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Urethrogenic Overactive Bladder: A Systematic Review of Pathophysiological Mechanisms and Clinical Implications

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Abstract

Purpose

While Overactive Bladder (OAB) is traditionally viewed as a detrusor-centric dysfunction, emerging evidence suggests the urethra plays a critical role in its pathogenesis. This review aims to evaluate the contribution of urethral mechanisms—including pressure variations, sensory thresholds, and morphological changes—to OAB symptoms and to explore the efficacy of urethra-targeted interventions.

Methods

A comprehensive review of clinical studies was conducted, analysing urodynamic data, Current Perception Thresholds (CPT), and magnetic resonance imaging (MRI) findings across cohorts of patients with OAB, mixed urinary incontinence (MUI), and asymptomatic controls. Therapeutic outcomes from sacral neuromodulation (SNM), urethral calibration, and micro-radiofrequency (RF) therapy were also synthesized.

Results

Patients with OAB and MUI frequently exhibit significant ‘urethral instability’ and pressure fluctuations compared to those with pure SUI. Sensory testing demonstrated that OAB is associated with altered urethral perception thresholds, suggesting a state of hypersensitivity or neural dysfunction in the lower urinary tract. Furthermore, imaging data identified distinct structural and morphological differences in the urethral sphincter and surrounding musculature of symptomatic patients. Finally, clinical outcomes indicate that interventions specifically targeting the urethra—ranging from mechanical calibration to neuromodulation and thermal therapies—result in a meaningful reduction of urgency episodes and an overall improvement in quality of life.

Conclusions

The urethra acts as a dynamic modulator of the micturition reflex rather than a passive conduit. Urethral sensory and mechanical dysfunctions are key components of OAB, and therapies targeting these urethral pathways offer promising alternatives for patients who do not respond to traditional detrusor-focused treatments.

1. Introduction

Overactive bladder (OAB) was defined by the International Continence Society (ICS) as a storage symptom syndrome characterised by ‘urgency, with or without urgency urinary incontinence (UUI),

usually with increased daytime frequency and nocturia in the absence of urinary tract infections or other pathology' [1].

In approximately 50% of cases, OAB is associated with detrusor overactivity (DO) observed during invasive urodynamic studies (iUDS) [2]. However, DO and OAB should not be considered synonymous and multiple mechanisms—linked to the urothelium, suburothelium, urethra, and central nervous system (CNS)—are believed to contribute to the pathogenesis of OAB [2,3]. Among these, the urethrogenic hypothesis proposes that urgency originates in the urethra. In the early 20th century, Barrington and other authors described various micturition reflexes in animal models [4]. They defined that micturition reflexes could be evoked by running water through the urethra or by the entry of urine into its proximal part. In patients with stress urinary incontinence (SUI), stimulation of urethral afferents may induce or exacerbate DO. In this case, OAB might seem to originate from the bladder neck [5].

Other potential urethral contributors to OAB include diminished urethral tone—often related to oestrogen deficiency in females—and urethral pressure variations during bladder filling (urethral instability) [6]. In patients with pelvic organ prolapse (POP), a vagina, incapable of supporting the bladder neck/proximal urethra stretches receptor and activates prematurely the micturition reflex [7].

The current European Association of Urology (EAU) Guidelines recommend a stepwise approach to OAB treatment, progressing from behavioural therapies to pharmacological interventions and ultimately surgical options [8,9]. However, phenotyping OAB or DO may lead to more individualized and effective management strategies.

Recently, Peyronnet et al proposed many possible OAB phenotypes according to pathophysiological factors or to urodynamic demonstration of DO [3]. Furthermore, at the ICI-RS 2023 meeting, Finazzi Agrò et al. emphasised the importance of adopting a comprehensive and personalised approach to phenotyping patients with lower urinary tract symptoms (LUTS), including both OAB and underactive bladder [10,11].

According to the concept of a future tailored approach to the treatment of OAB, this systematic review aims to summarise the current evidence on the pathophysiology, diagnostic considerations, and therapeutic approaches related to urethrogenic OAB.

2. Methods

The present SR was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[12].

2.1. Search strategy

After registering the protocol with PROSPERO (registration number CRD420250548418), we conducted a comprehensive literature search in PubMed, Embase, and Cochrane CENTRAL, including peer-reviewed studies published between January 2003 and December 2025. The search strategy employed both Medical Subject Headings (MeSH) and free-text terms. Full details of the search protocol are provided in **Supplementary File 1**.

2.2. Inclusion and exclusion criteria

Two authors (SM and LM) independently screened all titles, abstracts, and full-text records against the eligibility criteria by collecting them in an Excel sheet. In case of any disagreement, a third author (ER) solved the divergence. No automation tools were used.

For this systematic review, we included randomized controlled trials, cohort studies, and case-control studies enrolled both sex. We excluded case reports, surveys, expert opinions, editorials, abstracts, guidelines, review articles, and meta-analyses. Studies involving paediatric populations, neurological patients, or animal/cadaveric models were also excluded. Additionally, studies not addressing overactive bladder in relation to urethral physiology or pathophysiology were not considered. Patients affected by pure SUI were excluded while patients with urge urinary incontinence (UUI) or mixed incontinence (MUI) were considered.

2.3. Data collection process and data items

We collected information on the authors, year of publication, and the institution where the study was conducted. The study design (retrospective, prospective, randomized controlled trial [RCT], or non-randomized controlled trial [NRCT]) was also recorded. For each included study, we extracted data on the number of participants, their age (mean ± standard deviation, range, and median), and sex distribution (male and female). Finally, we reported the study objectives and a summary of the main results.

2.4. Reporting bias assessment

The risk of bias of each included study was assessed by two review authors working independently using the Cochrane Collaboration Risk of Bias Tool for Randomized Controlled Trials (Rob 2) and the Risk of Bias In Non-randomised Studies of Interventions Version 2 (ROBINS-IV 2) scale for randomized and non-randomized observational studies, respectively.

3. Results

3.1. Study inclusion

A total of 292 publications were initially identified through database searches. Figure 1 illustrates the flow of information through the different phases of this systematic review, in accordance with PRISMA guidelines [12]. Ultimately, 18 manuscripts met the eligibility criteria and were included in the final analysis.

3.2. Study Characteristics

Among included eighteen studies, 11 (61.1%) were prospective and 7 (38.9%) retrospective in design. The majority (83.3%, n = 15) obtained Institutional Review Board (IRB) approval, while 3 studies (16.7%) did not report ethical approval.

The total population across all studies comprised 1,134 patients, with individual sample sizes ranging from 10 to 230. Female participants represented the vast majority (81.9%, n = 16 studies included only women), whereas 2 studies (18.1%) enrolled both sexes. The mean or median age of participants varied between 42 and 69 years.

All details are reported in Table 1 and Table 2.

