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Associations of delirium with urinary tract infections and asymptomatic bacteriuria in adults aged 65 and older: A systematic review and meta-analysis

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Abstract

Objective: To determine the associations of delirium with urinary tract infection (UTI) and asymptomatic bacteriuria (AB) in individuals aged 65 and older.

Methods: The protocol for this systematic review and meta-analysis was published on PROSPERO (CRD42020164341). Electronic databases were searched for relevant studies, professional associations and experts in the field were additionally contacted. Studies with control groups reporting associations between delirium and UTI as well as delirium and AB in older adults were included. The random effects model meta-analysis was conducted using odds ratios (ORs) with 95% confidence intervals (CIs) as effect size measures. The Newcastle-Ottawa scale was used to rate the studies' quality. Heterogeneity was assessed using the Q and I^2 tests. The effects of potential moderators were investigated by both subgroup and meta-regression analyses. The risk of publication bias was evaluated using the funnel plot and Egger's test.

Results: Twenty nine relevant studies (16,618 participants) examining the association between delirium and UTI in older adults were identified. The association between delirium and UTI was found to be significant (OR 2.67; 95% CI 2.12–3.36; $p < 0.001$) and persisted regardless of potential confounders. The association between delirium and AB in older adults in the only eligible study found (192 participants) was insignificant (OR 1.62; 95% CI 0.57–4.65; $p = 0.37$). All included studies were of moderate quality.

Conclusion: The results of this study support the association between delirium and UTI in older adults. Insufficient evidence was found to conclude on an association between delirium and AB in this age group. These findings are limited due to the moderate quality of the included studies and a lack of available research on the association between delirium and AB. Future studies should use the highest quality approaches for defining both delirium and UTI and consider AB in their investigations.

KEYWORDS
asymptomatic bacteriuria, delirium, urinary tract infection

INTRODUCTION

The prevalence of delirium in persons aged 65 and older (older adults) varies, depending on the method of assessment and the population studied, from 18%–35% in the general medical ward, to 20%–22% in nursing homes, 25% in geriatric units, and 7%–50% in intensive care units.[1] Delirium in older adults is associated with prolonged hospital stays, complexity of care, institutionalization and high mortality rates as well as considerable difficulties for caregivers and increased healthcare costs.[2–4]

Urinary tract infection (UTI) among older adults is also associated with a high number of cases annually and high healthcare costs.[5,6] The diagnosis of UTI requires not only confirmed bacteriuria but also the presence of genitourinary symptoms, which often cannot be reliably confirmed in the many delirious individuals who are unable to adequately express themselves, thus posing a challenge to the clinical assessment of such patients.[7] When bacteriuria is detected in older adult patients, many clinicians consider behavioral or mental changes, including delirium, as non-urinary (also called "non-specific") manifestations of UTI,[8,9] especially in patients with cognitive impairment, from whom local urinary tract symptoms are often difficult to obtain.[10] Clinicians often prescribe antibiotics for delirium in patients with confirmed bacteriuria, based on the assumption that antibacterial treatment will manage non-specific psychiatric symptoms and improve patient outcomes.[11,12]

The available evidence suggests that there is no clinical benefit (both in terms of preventing further urological problems, in terms of mental disturbances, and in terms of mortality) from the treatment of asymptomatic bacteriuria (AB), which usually has a benign natural course and may resolve on its own or persist despite treatment.[13,14] Moreover, such treatment may lead to serious side effects and the possibility of antibiotic-resistant bacteria.[15–17] There is also evidence that the administration of antibiotics itself is associated with an increased risk of delirium.[18,19]

However, the studies addressing the association between delirium and UTI in older adults are contradictory.[20–23] Furthermore, there are limited data on the association between delirium and AB in older adults.[13]

There have been three systematic reviews published to date[24–26] that have addressed the relationship between delirium and UTI. Balogun and Philbrick[24] in their systematic review concluded that there may be an association between UTI and delirium in older adults, but the studies reviewed had methodological flaws that may have led to biased results. Chae and Miller[25] did not limit their study to older adults and suggested a potential relationship between UTI and delirium. Mayne and colleagues[26] used the less specific diagnostic category of confusion rather than delirium in their study. The authors concluded that there were insufficient data to determine the relationship between confusion and UTI in older adults, explaining this by poor confusion or UTI definitions as well as inadequate control of confounding factors in individual studies. Previous reviews used less comprehensive search approaches and did not provide a meta-analytical synthesis. The association between delirium and AB has not been separately systematically studied in any age group.

