

# Cranberries and Urinary Tract Infections: How Can the Same Evidence Lead to Conflicting Advice?<sup>1–3</sup>

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## ABSTRACT

Cranberry has been used traditionally to prevent urinary tract infections (UTIs), primarily among generally healthy women prone to recurrent UTIs. Results from a number of published clinical studies have supported this benefit; however, meta-analyses on cranberry and UTI prevention have reported conflicting conclusions. This article explores the methodological differences that contributed to these disparate findings. Despite similar research questions, the meta-analyses varied in the studies that were included, as well as the data that were extracted. In the 2 most comprehensive systematic reviews, heterogeneity was handled differently, leading to an  $I^2$  of 65% in one and 43% in the other. Most notably, the populations influencing the conclusions varied. In one analysis, populations with pathological/physiological conditions contributed 75.6% of the total weight to the summary risk estimate (RR: 0.86; 95% CI: 0.71, 1.04); another weighted the evidence relatively equally across UTI populations (RR: 0.62; 95% CI: 0.49, 0.80); and a third included only women with recurrent UTIs (RR: 0.53; 95% CI: 0.33, 0.83). Because women with recurrent UTIs are the group to whom most recommendations regarding cranberry consumption is directed, inclusion of other groups in the efficacy assessment could influence clinical practice quality. Therefore, conclusions on cranberry and UTIs should consider differences in results across various populations studied when interpreting results from meta-analyses. *Adv Nutr* 2016;7:498–506.

**Keywords:** cranberry, meta-analysis, systematic review, urinary tract infections, women

## Introduction

Urinary tract infections (UTIs)<sup>6</sup> are the second most common infection of any organ system and the most common urological disease in the United States, with a total annual cost of >\$3.5 billion (1). UTIs occur across myriad populations, from individuals with bladder dysfunction (e.g., neuropathic bladder, bladder cancer, spinal cord injuries) to normal, healthy women. Clinically, UTIs can be categorized as complicated, which occur under conditions of bladder dysfunction and during types of medical treatments such as chemotherapy, and uncomplicated (2). Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no physiological abnormalities. Among the generally healthy population, the risk of having an uncomplicated

UTI is ~50 times higher in adult women than in adult men (3). Approximately 50% of the general healthy female population will experience  $\geq 1$  UTI during their lifetime (3, 4). Furthermore, 25–35% of women who experience a UTI will have  $\geq 1$  recurrent UTI (rUTI) episode within the subsequent year (4, 5).

Antibiotics, which are commonly prescribed for UTIs, are efficacious for treatment and have also been used for prophylaxis of rUTIs (2, 3, 6). Repetitive use of antibiotics, however, is recognized as a factor in the development of multidrug resistance bacteria and recently is reported to affect the human commensal microbiota (7, 8). How to manage rUTIs without inducing multidrug resistance in women is an important consideration in clinical practice (6, 7, 9). Specifically, due to the common occurrence of rUTIs, recommendations to use diet and lifestyle approaches before prophylactic antibiotics are advocated (6, 7). Thus, identification of successful nonantibiotic strategies for the prevention of rUTIs in generally healthy women is of high importance.

Cranberries have historically been associated with urinary tract health, particularly among women with rUTIs (10–12). Results from several clinical studies have suggested that cranberries may decrease rUTIs in healthy women (11, 13–16). In addition, *in vitro* and *ex vivo* research has

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<sup>3</sup>Supplemental Data and Supplemental Table 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at <http://advances.nutrition.org>.

<sup>6</sup>Abbreviations used: cUTI, complicated urinary tract infection; rUTI, recurrent urinary tract infection; UTI, urinary tract infection.

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suggested that cranberry-derived compounds such as A-type proanthocyanidins and other polyphenols may interfere with adhesion of bacteria (including multidrug-resistant *Escherichia coli*) to epithelial cells of the urinary tract, attenuate the development of uropathogen reservoirs (i.e., in the gastrointestinal tract and intracellular pods within the urothelium), and suppress inflammatory cascades (13, 17, 18). These observations have indicated that cranberries may provide an option for prophylaxis in certain populations.

