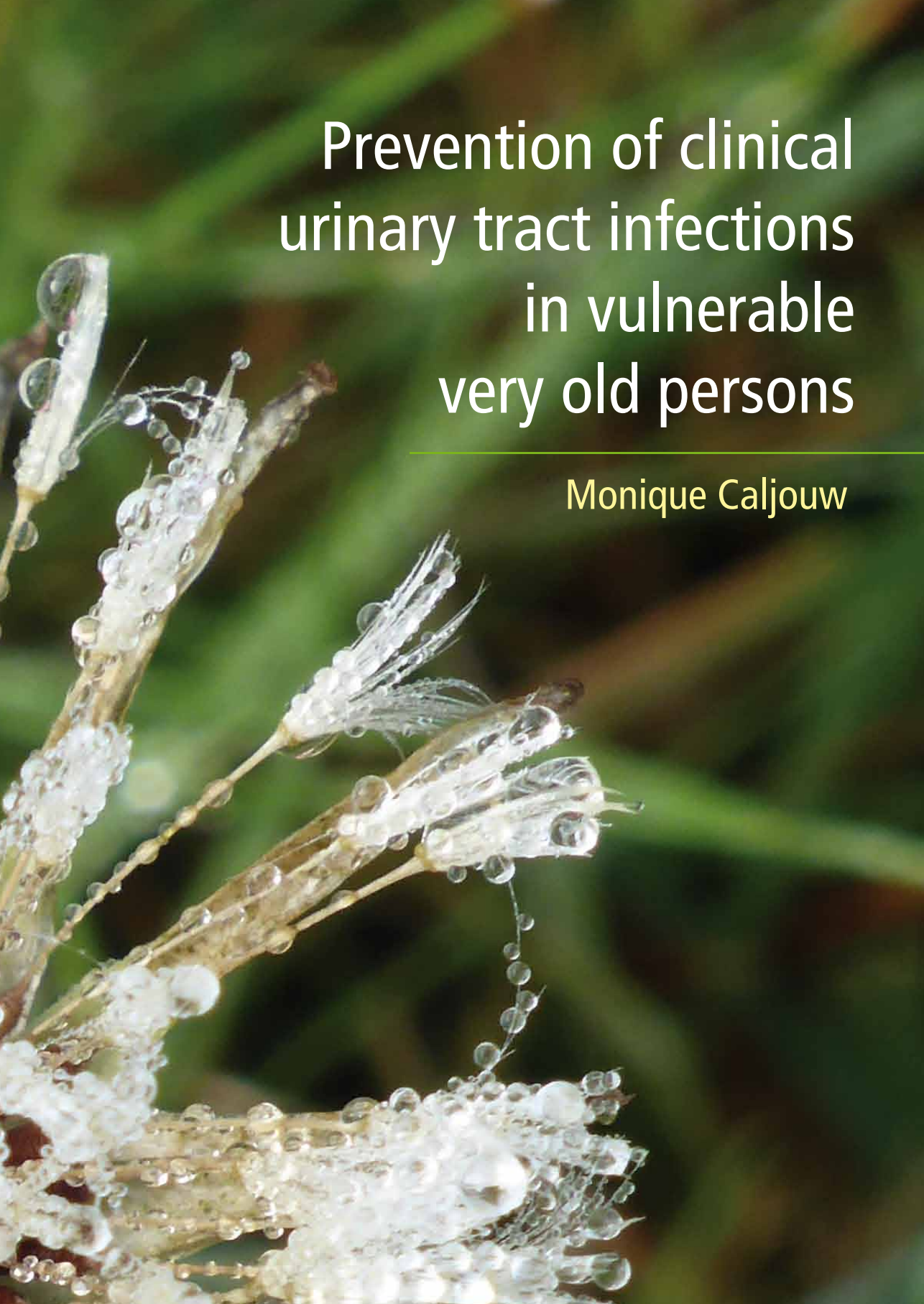

Prevention of clinical urinary tract infections in vulnerable very old persons

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ISBN: 978-94-6169-605-2

Layout and printing: Optima Grafische Communicatie, Rotterdam, the Netherlands
Cover photo: 'Faded dandelion with dew' by Monique Caljouw

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 10 februari 2015
klokke 15.00 uur

door

Monique Adriana Anna Caljouw

geboren te Middelburg
in 1967

PROMOTIECOMMISSIE

Promotores:	Prof.dr. J. Gussekloo
	Prof.dr. H.J.M. Cools
Overige leden:	Prof.dr. P.J. van den Broek
	Prof.dr. J.M.G.A. Schols (Universiteit Maastricht)
	Prof.dr. M.J. Schuurmans (Universiteit Utrecht)