By answering the main study question, what are the associations of delirium with UTI and AB in older adults, this review should improve the available evidence on these associations.

Key Points

- There is a significant association between delirium and UTI in older adults.
- The association between delirium and AB in older adults in the only study we could find was statistically insignificant.

Why Does this Paper Matter?

Clinicians should be aware of the importance of assessing UTI symptoms in older adults with delirium and of the possible presence of delirium in older adults referred for treatment of UTI.

METHODS

Methods for this systematic review and meta-analysis have been developed based on recommendations from the PRISMA statement.[27] The protocol for this study, including the definition of the study questions, description of the search strategy, definition of the inclusion and exclusion criteria, description of the approach to assessing risk of bias, and a plan for meta-analytic

synthesis, has previously been published on PROSPERO under number CRD42020164341.[28]

Search methods

An electronic search was conducted on January 5, 2021 in the following databases: PubMed, Ovid databases (Ovid Medline, PsycINFO, Embase), Cochrane Library, Scopus, CINAHL, Web of Science (Web of Science Core Collection, KCI-Korean Journal Database, Medline, Russian Science Citation Index, SciELO Citation Index), Networked Digital Library of Theses and Dissertations, and ProQuest Dissertations & Theses Global. When necessary, authors of potentially relevant publications were contacted directly to request complete usable data. A manual search was also conducted both in journals and in the proceedings of conferences and congresses with the highest impact in the field. We also contacted professional associations and experts in the field to request any further relevant data. Further details can be found in Text S1.

Selection criteria

Study type

Original studies with a control group regardless of their publication type and design (with the exception of case series and case studies) were considered. We included studies reporting the degree of associations, expressed as odds ratios (ORs), between delirium and UTI as well as between delirium and AB, or data to calculate these ORs. We considered studies of individuals (a) with delirium compared with non-delirium controls, (b) with UTI compared with non-UTI controls, and (c) with AB compared with non-bacteriuric controls.

Population

Older adults (aged 65 and older) with a diagnosis of delirium, UTI or AB. Comparison subjects were participants without delirium, UTI, or AB respectively. The diagnosis of delirium could have been made either (1) according to DSM or ICD diagnostic criteria (any version); or (2) using a symptom threshold on validated delirium rating scales; or (3) based on records in medical files/registries. The diagnosis of UTI could have been made either (1) on the basis of presence of 1 or more species of bacteria growing in the urine specimen at specified quantitative counts ($\geq 10^5$ colony-forming units [CFU]/ml or $\geq 10^8$ CFU/L) in the presence of classic signs or symptoms of (a) cystitis (dysuria, urinary frequency and/or urgency, suprapubic pain or tenderness, hematuria) or (b) pyelonephritis (flank pain, costovertebral angle pain or tenderness) or (c) systemic illness (fever, chills, rigors, marked fatigue, malaise beyond baseline) or (2) based on a listing of the diagnosis of UTI in medical records without additional data on tests performed and presence of UTI symptoms. The diagnosis of AB could have been made either (1) on the basis of presence of 1 or more species of bacteria growing in the urine specimen at specified quantitative counts ($\geq 10^5$ CFU/ml or $\geq 10^8$ CFU/L) in the absence of signs or symptoms attributable to UTI or (2) on the basis of study-defined criteria or (3) based on a listing of the diagnosis of AB in medical records.

Outcomes

The outcome measures were ORs expressing the association between delirium and UTI, and between delirium and AB in older adults.

Identification and selection of studies, data extraction, assessment of study quality

These steps were performed blindly by D.K. and R.K. and are described in detail in Text S1. The quality of the studies was assessed using the Newcastle-Ottawa scale[29] (see Text S2 with the scale content and Table S4 with the detailed results of each study assessment).