Cranberries and UTIs have been evaluated in evidence-based systematic reviews and meta-analyses, but instead of providing clarity on the efficacy of the cranberry for prevention of rUTIs, these systematic reviews have resulted in conflicting conclusions. Specifically, a meta-analysis by Wang and colleagues published in 2012 concluded that “cranberry products were associated with protective effects against UTIs (RR: 0.62; 95% CI: 0.49, 0.80), particularly for women with rUTIs (RR: 0.53; 95% CI: 0.33, 0.83)” (19). In contrast, a meta-analysis by the Cochrane Collaboration, also published in 2012, concluded that “...cranberry juice is less effective than previously indicated...cranberry juice cannot currently be recommended for the prevention of UTIs” (20). It is interesting that the Cochrane analysis was an update of a 2008 report that resulted in a conclusion similar to that derived by Wang et al., indicating a shift in the conclusions from this group (20, 21).

In theory, meta-analysis of results from randomized clinical trials examines the consistency of data across studies and is considered to be the strongest level of evidence that guides relevant practice decisions (22). When divergent conclusions are drawn from meta-analyses of a similar pool of original trials, it becomes a challenge for clinicians and policymakers to make the most appropriate or relevant recommendations to the public and clinicians. The present review was conducted to characterize the status of evidence-based assessments on the use of cranberry and prevention of rUTIs in healthy women. In addition, this review explores methodological differences that may be related to these conflicting findings.

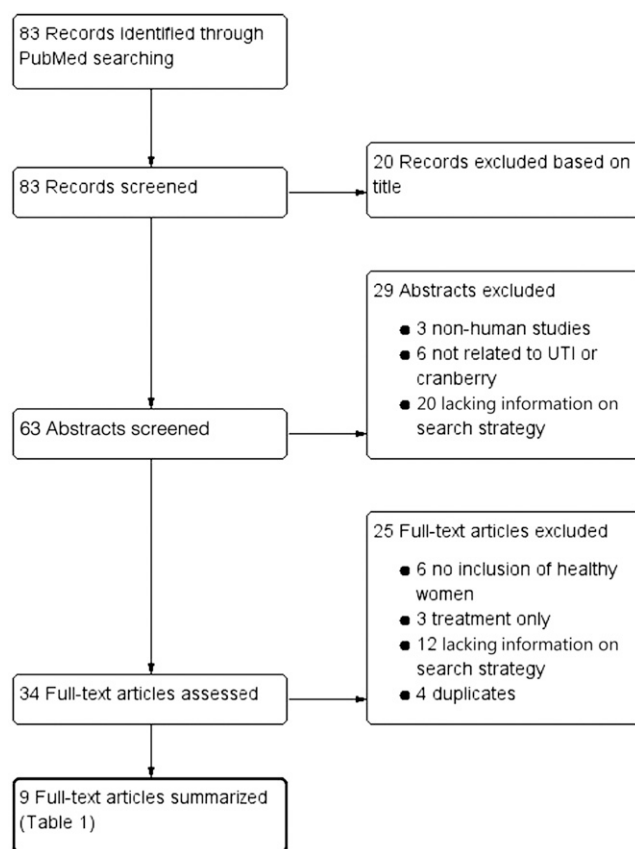
## Methods

A literature search was conducted to identify eligible systematic reviews and meta-analyses to be included in this assessment (see **Supplemental Data**). The identified meta-analyses from the literature search were selected for further detailed review. An evidence assessment was performed on the selected reports that evaluated the efficacy of the cranberry for rUTI prevention in women with rUTIs. The comparisons on methodologies included inclusion/exclusion criteria, extracted data, and statistical methods. The influences of specific studies on the overall conclusions were also explored.

## Results

### Identification of literature

The literature search identified 83 records (**Figure 1**), and 9 systematic reviews met the inclusion criteria for the evidence assessment (**Table 1**). Of these 9 reviews, 5 were systematic reviews with meta-analyses: 3 were from the Cochrane Collaboration (20, 21, 28), the latest of which was published in 2012 as an update of previous publications; 2 others were by Wang et al. (19) and Beerepoot et al. (27).



**FIGURE 1** Flow diagram of literature search. UTI, urinary tract infection.

### Assessment of meta-analysis methods

**Differences in selection of studies.** **Table 2** summarizes studies and populations that were included in 3 Cochrane systematic reviews (20, 21, 28), Wang et al. (19) and Beerepoot et al. (27), to compare cranberry products to placebo/control on UTI incidence. Overall, 21 studies were identified across all analyses; however, each analysis included only a subset of 2–13 studies. Only 2 studies were included in all analyses (**Table 2**), with another 5 studies included in both the Jepson et al. (20) and Wang et al. (19) analyses (**Table 2**).

