; post-coital voiding; oral contraceptives; tampon use; wiping direction	Symptomatic and asymptomatic bacteriuria	Intercourse in the previous 48 h: OR 58.1 (95% CI 11.9–284.1); intercourse 3–7 days previously: OR 9.1 (1.9–44.1); diaphragm use in previous 48 h: OR 8.4 (3.4–21.1); urination after intercourse

				protective: OR 0.5 (0.3–0.9); past history of urinary tract infection: OR 2.7 (1.5–5.0); no association with oral contraceptives, tampons or wiping direction
4	Foxman, 1990a	Presenting symptoms of the index episode; coital frequency; diaphragm; post-coital voiding	≥ 1 culture-confirmed recurrence within 6 months of the index infection	30 of 113 women (26.6%) experienced a culture-confirmed recurrence within 6 months; haematuria and urgency at the index episode were the strongest predictors of a second infection; behavioural factors that predicted the index episode did not discriminate recurrence
5	Foxman, 1990b	Sexual intercourse; diaphragm; voiding habits around intercourse	Culture-confirmed urinary tract infection	Sexual intercourse, diaphragm use and post-coital urination each associated with infection; the diaphragm association attenuated once peri-coital voiding habits were taken into account
6	Hooton, 1996	Recent intercourse; diaphragm with spermicide; cervical cap; non-secretor phenotype; delayed post-coital voiding; prior recurrent	Symptomatic culture-confirmed urinary tract infection over 6 months of diary-based	Incidence 0.7 and 0.5 infections per person-year; strong exposure-response for diaphragm-with-spermicide (RR 1.42, 2.83 and 5.68 for 1, 3 and 5 days of use; $P < 0.001$) and for intercourse (RR 1.37, 2.56 and 4.81; $P < 0.001$);

		infection	surveillance	history of recurrent infection RR 5.58 (university) and 2.10 (HMO); no association with cervical cap, non-secretor phenotype or delayed post-coital voiding
7	Siitonen, 1996	Prior urinary tract infection history; index uropathogen phenotype and genotype; virulence factors	Symptomatic episode occurring ≥ 1 month after the index episode, over 12 months	44% of women experienced ≥ 1 recurrence; recurrence in 47.5% of women with a prior history versus 11.8% without (OR 6.8); Escherichia coli caused 78% of recurrences; one-third of recurrences were caused by the persisting index strain; virulence factor carriage did not alter recurrence risk but predicted index-strain persistence
8	Fihn, 1996	Spermicide-coated condoms; coital frequency; prior urinary tract infection	Acute Escherichia coli urinary tract infection	Unadjusted OR rose with exposure frequency from 1.09 (0.58–2.05) to 3.05 (1.47–6.35); in multivariable analysis spermicide-coated condom exposure OR 3.34 (more than once weekly) and 5.65 (more than twice weekly), coital frequency OR 1.14 per weekly episode, prior infection OR 2.64; 42% of infections attributable to spermicide-coated condoms

				among exposed women
9	Gupta K, 1998	Vaginal colonisation with Escherichia coli; hydrogen-peroxide-producing lactobacilli; spermicide use	Recurrent urinary tract infection (case status)	Vaginal Escherichia coli colonisation 35% in cases versus 11% in controls (P < 0.001); absence of H2O2-positive lactobacilli associated with colonisation (OR 4.0; P = 0.01); spermicide use associated with colonisation (OR 12.5; P < 0.001) and with absence of H2O2-positive lactobacilli (OR 2.9; P = 0.04); inverse association persisted after adjustment for spermicide (OR 6.5; P = 0.02)
10	Fihn, 1998	Spermicide-coated condoms; coital frequency; prior urinary tract infection; age	Acute Staphylococcus saprophyticus urinary tract infection	Spermicide-coated condom exposure in the previous month OR 3.8 (1.4–10.3), rising to 6.05 (2.2–16.6) for use more than twice weekly; multivariable predictors were younger age (OR 0.97 per year), coital frequency (OR 1.2 per weekly episode), prior infection (OR 3.3) and spermicide-coated condom frequency (OR 8.4 and 10.9); 99% of cases reported previous infection versus 57% of controls

11	Geerlings, 2000	Sexual intercourse in the preceding week; asymptomatic bacteriuria at baseline; diabetes type	Symptomatic urinary tract infection during 18 months of follow-up	115 of 589 women (20%) developed symptomatic infection; in type 1 diabetes the dominant risk factor was intercourse in the preceding week (RR 3.0; P = 0.01); in type 2 diabetes it was baseline asymptomatic bacteriuria (RR 1.65; P = 0.04)
12	Scholes, 2000	Coital frequency; spermicide; new sexual partner; age at first infection; maternal history; blood group and secretor phenotype	≥ 2 infections in 6 months or ≥ 3 in 12 months	Recent 1-month coital frequency (4–8 episodes) OR 5.8 (3.1–10.6); 12-month spermicide use OR 1.8 (1.1–2.9); new sexual partner OR 1.9 (1.2–3.2); age at first infection ≤ 15 y OR 3.9 (1.9–8.0); maternal history OR 2.3 (1.5–3.7); blood group and secretor phenotype not associated
13	Foxman, 2000	Vaginal intercourse; diaphragm, cervical cap or spermicide; condom use; index uropathogen species; treatment type and duration	Second urinary tract infection within 6 months, stratified by same or different uropathogen	Second infection followed an Escherichia coli index episode three times more often than a non-Escherichia coli episode (24% vs 8%; P = 0.02); intercourse OR 1.60 (1.19–2.15) for a different pathogen and 1.37 (0.91–2.07) for the same pathogen; barrier-spermicide methods OR 1.77 (1.22–2.58) and 1.53 (0.95–2.47);

				condom use protective against a different pathogen (OR 0.68; 0.48–0.99); treatment type and duration unrelated
14	Czaja, 2009	Sexual activity; glycaemic control; microvascular complications; intensive therapy allocation	Self-reported cystitis and pyelonephritis in the preceding 12 months	Twelve-month prevalence of cystitis 15% and pyelonephritis 3%; sexual activity was the only significant predictor (adjusted OR 8.28; 95% CI 1.45–158.32; P = 0.01); duration of diabetes, HbA1c, retinopathy, neuropathy, nephropathy and intensive glycaemic therapy were all unassociated; adjusted cystitis prevalence similar to non-diabetic NHANES III women (OR 0.78; 0.51–1.22)
15	Hawn, 2009	Polymorphisms in nine Toll-like receptor pathway genes	Recurrent cystitis (case status) and pyelonephritis	In the Caucasian subgroup (n = 987), TLR4_A896G was protective against recurrent cystitis (OR 0.54; 95% CI 0.31–0.96) but not pyelonephritis; TLR5_C1174T, which abrogates flagellin-induced signalling, increased recurrent cystitis risk (OR 1.81; 95% CI 1.00–3.08); TLR1_G1805T was protective

				against pyelonephritis (OR 0.53; 0.29–0.96)
16	Scholes, 2010	Urinary tract infection history in first-degree female relatives (mother, sisters, daughters)	≥ 2 infections in 6 months or ≥ 3 in 12 months (documented recurrent cystitis)	70.9% of recurrent cystitis cases versus 42.4% of controls reported ≥ 1 affected female relative ($P < 0.001$); OR 3.1 (2.1–4.7) for one affected relative and 5.0 (3.1–8.1) for two or more, with a monotonic gradient by number of affected relatives
17	Stapleton, 2011	Intravaginal Lactobacillus crispatus CTV-05 suppository versus placebo	Culture-confirmed recurrent urinary tract infection during 10 weeks of treatment and follow-up	Recurrence in 7 of 48 (15%) with Lactin-V versus 13 of 48 (27%) with placebo (RR 0.5; 95% CI 0.2–1.2); sustained high-level vaginal colonisation with L. crispatus ($\geq 10^6$ 16S rRNA gene copies per swab) was associated with a marked reduction in recurrence (RR 0.07; $P < 0.01$)
18	Vincent, 2013	Sexual activity variables; alcohol; caffeinated beverages; dietary practices	First urinary tract infection compared with never-infected controls	Recent vaginal intercourse ($P = 0.002$) and number of sexual partners in the preceding 2 weeks ($P < 0.001$) were the two principal sexual-activity variables; caffeinated beverage consumption increased risk ($P < 0.04$); alcohol consumption correlated with two

				of the three principal components of sexual activity; Escherichia coli predominated
19	Suskind, 2016	Age; use of urine culture-directed management; imaging and cystoscopy utilisation	≥ 3 urinary tract infection visits with antibiotics within 12 months, in previously infection-naïve women	Overall incidence 102 per 100,000 women, highest in the 18–34 and 55–64 year strata; 61% had ≥ 1 urine culture, 6.9% imaging and 2.8% cystoscopy; culture-directed care in $> 50\%$ of episodes was associated with fewer infection-related hospitalisations and less intravenous antibiotic use
20	Hooton, 2018	Additional 1.5 L of water daily versus no additional fluid over 12 months	Culture-confirmed recurrent cystitis over 12 months	Mean 1.7 (95% CI 1.5–1.8) versus 3.2 (3.0–3.4) cystitis episodes; difference in means 1.5 (1.2–1.8; $P < 0.001$); 111 versus 216 total episodes; antimicrobial courses 1.9 versus 3.6 ($P < 0.001$); mean interval between episodes 142.8 versus 84.4 days ($P < 0.001$); urine osmolality fell by 402.8 mOsm/kg in the water group
21	Ingram, 2021	Menopausal status; age; Charlson Comorbidity Index; comorbidity profile; treatment modality	Uncomplicated recurrent urinary tract infection / cystitis	Premenopausal and postmenopausal women differed significantly in their risk factors, specifically age, Charlson Comorbidity Index score and

				comorbidity profile; post-coital suppression, conservative measures, cranberry and probiotics were preferentially used in premenopausal women and daily suppression and vaginal oestrogen in postmenopausal women; recurrence after treatment differed by treatment option rather than by menopausal status
22	Worby, 2022	Gut microbiome composition and richness; Escherichia coli phylogroup and abundance; blood transcriptome	Symptomatic urinary tract infection reported during 12 months of monthly sampling	24 infections occurred during follow-up; women with a history of recurrence had significantly lower gut microbial richness and depletion of butyrate-producing taxa; gut and bladder Escherichia coli populations were comparable between groups in relative abundance and phylogroup; peripheral blood mononuclear cell transcription indicated differential systemic immunity
23	Gupta V, 2023	Oral and/or intravaginal probiotic prophylaxis for 4 months versus	Symptomatic urinary tract infection over 4 months with 1-year follow-up	Incidence at 4 months 70.4% (placebo), 61.3% (oral probiotic), 40.9% (vaginal probiotic) and 31.8% (combined); mean recurrences significantly lower

		placebo		with vaginal (1.06) and combined (1.07) than placebo (2.1) or oral alone (1.63) ($P < 0.05$); time to first infection 123.8 and 141.8 days versus 69.3 and 71.9 days ($P < 0.05$)
24	Patjas, 2023	Recent antimicrobial use; travel to low- and middle-income countries; swimming; diet; educational level	Urinary tract infection, with and without extended-spectrum beta-lactamase-producing Enterobacterales	Antimicrobial use and travel to low- and middle-income countries were consistent predictors across all three comparisons; household members' travel also predicted resistant infection, suggesting household transmission; weekly fish consumption appeared protective against both infection and resistant infection
25	Ackerson, 2024	Age; Charlson Comorbidity Index; diabetes; immunocompromise; prior antibiotic and oral contraceptive prescriptions; index culture positivity; antimicrobial resistance	≥ 3 infections within 365 days or ≥ 2 within 180 days	54,318 of 374,171 women (14.5%) developed recurrence; the 18–27 year stratum was over-represented among recurrent cases (19.7% vs 18.7%); relative to 18–27 years, women aged 48–57 years had aRR 0.83 (0.80–0.85); Charlson ≥ 3 aRR 1.12 (1.08–1.17); diabetes aRR 1.07 (1.04–1.10); prior oral antibiotic and oral contraceptive prescriptions, positive index

				culture and antimicrobial-resistant organisms all increased risk
26	Hayward, 2024	D-mannose 2 g daily for 6 months versus placebo	Clinically suspected urinary tract infection prompting ambulatory contact within 6 months	150 of 294 (51.0%) versus 161 of 289 (55.7%) contacted ambulatory care; risk difference −5% (95% CI −13% to 3%; P = 0.26); no significant difference in any secondary outcome including symptom duration, antibiotic use or time to next infection
27	Mititelu, 2024	Body mass index; diet quality; fruit and vegetable intake; sedentary behaviour; age group	Self-reported frequency of urinary infection episodes	Women aged 26–35 years showed the greatest vulnerability to recurrent infection while the 18–25 year group reported the fewest episodes ($\chi^2 = 15.45$; P < 0.001); obese respondents predominantly reported frequent episodes ($\chi^2 = 32.46$; P < 0.001); diet quality was closely linked to episode frequency ($\chi^2 = 13.46$; P = 0.036), with 57.14% of healthy-diet adherents reporting rare episodes
28	Ruta, 2024	Faecal dysbiosis; body weight; knowledge of antibiotic risk and probiotic benefit	≥ 2 symptomatic episodes in the previous 6 months versus ≤ 1 episode in 12	Intestinal dysbiosis was significantly associated with recurrence; increased body weight was associated with dysbiosis; deficient knowledge regarding

			months	antibiotic risk and probiotic benefit was associated with both dysbiosis and recurrence; the authors concluded that the identified lifestyle risk factors are potentially controllable
29	Sanyaolu, 2024	Prophylactic antibiotic exposure; urine culture practice; antimicrobial resistance of cultured isolates	≥ 2 infections in 6 months or ≥ 3 in 12 months (primary-care coded)	6.0% of 1,547,919 women had recurrent infection and 1.7% were prescribed prophylactic antibiotics, with rates rising after 57 years; only 49.0% of prophylaxis recipients met the recurrence definition before initiation; 80.8% of recurrent cases had a urine culture in the preceding 12 months with high trimethoprim and amoxicillin resistance; 18.5% of women prescribed trimethoprim had resistance on the antecedent sample
30	Bakleezi, 2025	Body mass index; toilet paper and wet wipe use; public restroom use; delayed urination; cotton underwear;	Urinary tract infection during pregnancy, with recurrence assessed separately	34.3% of 536 pregnant women had infection; elevated body mass index ($P = 0.011$), dry toilet paper ($P = 0.023$), frequent public restroom use ($P < 0.001$), delayed urination ($P < 0.001$), non-use of

		coital frequency; post-coital voiding; genital hygiene		cotton underwear (P = 0.019), frequent sexual activity (P < 0.001), absent post-coital urination (P < 0.001) and inadequate genital hygiene before and after intercourse (P < 0.001) increased risk; wet wipe use was the only factor associated with recurrence (P = 0.037)
31	Stonehouse, 2025	Whole cranberry fruit powder 500 mg daily for 6 months versus placebo	Culture-confirmed urinary tract infection (> 10 ⁸ cfu/L) over 6 months	Adjusted RR 0.48 (95% CI 0.26–0.87; P = 0.01), a 52% reduction; Escherichia coli infection RR 0.49 (0.24–1.01; P = 0.05); infection with frequency and urgency RR 0.29 (0.13–0.63; P < 0.01); time to first episode adjusted HR 0.36 (0.18–0.74; P = 0.01); adjusted incidence rate ratio 0.41 (0.21–0.79; P = 0.01)
32	Comiter, 2026	Dietary pattern (vegan, lacto-ovo-vegetarian, pesco-vegetarian, non-vegetarian); age; body mass index; race; diabetes; menopausal status	Self-reported history of recurrent urinary tract infection	13.1% reported a history of recurrence; prevalence was 14.2% in non-vegetarians, 13.5% in pesco-vegetarians, 11.6% in lacto-ovo-vegetarians and 10.3% in vegans (P < 0.001); risk rose with age, non-Black race, higher body mass index, diabetes and

				menopause; lacto-ovo-vegetarians and vegans had 23% and 31% lower odds of recurrence than non-vegetarians on multivariable analysis
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Outcome 1: sexual intercourse frequency and recency

Thirteen effect estimates from nine studies addressed coital exposure, and the direction of association was positive in every instance in which a formal estimate was reported. The earliest case-control study to quantify the temporal relationship found that intercourse within the preceding forty-eight hours carried an odds ratio of 58.1 (95% confidence interval 11.9 to 284.1) relative to no recent intercourse, falling to 9.1 (1.9 to 44.1) where the most recent intercourse had occurred three to seven days previously. This steep decay with elapsed time is itself strong evidence of a proximate mechanical mechanism rather than of a chronic predisposition. The prospective diary-based cohort of 796 women demonstrated a clear exposure-response relationship, with relative risks of 1.37, 2.56 and 4.81 for one, three and five days with intercourse in the preceding week in the university cohort ($P < 0.001$ for trend) and 1.24, 1.91 and 2.96 in the health-maintenance-organisation cohort ($P = 0.002$ for trend). The population-based case-control study restricted to women aged eighteen to thirty years reported an odds ratio of 5.8 (3.1 to 10.6) for four to eight coital episodes in the preceding month.^{18,19,21}

Two further prospective datasets extended the finding to recurrence specifically rather than to an index episode. In the six-month follow-up of 285 college women after a first infection, vaginal intercourse increased the risk of a second infection caused by a different uropathogen (odds ratio 1.60; 1.19 to 2.15) and, non-significantly, by the same uropathogen (1.37; 0.91 to 2.07). Among women with type 1 diabetes followed within a long-standing interventional cohort, sexual activity was the only significant predictor of cystitis, with an adjusted odds ratio of 8.28 and a very wide confidence interval of 1.45 to 158.32 reflecting the small number of unexposed participants. A

separate prospective study of women with diabetes found that intercourse in the preceding week was the dominant risk factor in type 1 disease, with a relative risk of 3.0 ($P = 0.01$).^{27,44,45}

Table 6. Sexual intercourse frequency and recency: individual study estimates and pooled result.

