

# Meta-analysis

Cranberry-containing products for prevention of urinary tract infections in susceptible populations

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# Agenda

- A few words on meta-analysis
- Cranberry-containing products for prevention of urinary tract infections in susceptible populations (9 questions)

# Meta-analysis

- A meta-analysis combines the results of several studies that address a set of related research hypotheses
- Based on a common measure of effect size, for which a weighted average is estimated

# Meta-analysis based on literature review

- Identify variables of interest
- Identify studies for inclusion
- Obtain data from each study
- Perform meta-analysis (weighted average, Confidence intervals, heterogeneity)

# Types of effect measure

- Mean difference
- Odds ratio
- Hazard ratio
- Risk ratio

# From single study to population effect size

Studies vary in size

- An effect size based on 100 subjects is assumed to be a more "precise" estimate of the population effect size than an effect size based on 10 subjects
- Larger studies should carry more "weight" in a meta-analysis than smaller studies

**Simple approach:** weight each study effect size by its sample size

**Better approach:** weight each study effect size by the inverse variance

## From single study to population effect size

- The standard error (SE) is a direct index of the precision of the effect size
- The smaller the SE, the more precise is the effect size
- The optimal weights for meta-analysis are:

$$w = \frac{1}{SE^2} \quad , \text{ where } \quad SE = \frac{SD}{\sqrt{N}}$$

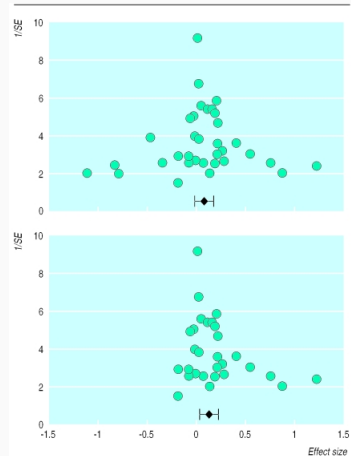
The Weighted  
Mean Effect Size

$$\overline{ES} = \frac{\sum (w \times ES)}{\sum w}$$

# Publication bias, funnel plots

Typical funnel plot generated from 35 simulated studies (top) and same data with five missing studies showing a typical manifestation of publication bias (bottom).

Sutton A J et al. BMJ  
2000;320:1574-1577





# Q1: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Describe the objectives. Are they clear and clinically relevant?

## A1: Describe the objectives. Are they clear and clinically relevant?

"The aims of this study were to evaluate cranberry-containing products for the **prevention** of UTI and to examine the factors influencing their effectiveness"

## Q2: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Describe the criteria for selection of studies. Are they reasonable?

## A2: Describe the criteria for selection of studies. Are they reasonable?

"Searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to November 2011 according to a prespecified protocol. Search terms included *cranberry*, *Vaccinium macrocarpon*, *Vaccinium oxycoccus*, *Vaccinium microcarpum*, *Vaccinium erythrocarpum*, *Vaccinium*, *urinary tract infection*, *pyelonephritis*, *cystitis*, *bacteriuria*, and *pyuria*"

"No language, population, or publication year restrictions were enforced"

"We manually checked bibliographies of relevant studies, reviews, and meta-analyses to identify references that may have been missed in our primary search"

## Q3: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Describe the procedures for selection of studies. Are they sufficient?

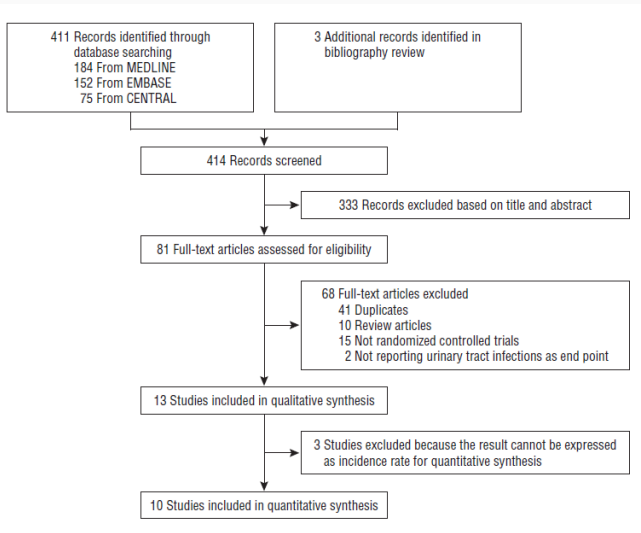
## **A3: Describe the procedures for selection of studies. Are they sufficient?**