The Jepson et al. (20) and Wang et al. (19) analyses had the same research questions, similar overall inclusion criteria for study selection, and comparable statistical models (**Table 3**). Surprisingly, studies included in these 2 meta-analyses were substantially different. It is notable that the Jepson et al. meta-analysis (20) was published as an update of the previous Cochrane analysis from 2008 (21), and yet only 4 of the studies were in common between the 2 analyses. Of 6 studies that were in Jepson and Craig (21), but not Jepson et al. (20), only 1 included women with rUTIs [because this was only a letter without additional data, it was excluded from Jepson et al. (20)]. Wang et al. (19) included 5 studies in common with Jepson and Craig (21) for overall risk estimates, only 2 of which were conducted in women with rUTIs. The impact of the differences in the study

**TABLE 1** Summary of systematic reviews on cranberry and UTI reporting search strategy and results<sup>1</sup>

Citation (reference)	Dates covered	Search strategy <sup>2</sup>	Objective	Inclusion criteria	Conclusions related to cranberry and UTI prevention
Systematic reviews <sup>3</sup>					
Micali et al., 2014 (23)	January 1994 to February 2011	Terms: cranberry, <i>Vaccinium macrocarpon</i> , UTI, natural drugs, cystitis, recurrent cystitis, PACs, and <i>Escherichia coli</i> ; databases: Medline	To present a broad overview of evidence on cranberry for the treatment of UTIs, and to summarize the evidence supporting its clinical use	Published in English	The cranberry efficacy-to-safety ratio strongly supports its use in the prevention of rUTIs in young and middle-aged women; clinical use in other groups remains controversial
Wang, 2013 (24)	2006– 2011	Terms: UTI, <i>Vaccinium macrocarpon</i> , and female searched using “OR” and “AND” as linkers; databases: PubMed Cumulative Index to Nursing and Allied Health Literature, Cochrane Library	To evaluate the research literature in which cranberry-based products are used to prevent or treat UTIs	Published in English; RCTs, comparative studies, meta-analyses, controlled clinical trials; includes clinical outcomes; human females	Some evidence suggests that cranberry products, especially in juice or cocktail form, prevent infections in some preliminary studies, but available evidence is limited
Jepson and Craig, 2007 (25)	Inception to December 2006	Terms: (1) <i>Vaccinium</i> , cranberry, fruit beverage, fruit drink, fruit juice, beverage; (2) UTIs, cystitis, bacteriuria, pyelonephritis, urinary infection, or bacterial infection; databases: Medline, Embase, Cochrane Controlled Trials Registry, CENTRAL, and others	To assess the effectiveness of cranberry or blueberry products in the prevention of symptomatic UTIs in susceptible populations	RCTs and quasi-RCTs; cranberry products vs. placebo, no treatment or any other treatment; studies in men, women, and children susceptible to UTIs; outcome: incidence of UTIs	There is some evidence from 4 good quality RCTs that cranberry juice may decrease the number of symptomatic UTIs over a 12-mo period, particularly in women with rUTIs; it's uncertain whether cranberry is effective in other groups
Systematic review and cost-effectiveness analysis					
Eells et al., 2014 (26)	1966 to January 2012	Terms: (1) recurrent, urine or urinary; and (2) infectious or infection(s); databases: Medline, Embase, Cochrane Library	To compare the effectiveness, cost, and health-related quality-of-life outcomes associated with commonly used strategies for management of rUTIs	Published in English; comparative clinical trial; placebo/untreated control; human study; nonpregnant female adults with $\geq 3$ UTIs/y; outcomes: incidence of UTI	Daily cranberry pills are effective at reducing UTIs and are cost effective; daily antibiotic use is more effective than cranberry pills
Meta-analyses					
Beerepoot et al., 2013 (27)	Published after 1984 to April 3, 2013	Terms: (1) prevention and control, prophylaxis; with (2) urinary tract infections, cystitis, pyelonephritis, UTI; databases: Medline, Embase, Cochrane Library	To assess the effectiveness, tolerability, and safety of nonantibiotic prophylaxis in adults with recurrent urinary tract infections	RCTs with parallel design; adults with recurrent UTIs; compared nonantibiotic prophylaxis to placebo or no treatment	Cranberry juice and tablets reduce the occurrence of UTIs vs. placebo
Wang et al., 2012 (19)	Inception to November 2011	Terms: (1) cranberry, <i>Vaccinium macrocarpon</i> , <i>Vaccinium oxycoccus</i> , <i>Vaccinium microcarpum</i> , <i>Vaccinium erythrocarpum</i> , <i>Vaccinium</i> ; with (2) UTI, pyelonephritis, cystitis, bacteriuria, pyuria; databases: Medline, Embase, CENTRAL	To evaluate cranberry-containing products for the prevention of UTIs	RCTs; compared cranberry products vs. placebo/control; outcome: incidence of UTIs	Cranberry-containing products are associated with protective effects against UTIs