Table 1
– Characteristics of the included studies, providing an overview of study designs, participating institutions, ethical approval status, and patient demographics.

Study	Institution	Design	Institutional Review Board (IRB) Approval	Number of patients	Sex	Age (years)
Mattiasson et al., 2006	Lund University Hospital, Lund, Sweden	Prospective	No	87	F	NA
Futyma et al., 2015	University of Lublin, Lublin, Poland	Retrospective	Yes	208	F	OAB Group 54.6 ± 14.57) MUI Group 58.03 ± 11.86
Rahmanou et al., 2011	St. Mary's Hospital, Imperial College, London, UK	Prospective	Yes	17	F	50 (20–80)
Cucchi et al., 2004	Policlinico S. Matteo, Pavia, Italy; Universita' di Trieste, Italy; Istituto di Medicina Fisica e Riabilitazione, Udine, Italy; Universita' di Pavia, Italy	Retrospective	No	40	F	Group 2 51 ± 13 Group 2A 49 ± 15 Group 2B 52 ± 12
Kulseng-Hanssen et al., 2013	Bærum Hospital, Rud, Norway Vestfold Hospital, Tønsberg, Norway	Retrospective	No	100	F	51.5
Kirschner-Hermanns et al., 2017	University Hospital Friederich Wilhelms, University Bonn, Germany; The Federal State Institute of Public Health, The Nikiforov Russian Center of Emergency and Radiation Medicine, Saint-Petersburg, Russian Federation;	Prospective	Yes	60	F	OAB Group 60.2 ± 13.6 MUI Group 58.5 ± 14.4

Study	Institution	Design	Institutional Review Board (IRB) Approval	Number of patients	Sex	Age (years)
	Laborie, Mississauga, ON, Canada					
Lowenstein et al., 2009	Loyola Medical Center, Chicago, Illinois;St. Luke's Medical Center, Chicago, Illinois; Rambam Medical Center, Faculty of Medicine, Haifa, Israel	Retrospective	Yes	33	Both	60 (36–82)
Kenton et al., 2007	Loyola University Medical Center, Maywood, Illinois	Prospective	Yes	13	F	62 ± 14
Ichiyanagi et al., 2017	Yamagata University; Yonezawa City Hospital,Yonezawa, Japan; Okitama General Hospital,Kawanishi town, Japan; Ishigooka Clinic, Yamagata, Japan	Retrospective	Yes	12	Both	69 (49–84)
Wenzler et al., 2014	INS, Oakland University, CA	Prospective	Yes	10	F	58.9 (31–73)
Vijaya et al., 2012	St. Mary's Hospital, Imperial College, London, UK	Prospective	Yes	20	F	46 (36–68)
Serati et al., 2014	Università dell'Insubria, Varese, Italy; IRCCS San Raffaele, Milano, Italy	Prospective	Yes	230	F	Group 1 65 (54–77) Group 2 62 (52–81)
Gleason et al., 2013	University of Alabama at Birmingham, Birmingham, AL, USA;	Prospective	Yes	26	F	61 ± 13

Study	Institution	Design	Institutional Review Board (IRB) Approval	Number of patients	Sex	Age (years)
	Loyola University Medical Center, Chicago, IL, USA					
Groenendijk et al., 2007	Leiden University, Leiden and Radboud University Nijmegen (JPFAH), Nijmegen, The Netherlands	Prospective	No	19	F	45.6 ± 7.7 (31–58)
Wang et al., 2022	Shanghai Fifth People's Hospital, Fudan University, Shanghai, China College of Biomedical Engineering and Medical Imaging, Army Medical University, Chongqing, China	Prospective	Yes	11	F	42 ± 15.5
Chen et al., 2023	The Queens Medical Center, Honolulu, HI John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI	Prospective	Yes	88	F	64.48 ± 13.15
Tang et al., 2023	The First Aliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China, Nanjing, Jiangsu, China Center for Global Health, School of Public Health,Nanjing Medical University, Nanjing, Jiangsu, China	Prospective	Yes	46	Both	41.11 ± 14.23
Xu et al., 2022	Zhejiang Provincial People's Hospital, Hangzhou, China,The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China Zhejiang-California International NanoSystems	Prospective	Yes	114	Both	43.37 ± 12.57

Study	Institution	Design	Institutional Review Board (IRB) Approval	Number of patients	Sex	Age (years)
	Institute, Hangzhou, China Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China					

Table 2
Summary of study objectives and clinical outcomes.

Study	N° of patients	Objectives of the study	Results
Mattiasson et al., 2006	87	To investigate the urethral motor function in incontinent women	UDS parameters in MUI (n = 46) vs. UUI (n = 21) patients MUP (cm_{H2O}): 58.6 ± 17.0 vs. 68.4 ± 25.3, p = ns MUCP (cm_{H2O}): 45.6 ± 18.0 vs. 62.7 ± 24.0, p = 0.006 FPL (mm): 29.2 ± 5.9 vs. 28.1 ± 5.5, p = ns All pressure falls provoked by squeeze (%): 62.2 vs. 57.1, p = ns Qmax (ml/sec): 30.1 ± 33.8 (range 5-175) vs. 19.5 ± 9.6 (range 2–40), p = ns Pdetmax (cm_{H2O}): 28.8 ± 14.2 vs. 36.5 ± 16.7, p = 0.04
Futyma et al., 2015	208	The study evaluated if uroflowmetry parameters can aid in diagnosing OAB using a new parameter, the flow index (FI, the ratio of average to maximum urine flow rate) proposed as a potential diagnostic marker	UDS parameters between OAB Group (n = 66) vs. MUI Group (n = 142) FI: 0.45 (0.08) vs. 0.48 (0.11) DO: 12/66 (18.2%) vs 18/142 (12.3%) AFL: 9.75 (4.3–26.5) vs. 10.50 (4.1–34.8) MUF: 22.35 (10.3–63.6) vs. 23.75 (10.7–64.5)
Rahmanou et al., 2011	17	To determine and compare reproducibility of UPP and MUCP in women with urodynamic USI without DO (Group 1) and USI with DO (Group 2)	There were no significant differences between the groups in terms of age, parity, body mass index, or menopausal status. Group 2 exhibited greater intra-subject variability in all UPP parameters (MUCP, MUP, FUL) compared with Group 1. However, none of these parameters showed statistically significant differences between the two groups.
Cucchi et al., 2004	40	To ascertain whether abdominal pressure transmission (APT) to the urethra would be affected by urgency in women with SUI	Groups 2A vs 2B duration of urge symptoms 9 ± 7 vs. 7 ± 6 months. P-values were < 0.001for differences in both PTR_{ave} and hMUP among