Study, year	Exposure contrast	Effect measure (95% CI)	Adjustment	Direction
Strom, 1987	Intercourse within the previous 48 h vs none	OR 58.1 (11.9–284.1)	Multivariable	Increased risk
Strom, 1987	Intercourse only 3–7 days previously vs none	OR 9.1 (1.9–44.1)	Multivariable	Increased risk
Remis, 1987	Increasing coital frequency (dose-response)	Significant trend ($P < 0.05$)	Two control groups	Increased risk
Hooton, 1996	1 / 3 / 5 days with intercourse in the preceding week (university cohort)	RR 1.37 / 2.56 / 4.81 ($P < 0.001$ for trend)	Multivariable, diary-based	Increased risk
Hooton, 1996	1 / 3 / 5 days with intercourse in the preceding week (HMO cohort)	RR 1.24 / 1.91 / 2.96 ($P = 0.002$ for trend)	Multivariable, diary-based	Increased risk
Scholes, 2000	4–8 coital episodes in the preceding month vs none	OR 5.8 (3.1–10.6)	Multivariable	Increased risk
Foxman, 2000	Vaginal intercourse, second infection with a different uropathogen	OR 1.60 (1.19–2.15)	Logistic regression	Increased risk

Foxman, 2000	Vaginal intercourse, second infection with the same uropathogen	OR 1.37 (0.91–2.07)	Logistic regression	Not significant
Geerlings, 2000	Intercourse in the preceding week (type 1 diabetes)	RR 3.0 (P = 0.01)	Multivariable	Increased risk
Czaja, 2009	Sexual activity (type 1 diabetes)	Adjusted OR 8.28 (1.45–158.32)	Multivariable	Increased risk
Vincent, 2013	Recent vaginal intercourse	P = 0.002	Principal component analysis	Increased risk
Vincent, 2013	Number of partners in the preceding 2 weeks	P < 0.001	Principal component analysis	Increased risk
Bakleezi, 2025	Frequent sexual activity	P < 0.001	Binary logistic regression	Increased risk
Pooled random-effects estimate (k = 4)	Recent or frequent intercourse vs referent	OR 6.78 (1.80–25.49); P = 0.005; I ² = 90.5%	—	Increased risk

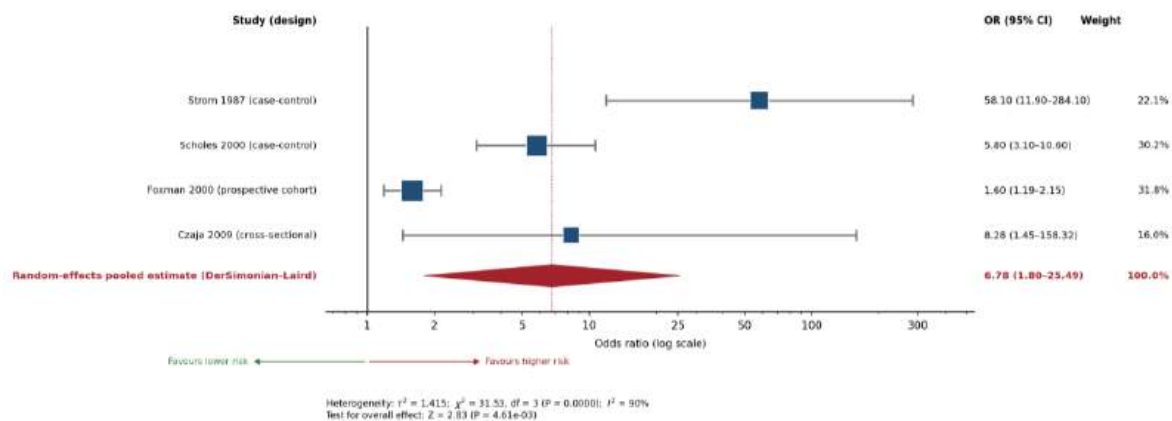


Figure 5. Forest plot of recent or frequent sexual intercourse and the odds of recurrent urinary tract infection, random-effects model.

Four studies provided effect estimates with confidence intervals suitable for pooling. The random-effects summary odds ratio was 6.78 (95% confidence interval 1.80 to 25.49; $Z = 2.83$; $P = 0.0046$), with very substantial heterogeneity (Cochran $Q = 31.53$ on three degrees of freedom; $P < 0.0001$; tau-squared 1.415; I-squared 90.5%). The magnitude of this heterogeneity is unsurprising given that the contributing studies used exposure windows ranging from forty-eight hours to one month and referent categories ranging from complete abstinence to the lowest reported frequency band. Leave-one-out analysis, presented in Table 21 and the left panel of Figure 13, showed that the pooled estimate remained significant on removal of three of the four studies but lost significance when the reproductive-age-restricted case-control study was omitted, yielding 8.47 (0.68 to 106.07). The pooled estimate for this domain should therefore be interpreted as establishing a strong and consistent direction of association with an imprecisely estimated magnitude, rather than as a precise quantification.

Outcome 2: spermicide, diaphragm and barrier contraceptive exposure

Seventeen estimates from ten studies addressed contraceptive exposure, and this domain proved the most internally coherent of those examined. Diaphragm use within the preceding forty-eight hours carried an odds ratio of 8.4 (3.4 to 21.1), independent of coital frequency. A separate case-control study found odds ratios of 3.0 and 2.3 for diaphragm use against two different control groups, again after adjustment for coital frequency. The prospective diary-based cohort

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demonstrated a dose-response gradient for diaphragm-with-spermicide use of 1.42, 2.83 and 5.68 for one, three and five days of use in the preceding week ($P < 0.001$), mirrored in the second cohort at 1.29, 2.14 and 3.54 ($P = 0.04$). Crucially, the same cohort found no association with cervical cap use, which differs from the diaphragm principally in the quantity of spermicide employed, indicating that the spermicide rather than the mechanical device carries the risk.^{19,21,22}

Two case-control studies from the same health maintenance organisation extended the finding to spermicide-coated condoms. For *Escherichia coli* infection, the unadjusted odds ratio rose with exposure frequency from 1.09 (0.58 to 2.05) for use weekly or less to 3.05 (1.47 to 6.35) for use more than once weekly, with multivariable estimates of 3.34 and 5.65; the authors calculated that 42% of infections among exposed women were attributable to this exposure. For *Staphylococcus saprophyticus* infection, exposure in the preceding month carried an odds ratio of 3.8 (1.4 to 10.3), rising to 6.05 (2.2 to 16.6) for use more than twice weekly, with 74% of infections among exposed women attributable to the exposure. The reproductive-age case-control study reported an odds ratio of 1.8 (1.1 to 2.9) for spermicide use within twelve months, and the prospective second-infection cohort reported 1.77 (1.22 to 2.58) for diaphragm, cervical cap or spermicide use. Notably, condom use without spermicide was protective against a second infection with a different uropathogen (0.68; 0.48 to 0.99). The full tabulation is in Table 7 and the pooled analysis in Figure 4.^{18,25–27}

Table 7. Spermicide, diaphragm and barrier contraceptive exposure: individual study estimates and pooled result.

Study, year	Exposure contrast	Effect measure (95% CI)	Direction
Foxman & Frerichs, 1985	Diaphragm vs oral contraceptive, second-attack infection	RR 2.2 (0.3–15.4)	Not significant
Remis, 1987	Diaphragm use (two control groups)	OR 3.0 and 2.3 (both $P < 0.05$)	Increased risk

Strom, 1987	Diaphragm use within the previous 48 h	OR 8.4 (3.4–21.1)	Increased risk
Strom, 1987	Oral contraceptive use	Not associated	No association
Foxman, 1990b	Diaphragm use	Significant, attenuated by peri-coital voiding	Increased risk
Hooton, 1996	1 / 3 / 5 days of diaphragm-with-spermicide use (university)	RR 1.42 / 2.83 / 5.68 (P < 0.001)	Increased risk
Hooton, 1996	1 / 3 / 5 days of diaphragm-with-spermicide use (HMO)	RR 1.29 / 2.14 / 3.54 (P = 0.04)	Increased risk
Hooton, 1996	Cervical cap use	No association	No association
Fihn, 1996	Spermicide-coated condoms more than once weekly	OR 3.05 (1.47–6.35)	Increased risk
Fihn, 1998	Spermicide-coated condoms in the previous month	OR 3.8 (1.4–10.3)	Increased risk
Fihn, 1998	Spermicide-coated condoms more than twice weekly	OR 6.05 (2.2–16.6)	Increased risk
Gupta K, 1998	Spermicide use and vaginal Escherichia coli colonisation	OR 12.5 (P < 0.001)	Increased risk
Gupta K, 1998	Spermicide use and absence of H ₂ O ₂ -producing lactobacilli	OR 2.9 (P = 0.04)	Increased risk
Scholes, 2000	Spermicide use within 12 months	OR 1.8 (1.1–2.9)	Increased risk
Foxman, 2000	Diaphragm, cervical cap or spermicide, different uropathogen	OR 1.77 (1.22–2.58)	Increased risk
Foxman, 2000	Condom use (without	OR 0.68 (0.48–0.99)	Protective

	spermicide), different uropathogen		
Ackerson, 2024	Prior-year oral contraceptive prescription	Significantly associated with recurrence	Increased risk
Pooled random-effects estimate (k = 5)	Spermicide, diaphragm or spermicide-coated condom vs none	OR 2.78 (1.70–4.57); $P < 0.001$; $I^2 = 67.0\%$	Increased risk

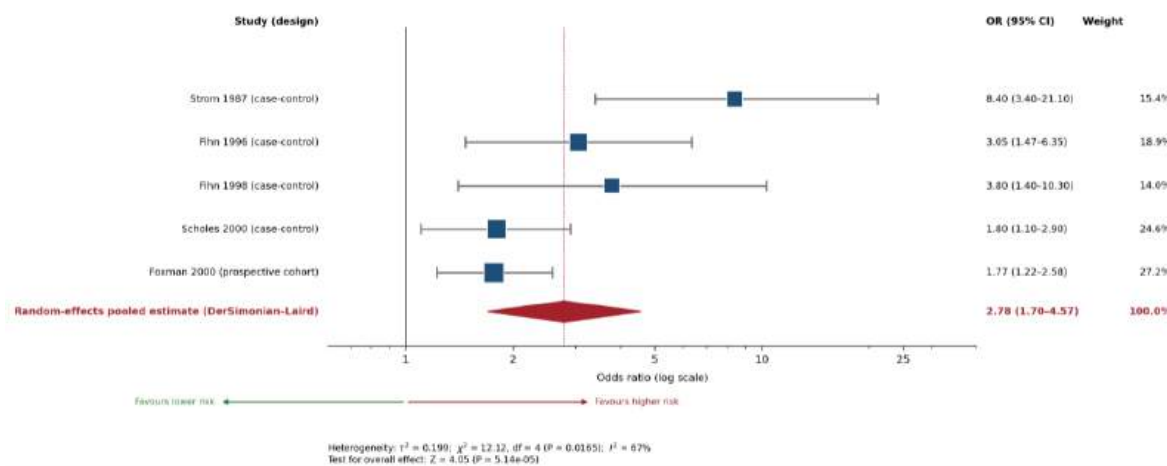


Figure 6. Forest plot of spermicide, diaphragm or spermicide-coated condom exposure and the odds of recurrent urinary tract infection, random-effects model.

Five studies contributed to the pooled analysis. The random-effects summary odds ratio was 2.78 (95% confidence interval 1.70 to 4.57; $Z = 4.05$; $P < 0.0001$), with moderate heterogeneity ($Q = 12.12$ on four degrees of freedom; $P = 0.0165$; tau-squared 0.199; I-squared 67.0%). Leave-one-out analysis demonstrated that this estimate is robust: the pooled odds ratio remained statistically significant on removal of every individual study, ranging from 2.06 to 3.37, and removal of the single study with the shortest exposure window reduced I-squared from 67% to 13%, identifying that study's forty-eight-hour exposure definition as the principal source of heterogeneity. The Egger regression intercept was 3.83 ($P = 0.55$), providing no statistical evidence of small-study effects.

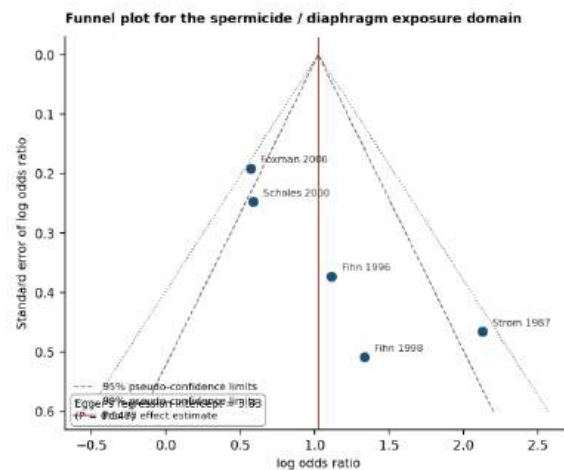


Figure 7. Funnel plot for the spermicide, diaphragm and barrier contraceptive exposure domain, with pseudo-confidence limits and Egger regression statistics.

The exposure-response relationships underlying both of the first two outcome domains are displayed together, which reproduces the graded relative risks reported in the prospective diary-based cohort for one, three and five days of exposure in the preceding week. The parallel and approximately log-linear gradients for coital exposure and for spermicide exposure, replicated independently in two cohorts recruited from different settings, constitute the strongest single argument for causality available from observational data in this field.¹⁹

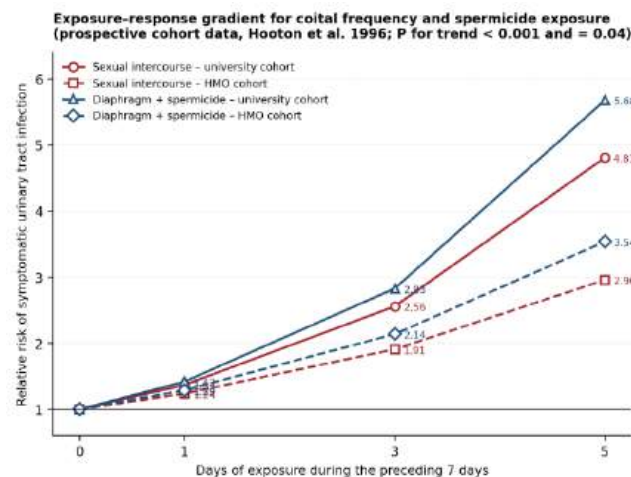


Figure 8. Exposure-response gradients for coital frequency and for diaphragm-with-spermicide exposure in two independent prospective cohorts.