(Continued)

**TABLE 1** (Continued)

Citation (reference)	Dates covered	Search strategy <sup>2</sup>	Objective	Inclusion criteria	Conclusions related to cranberry and UTI prevention
Jepson et al., 2012 (20)	July 2012; update of Cochrane 2008 review	Terms: (1) beverage, fruit beverage, fruit drink, fruit juice, cranberry, <i>vaccinium macrocarpum</i> , <i>vaccinium oxycoccus</i> , <i>vaccinium vitis-idaea</i> ; (2) UTIs, cystitis, bacteriuria, pyelonephritis, UTI, cystitis; (3) included terms for non-English language studies; databases: Medline, Embase, clinical trial registries <sup>4</sup> , etc.	To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations	RCTs and quasi-RCTs; comparison of cranberry products vs. placebo, no intervention, or other intervention; excluded studies on treatment of UTIs; excluded studies on UTIs not caused by bacterial infection; outcomes: incidence of UTIs	Cranberry juice is less effective than previously indicated; cranberry juice cannot currently be recommended for the prevention of UTIs
Jepson and Craig, 2008 (21)	September 2007; update of Cochrane 2004	Terms: (1) beverage, cranberry, fruit beverage, fruit drink, fruit juice, <i>vaccinium macrocarpum</i> , <i>vaccinium oxycoccus</i> , <i>vaccinium vitis-idaea</i> ; (2) UTIs, cystitis, bacteriuria, pyelonephritis, UTI, cystitis; (3) included terms for non-English language studies; databases: Medline, Embase, clinical trial registries <sup>4</sup> , etc.	To assess the effectiveness of cranberry in preventing UTIs in susceptible populations	RCTs or quasi-RCTs; cranberry products for the prevention of UTIs in all populations; studies men, women, or children susceptible to UTI; excluded studies on treatment of UTIs; excluded studies on UTIs not caused by bacterial infection; outcomes: incidence of UTIs.	Cranberry products significantly reduced the incidence of UTIs at 12 mo vs. placebo/control; cranberry products were more effective at reducing the incidence of UTIs in women with rUTIs than in elderly men and women or people requiring catheterization
Jepson et al., 2004 (28)	Search conducted November 2003	Terms: (1) beverage, cranberry, fruit beverage, fruit drink, fruit juice, <i>vaccinium macrocarpum</i> , <i>vaccinium oxycoccus</i> , <i>vaccinium vitis-idaea</i> ; (2) UTIs, cystitis, bacteriuria, pyelonephritis, UTI, cystitis; (3) included terms for non-English language studies; databases: Medline, Embase, clinical trial registries <sup>4</sup> , etc.	To assess the effectiveness of cranberry juice and other cranberry products in preventing UTIs in susceptible populations	RCTs and quasi-RCTs; cranberry products vs. placebo, no treatment or any other treatment; studies in men, women, and children susceptible to UTIs; outcome: incidence of UTIs	There is some evidence from 2 good quality RCTs that cranberry juice may decrease the number of symptomatic UTIs over a 12-mo period in women; effectiveness of cranberry in other groups, such as children and elderly men and women, is not clear

<sup>1</sup> CENTRAL, Cochrane Central Registry of Controlled Trials; PAC, proanthocyanidin; RCT, randomized controlled trial; rUTI, recurrent urinary tract infection; UTI, urinary tract infection.

<sup>2</sup> Does include noncranberry and non-UTI-related terms. Terms summarized for comparison of scope or search. See specific reports for full list of search terms.