Statistical analysis

ORs were extracted when they were available or calculated from the available data. We used random-effects model in our meta-analysis. First, we performed a meta-analysis of ORs across all studies addressing the association between delirium and UTI in older adults. Next, a sensitivity analysis was conducted by (1) removing the study with the highest relative weight and (2) removing the one clear outlier with the highest effect size. Then we conducted a subgroup meta-analyses of the studies (1) in which participants with delirium were compared with non-delirium controls, (2) in which participants with UTI were compared with non-UTI controls, (3) with a diagnosis of delirium based on DSM or ICD criteria, (4) with a diagnosis of UTI based on microbiological urine tests, (5) conducted in the clinical setting, (6) conducted in nursing homes, (7) of population-based samples.

Additionally, we performed meta-regression analyses including year of study publication, study country, type,

temporality and setting, delirium and UTI assessment method, rating on the Newcastle-Ottawa scale, age of study participants, their gender distribution and residence status, psychiatric and medical comorbidities, and received medications as regressors (for a complete list of all regressors, see Table S5).

We used Cochran's Q test and I^2 values to assess the heterogeneity of effect sizes. We used funnel plot as well as Egger's regression asymmetry test[30] to assess the presence of the publication bias. We used Duval and Tweedie's "trim and fill" method to examine the effect of the missing results caused by publication bias, if it was detected.[31] With this method, a pooled effect size is recalculated by including the hypothetical missing studies as if they actually existed to augment the observed data so that the funnel plot is more symmetrical.

In the only study found addressing the association between delirium and AB in older adults, the OR was calculated separately.

Analyses were performed using Comprehensive Meta-Analysis Version 3 (Biostat, Englewood, NJ 2013).

RESULTS

Figure 1 illustrates the study selection process, with 29 studies[20–23,32–56] being retained for a meta-analysis of the associations between delirium and UTI, comprising 16,618 participants, with 26 studies[20,21,23,32–38,40–55] comparing participants with delirium (4842 individuals) to those without delirium (10,849 individuals), and 3 studies[22,39,56] comparing participants with UTI (266 individuals) to those without UTI (661 individuals) (for details on each study, see Table 1 and Table S1). A study by Gau and colleagues[22] presented data on the association between delirium and UTI as well as on the association between delirium and AB (192 participants in total: 50 individuals with AB and 142 non-bacteriuric subjects) and this was the only study we could find that addressed this association: the OR with a 95% confidence interval (CI) for this association was calculated separately (for details see Table 1 and Table S2). Studies not included in the meta-analysis after evaluation of the full text are listed in Table S3, with reasons for exclusion.

The results of all analyses relating the associations between delirium and UTI in older adults are summarized in Table 2, which reports the effect sizes (ORs with 95% CI) as well as tests of heterogeneity and publication bias (Egger's test).

Our first analysis of all 29 available studies of associations between delirium and UTI found a significant pooled effect size (OR 2.67; 95% CI 2.12–3.36; p-value <0.001) (Figure 2). Heterogeneity was high and