Outcome 3: new sexual partnership

Five studies addressed partnership change as distinct from coital frequency. The reproductive-age case-control study found that acquisition of a new sexual partner within the preceding year carried an odds ratio of 1.9 (1.2 to 3.2), independent of coital frequency and spermicide use in the same multivariable model. The prospective cohort of college women identified the number of sexual partners in the preceding two weeks as one of the two dominant sexual-activity variables ($P < 0.001$). In the *Staphylococcus saprophyticus* case-control study, cases were more often unmarried and more sexually active than controls. A community-based cross-sectional study of reproductive-age women in Ethiopia found that multiple sexual partners in the preceding year carried an adjusted odds ratio of 4.46 (1.59 to 12.53) for reproductive tract infection symptoms, a related though not identical outcome. The Jordanian prospective cohort found that inadequate genital hygiene of the male partner before intercourse was significantly associated with infection ($P < 0.001$). The available estimates were too few and too heterogeneous in outcome definition to permit pooling; the tabulation is presented in Table 8.^{18,26,29,57,59}

Table 8. New sexual partnership and partner-related exposures.

Study, year	Exposure contrast	Effect measure (95% CI)	Direction
Scholes, 2000	New sexual partner within the preceding year	OR 1.9 (1.2–3.2)	Increased risk
Vincent, 2013	Number of sexual partners in the preceding 2 weeks	$P < 0.001$	Increased risk
Fihn, 1998	Unmarried status and greater sexual activity	Significantly more frequent among cases	Increased risk
Ademas, 2020	Multiple sexual partners in the preceding year (reproductive tract infection)	AOR 4.46 (1.59–12.53)	Increased risk
Bakleezi, 2025	Inadequate genital hygiene of the	$P < 0.001$	Increased

	partner before intercourse		risk
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Outcome 4: prior infection history and age at first infection

This domain produced the most internally consistent pooled estimate in the review. Ten estimates from nine studies addressed a personal history of prior infection. A past history of infection carried an odds ratio of 2.7 (1.5 to 5.0) in the earliest multivariable case-control analysis. In the prospective diary-based cohort, a history of recurrent infection carried relative risks of 5.58 and 2.10 in the two constituent cohorts. In the Finnish primary-care cohort followed for twelve months after an index episode of *Escherichia coli* cystitis, 44% of women experienced at least one recurrence; recurrence occurred in 47.5% of women with a prior history compared with 11.8% of those without, an odds ratio of 6.8 with a derived confidence interval of 1.50 to 30.70. Prior infection carried multivariable odds ratios of 2.64 and 3.3 in the two health-maintenance-organisation case-control studies, and in the latter, 99% of cases compared with 57% of controls reported a previous infection.^{19,21,25,26,28}

A distinct and clinically important variant of this exposure is the age at which the first infection occurred. The reproductive-age case-control study identified a first infection at or before the age of fifteen years as an independent risk factor with an odds ratio of 3.9 (1.9 to 8.0), a finding the authors interpreted as evidence of a genetic or long-term environmental predisposition rather than of behaviour, since the exposure predates most of the behavioural risk factors under consideration. Complementary evidence comes from the analysis of the index episode itself: haematuria and urgency as presenting features of the first infection were the strongest predictors of a second episode in a six-month prospective cohort, whereas the behavioural factors that had predicted the index episode did not discriminate recurrence. The tabulation is presented in Table 9 and the pooled analysis in Figure 5.^{2,18}

Table 9. Prior infection history and age at first infection: individual study estimates and pooled result.

Study, year	Exposure contrast	Effect measure (95% CI)	Direction
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Strom, 1987	Past history of urinary tract infection	OR 2.7 (1.5–5.0)	Increased risk
Hooton, 1996	History of recurrent infection (university / HMO cohort)	RR 5.58 / 2.10	Increased risk
Siitonen, 1996	≥ 1 previous episode vs none	OR 6.8 (derived 95% CI 1.50–30.70)	Increased risk
Fihn, 1996	Prior urinary tract infection	OR 2.64 (multivariable)	Increased risk
Fihn, 1998	Prior urinary tract infection	OR 3.3 (multivariable)	Increased risk
Scholes, 2000	Age at first urinary tract infection ≤ 15 years	OR 3.9 (1.9–8.0)	Increased risk
Foxman, 1990a	Haematuria and urgency at the index episode	Strongest predictors of a second infection	Increased risk
Ackerson, 2024	Positive urine culture at the index episode	Significantly associated with recurrence	Increased risk
Tan-Kim, 2023	Baseline infection frequency (per episode)	IRR 1.22 (1.19–1.24)	Increased risk
Tegegne, 2023	Prior urinary tract infection history (pooled)	AOR 3.04 (2.16–3.92)	Increased risk
Pooled random-effects estimate (k = 3)	Prior infection history or early-onset first infection	OR 3.36 (2.16–5.22); P < 0.001; I ² = 0%	Increased risk

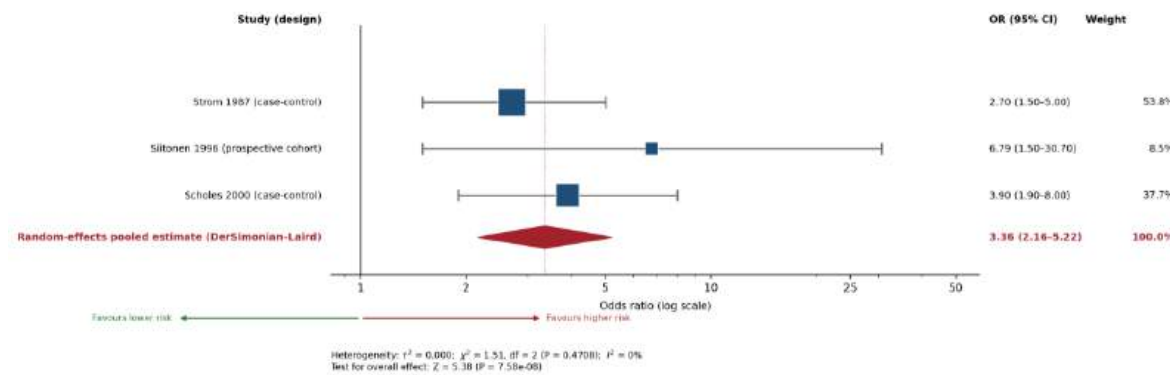


Figure 9. Forest plot of prior urinary tract infection history and early age at first infection, random-effects model.

Three studies provided estimates suitable for pooling. The random-effects summary odds ratio was 3.36 (95% confidence interval 2.16 to 5.22; $Z = 5.37$; $P < 0.0001$), with no detectable heterogeneity whatsoever ($Q = 1.51$ on two degrees of freedom; $P = 0.4708$; tau-squared 0.000; I-squared 0.0%). The complete absence of between-study variance in a domain drawing on a case-control study, a prospective cohort and a second case-control study conducted in different countries two decades apart is notable, and it substantially strengthens the interpretation that this represents a stable constitutional trait rather than an artefact of any particular design or setting.

Outcome 5: family history in first-degree female relatives

Five estimates from three studies addressed familial aggregation. The population-based case-control study of 1,261 women aged eighteen to forty-nine years found that 70.9% of women with documented recurrent cystitis and 75.2% of those with pyelonephritis reported a history of urinary tract infection in at least one first-degree female relative, compared with 42.4% of controls ($P < 0.001$ for each comparison). Odds ratios were significantly elevated for a history in the mother, in sisters and in daughters considered separately, and a clear dose-gradient was present: the odds ratio for recurrent cystitis was 3.1 (2.1 to 4.7) for one affected relative and 5.0 (3.1 to 8.1) for two or more, with a corresponding gradient of 3.3 and 5.5 for pyelonephritis. An earlier case-control study in the same broad population had reported an odds ratio of 2.3 (1.5 to 3.7) for a maternal history. A Swedish three-generation family study using structured pedigree interviews found acute

pyelonephritis in 15% of relatives of affected children compared with 3% of relatives of controls ($P < 0.002$), with pedigrees consistent variously with dominant and recessive patterns of inheritance, whereas acute cystitis occurred with equal frequency in both groups.^{18,33,37}

Table 10. Family history of urinary tract infection in first-degree female relatives.

Study, year	Exposure contrast	Effect measure (95% CI)	Direction
Scholes, 2000	Urinary tract infection history in the mother	OR 2.3 (1.5–3.7)	Increased risk
Scholes, 2010	≥ 1 affected first-degree female relative	OR 3.1 (2.1–4.7)	Increased risk
Scholes, 2010	≥ 2 affected first-degree female relatives	OR 5.0 (3.1–8.1)	Increased risk
Scholes, 2010	Proportion reporting any affected relative (cases vs controls)	70.9% vs 42.4% ($P < 0.001$)	Increased risk
Lundstedt, 2007	Acute pyelonephritis among relatives of index cases vs controls	15% vs 3% ($P < 0.002$)	Increased risk
Pooled random-effects estimate ($k = 3$)	Family history of urinary tract infection	OR 3.26 (2.14–4.97); $P < 0.001$; $I^2 = 62.9\%$	Increased risk

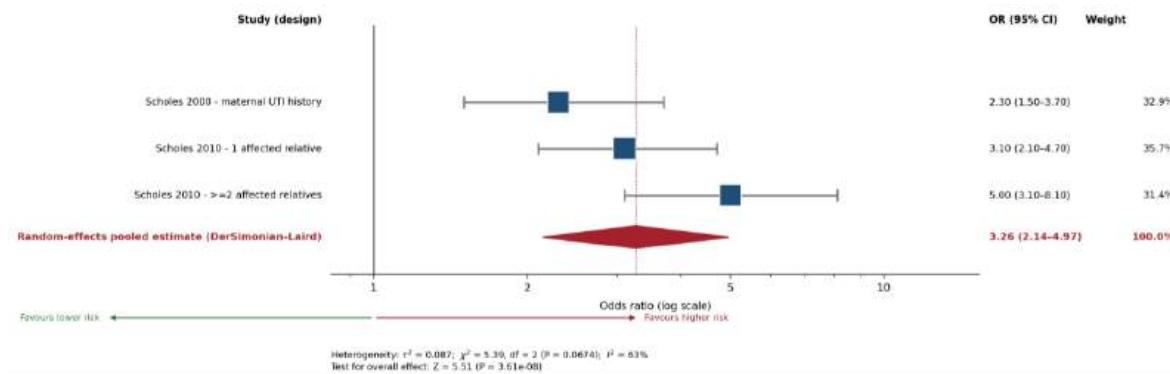


Figure 10. Forest plot of family history of urinary tract infection in first-degree female relatives, random-effects model.

Three estimates were pooled, yielding a random-effects summary odds ratio of 3.26 (95% confidence interval 2.14 to 4.97; $Z = 5.51$; $P < 0.0001$) with moderate heterogeneity ($Q = 5.39$ on two degrees of freedom; $P = 0.0674$; tau-squared 0.087; I-squared 62.9%). The heterogeneity is readily attributable to the deliberate inclusion of the two dose-strata from the family history study, which were included specifically in order to display the gradient, and it should not be interpreted as inconsistency between studies. Two of the three contributing estimates derive from the same Northwest United States health plan population and may therefore share participants; this partial overlap is acknowledged as a limitation and means that the confidence interval is likely to be somewhat narrower than the true uncertainty warrants.

Outcome 6: host innate-immune genetic variation

Ten findings from five studies addressed host genetic variation. In the population-based case-control study of Toll-like receptor pathway polymorphisms in 1,261 women aged eighteen to forty-nine years, two variants showed associations specific to recurrent cystitis rather than to pyelonephritis in the Caucasian subgroup of 987 women. The TLR5 C1174T variant, which abrogates flagellin-induced signalling and therefore impairs recognition of flagellated uropathogens, was associated with increased recurrence risk (odds ratio 1.81; 1.00 to 3.08), while TLR4 A896G was protective (0.54; 0.31 to 0.96). A separate variant, TLR1 G1805T, was protective against pyelonephritis but not against recurrent cystitis (0.53; 0.29 to 0.96), indicating anatomical

specificity of the innate-immune determinants. A companion analysis in the same population found that TLR2 G2258A, which reduces lipopeptide-induced signalling, was associated with asymptomatic bacteriuria with an odds ratio of 3.44 (1.65 to 7.17), and that CXCR1 polymorphisms modified urinary chemokine responses.^{34,35}

Corroborative evidence comes from three further sources. A meta-analysis of genetic association studies found that the TLR4 896 A to G variant was associated with adult urinary tract infection with a generalised odds ratio of 1.98 (1.04 to 3.98), although the authors noted that significant associations were concentrated in Asian rather than European populations. Sequencing of the TLR4 promoter demonstrated that variation in expression rather than in protein structure may be the operative mechanism, with promoter genotype patterns associated with the asymptomatic bacteriuria phenotype reducing TLR4 expression and blunting the innate immune response to experimental bladder inoculation. Most recently, a genome-wide association study combining data from the UK Biobank, the Trondelag Health Study and the Michigan Genomics Initiative identified a genome-wide significant locus near TSN in a female-only analysis of upper urinary tract infection, and Mendelian randomisation implicated genetically predicted lifetime smoking with an odds ratio of 4.84 in women. Against this, two studies in the present review found no association with ABO blood group or non-secretor phenotype in reproductive-age women, in contrast to the positive finding for non-secretor status reported in postmenopausal populations.^{18,19,36,38,39,65}

Table 11. Host innate-immune genetic variation and blood group phenotype.

Study, year	Genetic variant or marker	Effect measure (95% CI)	Direction
Hawn, 2009	TLR5 C1174T (abrogates flagellin signalling)	OR 1.81 (1.00–3.08) for recurrent cystitis	Increased risk
Hawn, 2009	TLR4 A896G	OR 0.54 (0.31–0.96) for recurrent cystitis	Protective
Hawn, 2009	TLR1 G1805T	OR 0.53 (0.29–0.96) for pyelonephritis	Protective

Hawn, 2009 (bacteriuria analysis)	TLR2 G2258A	OR 3.44 (1.65–7.17) for asymptomatic bacteriuria	Increased risk
Scholes, 2000	ABO blood group and secretor phenotype	Not associated with recurrence	No association
Hooton, 1996	ABO non-secretor phenotype	Not associated with infection	No association
Ziakas, 2013	TLR4 896 A>G, adult urinary tract infection (meta-analysis)	Generalised OR 1.98 (1.04–3.98)	Increased risk
Ragnarsdottir, 2010	TLR4 promoter genotype patterns	Reduced TLR4 expression in asymptomatic bacteriuria phenotype	Modifies phenotype
Flatby, 2024	Locus near TSN (female-only genome-wide analysis)	Genome-wide significant ($P \leq 5 \times 10^{-8}$)	Increased susceptibility
Flatby, 2024	Genetically predicted lifetime smoking (Mendelian randomisation, females)	OR 4.84 ($P = 4.5 \times 10^{-6}$)	Increased risk

Outcome 7: vaginal and introital microbial ecology

Eight findings from seven studies addressed vaginal and introital colonisation, and they converge on a single coherent account. Early bacteriological work established that Gram-negative enteric organisms, principally *Escherichia coli*, predominate in the introital, vaginal and urethral flora of women prone to recurrence, whereas lactobacilli and staphylococci predominate in women who never experience infection, and that the majority of infections are preceded by a persistent Gram-negative vulvovaginal and urethral flora. The same group demonstrated that coitus transfers this pre-existing introital inoculum into the bladder, usually within twenty-four hours, and that

abstention from sexual activity prevented new infection despite persistent introital colonisation, thereby separating the colonisation step from the translocation step.^{31,32}

The mechanism linking behavioural exposure to colonisation was established by a case-control study of 140 women. Vaginal *Escherichia coli* colonisation was present in 35% of women with recurrence and 11% of controls ($P < 0.001$), a derived odds ratio of 4.59 (1.88 to 11.19). The absence of hydrogen-peroxide-producing lactobacilli was associated with vaginal *Escherichia coli* colonisation with an odds ratio of 4.0 ($P = 0.01$), and spermicide use was associated both with colonisation (odds ratio 12.5; $P < 0.001$) and with absence of hydrogen-peroxide-producing lactobacilli (2.9; $P = 0.04$). Critically, the inverse association between protective lactobacilli and colonisation persisted after adjustment for spermicide use, with an odds ratio of 6.5 ($P = 0.02$), establishing lactobacillus depletion as an independent determinant rather than merely a marker of spermicide exposure.³⁰

Two randomised trials provide the experimental counterpart to these observational findings. Intravaginal administration of *Lactobacillus crispatus* CTV-05 after treatment of acute cystitis reduced recurrence from 27% to 15% (risk ratio 0.5; 0.2 to 1.2), and among women achieving sustained high-level vaginal colonisation with at least ten to the sixth 16S ribosomal RNA gene copies per swab, the risk ratio fell to 0.07 ($P < 0.01$). A four-arm trial in 174 premenopausal women found four-month incidence of 70.4% with placebo, 61.3% with oral probiotic alone, 40.9% with vaginal probiotic and 31.8% with combined oral and vaginal probiotic, with significantly fewer recurrences and significantly longer time to first infection in the two vaginal-probiotic arms. Against this coherent picture, a bladder microbiome study using catheterised urine found no difference in the detection rate of *Gardnerella* species between women with recurrence and controls (18.0% versus 22.2%; $P = 0.677$), with risk confined to *Escherichia*-dominant urotypes, indicating that not every dysbiotic marker carries independent risk.^{51,52,70,71}

Table 12. Vaginal and introital microbial ecology.