Study	N° of patients	Objectives of the study	Results
		(Group 1 = 40 patients) or MUI (Group 2 = 40 patients split in Group 2A and Group 2B for the ability to delay an urgent void at CMG for at least 2 minutes)	Groups 1–2, 1-2A, and 2A-2B. Differences among Groups 1-2B were not statistically significant.
Kulseng-Hanssen et al., 2013	28	To examine how often DO causes leakage during a stress test in women with mixed urinary incontinence MUI and if there are differences between patients with or without DO during the stress test (20 jumping jacks and three forceful coughs)	100% patients leaked during the stress test, 5% due to simultaneous stress test and DO, 87% due to the stress test only, and 8% during the stress test as well as due to DO before or after the stress test. Women with DO have a significantly higher Urgency Incontinence Index and 24-h pad-test leakage ($p = 0.001$ and $p = 0.046$).
Kirschner-Hermanns et al., 2017	60	To study urethral pressure variations during the filling phase of pressure/flow studies in OAB patients compared with SUI and MUI group	Characteristics of OAB Group (n = 29) vs. SUI Group (n = 19) vs. MUI Group (n = 31) Prevalence of urethral instability (%): 79.3% vs. 47.4% vs. 36.6% Post-menopausal rate (%): 79.3 vs. 84.2 vs.77.4 Mean Δ Pressure (cm_{H2O}): 36.5 vs. 14.9 vs. 19.3, $p < 0.05$ Maximum urethral closure pressure (cm_{H2O}): 202.1 vs. 114.5 vs. 89.0 Minimum urethral closure pressure (cm_{H2O}): 1.0 vs.3.0 vs.3.8 Functional Urethral Length (mm): 38.0 ± 7.9 vs. 33.9 ± 8.7 vs. 32.1 ± 6.6 AUC Urethral pressure curves: 1195.7 ± 985.6 vs. SUI 549.4 ± 273.0 vs. 429.3 ± 214.5 OAB Group with DO vs. OAB Group without DO Mean urethral pressure (cm_{H2O}): 85.5 ± 37.0 vs. 45.2 ± 30.65, $p < 0.05$
Lowenstein et al., 2009	33	To describe the temporal relationship between increases in bladder sensation and changes in detrusor and/or urethral pressures, and to explore quantitative relationships between the	DO vs. DOI: no difference in change in sensation level ($p > 0.5$), no dominant temporal pattern ($p = 0.84$), no evidence that the change in sensation level was more likely to occur before, during, or after DO/DOI episodes

Study	N° of patients	Objectives of the study	Results
		changes in detrusor pressures and changes in urgeometer level	UPP characteristic: the most common pattern seen was an increase in sensation level after a fall in urethral pressure, but no dominant pattern was seen.
Kenton et al., 2007	13	To compare CPT in the urethra and bladder of women with idiopathic OAB to asymptomatic controls	Women with UUI were significantly older (62 ± 14 vs. 44 ± 15, p < 0.0005) and more likely to be vaginally parous (92 and 51%, p = 0.007). Urethral CPT at 2,000, 250, and 5 Hz were significantly higher in women with UUI than controls, while bladder CPT were not different between groups (2,000 Hz: 1.15 (0.76–1.53) vs. 2.63 (1.31–5.39), p = 0.005; 250 Hz: 0.45 (0.33–0.56) vs. 1.39 (0.69–2.06), p < 0.0005; 5 Hz: 0.11 (0.7–0.24) vs. 1.14 (1.01–1.86), p < 0.0005). No statistically significant bladder findings.
Ichiyanagi et al., 2017	12	To investigate associations between urethral sensation and UUI in patients with and without DO	UDS parameters and urethral CPT of the patients with normal CMG (n = 11) vs. idiopathic DO (n = 12) First desire to void (mL): 85 (34–158) vs. 173 (5–230) MCC (mL): 403 (197–625) vs. 324 (28–511) Bladder compliance (mL/H2O): 104.7 (29.5–418.5) vs. 25.5 (0.4–191.4) Urethral CPT (mA): 2.8 (1.0–5.2) vs. 9.0 (2.0–28.0)
Wenzler et al., 2014	10	To investigate if SNM affects perception thresholds of afferent sensory nerve pathways on bladder and urethra after 1 month	OAB-q Score: 78.33 vs. 31.76 (p < 0.00001) OAB QoL: 30.32 vs. 73.39 (p = 0.022) CPT at 250 and 2000 Hz in the bladder: 335.75 mA +/- 358.036 (p = 0.033)
Vijaya et al., 2012	20	To evaluate the effect of Tolterodine vs. placebo on urethra and bladder afferent nerves by evaluating the CPT changes (mA)	Only in the tolterodine ER group (n = 10) there was a significantly CPT at 5 and 250 Hz for both urethral and bladder stimulation after 1 week of treatment Urethra CPT

Study	N° of patients	Objectives of the study	Results
			5 Hz from 1.12 (1.05–1.27) to 1.30 (1.19–1.30), p-value 0.04 250 Hz from 1.43 (0.95–1.88) to 1.84 (1.61–1.99), p-value 0.01 Bladder CPT 5 Hz from 0.73 (0.29–1.01) to 2.96 (2.07–2.78), p-value 0.01 250 Hz from 1.45 (0.91–1.90) to 1.76 (1.06–2.33), p-value 0.01
Serati et al., 2014	230	To evaluate Solifenacin efficacy in patients with de novo OAB after TOT (Group 1, n = 110) vs naive women with OAB (Group 2, n = 120)	Group 1 vs. Group 2 Median voided vol/micturition ml (IQR): 122 (67–142) vs 143 (123–187), (p < 0.0001) Median change urgency episodes/24h :1.1 vs 2.3, (p < 0.0001) Median change UUI episodes/24h: 0.2 vs 1.1, (p < 0.0001) Median micturitions/24 (%): 10 (6–15) vs 7, (5–12) (p < 0.0001) Median USS change: 1.5 vs.2.25, (p < 0.0001) PGI-I score ≤ 2 (%): 36 (32.7) vs. 85, (70.8) (p < 0.0001) Symptom severity at OAB-q SF: 28.50 vs. 40.25, (p < 0.0001) QoL at OAB-q SF:23.25 vs 34.50, (p < 0.0001)
Gleason et al., 2013	26	To characterize the effect of SNM on urethral neuromuscular function in women with refractory OAB	20/26 (76.9%) women responded to SNM with a significant improvements in the UDI-6 and UIQ-7 (p < 0.001). Pre-SNM urethral sensation was not significantly different between responders and non-responders. CPT and CNE parameters did not significantly differ from baseline after 2 weeks.