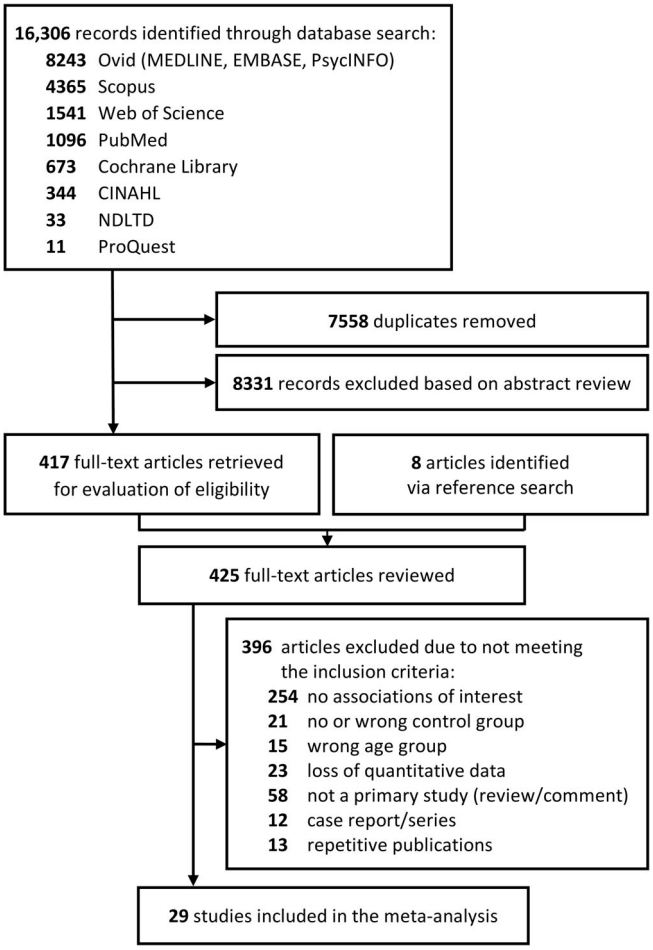

FIGURE 1 PRISMA diagram of included and excluded studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

significant, Egger's test was also significant, indicating publication bias. Correction of publication bias using Duval and Tweedie's method yielded the following result: OR 2.17; 95% CI 1.72–2.74 (see Figure S1).

After removing the study with the highest weight[34] as well as after removing one clear outlier with the highest effect size,[55] results remained significant. Subgroup meta-analyses of studies (1) in which participants with delirium were compared with non-delirium controls,[20,21,23,32–38,40–55] (2) in which participants with UTI were compared with non-UTI controls,[22,39,56] (3) with a diagnosis of delirium based on DSM or ICD criteria,[23,32,36–40,42,45,46,49,50,53–55] (4) with a diagnosis of UTI based on microbiological urine tests,[22,56] (5) conducted in the clinical setting,[21–23,32–38,41–46,48–50,52,54–56] (6) conducted in nursing homes,[20,47,51] and (7) of population-based samples[39,40] each found a statistically significant pooled OR (see Figures S2–S17). Thus, the results of all sensitivity and subgroup meta-analyses (see Table 2 and Figures S2–S17) were also statistically significant.

Meta-regression analysis showed that year of study publication, study country, type, temporality and setting,

TABLE 1 Main characteristics[a] of included studies reporting associations of delirium with urinary tract infections and asymptomatic bacteriuria in older adults

Study	Study design	Approaches to the diagnosis of delirium, UTI, and AB
Alvarez-Perez, 2017[32]	Retrospective cohort study	*Delirium*: DSM-5 criteria *UTI*: record in medical charts
Amado Tineo, 2013[33]	Prospective cross-sectional study	*Delirium*: CAM *UTI*: record in medical charts
Anderson, 2010[20]	Prospective cohort study	*Delirium*: CAM *UTI*: record in medical charts
Arshi, 2018[34]	Prospective cohort study	*Delirium*: record in medical charts *UTI*: record in medical charts
Brouquet, 2010[21]	Prospective cohort study	*Delirium*: CAM *UTI*: record in medical charts
de Bortoli Pereira, 2018[35]	Prospective cross-sectional study	*Delirium*: CAM *UTI*: record in medical charts
Edlund, 2001[36]	Prospective cohort study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Edlund, 2006[37]	Prospective cohort study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Elsamadicy, 2017[38]	Retrospective cohort study	*Delirium*: DSM-5 criteria *UTI*: record in medical charts
Eriksson, 2010[39]	Prospective cross-sectional study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Eriksson, 2011[40]	Prospective cross-sectional study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Gau, 2009[22]	Retrospective case–control study	*Delirium*: record in medical charts *UTI*: positive microbiological urine tests and presence of UTI symptoms *AB*: positive microbiological urine tests and absence of UTI symptoms
Gual, 2018[41]	Prospective cohort study	*Delirium*: CAM *UTI*: record in medical charts
Jitapunkul, 1992[23]	Prospective cohort study	*Delirium*: DSM-III-R criteria *UTI*: record in medical charts
Khurana. 2002[42]	Prospective cohort study	*Delirium*: ICD-10 research criteria *UTI*: record in medical charts
Kobayashi, 2017[43]	Retrospective cohort study	*Delirium*: record in medical charts *UTI*: record in medical charts
Large, 2013[44]	Prospective cohort study	*Delirium*: CAM *UTI*: record in medical charts
Lundström, 2004[45]	Control group from an RCT considered as a prospective cohort	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Lundström, 2005[46]	Control group from an RCT considered as a prospective cohort	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Marcantonio, 2005[47]	Prospective cohort study	*Delirium*: CAM *UTI*: record in medical charts
Morandi, 2019[48]	Retrospective cohort study	*Delirium*: CAM *UTI*: record in medical charts
Olofsson, 2005[49]	Prospective cohort study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts

TABLE 1 (Continued)

Study	Study design	Approaches to the diagnosis of delirium, UTI, and AB
Olofsson, 2018[50]	Prospective cohort study	*Delirium*: DSM-IV-TR criteria *UTI*: record in medical charts
Perez-Ros, 2018[51]	Retrospective case–control study	*Delirium*: DSM-IV criteria, CAM *UTI*: record in medical charts
Raats, 2015[52]	Prospective cohort study	*Delirium*: DSM-IV criteria, DOSS *UTI*: record in medical charts
Sandberg, 1999[53]	Prospective cross-sectional study	*Delirium*: DSM-III-R criteria *UTI*: record in medical charts
Schuurmans, 2003[54]	Prospective cohort study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Stroomer-van Wijk, 2016[55]	Prospective case–control study	*Delirium*: DSM-IV criteria *UTI*: record in medical charts
Wojszel, 2018[56]	Prospective cohort study	*Delirium*: DOSS *UTI*: positive microbiological urine tests and presence of UTI symptoms

Abbreviations: AB, asymptomatic bacteriuria; CAM, Confusion Assessment Method; DOSS, Delirium Observation Screening Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders (number refers to the edition); ICD, International Classification of Diseases (number refers to the edition); RCT, randomized controlled trial; UTI, urinary tract infection.
[a]For further details, see Tables S1 and S2.

TABLE 2 Summary of results demonstrating pooled odds ratios in the main meta-analysis, sensitivity analysis and subgroup meta-analysis of associations between delirium and urinary tract infections in older adults

				Heterogenity			Egger's test	
Type of analysis	***N***	**OR (95% CI)**	***p* value**	***Q***	***p* value**	I^2	***t***	***p* value**
All studies[20–23,32–56]	29	2.67 (2.12–3.36)	<0.001	70.87	<0.001	60.49	2.95	0.007
After removing the study with the highest weight[34]	28	2.77 (2.24–3.43)	<0.001	47.22	0.009	42.83	1.06	0.301
After removing one clear outlier[55]	28	2.57 (2.06–3.20)	<0.001	63.07	<0.001	57.19	2.62	0.014
Studies in which participants with delirium were compared with non-delirium controls[20,21,23,32–38,40–55]	26	2.62 (2.05–3.34)	<0.001	59.16	<0.001	57.74	2.81	0.010
Studies in which participants with UTI were compared with non-UTI controls[22,39,56]	3	3.07 (1.33–7.06)	0.008	10.29	0.006	80.56	1.03	0.490
Studies with a diagnosis of delirium based on DSM or ICD criteria[23,32,36–40,42,45,46,49,50,53–55]	15	3.01 (2.25–4.01)	<0.001	22.82	0.063	38.64	2.75	0.017
Studies with a diagnosis of UTI based on microbiological urine tests[22,56]	2	4.15 (1.32–13.05)	0.015	4.88	0.027	79.50	NA	NA
Studies conducted in the clinical setting[21–23,32–38,41–46,48–50,52,54–56]	23	3.22 (2.37–4.37)	<0.001	63.94	<0.001	65.59	3.11	0.005
Studies conducted in nursing homes[20,47,51]	3	1.64 (1.09–2.48)	0.018	2.14	0.343	6.60	0.52	0.696
Studies of population-based samples[39,40]	2	2.19 (1.52–3.14)	<0.001	1.19	0.276	15.90	NA	NA

Abbreviations: *N*, number of studies included in the analysis; NA, not applicable; OR, odds ratio; 95% CI, 95% confidence interval.