"Two authors independently scanned the titles and abstracts of all retrieved manuscripts to identify those pertinent to this review"

"The following prespecified inclusion criteria were used: 1) randomized controlled trials (RCTs); (2) comparison of cranberry-containing products vs placebo or nonplacebo control for prevention of UTI; and (3) outcomes reported as incidence of UTIs"

"After retrieving full reports of potentially relevant trials, the same reviewers independently assessed the eligibility of the studies on the basis of the inclusion criteria and settled differences of opinion by consensus or by consultation with a third investigator"

# Literature search flow diagram



## Q4: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Do you think all relevant studies were included in the overview?



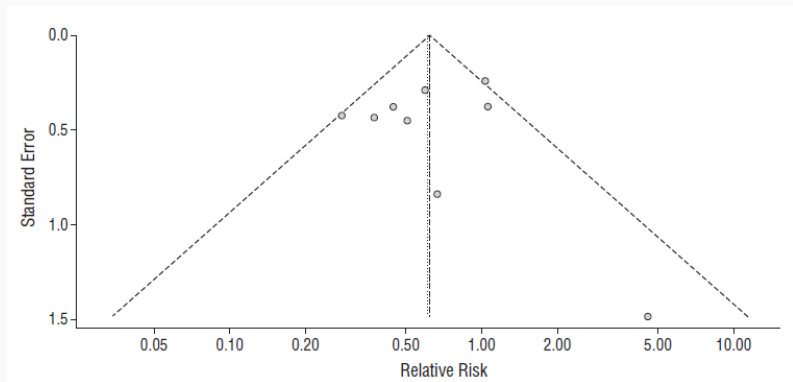
## A4: Do you think all relevant studies were included in the overview?

- Were all relevant and published studies identified?
- Were all relevant studies actually published?

"We did not search abstracts from conferences, proceedings, or clinical trial registries"

- A listing of excluded studies would be helpful

# Funnel plot



## Q5: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Describe how the validity of the individual studies included was evaluated

## A5: Describe how the validity of the individual studies included was evaluated

"The Cochrane risk of bias tool was adopted to assess the risk of bias for each trial, which was scored as *high risk*, *low risk*, or *unclear* based on methods of random sequence generation, allocation concealment, blinding process, incomplete outcome data, and selective reporting"

# Quality of reporting for included RCTs

Source	Risk of Bias Assessment				
	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting
Avorn et al, <sup>8</sup> 1994	High	High	Low	High	High
Foda et al, <sup>15</sup> 1995	Unclear	Unclear	Low	High	High
Walker et al, <sup>16</sup> 1997	Unclear	Unclear	Low	High	Unclear
Schlager et al, <sup>17</sup> 1999	Unclear	Unclear	Low	Low	High
Kontiokari et al, <sup>18</sup> 2001	Low	Unclear	Low	Low	High
McGuinness et al, <sup>19</sup> 2002	Unclear	Unclear	Low	High	High
Stothers et al, <sup>20</sup> 2002	Unclear	Unclear	Low	High	High
Waites et al, <sup>21</sup> 2004	Unclear	Unclear	Low	High	High
McMurdo et al, <sup>22</sup> 2005	Low	Low	Low	Low	High
Hess et al, <sup>23</sup> 2008	Unclear	Unclear	Low	Unclear	High
Wing et al, <sup>24</sup> 2008	Low	Unclear	Low	High	High
Ferrara et al, <sup>25</sup> 2009	Low	Unclear	Low	Low	Unclear
Barbosa-Cesnik et al, <sup>26</sup> 2011	Unclear	Low	Low	Unclear	Low