CONTENTS

CHAPTER 1

General introduction

Urinary tract infections (UTI) are among the most frequently reported infections among older persons.[1-6] The incidence of UTI increases with age in both men and women[7-9] and ranges from 12-29 per 100 person-years at risk in community-dwelling older people[9,10] up to 44-58 per 100 person-years at risk in long-term care facilities (LTCF).[11,12] UTI account for 25% to 40% of all bacterial infections in LTCF.[2,13-15] Infections in LTCF contribute to higher morbidity and mortality rates, to more infection outbreaks, higher antimicrobial use, and additional costs.[1,16]

However, it is still generally accepted that diagnosing UTI in vulnerable very old persons is challenging. Factors such as impaired communication due to dementia, high prevalence of incontinence, chronic genitourinary symptoms, and a high frequency of positive urine cultures due to bacteriuria without complaints,[17-19] makes diagnosing UTI even more difficult. In addition, since clinical symptoms of UTI are frequently absent,[20] this makes differentiation between asymptomatic and symptomatic UTI in this population rather complicated.[17,21] As a result, for LTCF populations, there is no generally accepted standard for the diagnosis of UTI.

In these older residents, most clinical symptoms to ascertain UTI are based on consensus as presented in clinical guideliness.[22-27] Currently, these guidelines define a clinical UTI as the presence of specific and non-specific symptoms and signs of UTI, such as dysuria, change in character of urine, and change in mental status, confirmed with a urinalysis to evaluate the evidence of the presence of nitrite and leukocyte esterase. A positive nitrite and leukocyte esterase test may indicate the presence of clinical UTI and treatment with antibiotics may start. Although UTI are often treated empirically,[28] a urine culture may be necessary in LTCF residents with recurrent UTI to confirm the diagnosis and guide antibiotic treatment.

In vulnerable LTCF residents, clinical UTI not only cause several days of illness, but may have more severe consequences such as delirium, dehydration, urosepsis, hospitalization, or even death.[4,29] Infections also lead to a general decline in functioning,[30] which is often irreversible and can cause a cascade of general deterioration, more care dependency, and a higher mortality risk. In addition, disability in activities of daily living (ADL) is independently associated with the development of infections.[3,30,31] The relation between infections and ADL disability seems to present a negative spiral. Older people with dependency in ADL, depression, urine incontinence and impaired cognition are at higher risk of being admitted to a LTCF.[32]

Different factors predispose older persons to infections, such as age-associated changes in the adaptive and innate immune system, the presence of multiple comorbid diseases, the use of indwelling devices (e.g. urinary catheter, feeding tubes), and 24-hour grouped living in close proximity (e.g. participating in social activities, and close contact between residents and staff).[28,33,34]

Considering this negative impact of clinical UTI, we are particularly interested in how to prevent clinical UTI in vulnerable very old persons. Since the incidence of clinical UTI in LTCF residents is high, general hygienic precautions are important in these facilities, e.g. hand hygiene, toilet hygiene, timely change of incontinence material, and urinary catheter care.[35,36] Also, ensuring adequate fluid intake (hydration), regular toilet visits, and sufficient urination

(bladder emptying), is essential to eliminate bacteria and prevent UTI in this population.[37] In addition, an adequate infection surveillance program can provide insight into the incidence and prevalence of infections in LTCF. Surveillance data should be frequently monitored and reviewed to identify changing trends in infections.[38,39] Surveillance results often provide tools for targeted infection prevention strategies.

To more efficiently prevent clinical UTI and their subsequent negative consequences, it is important to identify older persons at risk for UTI. Among vulnerable older persons, an increasing age,[7,34] diabetes mellitus,[40,41] stroke,[42] urine incontinence,[14,43,44] prior history of UTI,[14,43] and impaired functional and cognitive status[3,30,31,34,43] are predictive for the development of clinical UTI.