delirium and UTI assessment method, rating on the Newcastle-Ottawa scale, age of study participants, their gender distribution, and residence status did not significantly influence the pooled ORs. Among the comorbid psychiatric and medical conditions we examined as regressors only the presence of dehydration, urinary catheter, and urinary retention had a statistically significant effect on the pooled OR. In a meta-regression analysis,

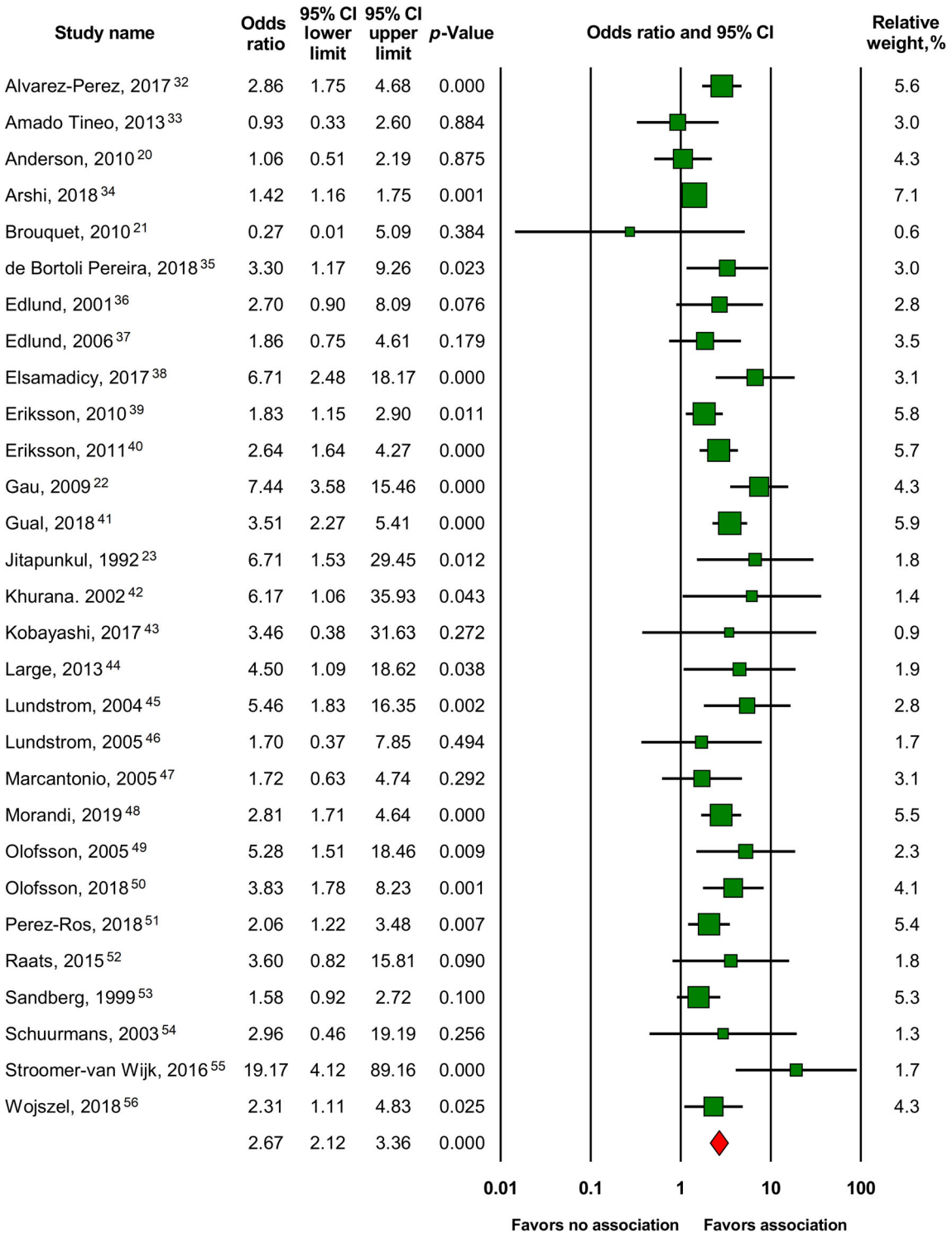

FIGURE 2 Forest plot of the main meta-analysis of 29 studies[20–23,32–56] expressing associations between delirium and UTI in older adults. 95% CI, 95% confidence interval

we also found a statistically significant effect of receiving benzodiazepines and drugs with anticholinergic properties on the pooled ORs. For details on meta-regression analysis, see Tables S5–S13.