<sup>3</sup> Authors provided details on search strategy but not inclusion/exclusion criteria and results of the search strategy.

<sup>4</sup> Clinical trial registries include Cochrane Controlled Trials Registry (CCTR), CENTRAL, clintrials.gov, and the International Clinical Trials Register (ICTR).

selection can be seen by reviewing the contributing weight of the studies (discussed below).

**Differences in population characteristics.** The overall conclusion on totality of evidence made by Jepson et al. (20) (RR: 0.86; 95% CI: 0.71, 1.04) was heavily influenced by results from studies in populations with complicated UTIs (cUTIs), particularly patients with neuropathic bladder, spinal cord injury, and radiotherapy. As shown in **Table 4**, people with neuropathic bladder or spinal injuries and radiotherapy

patients contributed 30.3% of the total weight to the overall RR estimate, whereas women with rUTIs contributed only 24.5% of the total weight. Although the analysis by Wang et al. (19) included similarly diverse populations (except radiotherapy patients), the evidence was weighted relatively equally across the populations as follows: cUTIs (40.9% of the total weight), women with rUTIs (32.3% of the total weight), and other populations including children, elderly, and pregnant women (26.8% of the total weight) (**Table 4**). The Wang et al. (19) report also addressed separate populations

**TABLE 2** Differences in selection of studies in 5 different analyses<sup>1</sup>

Citation (reference)	Population	Jepson et al. 2004 (28)	Jepson and Craig 2008 (21)	Jepson et al. 2012 <sup>2</sup> (20)	Wang et al. 2012 (19)	Beerepoot et al. 2013 (27)
Avorn et al., 1994 (29)	Elderly people (mean age: 78.5 y)		✓			
Haverkorn and Mandigers, 1994 (30)	The elderly in a hospital (mean age: 81 y)		✓			
Foda et al., 1995 (31)	Children with neuropathic bladder		✓			
Walker et al., 1997 (32)	Women with recurrent UTIs		✓			
Schlager et al., 1999 (33)	Participants with intermittent catheterization		✓		✓	
Kontiokari et al., 2001 (34)	Women with recurrent UTIs	✓	✓	✓	✓	✓
McGuinness et al., 2002 (35)	People with neuropathic bladder				✓	
Stothers, 2002 (36)	Women with recurrent UTIs	✓	✓	✓	✓	✓
Linsenmeyer et al., 2004 (37)	Patients with neurogenic bladder	NA	✓			
Waites et al., 2004 (38)	People with neuropathic bladder	NA	✓	✓	✓	
McMurdo et al., 2005 (39)	Elderly people	NA	✓	✓	✓	
Lee et al., 2007 (40)	Patients with spinal cord injuries	NA	NA	✓ <sup>3</sup>		
Hess et al., 2008 (41)	People with neuropathic bladder/spinal injuries	NA	NA		✓	
PACS Study, 2008 (42)	Elderly people	NA	NA	✓ <sup>3</sup>		
Wing et al., 2008 (43)	Pregnant women	NA	NA	✓	✓	
Ferrara et al., 2009 (44)	Children	NA	NA	✓	✓	
Essadi and Elmehashi, 2010 (45)	Pregnant women	NA	NA	✓ <sup>3</sup>		
Salo et al., 2012 (46)	Children	NA	NA	✓		
Barbosa-Cesnik et al., 2011 (47)	Women with recurrent UTIs	NA	NA	✓	✓	
Sengupta et al., 2011 (48)	Women with recurrent UTIs	NA	NA	✓		
Cowan et al., 2012 (49)	Radiotherapy patients	NA	NA	✓ <sup>3</sup>		
Total studies included, <i>n</i>		2	10	13	10/9 <sup>4</sup>	2

<sup>1</sup> NA, not applicable (studies were published after the search date); UTI, urinary tract infection.

<sup>2</sup> The studies depicted are those used for the comparison of cranberry compared with placebo/control among participants with  $\geq 1$  UTIs at follow-up.

<sup>3</sup> The 4 studies contributed the majority (53.7%) of total weight to the total RR estimate in Jepson et al., 2012 (20).

<sup>4</sup> Wang et al. (19) performed 2 analyses, 1 with Barbosa-Cesnik et al. (47) and 1 without. The main reporting used in the analysis was without Barbosa-Cesnik et al. (47), or 9 studies.

in their conclusions, noting that cranberry products appear to be more effective for prevention of rUTIs in women. These data suggest inclusion of groups with different pathophysiologic status (e.g., cUTIs) could modify the strength of overall risk estimates accorded to generally healthy at-risk populations.