Several options are available to reduce the risk of clinical UTI in those at high risk. With the discovery of penicillin by Fleming in 1928 and, later, other antibiotics for the treatment of infections, it became possible to cure and prevent UTI. For many years preventive treatment with antibiotics was the regular preventive care. However, an increasing problem arose with uropathogens that became resistant to antibiotic treatment. Also, prophylactic prevention with antibiotics in residents with recurrent UTI is not preferred because of side-effects, antibiotic resistance, and the related costs.[28,45]

With the expected increase in antimicrobial resistance there is a need for alternative non-antibiotic methods for UTI prevention. Prophylaxis with the vaginal application of estrogens is effective in post-menopausal women, but its safety and feasibility in geriatric populations has not yet been studied.[46,47] Methenamine hippurate is not effective for UTI prevention in patients with neurogenic bladder or renal tract abnormalities,[48] but is often present in LTCF residents. Also, other non-drug preventive measures can be considered, such as vitamin C, *Lactobacilli* and cranberry. However, vitamin C was shown to be not effective in the prevention of UTI,[49] and the use of *Lactobacilli* in post-menopausal women had no effect in UTI prevention compared with antibiotics.[50]

Centuries ago American Indians were aware of the medicinal working of cranberries and cranberry-containing products have long been used as a folk remedy to prevent clinical UTI. However, the question remains: are cranberry capsules a new alternative for the prevention of clinical UTI in LTCF residents? There is some evidence that prophylaxis with cranberry products is a potential prevention strategy.[51-55] Cranberries contain proanthocyanidins (PACs), which are stable compounds with anti-adhesion activity against e.g. *Escherichia coli*.[56-58] Two studies reported that cranberry juice may be protective in older adults[54,59] but the effectiveness of cranberry capsules in the protection against clinical UTI in vulnerable very old persons in LTCF has not yet been studied.

Aims of this thesis

The overall aim of this thesis is to study the possibilities for and effects of the prevention of clinical urinary tract infections in vulnerable very old persons.

The first part of this thesis investigates the effect of infections on functioning and explores which vulnerable very old persons would benefit most from UTI prevention. Chapter 2 describes a prospective follow-up study which explores the characteristics of LTCF residents on the natural course of care dependency. Within the Leiden 85-plus Study (a population-based prospective follow-up study of 85-year-old inhabitants of Leiden) we studied whether clinical infections predict an increase in disability in ADL among the oldest-old (Chapter 3), and which vulnerable older persons are at risk for UTI (Chapter 4).

The second part of this thesis describes the results of the effectiveness and costs of cranberry capsule use in the prevention of UTI in LTCF residents. The CRANBERRY study, a double-blind randomized placebo-controlled multi-center trial was conducted in 21 LTCF from the University Network for the Care sector in South Holland (UNC-ZH). The effectiveness of cranberry capsules in preventing UTI, stratified for UTI risk at baseline, is presented in Chapter 5. The use of cranberry capsules requires not only evaluation of its clinical effectiveness but also of its cost-effectiveness. The economic evaluation presented in Chapter 6 investigated the effect of UTI on health and related costs, and whether the preventive use of cranberry capsules in LTCF is cost-effective.

Chapter 7 presents a general discussion on the main results of the studies, considers the clinical implications of our findings for daily practice in long-term care, and makes some recommendations for future research.

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PART ONE

Correlates of clinical urinary tract infections

CHAPTER 2

Natural course of care dependency in residents of long-term care facilities: Prospective follow-up study

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BMC Geriatrics 2014, 14:67

ABSTRACT

Background Insight in the natural course of care dependency of vulnerable older persons in long-term care facilities (LTCF) is essential to organize and optimize individual tailored care. We examined changes in care dependency in LTCF residents over two 6-month periods, explored the possible predictive factors of change and the effect of care dependency on mortality.

Methods A prospective follow-up study in 21 Dutch long-term care facilities. 890 LTCF residents, median age 84 (Interquartile range 79–88) years participated. At baseline, 6 and 12 months, care dependency was assessed by the nursing staff with the Care Dependency Scale (CDS), range 15–75 points. Since the median CDS score differed between men and women (47.5 vs. 43.0, $P = 0.013$), CDS groups (low, middle and high) were based on gender-specific 33% of CDS scores at baseline and 6 months.

Results At baseline, the CDS groups differed in median length of stay on the ward, urine incontinence and dementia (all $P < 0.001$); participants in the low CDS group stayed longer, had more frequent urine incontinence and more dementia. They had also the highest mortality rate (log rank 32.2; df = 2; *P for trend* <0.001). Per point lower in CDS score, the mortality risk increased with 2% (95% CI 1%-3%). Adjustment for age, gender, cranberry use, LTCF, length of stay, comorbidity and dementia showed similar results. A one point decrease in CDS score between 0 and 6 months was related to an increased mortality risk of 4% (95% CI 3%-6%). At the 6-month follow-up, 10% improved to a higher CDS group, 65% were in the same, and 25% had deteriorated to a lower CDS group; a similar pattern emerged at 12-month follow-up. Gender, age, urine incontinence, dementia, cancer and baseline care dependency status, predicted an increase in care dependency over time.