The association between delirium and AB in older adults in the only study reporting this association that we could find[22] was statistically insignificant: OR 1.62; 95% CI 0.57–4.65; *p*-value 0.37.

DISCUSSION

To our knowledge, this is the first meta-analysis of the associations of delirium with UTI and AB. Only delirium and UTI were found to be significantly associated.

Through subgroup meta-analysis, the association between delirium and UTI persisted regardless of whether individuals with delirium were compared with non-delirium individuals, or individuals with UTI were compared with non-UTI individuals. This association remains significant when considering (1) only those studies in which delirium was diagnosed according to formal diagnostic criteria and (2) only those studies in which the diagnosis of UTI was based on positive results of microbiological urine tests combined with the presence of UTI symptoms, making it unlikely that our results were biased by non-optimal approaches to detecting delirium and UTI.

According to both subgroup meta-analysis and meta-regression analysis, the association between delirium and UTI in older adults was similar in clinical, nursing home, and population-based samples; thus, clinical referral bias cannot account for this association.

Meta-regression analysis showed that gender, age, and differences defining delirium and UTI also had no statistically significant effect on the association between delirium and UTI, which is consistent with the results of our subgroup meta-analysis. There was also no statistically significant effect of study design (cohort, case–control, cross-sectional) and temporality (prospective and retrospective) on the association we studied. The effect of the study country did not reach statistical significance. This observation should be interpreted with caution as only one or two studies were available for most countries.

It is noteworthy that preexisting dementia did not show a statistically significant impact on the association between delirium and UTI in older adults in the meta-regression analysis. It is conceivable that recognition of both delirium and UTI is more difficult in individuals with dementia, making such an association less detectable. This issue requires further study.

Among the moderators related to somatic conditions we found only dehydration, urinary retention, and the presence of a urinary catheter were found to have significant effects on the association between delirium and UTI in older adults. However, the use of a urinary catheter has previously been associated with both delirium and UTI.[57,58] The associations of delirium with dehydration and urinary retention have also been reported,[59–61] and there are some suggestions of a possible association between UTI and urinary retention.[62] Although data on the association between UTI and dehydration are contradictory, an adequate hydration is thought to improve the results of antimicrobial therapy for UTI.[63,64] In the meta-regression analysis focusing on medication status we found a statistically significant effect of benzodiazepines and drugs with anticholinergic properties on the association between delirium and UTI. However, the association between delirium and drugs from both of these groups has already been described previously.[65–67]

Study quality was not a significant predictor in the meta-regression analysis, which is consistent with our meta-analysis of subgroups demonstrating that significant results persisted when only the most rigorous studies were included, that is, studies in which the diagnosis of delirium was based on formal diagnostic criteria, and studies in which UTI was diagnosed based on results of microbiological urine tests.

There was statistically significant heterogeneity in both the main meta-analysis and most subgroup meta-analyses. However, in the sensitivity analysis with the removal of the study with the highest relative weight, the heterogeneity expressed by the I^2 value decreased from 60.49 (substantial) to 42.83 (moderate). The degree of heterogeneity was not significant in the subgroup meta-analysis that included studies with a diagnosis of delirium based on formal criteria, as well as in two smaller subgroup meta-analyses that included three studies conducted in nursing homes and two studies of population-based samples.

There was also statistically significant publication bias in both the main meta-analysis and most subgroup meta-analyses. However, the publication bias was insignificant in the sensitivity analysis with the removal of the study with the highest relative weight as well as in two small subgroup meta-analyses involving three studies in which participants with UTI were compared with non-UTI controls and three studies conducted in nursing homes. Where publication bias was observed, we attempted to correct the results obtained using Duval and Tweedie's "trim and fill" method, which identified potentially missing studies to add predominantly to the left side of the funnel plots to ensure symmetry. Adjusted ORs were slightly attenuated but remained significant (for details see Figures S1–S17).