# Study design of included RCTs

Source	Design	Washout Period	Analysis	Study Duration	Loss to Follow-up, No./Total No. (%)
Avorn et al, <sup>8</sup> 1994	Parallel	NA	ITT	6 mo	32/153 (21)
Foda et al, <sup>15</sup> 1995	Crossover	None	PP	12 mo	19/40 (48)
Walker et al, <sup>16</sup> 1997	Crossover	None	PP	6 mo	9/19 (47)
Schlager et al, <sup>17</sup> 1999	Crossover	None	ITT	6 mo	0/15 (0)
Kontiokari et al, <sup>18</sup> 2001	Parallel	NA	ITT	6 mo	9/50 (18)
McGuinness et al, <sup>19</sup> 2002	Parallel	NA	ITT	6 mo	12/135 (9)
Stothers et al, <sup>20</sup> 2002	Parallel	NA	ITT	12 mo	NR
Waites et al, <sup>21</sup> 2004	Parallel	NA	PP	6 mo	26/74 (35)
McMurdo et al, <sup>22</sup> 2005	Parallel	NA	ITT	35 d	115/376 (30.6)
Hess et al, <sup>23</sup> 2008	Crossover	None	PP	12 mo	10/57 (18)
Wing et al, <sup>24</sup> 2008	Parallel	NA	ITT	6 mo <sup>a</sup>	73/188 (39)
Ferrara et al, <sup>25</sup> 2009	Parallel	NA	PP	6 mo	3/57 (5)
Barbosa-Cesnik et al, <sup>26</sup> 2011	Parallel	NA	ITT	6 mo	89/319 (27.9)

a) Pregnant women were followed from prior to week 16 of gestation through delivery

# Study population of included RCTs

Source	No. of Patients	Study Region	Setting	Age, Range (Mean or Median), y	Subgroup	Female, %
Avorn et al, <sup>8</sup> 1994	153	US	Nursing homes	NA (78.6)	Elderly patients	100
Foda et al, <sup>15</sup> 1995	21	Canada	Hospital clinic	1.4-18 (NA)	Patients with neuropathic bladder	43
Walker et al, <sup>16</sup> 1997	10	US	Unclear	28-44 (37)	Women with recurrent UTIs	100
Schlager et al, <sup>17</sup> 1999	15	US	Hospital clinic	2-18 (NA)	Patients with neuropathic bladder	53
Kontiokari et al, <sup>18</sup> 2001	100	Finland	University health service	NA (30.5)	Women with recurrent UTIs	100
McGuinness et al, <sup>19</sup> 2002	135	Canada	Hospital clinic	NA (45.1)	Patients with neuropathic bladder	79
Stothers et al, <sup>20</sup> 2002	150	Canada	Unclear	21-72 (42.3)	Women with recurrent UTIs	100
Waites et al, <sup>21</sup> 2004	48	US	Hospital clinic	20-73 (40.9)	Patients with neuropathic bladder	13
McMurdo et al, <sup>22</sup> 2005	376	UK	Inpatients	>60 (81.4)	Elderly patients	68
Hess et al, <sup>23</sup> 2008	47	US	Hospital clinic	28-79 (53)	Patients with neuropathic bladder	0
Wing et al, <sup>24</sup> 2008	188	US	Hospital clinic	NA (26.4)	Pregnant women	100
Ferrara et al, <sup>25</sup> 2009	54	Italy	Hospital clinic	3-14 (NA)	Children	100
Barbosa-Cesnik et al, <sup>26</sup> 2011	319	US	University health service	18-40 (21.2)	Women with recurrent UTIs	100

# Interventions in included RCTs

Source	Baseline Bacteriuria Excluded?	Cranberry Group			Control Group	
		Form (Daily Dosage, mL)	Manufacturer	Cranberry Amount (g/d) (PAC Content, mg/d)	Dosing Frequency (Daily)	Formula
Avorn et al, <sup>8</sup> 1994	No	Juice (300)	Ocean Spray	NA	Not specified	Juice <sup>a</sup>
Foda et al, <sup>15</sup> 1995	No	Juice (15 mL/kg)	Ocean Spray	4.5 g/kg/d	3-4	Water
Walker et al, <sup>16</sup> 1997	No	Capsule	Solaray	0.4	Not specified	Dicalcium phosphate
Schlager et al, <sup>17</sup> 1999	No	Juice (60)	Ocean Spray	NA	Not specified	Juice <sup>a</sup>
Kontiokari et al, <sup>18</sup> 2001	Yes	Juice (50)	Marli	7.5	Not specified	No placebo
McGuinness et al, <sup>19</sup> 2002	No	Capsule	NOW Natural Foods	8	1	Beetroot
Stothers et al, <sup>20</sup> 2002	Yes	Tablet/juice (750)	Unclear	NA	2/3	Juice <sup>b</sup>
Waites et al, <sup>21</sup> 2004	No	Capsule	Aim This Way	4	2	Lactose
McMurdo et al, <sup>22</sup> 2005	No	Juice (300)	Ocean Spray	75 (0.838)	2	Juice <sup>c</sup>
Hess et al, <sup>23</sup> 2008	Yes	Tablet	Swiss Herbal	1	2	Rice flour
Wing et al, <sup>24</sup> 2008	Yes	Juice (240-720)	Ocean Spray	64.8-194.4 (80-240)	1-3	Juice <sup>a</sup>
Ferrara et al, <sup>25</sup> 2009	Yes	Juice (50)	Unclear	7.5	Not specified	No placebo
Barbosa-Cesnik et al, <sup>26</sup> 2011	Yes	Juice (480)	Ocean Spray	129.6 (224)	2	Juice <sup>a</sup>