Conclusion The majority of residents were stable in their care dependency status over two subsequent 6-month periods. Highly care dependent residents showed an increased mortality risk. Awareness of the natural course of care dependency is essential to residents and their formal and informal caregivers when considering therapeutic and end-of-life care options.

Keywords Care dependency, predictive factors, variability, mortality, long-term care facility, vulnerable older persons

BACKGROUND

The proportion of older people is steadily rising worldwide, people live longer and are managing their daily activities for longer than ever before.[1] But they have also a higher risk on negative health outcomes, like care dependency, being institutionalized and mortality.[2,3] Many vulnerable older people, heavily dependent on care, are living in long-term care facilities (LTCF) and place considerable constraints on healthcare professionals and healthcare budgets.

In the Netherlands 0.4% of the population; and around 2.7% of the population aged 65 years and above are living in LTCFs.[4,5] A typical Dutch LTCF accommodates 150–200 residents, has specialized psycho-geriatric wards for residents with dementia, somatic wards for residents with physical problems, and wards for rehabilitation.[6]

The daily nursing care in LTCF focuses on residents' care dependency as a process in which the residents' self-care decreases, and in which care demands make a person increasingly dependent on nursing care.[7] However, care dependency behaves like a dynamic process that is influenced by illness and disability,[8-10] i.e. care dependency can be a temporary, long-term or a permanent state.[11]

Two recent studies investigated the natural course of activities in daily living (ADL) among nursing home residents. Both studies showed that residents could improve, be stable or deteriorate in their ADL performance during 6 months of follow-up.[12,13] A study in a selected population of 68 females with Alzheimer's disease, living in a single Dutch LTCF and who survived a two-year period, care dependency showed a significant increase within that two-year period.[14]

Previous studies have shown that i.e. nutritional status,[12,13] cognitive impairment,[12,13,15] absence of daily contact with proxies,[12] depression,[12,16] neuropsychological deficits,[17] incontinence[12,13,18] and infections[19] were mentioned as predictors for deterioration in ADL performance of vulnerable older people. Deterioration in ADL will lead to more individual care demands and higher care dependency.

However, little is known about the natural course of care dependency in institutionalized older persons. It seems relevant to gain more insight in the stability and changes in care dependency to manage care and to provide better tailored care for individual LTCF residents. Therefore, we examined the changes in care dependency in LTCF residents over two 6-month periods, explored the possible predictive factors of change in care dependency, and the effect of care dependency on mortality.

METHODS

Setting and study population

The present prospective follow-up study was conducted within the framework of the CRANBERRY trial. The CRANBERRY trial is a double-blind randomized placebo-controlled multicenter trial, in which a total of 21 LTCFs from the University Nursing Home Research Network in South-Holland, the Netherlands, participated (trial registration NTR1266). The CRANBERRY study assesses the effectiveness of cranberry capsules to prevent urinary tract infections in vulnerable older persons living in intramural care settings in which care for the most vulnerable older persons is provided by a multidisciplinary team including elderly-care physicians, nursing assistants, licensed practical nurses, registered nurses and paramedical professionals. Residents aged 65 years and over were included. Excluded were residents with a life expectancy shorter than 1 month or using coumarin. For detailed information on the study design and outcomes we refer to the publication of the original trial.[20]

The Medical Ethics Committee of the Leiden University Medical Center approved the study. Written informed consent was obtained from all participants. For participants incapable of giving informed consent due to cognitive impairment, a guardian provided written consent.

Care dependency

At baseline, and at 6 and 12 months follow-up, an assessment was made of the care dependency status by interviewing the responsible nurses who care for the participants. For this the Care Dependency Scale (CDS) was used, which is a tool completed by nursing staff for assessment of the care dependency status of institutionalized residents.[21] The CDS has satisfactory reliability and validity,[22-24] and consists of 15 items, measuring basic care needs on a 5-point scale. The total CDS score ranges from 15 (completely dependent on care) to 75 (almost independent of care). The CDS 15 items are eating and drinking, continence, body posture, mobility, day and night pattern, getting (un)dressed, body temperature, hygiene, avoidance of danger, communication, contact with others, sense of rules and values, daily activities, recreational activities and learning ability.

Since women and men differ in their baseline care dependency status and the CDS scores were not normally distributed, women and men were separately ranked into gender-specific 33% groups according to their baseline CDS score. Thereafter, we combined the lowest, middle and highest 33% for women and men, to generate three gender-specific CDS groups. The 'low score' CDS group indicates participants most dependent on care and the 'high score' CDS group indicates participants the most independent of care.

Patient characteristics

Socio demographic factors
At baseline, a research nurse collected information on the participants' gender, age and length of stay on the ward.