Cross-sectional data are insufficient to identify causality in the association between delirium and UTI. The vast majority of the included longitudinal studies lack data on urine examination findings at baseline. However, in two studies[22,56] where such data are available, the number of individuals with and without delirium is pooled for the entire follow-up period. Thus, we cannot show whether one condition temporarily precedes another, thus contributing to its emergence.

In the absence of a clear signal from longitudinal studies, several possibilities arise: (1) UTI or related

factors may increase the risk of developing delirium; (2) delirium may increase the risk of developing UTI; (3) delirium and UTI share some biological risk factors. Regarding the first possibility, there is convincing evidence that inflammation, which is part of the infectious process, itself increases the risk of delirium.[68,69] As for the second hypothesis, we were unable to assess comprehensively the effect of delirium subtypes, its symptoms severity, or frequency on the association between delirium and UTI, because of the paucity of data. However, the administration of drugs with anticholinergic side effects, as well as benzodiazepines, which are known to increase the risk of delirium,[65–67] had a statistically significant effect on the association between delirium and UTI. It also seems reasonable that the inability of patients with delirium to maintain proper personal hygiene may increase the risk of UTI and complicate its treatment. This point represents an area for future research. The third hypothesis of shared biological dysfunction in delirium and UTI reflects the idea that many conditions traditionally thought to be nervous system disorders also involve changes in other physiological systems[70–73] including the immune system.

Despite extensive searching, we were unable to assess meta-analytically the association between delirium and AB in older adults: our results were limited to only one suitable study, which showed no statistically significant association between the two conditions.

Our results should be seen within the context of some limitations. First, we tried to include unpublished research data by contacting experts in the field, but were ultimately unable to obtain any unpublished data. Second, there were a group of studies whose results could potentially be used in our meta-analysis if the necessary quantitative data were reported in publications, but we were only able to obtain these data from a few authors. Third, we were unable to find any study in which both conditions (UTI or AB and delirium) were defined according to the highest diagnostic standards: in all publications one of the conditions was identified based on a record in the medical files. Fourth, the limited data available on the association between delirium and AB in the older adults should also be taken into account. All of the above suggests that our evidence is of moderate quality and further research is needed to investigate both the associations and the factors affecting them.

Some limitations are also related to the results of the meta-regression analysis. First, these results are mostly based on subsets of studies. Second, the influence of a number of somatic conditions on the association between delirium and UTI could not be properly assessed, as the individual studies did not report subtypes of the respective conditions (e.g., diabetes mellitus, type I or II) that were important for understanding such an effect. Third, we were only able to assess the effect of a small group of medications on the association we examined because many of the included studies did not report data on the medications taken by participants.

Our findings have important clinical and medical implications. Clinicians should be aware, of the importance of assessing UTI symptoms in older adults with delirium, and of the possible presence of delirium in older adults referred for treatment of UTI. Due to the lack of relevant data, no reliable conclusions can be drawn about the association between delirium and AB in older adults from our study, which points to the need for high-quality prospective research addressing this association.

The effects of treatment of UTI and AB on their associations with delirium are of particular interest for further research, as clinicians are ultimately interested in whether treatment of UTI and AB can improve delirium. In this context, the impact of treatment of usually benign AB in those subgroups of older adults who due to varying factors are at higher risk of developing UTI and urosepsis also merits further closer study. The influence of individual types of organisms (including those associated with a higher incidence of drug resistance) remains open to further research as well.

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CONFLICT OF INTEREST

None of the authors is affiliated with any organization or institution that has any financial interest in this publication. No author has any conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

D.K. led the project management. D.K. and R.K. implemented the search strategy, and performed all stages of study screening, quality assessment, and data extraction in a double-blind setting. D.K. performed the statistical processing of the data. D.K. and R.K. prepared the draft article. S.K. and E.L. accompanied the project as supervisors and contributed substantially to the interpretation of the results and the preparation of the final manuscript. All authors read and approved the final version of the manuscript.

SPONSOR'S ROLE

The study was not sponsored.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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