**Table 5** compares the RR estimates by subgroup in the meta-analyses by Jepson et al. (20), Jepson and Craig (21), and Wang et al. (19). Specifically, among women with rUTIs, RR for cranberry compared with placebo/control on rUTIs was reported to be 0.53 (95% CI: 0.33, 0.83) by Wang et al. (19) and 0.61 (95% CI: 0.40, 0.91) by Jepson and Craig (21). Beerepoot et al. (27) (not shown) only assessed cranberry compared with placebo in women with rUTIs and reported the RR to be 0.53 (95% CI: 0.33, 0.83). Although Jepson et al. (20) also found a similar trend for a reduction in RR in the same group, it was not statistically significant (RR = 0.74; 95% CI: 0.42, 1.31). Reasons for this nonsignificant RR in Jepson et al. (20) are discussed below. Overall, however, the RR estimates for rUTI prevention in this subgroup of women are similar across the systematic reviews.

**Differences in data extraction.** The subpopulation analyses for cranberries and UTIs among healthy women with rUTIs were compared to understand the reason for lack of statistical significance in the Jepson et al. (20) analysis. In this comparison, it was noted that different values were extracted from 1 of the studies that was included in Jepson et al. (20), Wang et al. (19), and Beerepoot et al. (27). As shown

in **Table 6**, RR values extracted from the Kontiokari et al. study (34) were 0.62 (95% CI: 0.34, 1.12) by Jepson et al. (20) and 0.44 (95% CI: 0.21, 0.93) by both Wang et al. (19) and Beerepoot et al. (27). These differences were due to the selection of outcome measures at different time points (i.e., at 6- vs. 12-mo follow-up). Because the significance of RR estimates in the Kontiokari et al. study (34) differed at the 6- and 12-mo follow-up, such inconsistency in the timing of outcome measurements could influence the strength of the summary RR estimates in the meta-analyses.

**Handling of heterogeneity.** Both Jepson et al. (20) and Wang et al. (19) reported substantial heterogeneity with inclusion of 1 specific study by Barbosa-Cesnik et al. (47), in the analysis of the use of cranberry to treat women with rUTIs (**Supplemental Table 1**). Both Jepson et al. (20) and Wang et al. (19) noted that the inclusion of the Barbosa-Cesnik et al. study (47) introduced substantial heterogeneity ( $I^2 = 65\%$  and  $59\%$ , respectively). Wang et al. (19) reported a reduction in heterogeneity to  $I^2 = 43\%$  when the study was excluded. Jepson et al. (20) did not report the change in heterogeneity upon exclusion of the study, but did indicate a significant RR reduction (from RR = 0.74; 95% CI: 0.42, 1.31 to RR = 0.58; 95% CI: 0.39, 0.86) after exclusion of the Barbosa-Cesnik et al. study (47). Despite significant heterogeneity with inclusion of the Barbosa-Cesnik et al. study (47), Jepson et al. (20) did not exclude this study, mainly because of its large sample size, whereas Wang et al. (19) further conducted a sensitivity analysis that identified the study

**TABLE 3** Similar research designs with conflicting conclusions<sup>1</sup>

Meta-analysis	Search date	Objective	Inclusion criteria	Statistical analysis	Conclusions
Jepson et al., 2012 (20)	July 2012	To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations	RCTs and quasi-RCTs; comparison of cranberry products vs. placebo, no treatment, or any other treatment; outcomes: incidence of UTIs	Software: Review Manager; random-effects models	Cranberry juice is less effective than previously indicated; cranberry juice cannot currently be recommended for the prevention of UTIs
Wang et al., 2012 (19)	November 2011	To evaluate cranberry-containing products for the prevention of UTIs	RCTs; comparison of cranberry products vs. placebo/nonplacebo control; outcome: incidence of UTIs	Software: R; random-effects models (DerSimonian-Laird method) when <i>P</i> for heterogeneity ≤0.05; fixed-effect model (Mantel-Haenszel method) when <i>P</i> for heterogeneity >0.05	Cranberry-containing products are associated with protective effect against UTIs

<sup>1</sup> RCT, randomized clinical trial; UTI, urinary tract infection.

by Barbosa-Cesnik et al. (47) as an outlier and excluded this study from the analysis on which their final conclusion was based. The discussion section in both systematic reviews explored potential reasons that findings by Barbosa-Cesnik et al. (47) were different from other studies, including a lower threshold for UTI diagnosis ( $10^3$  cfu/mL compared to a common threshold:  $10^5$  cfu/mL). A lower cutoff used to define UTI may increase the sensitivity but decrease the specificity of a test, which may bias the overall RR of treatment compared with the control/placebo toward a null effect.