Study	N° of patients	Objectives of the study	Results
Groenendijk et al., 2007	19	To evaluate the predictive value of urethral instability and other urodynamic parameters on the efficacy of SNM	13/19 (68%) responded to SNM, 6/15 patients with UI were completely dry and 5/15 had more than a 50% decrease in leakage episodes. At 6 months (baseline vs. follow-up) n. leaks/24h 13 ± 10 vs. 6 ± 8, p = 0.001 Leakage severity 2.2 ± 0.68 vs. 1.5 ± 0.45, p = 0.019 n. pads/24h 8.4 ± 7.0 vs. 4.0 ± 6.2, p = 0.002 At 6 months (SNM device on vs. SMN device off) URI + DO: 4 vs. 8 URI, no DO: 5 vs. 7 No URI, DO: 1 vs. 0 No URI or DO: 7 vs. 2 At 6 months UDS parameters (baseline vs. follow-up) FSF bladder vol (ml): 98 ± 88 vs. 235 ± 159, p = 0.002 MCC (ml): 284 ± 108 vs. 346 ± 166, p = 0.061 Peak detrusor pressure (cm_{H2O}): 42 ± 33 vs. 25 ± 14, p = 0.028 Volume at peak bladder pressure (ml): 239 ± 140 vs. 317 ± 153, p = 0.041 Peak urethral pressure during cystometry (cm_{H2O}): 121 ± 42 vs. 113 ± 42, p = 0.15
Wang et al., 2022	11	To examine the 3D morphological changes of the urination and urinary continence anatomical structures in OAB patients (n = 11) compared with healthy volounteers (n = 9) in MRI scans	MRI parameters in patients with (n = 11) and without (n = 9) OAB Thickness of bladder detrusor (mm): 3.1 ± 0.7 vs. 1.9 ± 0.3, p = 0.000 Volume of bladder detrusor (mm^3): 50,632.0 ± 19,724.7 vs. 23,386.6 ±

Study	N° of patients	Objectives of the study	Results
			7826.3, p = 0.001 Thickness of main part of urethral sphincter (mm): 2.2 ± 0.5 vs. 2.7 ± 0.3, p = 0.018 Volume of main part of urethral sphincter (mm^3): 2558.6 ± 703.2 vs. 3267.3 ± 681.9, p = 0.035 Diameter of the urethra (mm): 15.7 ± 1.6 vs. 15.7 ± 1.2, p = 0.982 Thickness of compressor urethral (mm): 3.6 ± 0.7 vs. 3.7 ± 1.0, p = 0.928 Length of compressor urethral (mm): 34.5 ± 6.6 vs. 38.2 ± 11.6, p = 0.416 Volume of compressor urethral (mm^3): 630.3 ± 301.2 vs. 866.1 ± 514.2, p = 0.247 Length of the anterior part of LAM hiatus (mm): 41.4 ± 3.3 vs. 39.0 ± 5.,p = 0.279 Length of middle part of LAM hiatus (mm): 37.7 ± 5.0 vs. 36.7 ± 4.3, p = 0.641 Length of posterior part of LAM hiatus (mm): 23. ± 6.0 vs. 21.2 ± 4.6, p = 0.451 Volume of LAM (mm^3): 27,089.4 ± 5015.0 vs. 27,294.4 ± 4461.4, p = 0.924
Chen et al., 2023		To investigate if urethral calibration with Walther's urethral sounds may be an effective treatment for OAB syndrome in a prospective placebo-controlled trial	Urethral calibration Group (n = 45) vs. control Group (n = 43) at 2 weeks Responsive patients: 14 (31.1%) vs. 4 (9.3%), p < 0.0001 Partially responsive 24 (53.3%) vs. 8 (18.6%), p < 0.0001 Failed 7 (15.6%) vs. 31 (72.1%), p < 0.0001 Urethral calibration Group (n = 45) vs. control Group (n = 43) at 8 weeks

Study	N° of patients	Objectives of the study	Results
			Responsive: 14 (31.1%) vs. 4 (9.3%), p < 0.001 Partially responsive 23 (51.1%) vs. 9 (20.9%), p < 0.001 Failed 8 (17.8%) vs. 30 (69.8%), p < 0.001
Tang et al., 2023	46	To compare the efficacy and safety of micro-radiofrequency (RF) therapy through the urethra vs. oral tolterodine tartrate in the treatment of newly diagnosed OAB	Pre-treatment parameters between micro-RF group (n = 23) vs. tolterodine group (n = 23) Voiding times/24h: 17 (15, 20) vs. 16 (14, 21) Urgency episodes/24h: 3 (1, 3) vs. 2 (2, 3) UUI episodes/24: 0 (0, 1) vs. 0 (0, 1) Mean volume per micturition: 97 (75,115) vs. 97 (84, 121) OABSS: 10 (9, 12) vs. 11 (9, 11) QoL score: 6 (5, 6) vs. 6 (6, 6) Post-treatment parameters between micro-RF group (n = 23) vs. tolterodine group (n = 23) Voiding times/24h: 10 (9, 11) vs. 13 (11, 15) Urgency episodes/24h: 1 (0, 1) vs. 2 (1, 2) UUI episodes/24: 0 (0, 0) vs. 0 (0, 0) Mean volume per micturition: 160 (145, 182) vs. 130 (110, 150) OABSS: 6 (5, 7) vs. 8 (7, 10) QoL score: 3 (2, 3) vs. 4 (3, 5)
Xu et al., 2022		To evaluate the efficacy and safety of low power micro radiofrequency (RF) therapy (μRFthera®) through urethra in the treatment of OAB through a prospective, single-blind, placebo-controlled, multi-center clinical protocol	Trial Group (n = 76) vs. control Group (n = 38) FAS 51(67.1%) vs. 10 (26.3%), p = 0.00 PPS 51(76.1%) vs. 10(26.3%), p = 0.00

Study	N° of patients	Objectives of the study	Results
			SA 46(60.5%) vs. 10(26.3%), p = 0.001 Micturition/24h 10.38 ± 4.29 vs. 13.51 ± 6.87, p = 0.0066 Urgency episodes/24h 7.44 ± 4.64 vs. 12.26 ± 7.64, p = 0.004 Quality of life score − 2.11 ± 1.49 vs. -0.60 ± 0.86, p < 0.001 Adverse events 28.9% (22/76) vs. 50.0% (19/38)

3.3. Anatomical changes in urethral complex and correlation with OAB

Wang et al. reported that OAB is associated with structural alterations in urethral continence mechanisms. OAB patients showed reduced urethral sphincter thickness (2.2 ± 0.5 mm vs. 2.7 ± 0.3 mm) and volume (2558.6 ± 703.2 mm^3 vs. 3267.3 ± 681.9 mm^3), lower compressor urethrae volume (630.3 ± 301.2 mm^3 vs. 866.1 ± 514.2 mm^3), and a more relaxed anterior levator ani muscle hiatus compared to healthy controls. The bladder detrusor was also significantly thicker (3.1 ± 0.7 mm vs. 1.9 ± 0.3 mm) and more voluminous (50,632.0 ± 19,724.7 mm^3 vs. 23,386.6 ± 7826.3 mm^3), likely reflecting frequent contractions [13].