- a) Specially designed juice to imitate cranberry juice
- b) Filtered water with food coloring plus 20-mL pineapple juice
- c) Containing water, sucrose, elderberry extract, quinic acid, citric acid, malic acid, vitamin C, and aspartame



# Definitions and outcomes

Source	Outcome Assessment			UTI Cumulative Incidence Rate, No./No. (%) <sup>a</sup>		UTI Incidence Rate (Episodes/Patient-year) <sup>b</sup>		Intervention Duration <sup>c</sup>
	Threshold of Bacteriuria (CFU/mL)	Pyuria Required in Definition of UTI	Symptoms Required in Definition of UTI	Cranberry	Control	Cranberry	Control	
Avorn et al. <sup>8</sup> 1994	100 000	Yes (undefined)	No	15% <sup>f</sup>	28.1% <sup>f</sup>	NA	NA	6 mo
Foda et al. <sup>15</sup> 1995	100 000	No	Yes (undefined) <sup>d</sup>	NA	NA	1.8	1.9	6 mo <sup>c</sup>
Walker et al. <sup>16</sup> 1997	Undefined	No	Yes (undefined)	NA	NA	2.4	6.0	3 mo <sup>c</sup>
Schlager et al. <sup>17</sup> 1999	10 000	No	Yes (defined)	2/15 (13)	3/15 (20)	0.8	0.8	3 mo <sup>c</sup>
Kontiohari et al. <sup>18</sup> 2001	100 000	No	Yes (defined)	8/50 (16)	18/50 (36)	NA	NA	6 mo
McGuinness et al. <sup>19</sup> 2002	1 000 000	Yes (undefined)	No	21/62 (34)	24/73 (33)	NA	NA	6 mo
Stothers et al. <sup>20</sup> 2002	100 000	No	Yes (undefined)	19/100 (19)	16/50 (32)	0.4	0.7	12 mo
Waites et al. <sup>21</sup> 2004	10 000	No	Yes (defined)	10/26 (34)	8/22 (36)	1.2	1.3	6 mo
McMurdo et al. <sup>22</sup> 2005	10 000	No	Yes (defined) <sup>e</sup>	7/187 (4)	14/189 (7)	NA	NA	35 d
Hess et al. <sup>23</sup> 2008	10 000	Yes (defined)	Yes (defined)	6/47 (13)	16/47 (34)	0.3	0.9	6 mo <sup>c</sup>
Wing et al. <sup>24</sup> 2008	100 000	Yes (defined)	Yes (defined)	4/125 (3)	0/63 (0)	NA	NA	6 mo <sup>c</sup>
Ferrara et al. <sup>25</sup> 2009	100 000	Yes (defined)	Yes (defined)	5/27 (19)	18/27 (67)	NA	NA	6 mo
Barbosa-Cesnik et al. <sup>26</sup> 2011	1000	Yes (defined)	Yes (defined)	31/155 (20)	23/164 (14)	NA	NA	6 mo

- a) Cumulative incidence rate: number of patients who experienced at least 1 episode of UTI/number of patients at risk during the intervention period
- b) Incidence rate: number of total episodes of UTIs during the intervention period/number of person-years at risk during the intervention period
- c) Intervention duration: In crossover trials, intervention duration of each intervention was half of the study duration
- d) Definition of UTI: bacteriuria or any growth in a symptomatic patient or any growth of *Proteus* or *Pseudomonas* species
- e) Definition of UTI: bacteriuria in a symptomatic patient and presence of leukocyte esterase and nitrite
- f) This percentage represented urine samples of bacteriuria with pyuria in all screened urine samples. The odds ratio was 0.42 (95% CI, 0.23-0.76) for bacteriuria with pyuria in cranberry relative to the control group (P = .004)