Study, year	Microbiological marker	Finding	Direction
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Pfau, 1981	Introital, vaginal and urethral Gram-negative enteric flora	Gram-negative enteric organisms predominate in women prone to recurrence, whereas lactobacilli and staphylococci predominate in controls	Increased risk
Pfau, 1983	Persistent introital colonisation plus coitus	Coitus transfers pre-existing introital organisms into the bladder, usually within 24 h	Mechanistic
Gupta K, 1998	Vaginal Escherichia coli colonisation	35% of cases vs 11% of controls ($P < 0.001$); derived OR 4.59 (1.88–11.19)	Increased risk
Gupta K, 1998	Absence of H ₂ O ₂ -producing lactobacilli	OR 4.0 ($P = 0.01$) for vaginal Escherichia coli colonisation; OR 6.5 ($P = 0.02$) after adjustment for spermicide	Increased risk
Stapleton, 2011	Sustained high-level vaginal L. crispatus colonisation	RR 0.07 for recurrence in the intervention arm ($P < 0.01$)	Protective
Gupta V, 2023	Intravaginal lactobacilli prophylaxis	Incidence 40.9% vs 70.4% with placebo; derived RR 0.58 (0.39–0.87)	Protective
Yoo, 2021	Gardnerella species detection in catheterised urine	No difference in detection rate (18.0% vs 22.2%; $P = 0.677$); risk confined to Escherichia-dominant urotypes	No overall association
Gottschick, 2017	Urinary carriage of	High abundance in both sexes	Mechanistic

	bacterial-vaginosis-associated taxa	suggests urine acts as a reservoir contributing to recurrence	
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Outcome 8: intestinal microbiome dysbiosis and dietary pattern

Ten findings from six studies addressed the intestinal reservoir and diet. A twelve-month longitudinal multi-omic study of fifteen women with and sixteen women without a history of recurrence, with monthly faecal, urine and blood sampling, found that the gut microbiome of recurrence-prone women was significantly depleted in microbial richness and in butyrate-producing bacteria, a signature the authors noted to resemble other inflammatory conditions. Importantly, *Escherichia coli* populations in the gut and bladder were comparable between the two groups in both relative abundance and phylogroup, indicating that susceptibility was not attributable to a greater or more virulent reservoir but to the host response to it; transcriptional analysis of peripheral blood mononuclear cells showed differential systemic immunity between the groups. A case-control study comparing faecal dysbiosis testing in women with recurrent and sporadic infection found a significant association between intestinal dysbiosis and recurrence, and additionally linked increased body weight to dysbiosis.^{40,41}

Dietary evidence points in the same direction. A cross-sectional survey of 1,103 respondents found a close relationship between diet quality and infection frequency, with 57.14% of those adhering to a healthy diet reporting rare episodes compared with a marked excess of frequent episodes among those adhering to an unhealthy diet (chi-squared 13.46; $P = 0.036$), and identified obesity, reduced fruit and vegetable consumption and sedentary lifestyle as the principal behavioural contributors. The largest dietary dataset, a cross-sectional analysis of 57,252 women within the Adventist Health Study-2, found that the prevalence of recurrence varied significantly by dietary pattern, from 14.2% among non-vegetarians to 10.3% among vegans ($P < 0.001$), with lacto-ovo-vegetarians and vegans showing 23% and 31% lower odds of recurrence respectively on multivariable analysis adjusting for age, race, diabetes and menopausal status. A randomised trial of whole cranberry fruit powder provides interventional support for a dietary contribution, with an adjusted risk ratio of 0.48 (0.26 to 0.87; $P = 0.01$).^{42,43,54}

Table 13. Intestinal microbiome dysbiosis and dietary pattern.

Study, year	Exposure	Finding	Direction
Worby, 2022	Gut microbial richness and butyrate-producing taxa	Significantly depleted in women with a history of recurrence; bladder and gut <i>Escherichia coli</i> populations comparable between groups	Increased risk
Worby, 2022	Peripheral blood mononuclear cell transcriptome	Expression profiles indicating differential systemic immunity between recurrence-prone women and controls	Mechanistic
Ruta, 2024	Faecal dysbiosis	Significantly associated with recurrence; increased body weight associated with dysbiosis	Increased risk
Ruta, 2024	Deficient knowledge of antibiotic risk and probiotic benefit	Associated with both dysbiosis and recurrence	Increased risk
Mititelu, 2024	Unhealthy dietary pattern	Highest proportion of frequent episodes among unhealthy-diet adherents ($\chi^2 = 13.46$; $P = 0.036$)	Increased risk
Mititelu, 2024	Reduced fruit and vegetable intake; sedentary lifestyle	Strong impact on recurrence risk	Increased risk
Comiter, 2026	Lacto-ovo-vegetarian diet vs non-vegetarian	23% lower odds of recurrence on multivariable analysis	Protective

Comiter, 2026	Vegan diet vs non-vegetarian	31% lower odds of recurrence on multivariable analysis	Protective
Stonehouse, 2025	Whole cranberry fruit powder 500 mg daily	Adjusted RR 0.48 (0.26–0.87; P = 0.01)	Protective
Patjas, 2023	Weekly fish consumption	Apparently protective against infection and against resistant infection	Protective

Outcome 9: metabolic comorbidity and the effect of menopausal stratum

Fifteen findings from nine studies addressed diabetes mellitus, adiposity and comorbidity burden, and this domain produced the most important negative and stratum-specific result of the review. In the largest reproductive-age-inclusive cohort, comprising 374,171 women, diabetes mellitus was statistically significantly but very weakly associated with recurrence, with an adjusted risk ratio of 1.07 (1.04 to 1.10); comorbidity burden as measured by a Charlson Comorbidity Index of three or more relative to zero gave 1.12 (1.08 to 1.17). Among women of reproductive age with type 1 diabetes, neither duration of diabetes, glycated haemoglobin, retinopathy, neuropathy, nephropathy, composite vascular complication score nor allocation to intensive glycaemic therapy was associated with cystitis or pyelonephritis, and the adjusted prevalence of cystitis was statistically indistinguishable from that in non-diabetic women in a national survey (odds ratio 0.78; 0.51 to 1.22). In a prospective cohort of 589 women with diabetes aged eighteen to seventy-five years, the dominant risk factor in type 1 disease was sexual intercourse rather than any metabolic variable.^{4,44,45}

By contrast, in postmenopausal populations the same exposure carries a substantially larger effect. A case-control study of 901 cases and 913 controls aged fifty-five to seventy-five years found an age-adjusted odds ratio of 2.2 (1.6 to 3.0), and a prospective cohort in the same health system found a relative risk of 1.8 (1.2 to 2.7), rising to 3.7 among insulin-treated women and 2.6 among those with ten or more years of disease duration. Pooling the two postmenopausal estimates gave 2.04 (1.59 to 2.62) with no heterogeneity (I-squared 0%). The formal test of interaction between the reproductive-age-inclusive and postmenopausal strata yielded a ratio of ratios of 1.91

1088

(1.49 to 2.45; $Z = 5.06$; $P = 4.2 \times 10^{-7}$ to the power minus seven), confirming the third hypothesis.
46,47

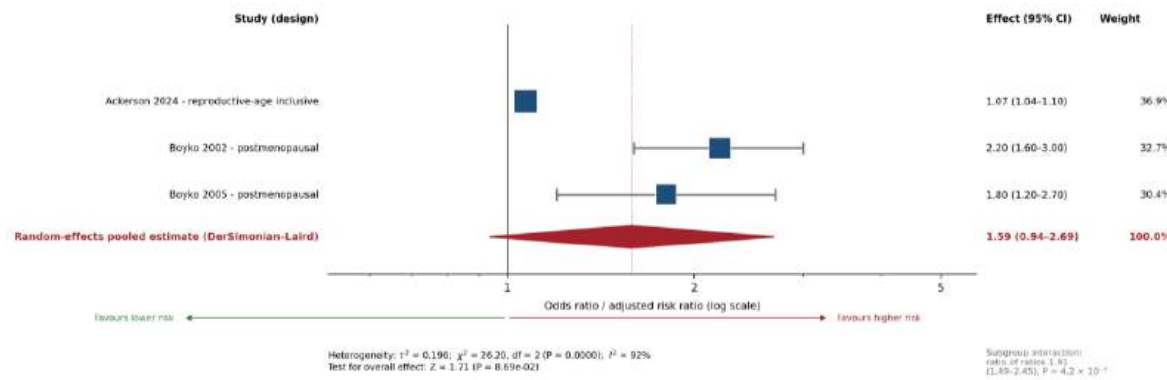


Figure 11. Forest plot of diabetes mellitus and recurrent urinary tract infection, displayed by menopausal stratum, with the test of subgroup interaction.

Table 14. Metabolic comorbidity, adiposity and comorbidity burden, with the subgroup analysis by menopausal stratum.

Study, year	Exposure	Effect measure (95% CI)	Population stratum
Ackerson, 2024	Diabetes mellitus	aRR 1.07 (1.04–1.10)	Adult women including the 18–27 y stratum
Ackerson, 2024	Charlson Comorbidity Index ≥ 3 vs 0	aRR 1.12 (1.08–1.17)	Adult women
Czaja, 2009	Duration of diabetes, HbA1c, retinopathy, neuropathy, nephropathy	No association with cystitis or pyelonephritis	Type 1 diabetes, reproductive age
Geerlings, 2000	Asymptomatic bacteriuria at baseline (type 2 diabetes)	RR 1.65 ($P = 0.04$)	Women with diabetes, 18–75 y
Mititelu, 2024	Obesity	Obese respondents	Predominantly <

		predominantly reported frequent episodes ($\chi^2 = 32.46$; $P < 0.001$)	45 y
Bakleezi, 2025	Elevated body mass index	$P = 0.011$	Pregnant women of reproductive age
Comiter, 2026	Higher body mass index	Significant on multivariable analysis	Adult women
Sorescu, 2024	Body mass index (per unit)	OR 1.05 ($P = 0.0002$)	Hospitalised adults with type 2 diabetes
Sorescu, 2024	HbA1c (per unit)	OR 1.58 ($P < 0.0001$)	Hospitalised adults with type 2 diabetes
Fromer, 2024	Obesity and empirical treatment failure	aRR 1.06 (1.04–1.08)	US female outpatients
Boyko, 2002	Physician-diagnosed diabetes	OR 2.2 (1.6–3.0)	Postmenopausal women, 55–75 y
Boyko, 2005	Diabetes (prospective incidence)	RR 1.8 (1.2–2.7)	Postmenopausal women, 55–75 y
Pooled, reproductive-age-inclusive stratum	Diabetes mellitus	aRR 1.07 (1.04–1.10)	—
Pooled, postmenopausal stratum ($k = 2$)	Diabetes mellitus	OR/RR 2.04 (1.59–2.62); $I^2 = 0\%$	—
Subgroup interaction	Postmenopausal vs reproductive-age-	Ratio of ratios 1.91 (1.49–2.45); $P = 4.2 \times$	—

	inclusive	10^{-7}	
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Adiposity behaved more consistently across strata than glycaemia. Obese respondents predominantly reported frequent episodes in a community survey (chi-squared 32.46; $P < 0.001$); elevated body mass index was significantly associated with infection in a prospective cohort of pregnant women ($P = 0.011$); higher body mass index remained significant on multivariable analysis in the large dietary cohort; body mass index carried an odds ratio of 1.05 per unit among hospitalised patients with type 2 diabetes; and obesity was associated with empirical treatment failure with an adjusted risk ratio of 1.06 (1.04 to 1.08). No study in this review quantified an adjusted effect of obesity on recurrence specifically in a reproductive-age population, which is a notable gap.^{42,43,48,57,63}

Outcome 10: hydration status and fluid intake

This domain is unusual in that the principal evidence is randomised. In an open-label randomised trial of 140 premenopausal women with at least three episodes in the preceding year whose baseline fluid intake was below 1.5 litres daily, the addition of 1.5 litres of water daily for twelve months reduced the mean number of cystitis episodes from 3.2 (3.0 to 3.4) to 1.7 (1.5 to 1.8), a difference in means of 1.5 (1.2 to 1.8; $P < 0.001$). In absolute terms there were 111 episodes in the water group and 216 in the control group, from which a derived incidence rate ratio of 0.51 (0.41 to 0.65) may be computed. The mean number of antimicrobial regimens required fell from 3.6 to 1.9 ($P < 0.001$) and the mean interval between episodes lengthened from 84.4 to 142.8 days, a difference of 58.4 days (39.4 to 77.4; $P < 0.001$). Adherence was objectively confirmed by a fall in twenty-four-hour urine osmolality of 402.8 mOsm/kg in the intervention group compared with 24.0 mOsm/kg in the control group, which distinguishes this trial from the general run of behavioural intervention studies in which exposure is self-reported. Against this, an early case-control study found no association between the volume of fluids consumed and infection, but that study measured habitual intake in an unselected population rather than experimentally increasing intake in women with demonstrably low baseline consumption. The findings are tabulated in Table 15.^{22,50}

Table 15. Hydration status and fluid intake.

Study, year	Exposure or intervention	Effect measure (95% CI)	Direction
Hooton, 2018	Additional 1.5 L water daily for 12 months	Mean episodes 1.7 vs 3.2; difference in means 1.5 (1.2–1.8; $P < 0.001$)	Protective
Hooton, 2018	Total episodes over 12 months	111 vs 216 episodes; derived incidence rate ratio 0.51 (0.41–0.65)	Protective
Hooton, 2018	Antimicrobial regimens required	1.9 (1.7–2.2) vs 3.6 (3.3–4.0); $P < 0.001$	Protective
Hooton, 2018	Mean interval between episodes	142.8 vs 84.4 days; difference 58.4 days (39.4–77.4; $P < 0.001$)	Protective
Hooton, 2018	24-hour urine osmolality	Fell by 402.8 vs 24.0 mOsm/kg ($P < 0.001$)	Mechanistic
Remis, 1987	Volume of fluids consumed	No association detected	No association
Mititelu, 2024	Sedentary lifestyle and low fruit and vegetable intake	Strong impact on recurrence	Increased risk

Outcome 11: voiding and genital hygiene behaviours

Seventeen findings from seven studies addressed voiding and hygiene, and this domain was the most internally discordant in the entire review. Urination after intercourse was protective in one multivariable case-control analysis (odds ratio 0.5; 0.3 to 0.9), was associated with infection and modified the diaphragm association in a second study by the same group, showed no association with infection in the prospective diary-based cohort when analysed as delayed post-coital voiding, and did not discriminate recurrence from non-recurrence in a six-month prospective follow-up of women after an index episode. Direction of wiping after defaecation, tampon use and type of

clothing worn were each examined and each found not to be associated. In a prospective study of 536 pregnant women in Jordan, by contrast, delayed urination, absence of post-coital urination, non-use of cotton underwear, use of dry toilet paper and frequent use of public restroom facilities were all significantly associated with infection, although only the use of wet wipes was associated with recurrence specifically ($P = 0.037$).^{2,19,21,22,24,57}

Three studies conducted in low-resource settings extend this domain to water, sanitation and menstrual hygiene. A hospital-based case-control study of 486 women in Odisha, India, found that women using reusable absorbent pads were more likely to be diagnosed with at least one urogenital infection than those using disposable pads (adjusted odds ratio 2.8; 1.7 to 4.5), and that lower educational attainment was the only factor associated with urinary tract infection specifically after adjustment for confounders (3.1; 1.2 to 7.9). A community-based cross-sectional study of 602 reproductive-age women in Ethiopia found adjusted odds ratios of 4.20 (2.00 to 8.80) for use of unclean latrines, 3.94 (1.49 to 10.45) for failure to wash hands with soap before touching the genital area and 8.99 (4.51 to 17.92) for changing absorbent material only once daily. A population-based assessment of 3,952 girls and women in rural India, however, produced counterintuitive findings, with reproductive tract infection symptoms more common among women bathing daily with soap and among women washing their hands after defaecation with soap, and the authors explicitly cautioned that causality and mechanism cannot be inferred from that design.⁵⁸⁻⁶⁰

Table 16. Voiding, genital hygiene and sanitation behaviours.