## Discussion

Traditionally, the cranberry has been used to prevent rUTIs among generally healthy women. Although results from a number of clinical studies have been published supporting its benefits, the efficacy of the cranberry on prevention of rUTIs remains controversial, in part because of conflicting conclusions from meta-analyses.

Inconsistency in meta-analysis methodologies, including clinical (i.e., participants, outcome, and intervention) and methodological heterogeneity (i.e., trial design and execution including inclusion/exclusion criteria), can lead to varying results and interpretations, as appears to have been the case here. Standard checklists, including Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), have been developed to evaluate the evidence quality that is linked to clinical recommendations, clarify meta-analysis

methodology, and minimize possible bias (28, 50). Despite these guidelines toward the best evidence syntheses, the presence of substantial heterogeneity in systematic reviews has made it a challenge for health care professionals and policymakers to apply such nonspecific findings (50). As observed in our review, the variability of participants in Jepson et al. (20) and Wang et al. (19) ranged from patients with complicated disease conditions to otherwise healthy women to special groups (elderly, children, and pregnant women). Similarly, outcome measures differed in the diagnosis of a UTI (e.g., lower threshold of bacteria for UTI diagnosis) and varied in the timing of UTI assessments (e.g., 6- vs. 12-mo follow-up). Inadequately addressing issues such as clinical heterogeneity in studies used in a meta-analysis may contribute to increased variability in the summary effect estimates and lead to different conclusions.

In terms of efficacy assessment of the cranberry on UTI prevention, population definition is a key methodological element for consideration in performing a meta-analysis. For example, the FDA has recently published a guidance document “identifying cUTIs, which occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization,” as distinct from uncomplicated UTIs for purposes of research on therapies (51). Early reviews on the cranberry and UTIs have noted that efficacy was observed in clinical trials assessing prevention of rUTIs in generally healthy women, but not against cUTIs or as a treatment for UTIs (11, 13). In our comparison, more similarity in results was present among

**TABLE 4** Differences in subgroup contributions to overall relative risk estimates

Subgroup	Jepson et al., 2012 (20)			Wang et al., 2012 (19)		
	Trials, <i>n</i>	Sample size, <i>n</i>	Weight, %	Trials, <i>n</i>	Sample size, <i>n</i>	Weight, %
Women with recurrent urinary tract infections	4	594	24.5	2	250	32.3
Elderly men and women	2	413	13.7	1	376	11.4
Children	2	309	12.5	1	54	14.8
Pregnant women	2	674	19.1	1	188	0.5
People with neuropathic bladder/spinal injuries	2	353	20.2	4	307	40.9
Radiotherapy patients	1	119	10.1	—	—	—
Total	13	2462	100	9	1175	100