Complementing these findings, Chen et al. showed that urethral obstruction contributes to OAB symptoms and that restoring urethral patency through calibration improved outcomes: at eight weeks, 31.1% (n = 14) of women in the treatment group were fully responsive versus 9.3% (n = 4) in the placebo group, and at least partial response was observed in 51.1% (n = 23) versus 20.9% (n = 9)[14].

The integration of these findings suggests that while OAB is often associated with specific anatomical weaknesses of the urethral sphincter, de novo OAB following mid-urethral sling surgery represents a distinct clinical entity primarily driven by iatrogenic factors. As demonstrated by Serati et al., the significantly higher PdetQmax values in non-responders (30.6 ± 8.2 vs. 19.9 ± 4.5 cmH_2O, p = 0.003) confirm that this postoperative urgency is frequently a result of increased outflow resistance and the efficacy of pharmacological therapy is markedly reduced, with a success rate of only 29.3%[15].

3.4. Correlation between urethrogenic OAB and pelvic floor

In an earlier study, Shafik et al. demonstrated the role of pelvic floor muscle (PFM) contractions in patients with OAB, suggesting that their therapeutic effect is mediated through the voluntary urinary inhibition refle [16]. Urgency typically triggers pelvic floor contractions, which contribute to the active component of abdominal pressure transmission (a.p.t.). Urodynamic assessments by Cucchi et al. in

women with stress urinary incontinence (SUI, Group 1) and mixed urinary incontinence (MUI, Group 2) showed that MUI patients exhibited both leaks due to abdominal pressure rises and involuntary detrusor contractions preceded by urgency, which could initially be voluntarily inhibited. Pressure transmission ratio (PTR) and maximum urethral pressures during holding (hMUP) differed significantly between the groups ($P < 0.001$), highlighting the critical role of the pelvic floor in modulating OAB symptoms[17].

3.5. Urethral function and urodynamic parameters

Recent studies have investigated urethral pressure variations and urodynamic parameters in women with OAB with or without incontinence. Continuous urethral pressure profiling revealed that 'urethral instability' —defined as pressure changes > 15 cmH_2O—was highly prevalent, particularly among women with OAB (36.5 cmH_2O) compared with stress urinary incontinence (SUI, 14.9 cmH_2O) and mixed incontinence (19.3 cmH_2O) ($p < 0.05$)[18]. Urodynamic studies introduced a novel flow index (FI), calculated as the ratio of average to maximum urine flow, which was significantly lower in pure OAB patients compared with pure SUI patients (0.45 ± 0.08 vs. 0.53 ± 0.09, $P < 0.001$), and similarly lower in combined OAB groups (pure OAB + MUI-OAB) versus combined SUI groups (0.47 ± 0.11 vs. 0.53 ± 0.09, $P < 0.001$), while no significant difference was found between MUI-SUI and pure SUI groups ($P > 0.5$)[19]. Some studies reported that intraurethral pressure falls during or immediately after a squeeze occurred more frequently in women with established incontinence (66%) compared with treatment-naïve incontinent women (35%) and asymptomatic controls (25%, $P < 0.001$)[20,21].

However, studies examining the temporal relationship between lower urinary tract sensation and detrusor or urethral pressure changes found no consistent pattern, indicating that heightened sensation during detrusor overactivity or incontinence episodes cannot be reliably explained by measurable changes in bladder or urethral pressures[22,23].

3.6. Treatment effects on urethral and bladder physiology

Current perception threshold (CPT) testing, which evaluates A-β, A-δ, and C fiber function, has been widely used to assess urethral and bladder sensory abnormalities in women with OAB and UUI [24–26].

Kenton et al. compared 13 women with idiopathic UUI to 48 asymptomatic controls and found significantly higher urethral CPTs at 2000, 250, and 5 Hz in the UUI group, whereas bladder CPTs were similar[24]. After adjusting for age and parity, urethral CPT at 5 Hz remained significantly elevated ($p = 0.013$), reinforcing the impact of urethral sensory dysfunction, particularly C-fibers, in aging-related OAB[24].

Ichiyanagi et al. retrospectively analysed 53 patients with and without DO and observed that median proximal urethral CPT at 3 Hz was significantly higher in neurogenic and idiopathic DO (11.3 and 9.0 mA) compared to normal controls (2.8 mA; $P < 0.05$), and in patients with UUI versus non-UUI (12.5 vs. 5.4 mA; $P < 0.05$). CPTs were not associated with bladder capacity, highlighting that hyposensitive C-fibers of the proximal urethra contribute to the development of both urodynamic DO and UUI[25]. Finally, a

randomized placebo-controlled study by Vijaya et al. evaluated the effect of tolterodine on urethral and bladder CPT in 20 women with idiopathic DO. After one week of treatment, tolterodine significantly increased urethral and bladder CPTs at 5 Hz and 250 Hz, whereas no changes were observed in the placebo group. Bladder CPT at 5 Hz was significantly higher compared to placebo ($P < 0.05$), indicating that antimuscarinic therapy can modulate urethral and bladder sensory function, particularly C- and Aδ-fiber-mediated pathways. Collectively, these studies demonstrate a consistent association between elevated urethral CPTs, C-fiber dysfunction, and impaired urethral sensory function in OAB/UUI, and suggest that both aging and pharmacologic modulation can influence urethral afferent signaling.

3.7. Urethrogenic OAB and Sacral neuromodulation (SNM)

Across the included studies, sacral neuromodulation (SNM) achieved clinical response rates ranging from 68% to 76.9%, with significant improvements in urinary symptoms, pad use, and quality-of-life measures[27]. Pathological urethral pressure fluctuations during bladder filling were highly prevalent at baseline (> 31 cm H_2O in 84% of patients) and decreased to 29% after six months of SNM[27]. In another cohort, urethral instability (> 15 cm H_2O) was present in 18 of 19 patients at baseline and in 12 of 13 successfully treated patients; after six months, urethral instability resolved in 7 responders, whereas detrusor DO resolved in only one[28]. Short-term assessments before and two weeks after stage 1 SNM implantation showed no significant changes in periurethral sensory thresholds or electromyographic parameters, and baseline urethral sensory function was similar between responders and non-responders; however, responders exhibited trends toward larger, longer, and more complex urethral motor unit action potentials at baseline[28]. In Wenzler et al study, CPT testing one month after SNM showed significant increases in bladder values at 2000 Hz ($p = 0.033$) and changes at 250 Hz, while urethral CPT values and 5 Hz measurements showed minimal or no change[29]. Overall, the included studies reported frequent baseline urethral abnormalities in OAB and variable modulation of both bladder and urethral function during SNM.