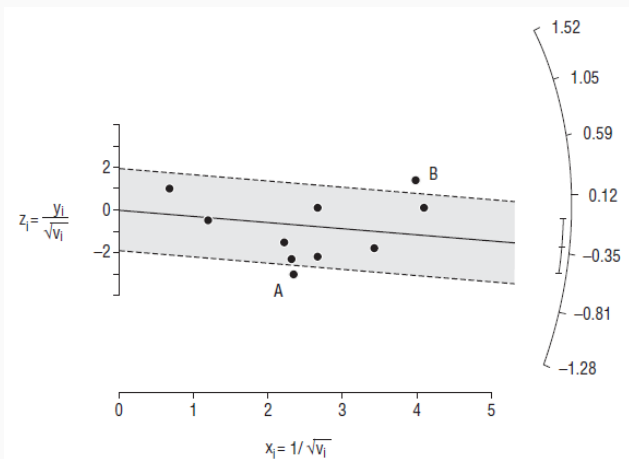
## Q6: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Describe how the validity of all the included studies together was evaluated regarding consistency of results and heterogeneity

## **A6: Describe how the validity of all the included studies together was evaluated regarding consistency of results and heterogeneity**

"There was significant heterogeneity among trials. The Galbraith plot indicated that the trials by Ferrara et al and Barbosa-Cesnik et al were potential sources of heterogeneity. Influential plot further demonstrated that the trial by Barbosa-Cesnik et al had the most significant impact on the pooled summary estimate, justifying its exclusion from the main analysis"

# Galbraith plot



- Y-axis: Individual effect estimate divided by its standard error (SE)
- X-axis:  $1/SE$
- Larger studies (with smaller SE and larger  $1/SE$ ) will be observed to aggregate away from the origin

# Influential plot

## Study omitted

Schlager et al,<sup>17</sup> 1999

Kontiokari et al,<sup>18</sup> 2001

McGuinness et al,<sup>19</sup> 2002

Stothers et al,<sup>20</sup> 2002

Waites et al,<sup>21</sup> 2004

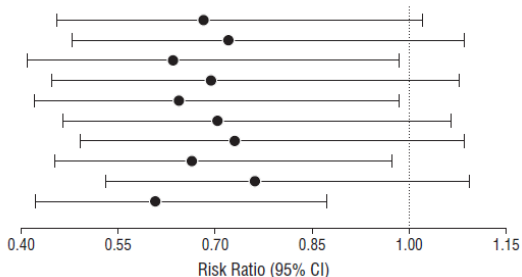
McMurdo et al,<sup>22</sup> 2005

Hess et al,<sup>23</sup> 2008

Wing et al,<sup>24</sup> 2008

Ferrara et al,<sup>25</sup> 2009

Barbosa-Cesnik et al,<sup>26</sup> 2011



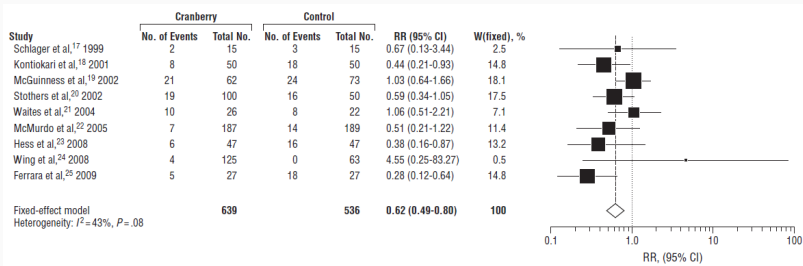
## Q7: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Describe how the pooled summary effect estimated was calculated. Could other methods be used?

## **A7: Describe how the pooled summary effect estimated was calculated. Could other methods be used?**

"Random effects summary estimates (DerSimonian-Laird method) were reported if the heterogeneity was significant in either test of heterogeneity; otherwise, fixed-effect summary estimates (Mantel-Haenszel method) were reported"

# Forest plot



- What about a random effect model based on 10 studies?