Comorbidity
Information on participants' medical history was obtained by examination of the medical records, and interviews with the elderly care physician. Within the CRANBERRY trial we obtained clinical information on the presence of myocardial infarction, stroke, cancer, diabetes mellitus, chronic pulmonary disease (COPD) and dementia, as well as information on urine incontinence and urinary tract infections in the preceding year.

Statistical analysis

Comparisons were made between the CDS groups using Chi-square tests in case of categorical data and Kruskal-Wallis tests to compare the three groups for non-normally distributed continuous variables. *P*-values < 0.05 were considered significant and should be interpreted as nominal ones.

The difference in the cumulative incidence of mortality between the CDS groups was explored with Kaplan-Meier curves, with corresponding log-rank test. Cox proportional hazards models, adjusted for age, gender, cranberry use, LTCF, length of stay on the ward, somatic comorbidity (myocardial infarction, stroke, cancer, diabetes mellitus, COPD, urine incontinence, and urinary tract infection in the preceding year) and dementia were used to present mortality risks based on continuous CDS score at baseline.

The change in care dependency for survivors between 0–6 months and 7–12 months is presented by the number of participants in the three CDS groups who improved, stayed stable, or degraded to another CDS group during the two 6-month periods. For the analysis of CDS change in the subsequent 7–12 months, participants were newly classified in gender-specific 33% groups at the 6-month CDS assessment.

A crude and adjusted multivariate linear regression analysis was performed to estimate the predicted CDS score for survivors at 6-month follow-up. The CDS score at 6-month follow-up was considered as a dependent variable, while gender, age, cranberry use, LTCF, length of stay on the ward, CDS score at baseline, somatic comorbidity (myocardial infarction, stroke, cancer, diabetes mellitus, COPD, urine incontinence, and urinary tract infection in the preceding year) and dementia were considered to be independent variables. Except gender and age, all other variables with a *P*-value ≥ 0.05 were excluded from the adjusted model. Co-linearity between the independent variables and dependent variable (CDS score at 6 months) will be investigated with the Variance Inflation Factor (VIF). A VIF of 5 or above indicates co-linearity.

Analyses were performed with IBM SPSS Statistics for Windows, version 20.0.

RESULTS

In the original trial, 928 residents were included.[20] In 38 participants the baseline CDS score was missing due to technical reasons, resulting in a total of 890 participants eligible for the present study. There were no differences is gender, age and comorbidity between the participants and the 38 non-participants.

At 6 months follow-up, 132 participants (14.8%) had died and in 44 participants (4.9%) the CDS scores were missing, resulting in 714 participants (80.2%) at 6 months. At 12 months follow-up, another 129 participants (18.1%) died and in 21 participants (2.9%) the CDS scores were missing, resulting in 564 participants with complete measurements (79.0%) at 12 months.

Study population

Table 1 presents the baseline characteristics of the total population and of the three CDS groups. Overall, almost 75% of the study population was female and the median age was 84 (IQR 79–88) years. The median CDS score was 44 (IQR 30–56). At baseline, women had a lower CDS score compared with men: 43 (33rd percentile 34, 66th percentile 51) vs. 47.5 (33rd percentile 37,66th percentile 55); Mann–Whitney U-test; $P = 0.013$.

There was no significant difference in age between the CDS groups (Kruskal-Wallis test; $P = 0.180$). The CDS score was negatively correlated with the length of stay on the ward: participants who stayed the longest had the lowest CDS scores (Kruskal-Wallis test; $P < 0.001$). There were no significant differences between the CDS groups for cranberry use, myocardial infarction, stroke, cancer, diabetes mellitus, COPD and urinary tract infection in the preceding year. However, urine incontinence and dementia were more frequently present in the low CDS group compared with the other groups (Table 1).

Care dependency and mortality

Figure 1 presents the mortality rate for the three CDS groups; the highest mortality rate was in the group with the lowest CDS score (log rank 32.2; df = 2; *P for trend* <0.001).

The mortality risk at 12-month follow-up, based on continuous CDS scores at baseline are presented in Table 2. The crude analysis shows, that per point decrease in CDS score, the mortality risk increased with 2% (HR 1.02; 95% CI 1.01-1.03). The adjusted models showed similar results.

Additional analysis showed that a one point decrease in CDS score between 0 and 6 months was related to an increased mortality risk of 4% during the subsequent 6 months follow-up, adjusted for baseline CDS score (HR 1.04; 95% CI 1.03-1.06).