3.8. Micro-radiofrequency (mRT) and urethrogenic OAB

Recent clinical trials have shown that micro-radiofrequency (mRF) therapy is a safe and effective treatment for overactive bladder (OAB), with outcomes superior or comparable to standard pharmacotherapy[30,31]. The therapy applies low-temperature energy (40–55°C) to urethral and vaginal wall tissues, inducing collagen contraction and remodelling, which enhances urethral support and stability. These anatomical and tissue-level effects likely contribute to modulation of urethral sensory input and reinforcement of the urethra-bladder inhibitory reflex, resulting in improved urethral closure, suppression of detrusor overactivity, and enhanced pelvic floor stability[30,31].

Xu et al. reported a 75.4% response rate in the mRF group at 12 weeks, defined as a ≥ 50% reduction in urgency episodes, compared to 20% in the control group ($p = 0.001$)[30].

Similarly, Tang et al. demonstrated significant reductions in micturition frequency (from 12.33 ± 3.01 to 8.07 ± 1.62) and urgency episodes, outperforming tolterodine ($p = 0.012$)[31].

3.9. Bias assessment

Fifteen non-randomized studies were assessed using the ROBINS-I tool and were found to have an overall high risk of bias (Fig. 2A **and B**). Eleven studies (73%) were judged at serious risk, while four (27%) were rated as having a critical risk of bias[19,20,27,29]. The main sources of bias were confounding and participant selection, which raised serious or critical concerns in nearly all studies. In contrast, bias due to deviations from intended interventions was generally low.

Three randomized controlled trials, evaluated with the RoB 2 tool, showed an overall judgment of “some concerns”[14,26,30]. These trials demonstrated low risk of bias for randomization, intervention adherence, and missing outcome data, but consistently raised concerns regarding outcome measurement and selective reporting (Fig. 3A **and B**).

4. Discussion

To our knowledge, this systematic review represents the first structured analysis exploring the functional role of the urethra in the pathophysiology and treatment of OAB. The findings collectively challenge the traditional view of the urethra as a passive conduit for urine and support the concept that it actively participates in bladder regulation through reflex mechanisms, neuromuscular interactions, and structural support[7,32]. In this context, the term "urethrogenic OAB" may identify a clinically meaningful phenotype within the broader OAB spectrum, with distinct pathophysiological underpinnings and potentially distinct therapeutic implications[3,33,34].

Structural evidence from Wang et al. suggested that urethral anatomical changes (reductions in urethral sphincter thickness and volume) are not merely a consequence of OAB but may actively contribute to its onset and perpetuation[13]. These findings are consistent with the concept that a mechanically compromised urethra may fail to adequately modulate afferent signalling from the lower urinary tract, thereby facilitating premature activation of the micturition reflex[7,35].

A converging body of evidence from CPT studies highlights the importance of urethral sensory dysfunction in OAB. Kenton et al. demonstrated significantly elevated urethral CPTs at multiple frequencies in women with UUI compared to asymptomatic controls, with the most pronounced differences at 5 Hz, reflecting C-fibre dysfunction, even after adjustment for age and parity[24]. Ichiyanagi et al. similarly reported higher proximal urethral CPTs in patients with detrusor overactivity and UUI, specifically implicating hyposensitive C-fibres as contributors to the development of both urodynamic DO and urge incontinence[25]. In this context, Vijaya et al. demonstrated that antimuscarinic therapy significantly increased CPTs at both urethral and bladder levels indicating that pharmacological modulation of OAB acts through urethral afferent pathways[26].

Urethral pressure variations during bladder filling ($\Delta \geq 15$ cmH_2O), termed ‘urethral instability’, emerged as a clinically relevant finding in several included studies[4,6,27]. This condition was significantly more

prevalent in women with OAB than in those with SUI or mixed incontinence[36]. For these reasons, urethral pressure profiling, although not yet part of standard urodynamic assessment, may offer additional diagnostic value in selected patients with refractory OAB[34].

The interaction between the urethra and the pelvic floor musculature represents another important dimension of urethrogenic OAB. Cucchi et al. demonstrated that women with MUI exhibit distinct urethral pressure transmission patterns compared to those with pure SUI, with the pelvic floor playing a critical role in modulating urgency through active pressure transmission mechanisms[17]. These findings reinforce the importance of pelvic floor rehabilitation not only in stress incontinence but also in OAB, particularly when a urethrogenic component is suspected[8,16]. They also support the rationale for emerging approaches that target urethral and pelvic floor support, such as micro-radiofrequency (mRF) therapy. Micro-radiofrequency therapy offers a mechanistically coherent approach to urethrogenic OAB by targeting collagen remodelling and urethral wall stability. The randomised trial by Xu et al. demonstrated a 75.4% response rate in the mRF group compared to 20% in controls, while Tang et al. reported significant reductions in urgency and micturition frequency, with outcomes superior to tolterodine[30,31]. SNM has also shown promising effects on urethral function; however, current data remain inconsistent, limiting definitive pathophysiological interpretations and clinical implications[27–29].

An often-overlooked contributor to OAB symptoms is anatomical urethral obstruction. Chen et al. reported that urethral calibration in women with OAB resulted in significantly higher clinical response rates compared with placebo, supporting the concept that increased urethral resistance and altered afferent signalling may contribute to bladder overactivity through a mechanically mediated urethrogenic mechanism[14]. A clinically analogous scenario is represented by de novo OAB following mid-urethral sling insertion, where iatrogenic outlet obstruction, rather than primary DO, appears to drive urgency symptoms, as reflected by the markedly reduced efficacy of antimuscarinic therapy reported by Serati et al. (success rate 29.3%) [15].

Several limitations of the included studies must be acknowledged when interpreting the findings of this review. Firstly, the overall evidence quality was low: most non-randomised studies showed serious or critical risk of bias (ROBINS-I), mainly due to confounding and participant selection, while the three RCTs had ‘some concerns’ (RoB 2), particularly regarding outcome measurement and selective reporting. Marked methodological heterogeneity, across OAB definitions, ‘urethral instability’ thresholds, CPT protocols, and reported outcomes, precluded meta-analysis and limited generalisability. Most studies included exclusively or predominantly women, leaving the urethral role in male OAB largely unexplored. This gap is relevant, as male OAB is often associated with bladder outlet obstruction due to benign prostatic enlargement, where urethral mechanisms may be equally or more important.

Future research should prioritise the development of standardised diagnostic criteria for urethrogenic OAB, including validated thresholds for ‘urethral instability’. Well-designed RCTs specifically enrolling patients with a suspected urethrogenic phenotype are needed to evaluate the efficacy of targeted interventions, including mRF therapy, pelvic floor rehabilitation, and SNM. The urethral contribution to

male OAB also warrants dedicated investigation. Finally, the integration of urinary biomarkers and microbiome data, as advocated in the ICI-RS 2023 recommendations, with urethral functional parameters may ultimately enable a truly personalised approach to OAB management[33,34].