# Sensitivity analyses

Sensitivity Analysis According to:	No. of Trials	Pooled Cumulative Incidence Rate of UTI, No./No. <sup>a</sup>		Heterogeneity <i>I</i> <sup>2</sup> , % ( <i>P</i> Value)	Risk Ratio (95% CI)	<i>P</i> Value in Meta-regression
		Cranberry	Control			
Study design						
Parallel	7	74/577	98/474	51 (.05)	0.64 (0.42-0.97)	.45
Crossover	2	8/62	19/62	0 (.54)	0.42 (0.20-0.89)	
Study analysis						
ITT	6	61/539	75/440	22 (.27)	0.70 (0.52-0.95)	.44
PP	3	21/100	42/96	69 (.04)	0.49 (0.21-1.13)	
Risk of random sequence generation						
Low risk	4	24/389	50/329	22 (.28)	0.46 (0.29-0.71)	.08
Unclear	5	58/250	67/207	31 (.21)	0.74 (0.55-1.00)	
Treatment in control group						
Placebo	7	69/562	81/459	25 (.23)	0.73 (0.55-0.97)	.05
No placebo	2	13/77	36/77	0 (.41)	0.36 (0.21-0.62)	
Incidence rate in control group						
≥30%	6	69/312	100/269	59 (.03)	0.59 (0.38-0.91)	.81
<30%	3	13/327	17/267	5 (.35)	0.69 (0.33-1.41)	
Bacteriuria threshold in definition of UTI						
10 000 CFU/mL	4	25/275	41/273	19 (.30)	0.58 (0.37-0.91)	.46
100 000 CFU/mL	4	36/302	52/190	34 (.21)	0.49 (0.34-0.73)	
Pyuria requirement in definition of UTI						
Pyuria unrequired	5	46/378	59/326	0 (.54)	0.60 (0.42-0.85)	.88
Pyuria required	4	36/261	58/210	72 (.01)	0.59 (0.25-1.40)	

- a) Pooled incidence rate: number of patients who experienced at least 1 episode of UTI/number of patients at risk during the intervention period

## Q8 + Q9: Cranberry-containing products for prevention of urinary tract infections in susceptible populations

- Could the results of this meta-analysis be used in the clinic?
- What advise would you give patients regarding the use of cranberry-containing products?

"The results of the present meta-analysis support that consumption of cranberry-containing products may protect against UTIs in certain populations. However, because of the substantial heterogeneity across trials, this conclusion should be interpreted with great caution. Cranberry-containing products tend to be more effective in women with recurrent UTIs, female populations, children, cranberry juice drinkers, and people using cranberry-containing products more than twice daily"

# Subgroup analyses

Subgroup Analysis According to:	No. of Trials	Pooled Cumulative Incidence Rate of UTI, No./No. <sup>a</sup>		Heterogeneity <i>I</i> <sup>2</sup> , % ( <i>P</i> Value)	Risk Ratio (95% CI)	<i>P</i> Value in Meta-regression
		Cranberry	Control			
Population type						
Women with recurrent UTIs	2	27/150	34/100	0 (.54)	0.53 (0.33-0.83)	NA
Neuropathic bladder	4	39/150	51/157	37 (.19)	0.80 (0.57-1.14)	
Children	1	5/27	18/27	NA	0.28 (0.12-0.64)	
Elderly patients	1	7/187	14/189	NA	0.51 (0.21-1.22)	
Pregnant patients	1	4/125	0/63	NA	4.57 (0.25-83.60)	
Age						
<18 y	2	7/42	21/42	0 (.35)	0.33 (0.16-0.69)	.15
≥18 y	7	75/597	96/494	39 (.14)	0.68 (0.52-0.89)	
Sex						
Female	4	36/302	52/190	34 (.21)	0.49 (0.34-0.73)	.17
Form of cranberry-containing products						
Cranberry juice	5	26/404	53/344	2 (.39)	0.47 (0.30-0.72)	.07
Capsule or tablet	3	37/135	48/142	57 (.10)	0.79 (0.44-1.44)	
Dose frequency						
More than twice daily	4	42/360	54/308	18 (.30)	0.58 (0.40-0.84)	.12
Once daily	1	21/62	24/73	NA	1.03 (0.64-1.66)	

- a) Pooled incidence rate: number of patients who experienced at least 1 episode of UTI/number of patients at risk during the intervention period