**TABLE 5** RR (cranberry vs. placebo/control) by subgroup in 3 meta-analysis reviews<sup>1</sup>

Subgroup	Jepson and Craig, 2008 (21)		Jepson et al., 2012 (20)		Wang et al., 2012 (19)	
	Studies included	RR (95% CI)	Studies included	RR (95% CI)	Studies included	RR (95% CI)
Women with recurrent UTIs	Kontiokari et al., 2001 (34), Stothers, 2002 (36)	0.61 <sup>2</sup> (0.40, 0.91)	Barbosa-Cesnik et al., 2011 (47), Kontiokari et al., 2001 (34), Stothers, 2002 (36), Sengupta et al., 2011 (48)	0.74 (0.42, 1.31)	Kontiokari et al., 2001 (34), Stothers, 2002 (36)	0.53 (0.33, 0.83)
Elderly men and women	McMurdo et al., 2005 (39)	0.51 (0.21, 1.22)	McMurdo et al., 2005 (39), PACS study, 2008 (42)	0.75 (0.39, 1.44)	McMurdo et al., 2005 (39)	0.51 (0.21, 1.22)
People with neuropathic bladder [and spinal injuries in Jepson et al., 2012 (20)]	NA	NA	Waites et al., 2004 (38), Lee et al., 2007 (40)	0.95 (0.75, 1.20)	Schlager et al., 1999 (33), McGuinness et al., 2002 (35), Waites et al., 2004 (38), Hess et al., 2008 (41)	0.80 (0.57, 1.14)
Pregnant women	NA	NA	Wing et al., 2008 (43), Essadi and Elmehashi, 2010 (45)	1.04 (0.93, 1.17)	Wing et al., 2008 (43)	4.57 (0.25, 83.60)
Children	NA	NA	Ferrara et al., 2009 (44), Salo et al., 2012 (46)	0.48 (0.19, 1.22)	Ferrara et al., 2009 (44)	0.28 (0.12, 0.64)
Radiotherapy patients	NA	NA	Sengupta et al., 2011 (48)	1.15 (0.75, 1.77)	NA	NA
Participants with catheterization (intermittent or indwelling)	Foda et al., 1995 (31), Schlager et al., 1999 (33), Linsenmeyer et al., 2004 (37), Waites et al., 2004 (38)	1.06 (0.51, 2.21)	NA	NA	NA	NA
Total <sup>3</sup>	Kontiokari et al., 2001 (34), Stothers, 2002 (36), Waites et al., 2004 (38), McMurdo et al., 2005 (39)	0.66 (0.47, 0.92)	All 13 studies listed above	0.86 (0.71, 1.04)	9 studies [excluding Barbosa-Cesnik et al., 2011 (47)]; 10 studies [including Barbosa-Cesnik et al., 2011 (47)]	0.62 (0.49, 0.80); 0.68 (0.47, 1.00)

<sup>1</sup> NA, not applicable; UTI, urinary tract infection.

<sup>2</sup> RR was for participants with a history of recurrent lower UTIs or women with a UTI.

<sup>3</sup> The outcome was incidence of UTIs at 12 mo (21). The outcome was cumulative incidence rate of 1 or more UTIs at the end of follow-up period (19, 20).

uncomplicated UTI subgroups, which helps explain the null effects reported in the Jepson et al. review (20) when subjects with cUTIs and uncomplicated UTIs were combined in the overall risk estimates. This further points out that the biology and clinical relevance should be considered when identifying populations for assessment.

The methodological challenges discussed in the present review are consistent with literature in a broader context

of clinical practice guidelines. During the development of primary care recommendations both in Europe and in the United States, the relevance of evidence to patient subgroups is deemed to be a challenge (52). Generalization of research evidence from high-risk populations to low-risk groups should be avoided to ensure the integrity of guidelines and reduce unwanted harm on patients, which is yet to be enhanced (52). Because these recommendations are usually

**TABLE 6** Differences in data extraction<sup>1</sup>

Meta-analysis	Population definition	Cranberry, UTI number/n	Control, UTI number/n	RR (95% CI)
Jepson et al., 2012 (20)	Number of women with recurrent UTI in 12 mo; total number completing the study	12/46	19/45	0.62 (0.34, 1.12)
Wang et al., 2012 (19), Beerepoot et al., 2013 (27)	Number of women with ≥1 UTI in 6 mo; intent-to-treat population	8/50	18/50	0.44 (0.21, 0.93)

<sup>1</sup> From the Kontiokari et al. study (34) in Jepson et al., 2012 (20), Wang et al., 2012 (19), and Beerepoot et al., 2013 (27). UTI, urinary tract infection.

based on the best available evidence including systematic reviews and meta-analysis, how to define the relevant population and to generalize the findings in such systematic reviews may indirectly influence the quality and efficacy of clinical practice.

Women with rUTIs represent a clinically relevant population, particularly because the alternative choices other than antibiotics are very limited and cranberry prophylaxis seems to be promising. To our knowledge, this is the first assessment of evidence-based systematic reviews on cranberries and the prevention of rUTIs, with evaluation of methodological discrepancies between the high profile meta-analyses. In particular, our analysis suggests consideration should be given to completion of additional research on cranberries for UTI prevention among women with rUTIs. A meta-analysis with focus on this most relevant population is warranted. This is particularly important for women with uncomplicated rUTIs who have developed antimicrobial resistance.

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