5. Conclusions

This review supports an active role of the urethra in bladder regulation and OAB pathophysiology. Based on current evidence, a clinical framework for suspected urethrogenic OAB may include history of pelvic organ prolapse, stress urinary incontinence, pelvic surgery (especially mid-urethral sling), or oestrogen deficiency; urodynamic evidence of urethral instability or increased outflow resistance; elevated urethral CPTs; and poor response to antimuscarinics or β3-agonists. Although no validated algorithm exists, the coexistence of these features should prompt consideration of a urethral aetiology and tailored management (e.g., hormonal therapy, pelvic floor rehabilitation, SNM or mRF). However, conclusions are limited by heterogeneous designs, small samples, and predominantly female populations. Larger, methodologically standardised studies including more diverse cohorts are needed.

Declarations

Authors' contribution: E.R. conceptualization, writing - original draft and writing - review&editing; S. M.: data collection and management, data analysis; L.M.: data collection and management, data analysis; P.V. methodology and data analysis; G. F.: conceptualization and methodology; A.T.: writing - original draft and writing - review&editing; E.F.A.: supervision, writing - review&editing.

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Figures

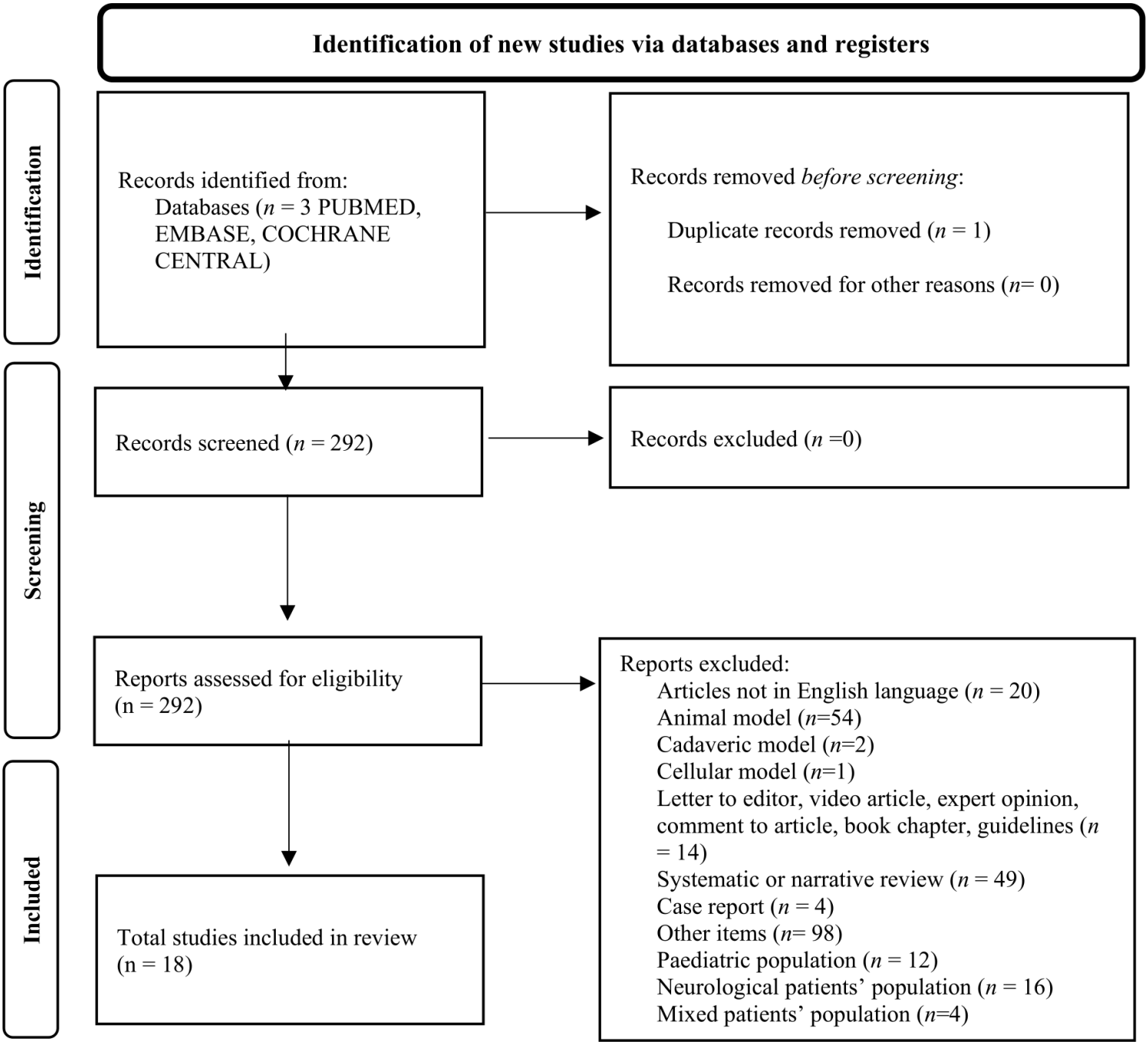
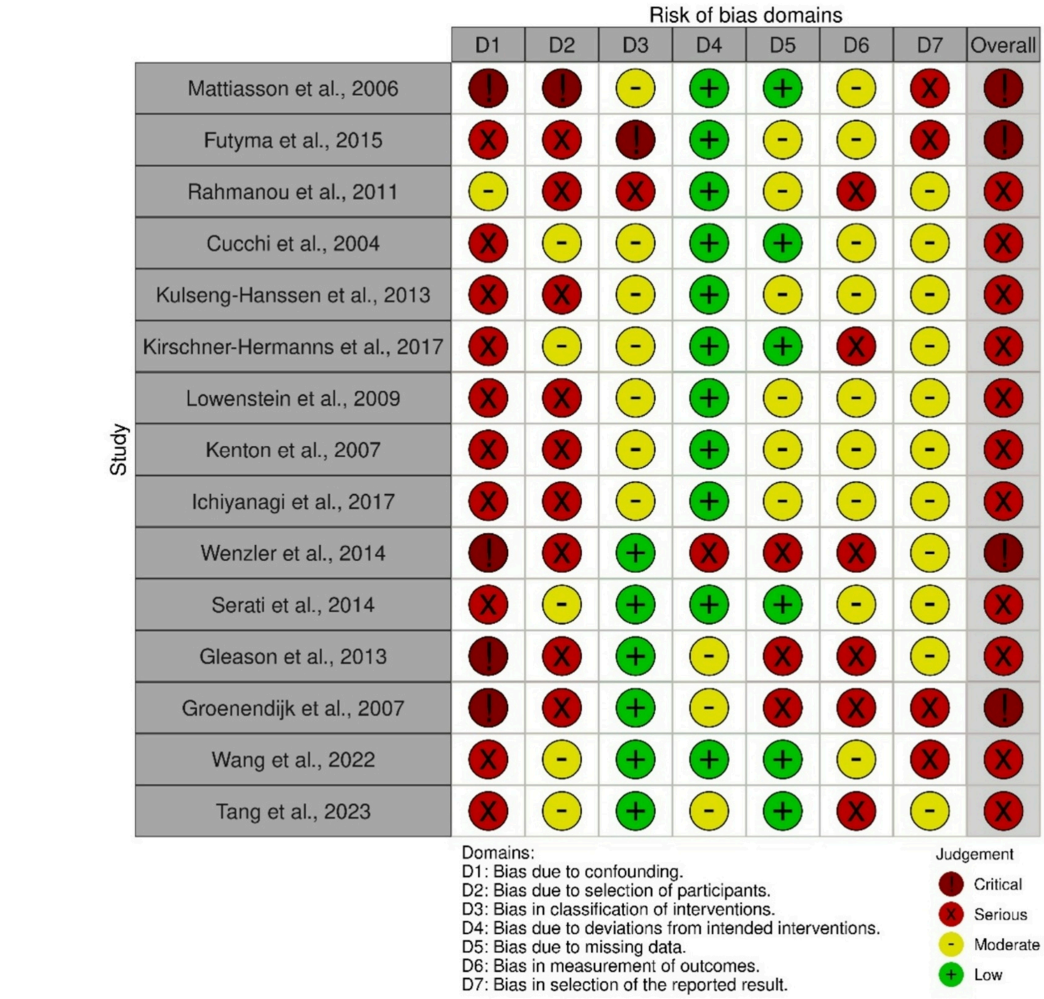