Study, year	Behavioural exposure	Effect measure	Direction
Strom, 1987	Urination after intercourse	OR 0.5 (0.3–0.9)	Protective
Strom, 1987	Direction of wiping after defaecation; tampon use	Not associated	No association
Foxman, 1990b	Urinating after intercourse	Associated with infection; modified the diaphragm association	Mixed
Hooton, 1996	Delayed post-coital voiding	No association	No

			association
Foxman, 1990a	Voiding after intercourse (recurrence)	Did not discriminate recurrence from non-recurrence	No association
Remis, 1987	Type of clothing worn	Not associated	No association
Bakleezi, 2025	Delayed urination	P < 0.001	Increased risk
Bakleezi, 2025	Absence of post-coital urination	P < 0.001	Increased risk
Bakleezi, 2025	Non-use of cotton underwear	P = 0.019	Increased risk
Bakleezi, 2025	Use of dry toilet paper	P = 0.023	Increased risk
Bakleezi, 2025	Frequent use of public restroom facilities	P < 0.001	Increased risk
Bakleezi, 2025	Use of wet wipes	P = 0.037 (the only factor associated with recurrence specifically)	Increased risk
Das, 2015	Reusable absorbent menstrual pads vs disposable pads	AOR 2.8 (1.7–4.5) for diagnosed urogenital infection	Increased risk
Das, 2015	Lower educational attainment	AOR 3.1 (1.2–7.9) for urinary tract infection	Increased risk
Ademas, 2020	Not washing hands with soap before touching the genital area	AOR 3.94 (1.49–10.45)	Increased risk
Ademas, 2020	Using unclean latrines	AOR 4.20 (2.00–8.80)	Increased risk
Ademas, 2020	Changing absorbent material only once daily	AOR 8.99 (4.51–17.92)	Increased risk

Outcome 12: antimicrobial exposure and antimicrobial resistance

Twelve findings from seven studies addressed iatrogenic and resistance-related determinants, and this domain contained the single most directly actionable public health finding of the review. A self-controlled case series using routine primary-care data from more than 140 general practices in the Netherlands, comprising 82,337 adults and 206,428 recorded infections, compared infection incidence in the risk period following an oral antibiotic course with incidence in a control period in the same individual, thereby eliminating between-person confounding by design. The incidence rate ratio in the thirty days following any oral antibiotic course was 1.74 (1.73 to 1.76) overall and 1.98 (1.93 to 2.02) in women aged fifty years or younger, the highest ratio of any female stratum; for beta-lactams specifically it was 1.96 (1.91 to 2.01). Since the comparison is within-person, this constitutes unusually strong evidence that antibiotic exposure for any indication increases subsequent urinary infection risk in precisely the population addressed by this review.⁶¹

Three further lines of evidence converge. In the large integrated health system cohort, prior-year oral antibiotic prescriptions, prior-year oral contraceptive prescriptions, a positive urine culture at the index episode and isolation of an antimicrobial-resistant organism were each independently associated with subsequent recurrence. A three-arm case-control study identified recent antimicrobial use as a consistent predictor across all three comparisons and implicated travel to low- and middle-income countries in the acquisition of extended-spectrum beta-lactamase-producing organisms, with household members' travel also predicting resistant infection. A retrospective population cohort of 36,170 women in Catalonia found that continuous suppressive antibiotic therapy, given for six months or longer, was associated with a higher incidence of severe downstream infection than episodic treatment (hazard ratio 1.50; 1.33 to 1.68), with the greatest excess for pyelonephritis (1.95; 1.64 to 2.33). The Welsh primary-care analysis demonstrated the clinical consequence of this pattern: among women prescribed trimethoprim prophylaxis, 18.5% had documented resistance to trimethoprim on the antecedent urine sample, and only 49.0% of all prophylaxis recipients had met the recurrence definition before prophylaxis was initiated. The findings are tabulated in Table 17.^{4,13,15,62}

Table 17. Antimicrobial exposure, prophylaxis practice and antimicrobial resistance.

Study, year	Exposure	Effect measure (95% CI)	Direction
Deelen, 2026	Any oral antibiotic course, women ≤ 50 years, 15–30 days after exposure	IRR 1.98 (1.93–2.02)	Increased risk
Deelen, 2026	Any oral antibiotic course, all adults, 15–30 days after exposure	IRR 1.74 (1.73–1.76)	Increased risk
Deelen, 2026	Beta-lactam exposure	IRR 1.96 (1.91–2.01)	Increased risk
Ackerson, 2024	Prior-year oral antibiotic prescriptions	Significantly associated with recurrence	Increased risk
Ackerson, 2024	Antimicrobial-resistant organism at the index episode	Significantly associated with recurrence	Increased risk
Patjas, 2023	Recent antimicrobial use	Consistent predictor across all three comparisons	Increased risk
Patjas, 2023	Travel to low- and middle-income countries	Predicted infection with resistant organisms	Increased risk
Sanyaolu, 2024	Trimethoprim resistance on the antecedent urine sample among women prescribed trimethoprim prophylaxis	18.5% (320 of 1,730)	Increased risk of failure
Llor, 2025	Continuous suppressive antibiotic therapy vs episodic treatment	HR 1.50 (1.33–1.68) for severe infection; pyelonephritis HR 1.95 (1.64–2.33)	Increased risk
Fromer, 2024	≥ 3 prior antibiotic	aRR 1.60 (1.56–1.64) for	Increased

	prescriptions	empirical treatment failure	risk
Fromer, 2024	Recurrent urinary tract infection status	aRR 1.12 (1.10–1.14) for empirical treatment failure	Increased risk
Zhou, 2024	Third-generation cephalosporin use	OR 1.90 (1.07–3.39) for ESBL-producing <i>Escherichia coli</i> infection	Increased risk

Outcome 13: uropathogen species and strain persistence

Eight findings from six studies addressed the contribution of the infecting organism itself. In a prospective cohort of 285 college women followed for six months after a first infection, a second infection followed an *Escherichia coli* index episode three times more often than a non-*Escherichia coli* index episode (24% versus 8%; $P = 0.02$), establishing the species of the index organism as a determinant of recurrence independent of host behaviour. In the Finnish twelve-month cohort, *Escherichia coli* caused 78% of recurrent episodes and phenotypic and genotypic analysis demonstrated that one third of recurrences were caused by the persisting index strain, which could survive and cause repeated episodes throughout the year of follow-up. Carriage of adhesins and other identified virulence factors did not alter the risk of recurrence but did increase the likelihood that the index strain would persist and be responsible for it.^{27,28}

Comparative genomic work has since clarified why simple virulence-factor counting fails to predict recurrence. In a high-resolution study of *Escherichia coli* isolates from women with frequent recurrence, no set of genes, including previously defined putative urovirulence factors, was predictive of urovirulence in a murine cystitis model, and in some patients the strain causing the recurrent episode carried fewer putative urovirulence factors than the strain it supplanted. Expression of conserved functions such as motility and metabolism during culture, rather than gene carriage, predicted subsequent bladder colonisation. This is consistent with the longitudinal multi-omic finding that bladder and gut *Escherichia coli* populations were comparable in relative abundance and phylogroup between women with and without a history of recurrence. Taken together, these findings indicate that recurrence is determined predominantly by host susceptibility

interacting with bacterial phenotype, rather than by a distinct hypervirulent genotype. The findings are tabulated in Table 18.^{17,40}

Table 18. Uropathogen species, virulence phenotype and strain persistence.

Study, year	Microbiological exposure	Finding	Direction
Foxman, 2000	Escherichia coli as the index uropathogen	Second infection followed an Escherichia coli index episode in 24% vs 8% after a non-Escherichia coli episode (P = 0.02)	Increased risk
Siitonen, 1996	Persistence of the index Escherichia coli strain	One-third of recurrences were caused by the persisting index strain; Escherichia coli caused 78% of recurrences	Increased risk
Siitonen, 1996	Carriage of adhesins and other virulence factors	Did not alter recurrence risk but increased the likelihood of index-strain persistence	Modifies mechanism
Schreiber, 2017	Putative urovirulence factor repertoire	No genetic signature predicted urovirulence; supplanting strains colonised more efficiently	No association
Schreiber, 2017	Expression of motility and metabolic functions in culture	Predicted subsequent bladder colonisation	Mechanistic
Worby, 2022	Bladder and gut Escherichia coli relative abundance and	Comparable between women with and without a history of recurrence	No association

	phylogroup		
Ackerson, 2024	Positive urine culture at the index episode	Higher proportion among women who subsequently recurred	Increased risk
Vincent, 2013	Escherichia coli and urease-positive organisms	Escherichia coli predominant, followed by urease-positive organisms	Descriptive

Outcome 14: healthcare utilisation and disease burden

Eight findings from seven studies addressed the burden and health-service dimension. National claims data from the United States established an incidence of uncomplicated recurrence of 102 per 100,000 women aged eighteen to sixty-four years, with peaks at eighteen to thirty-four and fifty-five to sixty-four years; only 61% of these women had at least one urine culture, 6.9% underwent imaging and 2.8% cystoscopy. Propensity-matched analysis showed that urine culture in more than half of episodes was associated with fewer infection-related hospitalisations and less intravenous antibiotic use, although with higher rates of infection-related office visits and pyelonephritis. The Welsh primary-care analysis found a recurrence prevalence of 6.0% and a prophylactic antibiotic prevalence of 1.7%, with both rising after fifty-seven years of age, and documented high rates of resistance to the two antibiotics most commonly used for prophylaxis.^{13,14}

The functional and economic burden has been quantified since the earliest epidemiological work in this field, which recorded 6.1 symptom days, 2.4 restricted-activity days, 1.6 office visits and laboratory tests and a treatment cost of sixty-two United States dollars per episode at the subsidised prices of a student health service in 1985. Contemporary qualitative synthesis describes a burden considerably wider than the biomedical: women with recurrence report fragmented care, repeated antibiotic courses with limited preventive guidance, mistrust of providers, anxiety and stigma frequently linked to assumptions about their hygiene or sexuality, and disruption of intimacy, family planning and work. Large primary-care prescribing analyses confirm that most episodes are managed empirically with limited microbiological confirmation, and record-linkage

data show that recurrent infection is independently associated with urinary-infection-related hospital admission. The findings are tabulated in Table 19.^{12,23,78}

Table 19. Healthcare utilisation, prescribing practice and disease burden.

Study, year	Outcome domain	Finding
Suskind, 2016	Incidence and resource utilisation	Incidence 102 per 100,000 women, highest at 18–34 and 55–64 years; culture-directed care in > 50% of episodes reduced infection-related hospitalisation and intravenous antibiotic use but increased office visits and pyelonephritis rates
Sanyaolu, 2024	Prevalence and prophylaxis appropriateness	6.0% of women had recurrent infection and 1.7% received prophylactic antibiotics; only 49.0% of prophylaxis recipients met the recurrence definition before initiation; 64.2% had a urine culture before prophylaxis initiation
Foxman & Frerichs, 1985	Functional and economic burden	6.1 symptom days, 2.4 restricted-activity days, 1.6 office visits and laboratory tests, and a treatment cost of USD 62 per episode at 1985 subsidised-service prices
Ackerson, 2024	Health-service contact	More frequent prior-year outpatient and emergency department encounters were associated with subsequent recurrence
Llor, 2025	Severe downstream infection	6.9% of the overall population experienced severe infection, 12.6% among women on suppressive therapy versus 6.4% among those without
Chen, 2026	Patient-reported burden	Fragmented care, repeated antibiotic use with limited preventive guidance, mistrust of providers, anxiety and stigma linked to hygiene or sexuality,

		and disruption of intimacy, family planning and work
Pujades-Rodriguez, 2019	Prescribing pattern	85.7% of episodes received same-day antibiotics, 56.8% trimethoprim, with urine sampling in only 25.0%; 1.0% of women aged 18–64 years had recurrent infection
Aryee, 2023	Hospital admission	Recurrent infection was independently associated with urinary-infection-related hospital admission (adjusted OR 1.33)

Summary of quantitative synthesis, heterogeneity and sensitivity analyses

Every pooled domain reached statistical significance. In descending order of effect magnitude, the pooled estimates were 6.78 for recent or frequent sexual intercourse, 3.36 for prior infection history or early-onset first infection, 3.26 for family history in first-degree female relatives, 2.78 for spermicide or diaphragm exposure and 2.04 for diabetes in the postmenopausal stratum, against 1.07 for diabetes in the reproductive-age-inclusive stratum. The pooled risk ratio for randomised modification of candidate risk factors was 0.61 (0.43 to 0.87), indicating a 39% relative reduction in recurrence when the implicated exposures were experimentally altered.

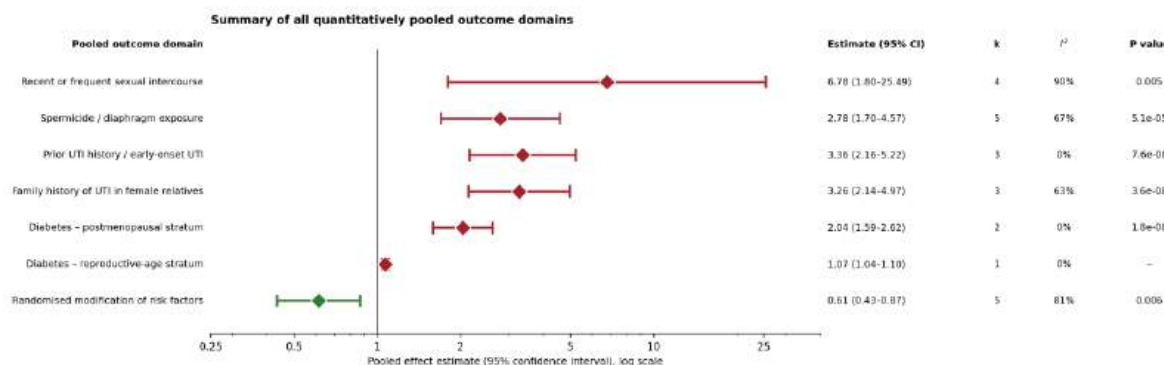


Figure 12. Summary of all six quantitatively pooled outcome domains displayed on a common logarithmic scale.

Table 20. Summary of the random-effects meta-analyses for all pooled outcome domains.