Table 1. Baseline characteristics of the total study population and the three care dependency groups based on their care dependency scores at baseline

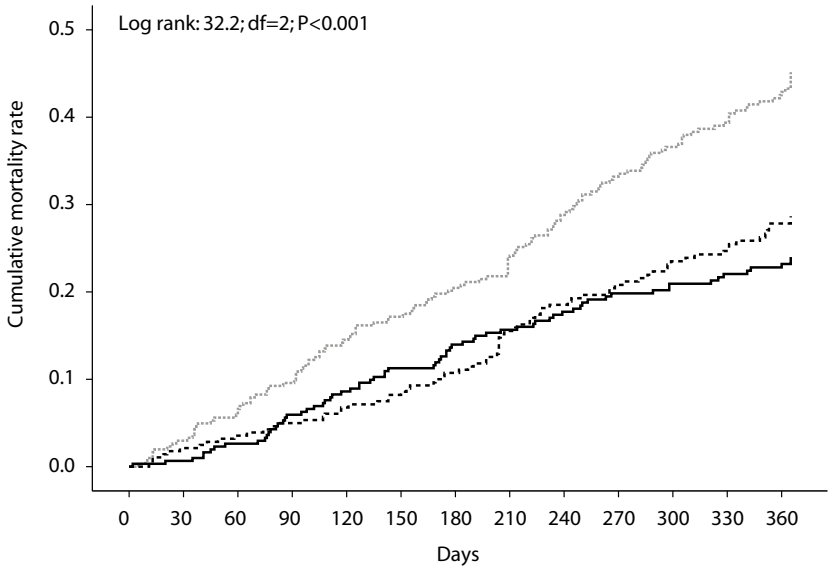
		Care Dependency groups[a]			
	Total population n = 890	**Low CDS group n = 303**	**Middle CDS group n = 282**	**High CDS group n = 305**	***P*-value***
Cut-off level of the CDS score (points)					
Men		≤ 37 points	>37 - <55	≥ 55 points	
Women		≤ 34 points	>34 - <51	≥ 51 points	
Socio demographic factors					
Female, n (%)	674 (75.7)	229 (75.6)	213 (75.5)	232 (76.1)	0.986
Age in years, median (IQR)	84 (79,88)	85 (79,89)	84 (79,88)	84 (79,88)	0.180**
Length of stay on ward in months, median (IQR)	18 (5,40)	31 (11,58)	17 (3,34)	12 (3,31)	<0.001**
CDS: median (IQR)	44 (30,56)	26 (21,31)	44 (39,48)	60 (55,64)	NA
Cranberry use	443 (49.8)	155 (51.2)	135 (47.9)	153 (50.2)	0.720
Comorbidities n (%)					
Myocardial infarction	78 (8.8)[b]	28 (9.3)	28 (10.0)	22 (7.3)	0.482
Stroke	204 (23.1)[b]	79 (26.3)	63 (22.5)	62 (20.4)	0.215
Cancer	164 (18.7)[b]	49 (16.4)	49 (17.7)	66 (21.8)	0.209
Diabetes mellitus	174 (19.6)	54 (17.8)	54 (19.1)	66 (21.6)	0.484
COPD	129 (14.8)[b]	47 (15.8)	46 (16.5)	36 (12.1)	0.274
Urine incontinence	563 (65.8)[b]	263 (88.3)	180 (67.4)	120 (41.4)	<0.001
Urinary tract infection preceding year	386 (43.4)[b]	136 (44.9)	120 (42.6)	130 (42.8)	0.817
Dementia	677 (76.8)[b]	262 (87.3)	224 (80.6)	191 (63.0)	<0.001

CDS, Care Dependency Scale (range 15–75 points); IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NA, not applicable.

[a]Low CDS group = most dependent on care; High CDS group = least dependent on care; [b]n = 1-17 missing; *Chi-square test;**Kruskal-Wallis test.

Change in care dependency during 12 months of follow-up

Table 3 shows the variation in care dependency among survivors for the CDS groups at 0–6 months (n = 714) and 7–12 months (n = 564) follow-up, based on the 33% gender-specific CDS score at baseline for the first 6 months and 33% gender-specific CDS score at 6-month follow-up. The pattern of 'improvement', 'being stable' and 'degradation' of care dependency was almost similar over the two 6-month periods.



High CDS group	305	245	209
Middle CDS group	282	236	193
Low CDS group	303	233	162
Total	890	714	564

Figure 1. Cumulative mortality rate depending on care dependency scores at baseline during 12-months of follow-up
Grey dotted line: low CDS-group; Black dotted line: middle CDS-group; Solid black line: high CDS-group.