Figure 1

PRISMA flow chart



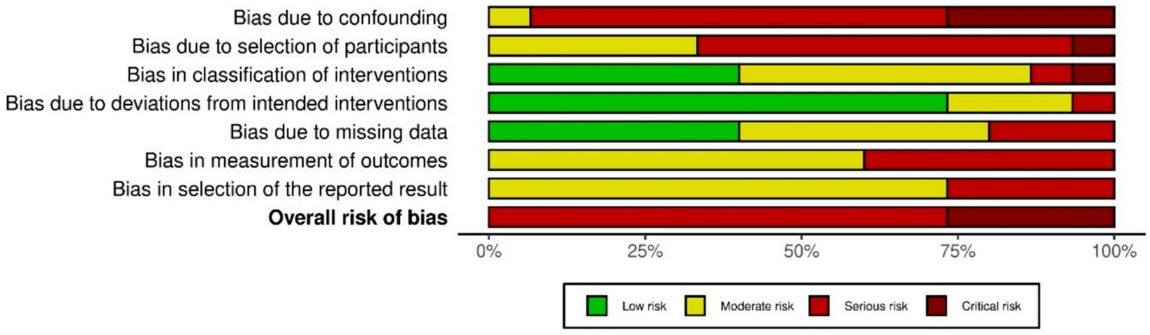


Figure 2

A and B- Bias assessment of non- randomized included studies using ROBINS-I.

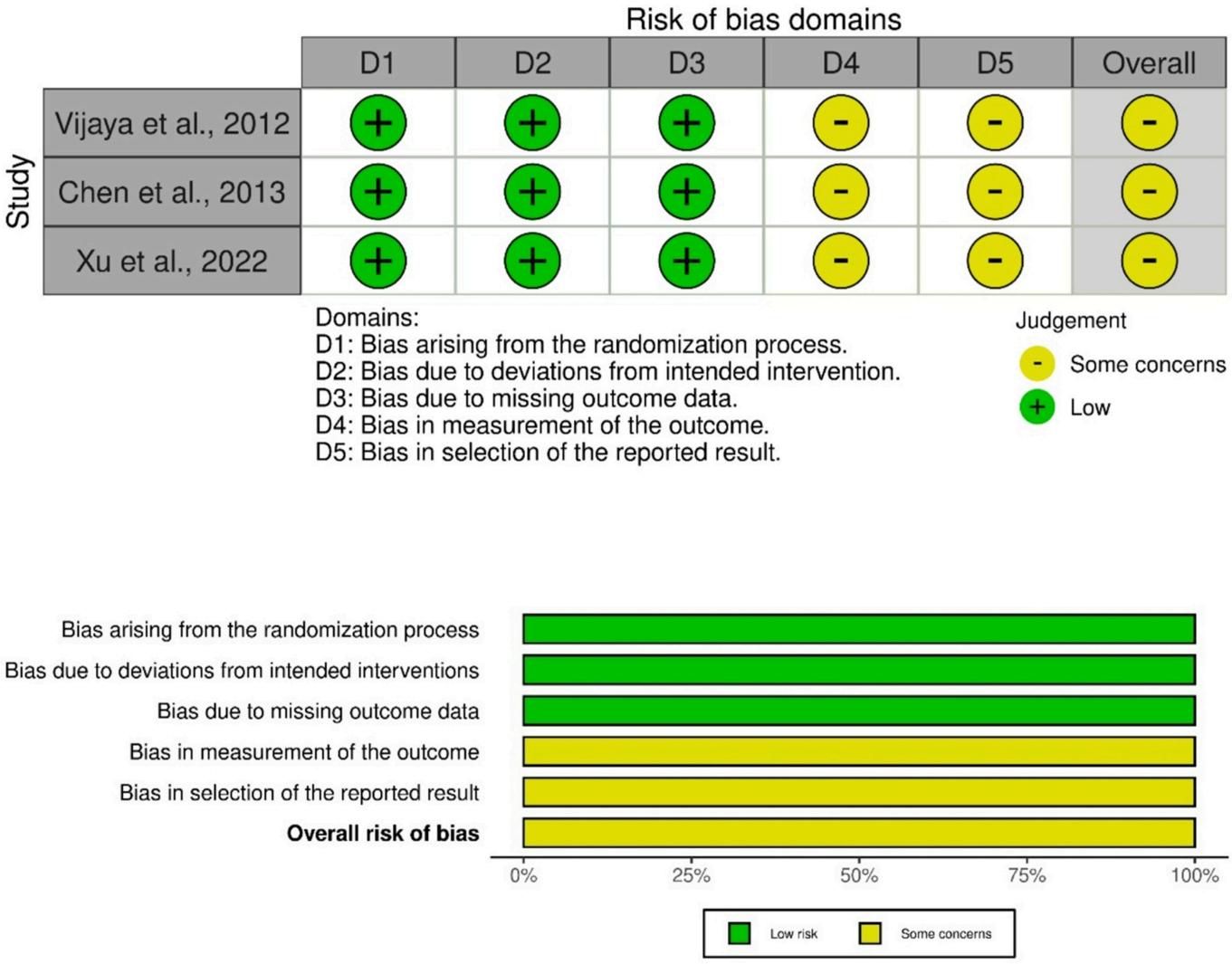


Figure 3

A and B- Bias assessment of randomized controlled included studies using ROB-2.