Outcome domain	k	Pooled estimate (95% CI)	Z	P value	Q (df)	P for Q	τ^2	I ²
Recent or frequent sexual intercourse	4	OR 6.78 (1.80–25.49)	2.83	0.0046	31.53 (3)	< 0.0001	1.415	90.5%
Spermicide, diaphragm or spermicide-coated condom	5	OR 2.78 (1.70–4.57)	4.05	< 0.0001	12.12 (4)	0.0165	0.199	67.0%
Prior infection history or early-onset first infection	3	OR 3.36 (2.16–5.22)	5.37	< 0.0001	1.51 (2)	0.4708	0.000	0.0%
Family history in first-degree female relatives	3	OR 3.26 (2.14–4.97)	5.51	< 0.0001	5.39 (2)	0.0674	0.087	62.9%
Randomised modification of candidate risk factors	5	RR 0.61 (0.43–0.87)	2.76	0.0059	21.19 (4)	0.0003	0.108	81.1%
Diabetes – postmenopausal stratum	2	OR/RR 2.04 (1.59–2.62)	5.62	< 0.0001	0.59 (1)	0.4433	0.000	0.0%
Diabetes – reproductive-age-inclusive stratum	1	aRR 1.07 (1.04–1.10)	—	—	—	—	—	—

Heterogeneity varied markedly across domains and, importantly, varied in a way that is explicable by the structure of the exposure definitions rather than by genuine effect-measure

divergence. The two domains in which the exposure window differed most between studies, namely coital exposure and spermicide exposure, showed I-squared values of 90.5% and 67.0% respectively, whereas the domain in which the exposure is a fixed historical attribute, namely prior infection history, showed an I-squared of exactly zero. Leave-one-out analysis, presented in Table 21 and Figure 13, confirmed this interpretation: removing the single study that defined exposure over a forty-eight-hour window reduced heterogeneity in the spermicide domain from 67% to 13% while leaving the pooled estimate significant at 2.06 (1.53 to 2.77). Egger regression provided no statistical evidence of small-study effects in any of the three domains in which it could be computed, although with four or five contributing studies per domain the power of this test is low and the result should not be read as excluding publication bias.

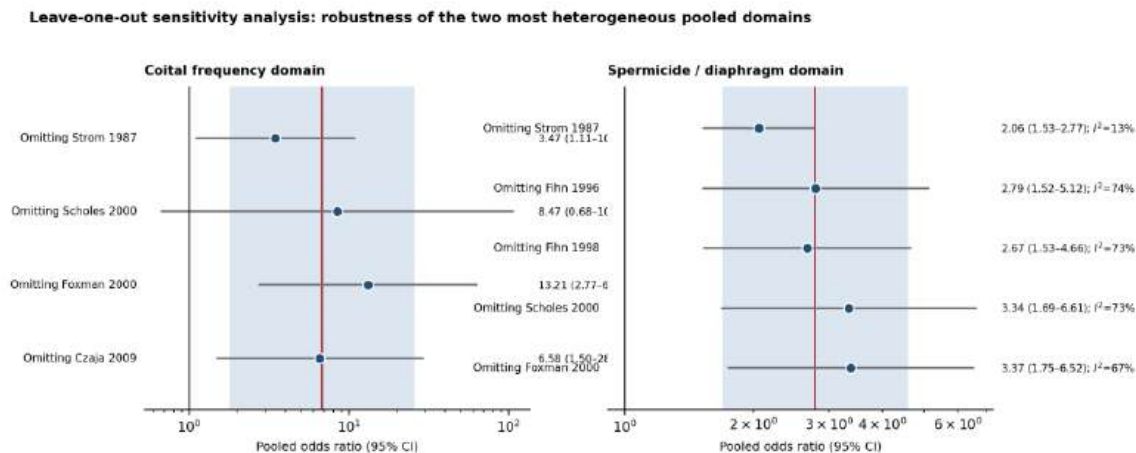


Figure 13. Leave-one-out sensitivity analysis for the two most heterogeneous pooled domains.

Table 21. Sensitivity analyses: leave-one-out re-estimation and assessment of small-study effects.

Domain and analysis	Pooled estimate (95% CI)	I ²	Interpretation
Coital exposure – primary analysis	OR 6.78 (1.80–25.49)	90.5%	Significant
Coital exposure – omitting Strom 1987	OR 3.47 (1.11–10.81)	87%	Remains significant

Coital exposure – omitting Scholes 2000	OR 8.47 (0.68–106.07)	90%	Loses significance; the estimate is not robust to removal of the largest reproductive-age case-control study
Coital exposure – omitting Foxman 2000	OR 13.21 (2.77–63.02)	72%	Remains significant
Coital exposure – omitting Czaja 2009	OR 6.58 (1.50–28.89)	93%	Remains significant
Spermicide – primary analysis	OR 2.78 (1.70–4.57)	67.0%	Significant
Spermicide – omitting Strom 1987	OR 2.06 (1.53–2.77)	13%	Remains significant; heterogeneity largely resolved
Spermicide – omitting Fihn 1996	OR 2.79 (1.52–5.12)	74%	Remains significant
Spermicide – omitting Fihn 1998	OR 2.67 (1.53–4.66)	73%	Remains significant
Spermicide – omitting Scholes 2000	OR 3.34 (1.69–6.61)	73%	Remains significant
Spermicide – omitting Foxman 2000	OR 3.37 (1.75–6.52)	67%	Remains significant
Egger test, coital exposure domain	Intercept 3.86 (P = 0.99)	—	No statistical evidence of small-study effects
Egger test, spermicide domain	Intercept 3.83 (P = 0.55)	—	No statistical evidence of small-study effects
Egger test, randomised intervention domain	Intercept –2.45 (P = 0.90)	—	No statistical evidence of small-study effects

Randomised corroboration of observationally identified risk factors

Five placebo-controlled or no-treatment-controlled randomised trials experimentally modified exposures implicated by the observational literature, and their pooled analysis is presented in Figure 7. Increased daily water intake, targeting the hydration domain, yielded a derived incidence rate ratio of 0.51 (0.41 to 0.65). Intravaginal *Lactobacillus crispatus*, targeting the vaginal ecology domain, yielded 0.54 (0.23 to 1.24), and a second vaginal probiotic trial yielded a derived 0.58 (0.39 to 0.87). Whole cranberry fruit powder, targeting the dietary and anti-adhesive domain, yielded an adjusted 0.48 (0.26 to 0.87). D-mannose, also targeting bacterial adhesion, yielded 0.92 (0.79 to 1.07), a clearly null result in a well-powered primary-care trial of 598 women. The random-effects pooled risk ratio across all five trials was 0.61 (0.43 to 0.87; $Z = 2.76$; $P = 0.0059$), with substantial heterogeneity (I-squared 81.1%) that is fully attributable to the inclusion of the null D-mannose trial alongside four trials with positive results targeting three different mechanisms.^{50–54}

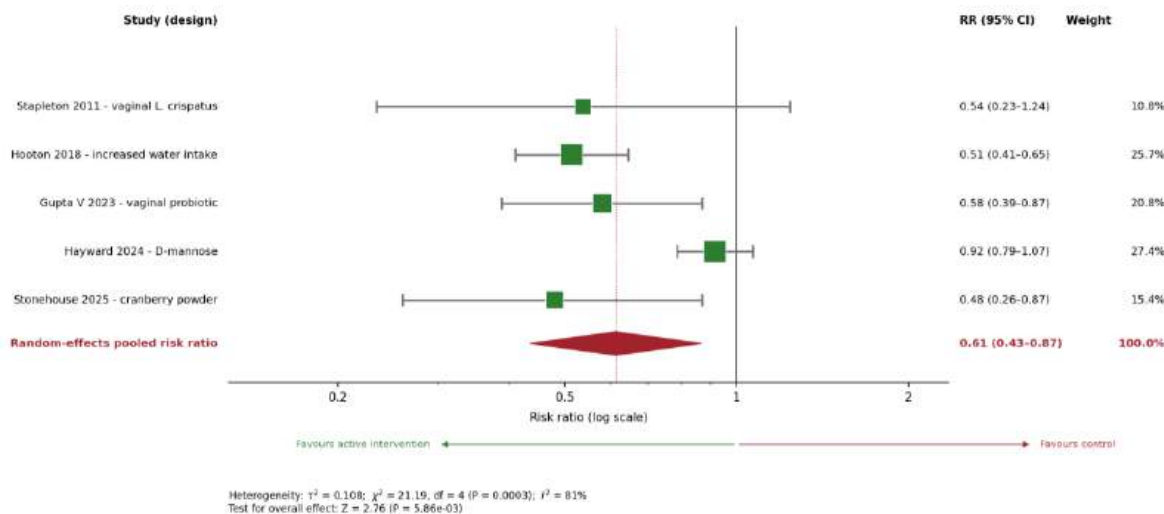


Figure 14. Forest plot of randomised modification of candidate risk factors and the risk of recurrent urinary tract infection, random-effects model.

The interpretive value of this analysis does not lie in the pooled number itself, which combines mechanistically distinct interventions and should not be read as the effect of any single strategy. It lies in the demonstration that when the specific mechanisms implicated by the observational synthesis, namely dilute urine and vaginal *Lactobacillus* depletion, are experimentally

reversed, recurrence falls; and that when a mechanism not implicated by the present synthesis is targeted instead, as with D-mannose-mediated inhibition of type 1 fimbrial adhesion, no benefit is observed. This internal consistency between the observational and the experimental evidence materially strengthens the causal interpretation of the corresponding observational domains.

Certainty of evidence

The GRADE assessment for all fourteen outcome domains is presented in Table 22. Certainty was rated as high for one domain, moderate for seven, low for four and very low for two. The single high-certainty domain was hydration status, where the evidence derives from a randomised trial with an objectively verified exposure marker. Moderate certainty was assigned to spermicide exposure, prior infection history, family history, vaginal ecology, diabetes in each of the two strata separately, antimicrobial exposure and healthcare utilisation. The coital exposure domain was rated low despite the large pooled effect, because very serious inconsistency and imprecision offset the upgrades awarded for effect magnitude and exposure-response gradient. The two very low domains were gut microbiome dysbiosis with dietary pattern, and voiding and genital hygiene behaviours, the latter reflecting serious risk of bias from recall and social-desirability effects together with directionally discordant findings across studies.

Table 22. GRADE summary of findings and certainty of evidence for all fourteen outcome domains.

Outcome domain	Studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
Recent or frequent sexual intercourse	4 (case-control, cohort, cross-sectional)	Not serious	Very serious ($I^2 = 90.5\%$)	Not serious	Serious (wide interval, non-robust to leave-	Large effect (+1); exposure-response gradient (+1)	Low

					one-out)		
Spermicide, diaphragm or spermicide-coated condom	5 (case-control, cohort)	Not serious	Serious ($I^2 = 67.0\%$)	Not serious	Not serious	Large effect (+1); exposure-response gradient (+1); confirmed by removal of exposure in clinical practice	Moderate
Prior infection history or early-onset first infection	3 (case-control, cohort)	Not serious	Not serious ($I^2 = 0\%$)	Not serious	Not serious	Large effect (+1)	Moderate
Family history in first-degree female relatives	3 (case-control)	Not serious	Serious ($I^2 = 62.9\%$)	Not serious	Not serious	Dose-gradient by number of affected relatives (+1); biological corroboration by	Moderate

						candidate-gene data (+1)	
Vaginal lactobacillus depletion and introital Escherichia coli colonisation	3 observational plus 2 randomised trials	Not serious	Serious	Not serious	Serious	Corroborated by randomised repletion of lactobacilli	Moderate
Gut microbiome dysbiosis and dietary pattern	4 (cohort, case-control, cross-sectional)	Serious (self-report exposure in two studies)	Serious	Not serious	Serious	—	Very low
Diabetes mellitus – reproductive-age stratum	1 (large retrospective cohort)	Not serious	Not applicable	Not serious	Not serious	Very large sample; effect small in magnitude	Moderate
Diabetes mellitus – postmenopausal stratum	2 (case-control, cohort)	Not serious	Not serious ($I^2 = 0\%$)	Serious (indirect for the review population)	Not serious	Large effect (+1)	Moderate

Low fluid intake and hydration status	1 randomised trial plus 1 case-control	Not serious (some concerns for open-label design)	Not applicable	Not serious	Not serious	Randomised evidence; exposure-response on urine osmolality	High
Voiding and genital hygiene behaviours	7 (case-control, cohort, cross-sectional)	Serious (recall and social-desirability bias)	Very serious (directionally discordant findings)	Not serious	Serious	—	Very low
Antimicrobial exposure and antimicrobial resistance	5 (self-controlled case series, cohort, case-control)	Not serious	Not serious	Not serious	Not serious	Very large samples; consistent direction	Moderate
Host innate-immune genetic variation	3 (case-control, genome-wide association)	Not serious	Serious	Not serious	Serious (borderline intervals)	Biological plausibility	Low

Index uropathogen species and strain persistence	4 (cohort, translation al)	Not serious	Serious	Not serious	Serious	—	Low
Healthcare utilisation and disease burden	6 (cohort, cross-sectional)	Not serious	Serious	Not serious	Not serious	Very large administrative samples	Moderate

The model distinguishes three upstream domains, namely non-modifiable host factors, behavioural exposures and metabolic or iatrogenic factors, which converge upon a single set of intermediate mechanisms comprising vaginal lactobacillus depletion, persistent periurethral colonisation, intestinal reservoir dysbiosis and attenuated urothelial innate immunity, and which in turn produce clinical recurrence. The model also represents the self-perpetuating character of the process, in which treatment of each episode further depletes the protective flora and selects for resistance, thereby raising the probability of the next episode.

Conceptual model of the interaction between risk-factor domains in recurrent urinary tract infection among women of reproductive age, as synthesised from the included studies

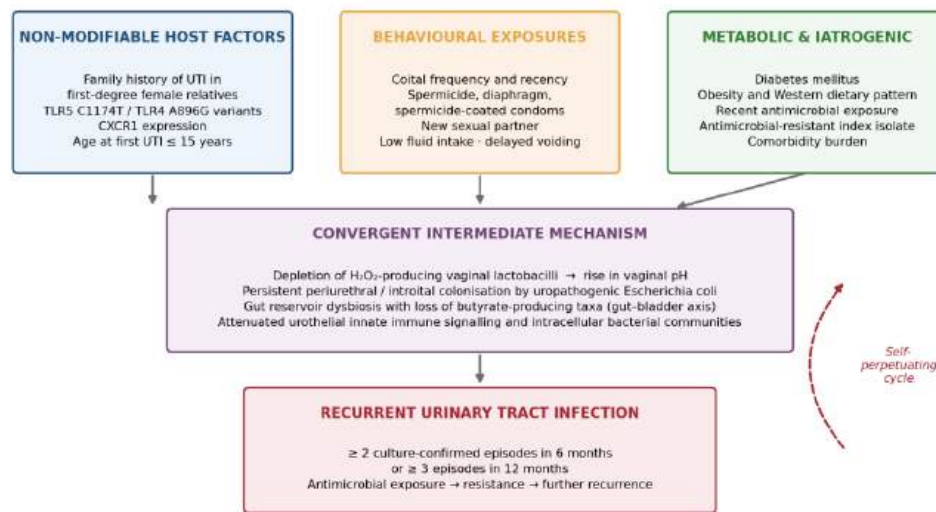


Figure 15. Conceptual model of the interaction between risk-factor domains in recurrent urinary tract infection among women of reproductive age.