Table 2. Mortality risk at 12-month follow-up depending on care dependency scores (continuous) at baseline

	Mortality risk per point decrease in CDS score	**95% CI**
Crude	1.02	1.01-1.03
Adjusted for age and gender	1.02	1.01-1.03
Adjusted for age, gender, cranberry use and LTCF	1.02	1.01-1.03
Adjusted for age, gender, cranberry use, LTCF, and length of stay on ward	1.02	1.01-1.03
Adjusted for age, gender, cranberry use, LTCF, length of stay on the ward and comorbidity[a]	1.03	1.02-1.04
Adjusted for age, gender, length of stay, cranberry use, LTCF comorbidity[a] and dementia	1.03	1.02-1.04

CDS, Care Dependency Scale (range 15–75 points); LTCF, Long-term care facility.
Data are presented as risk per point decrease (hazard ratio and corresponding 95% confidence intervals (CI)); estimated by Cox regression analysis.
[a]Comorbidity (including myocardial infarction, stroke, cancer, diabetes mellitus, COPD, and urine incontinence, urinary tract infection preceding year).

Table 3. Variation in care dependency in survivors during 2 subsequent periods of 6 months of follow-up for the three CDS groups

	Low CDS group	Middle CDS group	High CDS group	Total group
0-6 months: n (%)				
n	233	236	245	714
Improved	41 (17.6)	30 (12.7)	--	71 (9.9)
Stable	192 (82.4)	120 (50.8)	155 (63.3)	467 (65.6)
Deterioration	--	86 (36.4)	90 (36.7)	176 (24.6)
7-12 months: n (%)				
n	210	184	170	564
Improved	42 (20.0)	22 (12.0)	--	64 (11.3)
Stable	168 (80.0)	98 (53.3)	109 (64.1)	375 (66.5)
Deterioration	--	64 (34.8)	61 (35.9)	125 (22.2)

CDS, Care Dependency Scale (range 15–75 points).

Predictive factors for increase in care dependency

Table 4 presents the results of the crude and adjusted multivariate linear regression analysis at 6 months. The adjusted model at 6 months showed that gender, age, baseline CDS score,

Table 4. Predictors of the care dependency score for survivors at 6-month follow-up (n = 659)

	Crude model[a]			Adjusted model[b]		
	B	**SE**	***P*-value**	**B**	**SE**	***P*-value**
Constant	22.37	5.18	<0.001	22.73	4.92	<0.001
Female	1.839	0.96	0.056	1.854	0.92	0.045
Age in years	−0.106	0.06	0.058	−0.122	0.06	0.027
Cranberry use	0.143	0.78	0.855			
Long-term care facility	−0.079	0.04	0.055	−0.075	0.04	0.063
Length of stay on ward in months	−0.009	0.01	0.486			
Baseline CDS score	0.685	0.03	<0.001	0.693	0.03	<0.001
Myocardial infarction	−0.819	1.38	0.552			
Stroke	−0.539	0.96	0.576			
Cancer	−2.927	1.01	0.004	−2.969	1.00	0.003
Diabetes mellitus	0.163	0.99	0.869			
COPD	0.756	1.13	0.497			
Urine incontinence	−3.109	0.93	0.001	−3.171	0.92	0.001
Urinary tract infection preceding year	−0.634	0.81	0.432			
Dementia	−3.779	1.03	<0.001	−3.543	0.97	<0.001

CDS, Care Dependency Scale (range 15–75 points); SE, Standard Error; COPD, Chronic obstructive pulmonary disease.

[a]multivariate linear regression model.

[b]excluded from the model: cranberry use, myocardial infarction, stroke, diabetes mellitus, COPD, urinary tract infection preceding year.

cancer, urine incontinence and dementia predicted an accelerated decrease of dependency scores at 6 months. Cranberry use, LTCF, myocardial infarction, stroke, diabetes mellitus, COPD, and urinary tract infection in the preceding year, were not associated with the CDS score at 6 months. We did not find co-linearity between the dependent variable (CDS-score at 6 months) and the independent variables in both the crude and adjusted model. The Variance Inflation Factors ranges between 1.0 and 1.4. The multivariate linear regression model for men and women separately showed similar results (data not shown).

DISCUSSION

The main purpose of this study was to gain insight in the stability and changes in the care dependency status of LTCF residents, to explore possible predictive factors of change in care dependency, and examine the effect of care dependency on mortality. Changes in care dependency were examined to shed light on how to manage care and provide better tailored care for individual LTCF residents.