DISCUSSION

Summary of principal findings

This systematic review and meta-analysis assembled 32 primary analytical studies published between up to 2026 and synthesised fourteen outcome domains, six of them quantitatively, in order to establish which determinants govern recurrent urinary tract infection specifically in women of reproductive age. Every pooled domain reached statistical significance. The dominant determinants, ranked by pooled effect magnitude, were recent or frequent sexual intercourse (odds ratio 6.78), a prior personal history of infection or a first infection at or before the age of fifteen years (3.36), a family history of infection in first-degree female relatives (3.26) and exposure to spermicide-containing contraception (2.78). Randomised modification of the implicated exposures reduced recurrence by 39% (risk ratio 0.61). Diabetes mellitus, which occupies a prominent position in guidance written for older women, was associated with an adjusted risk ratio of only 1.07 in a reproductive-age-inclusive cohort of 374,171 women, compared with 2.04 in pooled

postmenopausal data, a statistically robust difference between strata (ratio of ratios 1.91; $P = 4.2 \times 10$ to the power minus seven). All four pre-specified hypotheses were therefore supported, including the fourth, which predicted that voiding and genital hygiene behaviours would not be consistently associated with recurrence once coital exposure was accounted for.^{4,18,33,46,47}

The overall picture that emerges is of a condition in the reproductive years that is driven by the intersection of a constitutional susceptibility, which the woman cannot alter, with a small number of proximate exposures, most of which she can. This differs fundamentally from the picture that dominates the contemporary literature, in which recurrence is presented principally as a consequence of oestrogen deficiency, urogenital atrophy, impaired bladder emptying and accumulated comorbidity. Both pictures are accurate for their respective populations; the difficulty arises when guidance derived from one is applied to the other.^{20,65,72,73}

Sexual and contraceptive exposure: mechanism and interpretation

Coital exposure produced the largest pooled effect in this review and also the most heterogeneous. Both features are explicable by the same underlying property of the exposure, namely that its effect is intensely time-dependent. Where exposure was defined over a forty-eight-hour window, the odds ratio was 58.1; where it was defined over three to seven days, it fell to 9.1 in the same study and the same participants; where it was defined over one month, it was 5.8; and where it was defined simply as any vaginal intercourse during six months of follow-up, it was 1.60. This is not inconsistency between studies but a coherent decay function, and it is precisely what would be predicted by a mechanism in which coitus mechanically translocates a pre-existing introital inoculum into the bladder within approximately twenty-four hours. The experimental demonstration that abstention from sexual activity prevented new infection in women whose introital Gram-negative colonisation persisted unchanged separates the two steps of this mechanism with unusual clarity.^{18,21,27,32}

The heterogeneity in this domain therefore does not undermine the finding; it characterises it. The practical implication is that the appropriate clinical question is not whether a woman is sexually active but when, relative to her episodes, she last had intercourse. A woman whose recurrences cluster within a day or two of coitus has a different and more tractable problem than

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one whose episodes bear no temporal relation to sexual activity, and the two warrant different preventive strategies, namely post-coital single-dose prophylaxis in the former and continuous low-dose or non-antimicrobial prophylaxis in the latter. This distinction is made explicitly in the rapid review that informed contemporary practice recommendations and is reflected in the major guidelines, and the present synthesis provides the quantitative underpinning for it.^{5-7,75}

The spermicide domain is, from the standpoint of clinical utility, the more valuable of the two, because it is fully modifiable at no cost to the patient's sexual life. Its pooled estimate of 2.78 was robust to removal of every individual study, showed a clear exposure-response gradient across one, three and five days of weekly use in two independently recruited prospective cohorts, and was mechanistically corroborated by the finding that spermicide use was associated with an odds ratio of 12.5 for vaginal *Escherichia coli* colonisation and 2.9 for absence of hydrogen-peroxide-producing lactobacilli. The observation that the cervical cap, which is mechanically similar to the diaphragm but employs substantially less spermicide, carried no detectable risk provides an elegant internal control that isolates the chemical rather than the mechanical component of the exposure. So does the finding that condoms without spermicide were protective against a second infection with a different uropathogen, whereas spermicide-coated condoms carried odds ratios rising to 6.05 with frequent use.^{19,25-27,30}

Two caveats attach to this domain. The first is temporal. Most of the spermicide evidence derives from North American populations studied between 1985 and 2000, when the diaphragm and spermicidal preparations occupied a much larger share of contraceptive practice than they do today. The absolute population attributable fraction of spermicide exposure is therefore almost certainly lower now than these studies imply, even though the relative risk in an individual woman who does use these methods is unlikely to have changed. The second caveat concerns oral contraception. One classical case-control study found no association with oral contraceptive use, whereas the largest contemporary cohort found that prior-year oral contraceptive prescription was significantly associated with recurrence. This discordance is most plausibly explained by confounding by indication in the administrative dataset, in which a prescription for oral contraception is a marker of

sexual activity rather than an independent exposure, and it should not be interpreted as evidence that oral contraceptives cause recurrence.^{4,21}

Constitutional susceptibility: personal history, family history and host genetics

Two of the four strongest determinants identified in this review are not behavioural at all. A prior history of infection produced a pooled odds ratio of 3.36 with an I-squared of exactly zero across a case-control study, a prospective cohort and a second case-control study conducted in different countries two decades apart. Such complete absence of between-study variance is rare in observational synthesis and argues strongly that the underlying trait is stable and design-independent. The related finding that a first infection at or before the age of fifteen years carried an odds ratio of 3.9 is particularly informative, because that exposure predates almost all of the behavioural risk factors under consideration and therefore cannot be explained by them.^{18,21,28}

Family history produced a pooled odds ratio of 3.26 with a clear monotonic gradient from 3.1 for one affected first-degree female relative to 5.0 for two or more. Dose-gradients of this kind are among the strongest non-experimental arguments for a genuine underlying determinant, and the finding is corroborated by pedigree analysis in a three-generation family study in which acute pyelonephritis was five times more common among relatives of affected probands than among relatives of controls, with pedigrees consistent variously with dominant and recessive inheritance. It is important to acknowledge that familial aggregation may reflect shared environment and shared behaviour as well as shared genotype, and the present review cannot separate these. The candidate-gene and genome-wide evidence, however, supplies a plausible genetic component.^{33,34,37,39}

The genetic evidence is biologically coherent but quantitatively modest. The TLR5 C1174T variant, which abrogates flagellin-induced signalling and would therefore be expected to impair recognition of flagellated uropathogens, was associated with recurrent cystitis with an odds ratio of 1.81 whose lower confidence limit touched unity. TLR4 A896G was protective for recurrent cystitis while TLR1 G1805T was protective for pyelonephritis, an anatomical specificity that is itself informative and that argues against a generic immunodeficiency explanation. Work on the TLR4 promoter indicates that variation in receptor expression rather than in protein structure may be the operative mechanism, and genome-wide analysis has identified a female-specific locus near TSN

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together with Mendelian randomisation evidence implicating lifetime smoking. None of this is remotely ready for clinical genotyping, and the honest conclusion is that host genetic variation is established as a contributor to the constitutional susceptibility revealed by family history, but that the specific variants so far identified account for only a small fraction of it.^{34,36,38,39}

It is also notable that two exposures with a long history in clinical teaching, namely ABO blood group and non-secretor phenotype, were not associated with recurrence in either the reproductive-age case-control study or the prospective diary-based cohort, despite non-secretor status being a significant independent predictor in postmenopausal women with an odds ratio of 2.9. This is a further instance of the stratum-specificity that runs through the present review.^{18,19,65}

Vaginal microbial ecology as the convergent intermediate mechanism

The most satisfying feature of the present synthesis is that the behavioural and the constitutional domains converge upon a single, experimentally accessible intermediate mechanism. Women prone to recurrence carry a periurethral and vaginal flora dominated by Gram-negative enteric organisms rather than by lactobacilli; vaginal *Escherichia coli* colonisation was present in 35% of women with recurrence and 11% of controls; the absence of hydrogen-peroxide-producing lactobacilli was associated with that colonisation with an odds ratio of 4.0, rising to 6.5 after adjustment for spermicide use; and spermicide exposure was itself associated with both colonisation and lactobacillus depletion. Coitus then translocates the established inoculum into the bladder. Every element of this chain is documented, and the chain accounts for both of the leading behavioural determinants.³⁰⁻³²

What elevates this from a plausible narrative to a supported causal account is the randomised evidence. Intravaginal repletion of *Lactobacillus crispatus* after treatment of acute cystitis reduced recurrence from 27% to 15%, and among women who achieved sustained high-level colonisation the risk ratio fell to 0.07. An independent four-arm trial in 174 premenopausal women found that vaginal and combined vaginal-plus-oral probiotic arms reduced four-month incidence from 70.4% to 40.9% and 31.8% respectively and approximately doubled the time to first recurrence, whereas the oral-only arm did not differ significantly from placebo. The route-specificity of that result is itself strong evidence that the operative mechanism is vaginal rather than

systemic. The contrast with D-mannose, which targets type 1 fimbrial adhesion rather than vaginal ecology and produced a clearly null result in a well-powered primary-care trial of 598 women, further supports mechanistic specificity rather than a non-specific placebo effect.⁵¹⁻⁵³

Not every dysbiotic marker carries independent risk. A bladder microbiome study using catheterised urine found no difference in the detection rate of *Gardnerella* species between women with recurrence and controls, with risk confined to *Escherichia*-dominant urotypes, and work on the urinary microbiota in bacterial vaginosis suggests that urine may act as a reservoir for vaginosis-associated taxa without that carriage necessarily translating into symptomatic urinary infection. The discipline required here is to distinguish markers of a disturbed community from members of the causal pathway, and the randomised repletion data currently provide the only reliable means of doing so.^{70,71}

The gut-bladder axis and dietary pattern

The intestinal reservoir contributes in a manner that is more subtle than the simple model of a larger or more virulent faecal *Escherichia coli* population would predict. In the twelve-month multi-omic cohort, gut and bladder *Escherichia coli* populations were comparable between women with and without a history of recurrence in both relative abundance and phylogroup; what differed was the richness of the surrounding community, the abundance of butyrate-producing taxa and the transcriptional signature of circulating mononuclear cells. Susceptibility therefore appears to reside in the host response to a common reservoir rather than in the reservoir itself, a conclusion independently supported by the comparative genomic finding that no set of putative urovirulence genes predicted urovirulence and that supplanting strains sometimes carried fewer such genes than the strains they displaced.^{17,40}

Dietary evidence is directionally consistent but methodologically weaker. The largest dataset, comprising 57,252 women, found recurrence prevalence falling monotonically from 14.2% in non-vegetarians to 10.3% in vegans, with 23% and 31% lower adjusted odds for lacto-ovo-vegetarians and vegans respectively; a community survey linked unhealthy dietary pattern, low fruit and vegetable intake, sedentary behaviour and obesity to more frequent episodes; and a case-control study linked faecal dysbiosis to recurrence and increased body weight to dysbiosis. All of these rely

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on self-reported outcome ascertainment and on dietary self-classification, and residual confounding by socioeconomic position, healthcare access and health-consciousness is difficult to exclude. The randomised cranberry trial, with a culture-confirmed endpoint and an adjusted risk ratio of 0.48, provides the only interventional support in this domain, and it targets bacterial adhesion rather than the gut community as such. This domain was accordingly graded as very low certainty, and the appropriate clinical posture is to discuss diet quality as part of general health rather than to advise a specific diet for the prevention of recurrence.^{41–43,54}

Metabolic comorbidity and the divergence between reproductive-age and postmenopausal women

The stratum-specific finding for diabetes mellitus is, in the authors' view, the single most clinically consequential result of this review. Within a reproductive-age-inclusive cohort of 374,171 women, the adjusted risk ratio for diabetes was 1.07, an estimate that is statistically significant only because of the extraordinary sample size and that corresponds to a 7% relative increase in a condition whose baseline recurrence rate was 14.5%. Among reproductive-age women with type 1 diabetes studied in detail, no measure of glycaemic control or of microvascular complication was associated with cystitis or pyelonephritis, and the adjusted prevalence of cystitis was statistically indistinguishable from that in non-diabetic women; the dominant risk factor in that population was sexual activity, with an adjusted odds ratio of 8.28. In a prospective cohort of women with diabetes aged eighteen to seventy-five years, intercourse in the preceding week was again the dominant factor in type 1 disease, while in type 2 disease it was baseline asymptomatic bacteriuria rather than any glycaemic measure.^{4,44,45}

In postmenopausal women the same exposure behaves quite differently, with a pooled estimate of 2.04 and no heterogeneity, rising to a relative risk of 3.7 among insulin-treated women and 2.6 among those with ten or more years of disease duration. The formal test of interaction was highly significant. The most economical explanation is that diabetes contributes to recurrence principally through pathways that require additional age-related substrate, such as impaired bladder emptying, autonomic neuropathy, elevated post-void residual volume and a urogenital environment already depleted of lactobacilli by oestrogen withdrawal, none of which is typically present in a

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thirty-year-old woman with well-controlled diabetes. Contemporary syntheses of the postmenopausal urogenital microbiome-metabolic interface describe exactly this constellation.^{46,47,65,72}

The practical corollary is that a clinician counselling a reproductive-age woman with diabetes and recurrent cystitis should not present her diabetes as the principal explanation, and should not allow attention to glycaemic optimisation, which is of course warranted for its own reasons, to displace enquiry into contraceptive method, coital timing, fluid intake and antimicrobial history. Adiposity appears to behave more consistently across strata than glycaemia, being associated with infection frequency in a community survey, with infection in pregnancy, with recurrence in the large dietary cohort and with empirical treatment failure; but no study in this review provided an adjusted estimate for obesity and recurrence in a purely reproductive-age population, which is a clear gap.^{42,43,57,63}

Hydration status

The hydration domain is the only one in this review to attract high certainty, and it does so because the pivotal evidence is randomised, the population was precisely the review population, and adherence was objectively verified. Among 140 premenopausal women of mean age 35.7 years with at least three episodes in the preceding year and baseline intake below 1.5 litres daily, an additional 1.5 litres of water daily halved the episode rate, almost halved antimicrobial consumption and lengthened the mean interval between episodes by 58 days, with a 403 mOsm/kg fall in twenty-four-hour urine osmolality confirming that the intervention was actually delivered. The apparently contradictory finding from an early case-control study, that fluid volume was not associated with infection, is not in fact contradictory: that study measured habitual intake across an unselected population in whom most women were presumably already adequately hydrated, whereas the trial experimentally increased intake in women selected for low baseline consumption. The two results together define the clinically useful proposition, which is that increasing intake benefits women who drink little, not that drinking more benefits everyone.^{22,50}

Voiding and genital hygiene: discordance and its clinical and ethical implications

No domain in this review produced more discordant findings than voiding and genital hygiene, and the discordance is itself the result. Post-coital urination was protective in one multivariable analysis, was associated with infection in a second study by the same group, showed no association in a prospective diary-based cohort and did not discriminate recurrence in a six-month follow-up study. Direction of wiping after defaecation, tampon use and clothing type were each examined and each found unassociated. A prospective study in pregnant women found numerous hygiene variables associated with infection but only one, the use of wet wipes, associated with recurrence specifically. Studies conducted in low-resource settings reported strong associations with unclean latrines, handwashing practice and menstrual absorbent management, yet a population-based assessment of 3,952 girls and women in rural India found reproductive tract infection symptoms to be more common among women who bathed daily with soap and among those who washed their hands with soap after defaecation, and the authors explicitly warned that causality could not be inferred.^{2,19,21,24,57–60}

The most probable explanation for this pattern is a combination of reverse causation, in which women who have already experienced symptoms intensify their hygiene practices, and social-desirability bias in the reporting of intimate behaviours, compounded in cross-sectional designs by the impossibility of establishing temporal order. The clinical and ethical implication deserves to be stated plainly. Hygiene-focused counselling that implies a woman's recurrences result from inadequate personal care is not supported by the pooled evidence, and qualitative synthesis documents that women with recurrence already experience substantial stigma frequently linked to assumptions about their hygiene or sexuality. Given that the demonstrably strong determinants in this population are a contraceptive method, a family history, a prior infection and an antibiotic prescription, the continued prominence of hygiene advice in patient-facing material is disproportionate to its evidential basis.¹²

Antimicrobial exposure as an iatrogenic determinant

The self-controlled case series design deserves particular emphasis because it eliminates by construction the between-person confounding that limits every other observational estimate in this

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review. Within 82,337 adults contributing 206,428 infections, the incidence rate ratio in the thirty days following any oral antibiotic course, for any indication, was 1.98 in women aged fifty years or younger. Each woman serves as her own control, so the finding cannot be attributed to the possibility that women who receive more antibiotics are constitutionally more infection-prone. The mechanism is presumably disruption of the protective vaginal and intestinal communities identified in the microbial domains of this review, and the finding closes the loop of the conceptual model in Figure 14: each treated episode raises the probability of the next.^{30,40,61}

The corroborating evidence is consistent. Prior-year antibiotic prescriptions and isolation of an antimicrobial-resistant organism were both independently associated with recurrence in the largest cohort; recent antimicrobial use was a consistent predictor across all three comparisons of a three-arm case-control study; three or more prior antibiotic prescriptions carried an adjusted risk ratio of 1.60 for empirical treatment failure; and continuous suppressive therapy of six months or longer was associated with a hazard ratio of 1.50 for severe downstream infection and 1.95 for pyelonephritis relative to episodic treatment. Alongside this sits evidence of substantial misapplication: in a Welsh primary-care population, only 49.0% of women commenced on prophylactic antibiotics had met the recurrence definition beforehand, and 18.5% of those prescribed trimethoprim had documented trimethoprim resistance on the antecedent urine sample.^{4,13,15,62,63}

It would be an overinterpretation to conclude that prophylaxis is harmful, since the suppressive-therapy cohort is subject to confounding by indication of a severity that no adjustment can fully address: women placed on suppression are by definition those with the worst disease. It is nevertheless reasonable to conclude that the threshold for initiating prophylaxis should be higher, that a culture should precede it, and that non-antimicrobial options with demonstrated randomised efficacy, namely increased fluid intake, vaginal lactobacillus repletion and cranberry proanthocyanidins, should be offered first in women who do not have a compelling indication for antibiotics. This is the direction in which the most recent guideline updates have moved.^{6,10,56,73}

Uropathogen species and strain persistence

The organism itself contributes independently. A second infection followed an *Escherichia coli* index episode three times more often than a non-*Escherichia coli* index episode, and one third of recurrences in a twelve-month cohort were caused by the persisting index strain, which survived and re-emerged repeatedly across the year. Carriage of adhesins and other virulence factors did not alter recurrence risk but did increase the likelihood of index-strain persistence, a distinction that comparative genomic work has since clarified: no gene set predicted urovirulence, and expression of conserved motility and metabolic functions during culture predicted bladder colonisation better than gene carriage did. Together with the multi-omic finding that bladder and gut *Escherichia coli* populations were comparable between recurrence-prone women and controls, these data indicate that recurrence is a property of the host-organism interaction rather than of a distinct hypervirulent lineage. The clinical implication is that the identity of the index organism carries prognostic information worth recording, and that speciation at the index episode is not merely of therapeutic relevance.^{17,27,28,40}

Burden, health-service factors and the case for structured care

The burden of this condition is systematically underestimated because each episode is individually minor. Even at the subsidised prices of a student health service in 1985, an episode generated 6.1 symptom days, 2.4 restricted-activity days and 1.6 office visits. Contemporary incidence in a national claims sample was 102 per 100,000 women aged eighteen to sixty-four years, yet only 61% of affected women had any urine culture, and culture-directed management in more than half of episodes was associated with fewer infection-related hospitalisations and less intravenous antibiotic use. Qualitative synthesis describes fragmented care, repeated antibiotic courses without preventive guidance, mistrust of providers, anxiety, stigma and disruption of intimacy, family planning and work. The combination of high prevalence, low investigative intensity, high antimicrobial consumption and substantial patient-reported burden constitutes a strong argument for a structured care pathway rather than repeated episodic management, and the risk-factor hierarchy established in this review provides the content such a pathway would require.^{12,14,23,78}

Comparison with existing guidance and previous syntheses

The present findings are broadly concordant with the major guidelines but differ in emphasis in ways that matter for the reproductive-age patient. Guideline syntheses agree in supporting either continuous or post-coital antimicrobial prophylaxis, in emphasising urine culture and in limiting cystoscopy and upper tract imaging in women without risk factors; they diverge chiefly on antibiotic-sparing strategies. Practice recommendations derived from rapid review specifically endorse low-dose post-coital antibiotics for premenopausal women whose recurrence is associated with sexual activity and low-dose daily prophylaxis for those in whom it is not, and this review supplies the quantitative justification for that bifurcation. The most recent guideline update has expanded non-antibiotic options, emphasised the value of a negative urinalysis in excluding infection and shifted towards clinician judgement rather than microbial detection in weighing the risks and benefits of antibiotics.^{5-7,75}

Where this review departs from the received account is in the weight it assigns to metabolic comorbidity before the menopause, which the interaction analysis shows to be small, and in the weight it declines to assign to hygiene behaviours, for which the pooled evidence is directionally discordant. It also differs from previous syntheses in scope: existing reviews have addressed prevention rather than aetiology, or have addressed the whole adult female population in which the postmenopausal stratum dominates. The finding that D-mannose was ineffective in a well-powered primary-care trial also stands in contrast to an earlier meta-analysis of three small studies that reported a pooled relative risk of 0.23 against placebo, and illustrates the familiar pattern in which small early trials overstate effects subsequently tested at scale.^{3,53,55}

Implications for clinical practice

Six practical propositions follow from this synthesis, and they are set out with their supporting evidence and certainty in Table 23. First, a contraceptive history should be taken at every consultation for recurrence, and spermicide-containing methods, including the diaphragm and spermicide-coated condoms, should be substituted where a woman is using them; this is the single most actionable modifiable determinant identified. Second, women whose baseline fluid intake is below 1.5 litres daily should be advised to add 1.5 litres of water daily, an intervention supported by

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randomised evidence with an objectively verified adherence marker. Third, the temporal relationship between episodes and intercourse should be established, because it determines whether post-coital or continuous prophylaxis is appropriate. Fourth, a structured family history in first-degree female relatives should be recorded, since it identifies a constitutionally susceptible phenotype and supports earlier and more intensive preventive counselling without implying that the woman has done anything wrong. Fifth, intravaginal lactobacillus preparations and cranberry proanthocyanidins should be offered as antibiotic-sparing options before prophylactic antibiotics in women without a compelling indication. Sixth, antimicrobial stewardship should be applied rigorously, including for non-urinary indications, given the within-person evidence that any oral antibiotic course nearly doubles urinary infection incidence in the following month in women aged fifty years or younger.^{19,33,50,51,61,75}

Table 23. Translation of the synthesised evidence into graded clinical actions.

Risk factor	Modifiable?	Strength of association in this review	Certainty (GRADE)	Recommended clinical action
Spermicide, diaphragm and spermicide-coated condoms	Yes	OR 2.78 (1.70–4.57)	Moderate	Take a contraceptive history at every consultation for recurrence and offer a non-spermicidal alternative; this is the single most actionable modifiable factor identified
Low fluid intake (< 1.5 L daily)	Yes	Incidence rate ratio 0.51 (0.41–0.65) for the	High	Advise an additional 1.5 L of water daily in women whose baseline intake is

		randomised increase		below 1.5 L
Coital frequency and post-coital exposure	Partially	OR 6.78 (1.80– 25.49)	Low	Offer post-coital single- dose antimicrobial prophylaxis where recurrence is temporally related to intercourse, rather than advising reduced sexual activity
Vaginal lactobacillus depletion	Yes	RR 0.58 (0.39– 0.87) for intravaginal repletion	Moderate	Consider intravaginal lactobacillus preparations as an antibiotic-sparing option; avoid agents that deplete lactobacilli
Dietary pattern and gut dysbiosis	Yes	23–31% lower odds with plant- predominant diets	Very low	Discuss diet quality as an adjunct; evidence is insufficient to recommend a specific diet for prevention
Cranberry-derived proanthocyanidins	Yes	RR 0.48 (0.26– 0.87)	Moderate	Reasonable antibiotic- sparing adjunct in women who prefer non- antimicrobial prophylaxis
D-mannose	Yes	RR 0.92 (0.79– 1.07)	Moderate	Not supported for routine prophylaxis in primary care
Recent	Partially	IRR 1.98 (1.93–	Moderate	Apply strict antimicrobial

antimicrobial exposure		2.02) in women $\leq$ 50 years		stewardship; avoid antibiotics for non-urinary indications where they are not required
Prior infection history and early-onset first infection	No	OR 3.36 (2.16–5.22)	Moderate	Use as a case-finding and risk-stratification variable, not as an indication for imaging in the absence of other features
Family history in first-degree female relatives	No	OR 3.26 (2.14–4.97)	Moderate	Record a structured family history; it identifies a constitutionally susceptible phenotype and supports earlier preventive counselling
Host innate-immune genetic variation	No	OR 1.81 (1.00–3.08) for TLR5 C1174T	Low	Not ready for clinical genotyping; relevant to research stratification only
Diabetes mellitus	Partially	aRR 1.07 (1.04–1.10) in reproductive-age-inclusive cohorts	Moderate	Optimise glycaemic control for its own sake; the magnitude of the recurrence effect before the menopause is small and should not dominate counselling
Obesity and elevated body mass	Yes	Consistent direction across	Very low	Address as part of general metabolic health rather

index		four studies		than as a specific recurrence intervention
Delayed voiding and genital hygiene practices	Yes	Directionally discordant across studies	Very low	Avoid presenting hygiene advice as established causation; the evidence does not support attributing recurrence to a woman's hygiene

Implications for low- and middle-income settings, including Indonesia

Fourteen of the 32 included studies were conducted in the United States and nine in Europe. Only three were conducted in Asia and none in Indonesia or in South-East Asia more broadly. This geographical concentration limits the direct transferability of several findings. The contraceptive exposure distribution differs markedly: in Indonesia, injectable progestogens, implants and the intrauterine device account for a far larger share of contraceptive practice than the diaphragm or spermicidal preparations, so the population attributable fraction of the spermicide determinant is likely to be small even though the individual-level relative risk should hold. Conversely, the water, sanitation and menstrual hygiene exposures that were examined chiefly in Indian and Ethiopian populations are considerably more relevant to parts of the Indonesian archipelago than to the North American college populations that generated most of the behavioural evidence, and those exposures carried some of the largest adjusted odds ratios reported in this review, including 4.20 for unclean latrine use and 8.99 for changing menstrual absorbent material only once daily.⁵⁸⁻⁶⁰

Two further considerations are specific to such settings. Antimicrobial availability without prescription increases the frequency of the exposure shown here to nearly double subsequent infection incidence, and locally prevalent resistance patterns determine whether empirical therapy succeeds. The demonstration that travel to low- and middle-income countries predicts infection with extended-spectrum beta-lactamase-producing organisms, and that household members' travel does so too, indicates that resistant uropathogens circulate within households rather than only within

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healthcare facilities. There is therefore a strong case for adequately powered prospective cohort studies of recurrence in Indonesian and wider South-East Asian populations, with culture-confirmed endpoints, locally relevant contraceptive and sanitation exposures and concurrent antimicrobial susceptibility surveillance.^{61,62,79}

Strengths

This review has five principal strengths. It is restricted a priori to the reproductive-age population, so that its estimates are not diluted by the numerically larger postmenopausal literature. It integrates observational risk-factor estimates with a pooled analysis of randomised trials in which the same exposures were experimentally modified, providing an internal consistency check on causal interpretation that observational syntheses rarely possess. It applies a formal test of subgroup interaction rather than merely presenting stratified estimates, thereby converting a clinical impression about age-dependence into a quantified and statistically evaluated finding. It grades all fourteen outcome domains explicitly with the GRADE framework, so that the reader can distinguish a moderate-certainty determinant from a very low-certainty one. Finally, every reference was identified and verified through an academic search platform restricted to peer-reviewed medical literature, and each is reported with both a digital object identifier and a persistent record link, so that the evidential basis of every statement can be independently retrieved.

Directions for future research

Five priorities follow. First, prospective cohort studies with culture-confirmed endpoints are needed in Asian and African populations, including Indonesia, with exposure sets that reflect local contraceptive practice and sanitation conditions. Second, the field requires methodological standardisation: the exposure window and referent category for coital and contraceptive exposure should be harmonised, since this review demonstrates that these choices account for most of the observed heterogeneity. Third, contraceptive substitution has never been evaluated as a randomised primary preventive strategy, despite being the most actionable determinant identified here, and a trial of substituting a non-spermicidal method in women with recurrence is both feasible and overdue. Fourth, the intravaginal lactobacillus data are promising but derive from trials of modest size, and a definitive adequately powered trial with a culture-confirmed endpoint and pre-specified

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colonisation stratification is warranted, given that the largest effect observed to date was confined to women achieving sustained high-level colonisation. Fifth, the iatrogenic contribution of antimicrobial exposure identified by the self-controlled case series should be quantified prospectively with concurrent vaginal and faecal microbiota sampling, in order to establish whether the microbial disruption hypothesis accounts for the observed increase in incidence.^{51,61}

CONCLUSION AND RECOMMENDATIONS

Conclusion

Recurrent urinary tract infection in women of reproductive age is governed by a small and identifiable set of determinants that differ substantially from those emphasised in guidance written for older women. In this synthesis of 32 primary studies and fourteen outcome domains, every quantitatively pooled domain reached statistical significance. Recent or frequent sexual intercourse carried a pooled odds ratio of 6.78, a prior personal history of infection or an early first infection 3.36, a family history in first-degree female relatives 3.26 and exposure to spermicide-containing contraception 2.78. Randomised modification of the implicated exposures reduced recurrence by 39%. Diabetes mellitus, by contrast, carried an adjusted risk ratio of only 1.07 before the menopause against 2.04 after it, a difference confirmed by a formal test of interaction.

These determinants are not independent of one another. Spermicide exposure depletes hydrogen-peroxide-producing vaginal lactobacilli, permitting periurethral colonisation by uropathogenic *Escherichia coli*; coitus translocates that established inoculum into the bladder; constitutional susceptibility, evidenced by a strong dose-graded family history and by innate-immune genetic variation, determines whether colonisation produces symptomatic infection; and each treated episode further depletes the protective flora and selects for resistance, raising the probability of the next. The randomised evidence that reversing two of these mechanisms, by increasing fluid intake and by repleting vaginal lactobacilli, reduces recurrence provides an unusual degree of experimental corroboration for an observational synthesis.

The central clinical message is that the questions which most need to be asked of a reproductive-age woman with recurrent cystitis concern her contraceptive method, the timing of her episodes relative to intercourse, her fluid intake, her family history and her recent antimicrobial

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exposure. The questions that dominate much current patient-facing material, concerning hygiene practice and wiping direction, are not supported by the pooled evidence, and framing recurrence as a consequence of inadequate personal care is both unjustified and, in light of the documented experience of stigma among affected women, harmful.

Recommendations

Recommendations for clinical practice

- Elicit a full contraceptive history at every consultation for recurrence and substitute a non-spermicidal method where a diaphragm, spermicidal preparation or spermicide-coated condom is in use (pooled odds ratio 2.78; moderate certainty).
- Advise an additional 1.5 litres of water daily where baseline fluid intake is below 1.5 litres, the only recommendation in this review supported by high-certainty randomised evidence with objectively verified adherence.
- Establish the temporal relationship between episodes and sexual intercourse, and select post-coital single-dose prophylaxis where episodes cluster after coitus, reserving continuous prophylaxis for women in whom no such relationship exists.
- Record a structured family history of urinary tract infection in first-degree female relatives, and use a positive history to justify earlier preventive counselling rather than to justify imaging.
- Offer intravaginal lactobacillus preparations or cranberry proanthocyanidin products as antibiotic-sparing options before initiating antimicrobial prophylaxis in women without a compelling indication; do not offer D-mannose for routine prophylaxis.
- Obtain a urine culture before initiating any prophylactic regimen, given documented resistance to the prescribed agent on the antecedent sample in a substantial minority of women.
- Do not present diabetes mellitus as the principal explanation for recurrence in a reproductive-age woman, and do not allow attention to it to displace enquiry into contraceptive, coital, hydration and antimicrobial exposures.
- Avoid hygiene-focused counselling that attributes recurrence to the woman's personal care, for which the pooled evidence is directionally discordant and the potential for harm through stigma is documented.

Recommendations for health policy and antimicrobial stewardship

- Incorporate the finding that any oral antibiotic course nearly doubles urinary infection incidence in the following month in women aged fifty years or younger into stewardship programmes covering all indications, not urinary indications alone.
- Audit the initiation of prophylactic antibiotics against the formal recurrence definition, since fewer than half of women commenced on prophylaxis in one large primary-care population met that definition beforehand.
- Support a structured care pathway for recurrence in primary care, incorporating the risk-factor hierarchy established here, in place of repeated episodic empirical management.
- Strengthen antimicrobial susceptibility surveillance for community-onset urinary isolates, particularly in settings where antimicrobials are available without prescription.

Recommendations for future research

- Conduct adequately powered prospective cohort studies with culture-confirmed endpoints in Indonesian and wider South-East Asian populations, incorporating locally relevant contraceptive, sanitation and menstrual hygiene exposures.
- Harmonise exposure windows and referent categories for coital and contraceptive exposure, which this review identifies as the principal source of statistical heterogeneity.
- Undertake a randomised trial of contraceptive substitution as a primary preventive strategy in women with recurrence, an intervention that has never been formally evaluated despite being the most actionable determinant identified.
- Conduct a definitive, adequately powered randomised trial of intravaginal lactobacillus repletion with a culture-confirmed endpoint and pre-specified stratification by achieved colonisation density.
- Quantify the iatrogenic contribution of antimicrobial exposure prospectively, with concurrent vaginal and faecal microbiota sampling, to test whether microbial disruption accounts for the observed increase in subsequent incidence.
- Establish an adjusted estimate for obesity and recurrence in a purely reproductive-age population, which no included study provided.

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