Care dependency and mortality

In studying the natural course of care dependency, the relation between care dependency and mortality is important. It can be hypothesized that higher care dependency leads to higher mortality risk. There are a few studies unraveling this relation. The study of Marengoni et al. showed that baseline disability was a strong predictor for mortality, independent of number of diseases.[25] Also Chen et al. showed that the sum of care problems, independent of comorbidity, is a predictor of 12-month mortality in LTCF residents[26], and Ferrucci et al. concluded that mortality after severe disability onset was high.[27] Within our study, we found similar results. A one point decrease in baseline CDS score was related to a 2% higher mortality risk in the forthcoming 12-months, also when adjusting for age, gender, cranberry use, LTCF, length of stay on the ward, comorbidity and dementia.

The course of care dependency

A recent Swiss study among 10,199 nursing home residents (70% women, 74 % aged 80 years and above) observed a decrease in activities of daily living (ADL) of 35% and an increase in ADL of almost 14% among residents, within a period of median 6 months (SD 3 months).[12] They used the Minimum Data Set Activities of Daily Living (MDS-ADL) and looked at ADL performance as primary outcome. Another study in low ADL-dependent LTCF residents in the USA, found that 69% of these LTCF residents with higher physical function remained stable in their ADL performance during 6 months of follow-up.[13] Our study shows a similar trend for care dependency. The majority of the LTCF residents remained stable in their care dependency status, only 10% improved and 25% deteriorated. The variability in the pattern of 'improve-

ment', 'being stable' and 'degradation' of care dependency varies in a similar pattern over two subsequent 6-month periods.

Predictors of change in care dependency

It is known that LTCF residents with cognitive impairment experience a deterioration in their ADL performance,[12,13,15] which make them increasingly dependent on nursing care. As mentioned earlier, nutritional status,[12,13] cognitive impairment,[12,13,15] absence of daily contact with proxies,[12] depression,[12,16] neuropsychological deficits,[17] incontinence[12,13,18] and infections[19] were mentioned as predictors for deterioration in ADL performance. The study of Dijkstra et al. showed that the degree of care dependency at entry to the study was one of the strongest predictors of follow-up CDS ratings.[14] Our study confirms that the baseline CDS score is predictive, but showed also that gender, age, urine incontinence, dementia and cancer; predict an increase in care dependency over time.

Strengths and limitations

The present study included a large sample of 890 residents residing in 21 Dutch LTCFs. Our study participants represent a vulnerable population; with a median age of 84 years and a high dependency on nursing care (median CDS score of 44 points). This median baseline CDS score is comparable with that of other studies in nursing homes.[11,28] Because a recent international comparison of the CDS demonstrated its usefulness for comparative research across countries[28], the results of the present study might be generalizable to LTCFs worldwide.

Daily nursing care in LTCF focuses on residents care dependency as a process in which the residents' self-care decreases, and in which care demands makes a person increasingly dependent on nursing care.[7] Although other instruments to assess care dependency are available (e.g. the MDS-ADL, Barthel index,[29] or Katz[30]) we decided to use the Care Dependency Scale. The CDS comprises all domains of nursing care; it is not limited to basic ADL, but also includes the individual's capacity for social contacts, recreational activities, and learning abilities. The CDS is easy to administer, the responsible nurse could assess the CDS usually in less than five minutes and has shown satisfactory reliability and validity.[22-24]

Our study was nested in the CRANBERRY trial. Since the CRANBERRY study is a randomized-controlled trial and half of the participants underwent treatment with cranberry, this could have influenced the course of care dependency. However, there was no cranberry effect on care dependency over time. Therefore the CRANBERRY trial gives us the possibility to explore whether there are predictive factors of changes in care dependency. However, this means that not all earlier mentioned predictors of change in ADL were included in the dataset.

Within this study we were particularly interested to explore the personal characteristics of LTCF residents on the natural course of care dependency. An institutional effect on mortality and care dependency was not found. Other factors dependent on organizational characteristics of the long-term care facilities would be of interest for further research, since these char-

acteristics could influence the care dependency status of LTCF residents as well. However, this was outside the scope of our study.

Another possible limitation of the present study is that we studied a selected period of 12 months. Classification of the participants into the three CDS groups was based on the prevalent CDS score at baseline, and we have no data on the CDS score of the residents at admission to the LTCF. Because care dependency is a dynamic process, the change in CDS score (and therefore the results) might be different if we had known the care dependency status when the residents were first admitted.

Implications for practice

A regular and simple assessment of care dependency can be valuable, since this allows nursing staff to become more aware of the variability in the care dependency status of their residents, manage care, and provide better tailored care for individual residents. In daily nursing care, they are the first professionals who might observe subtle changes in the care dependency status of residents and therefore can better anticipate residents' care needs. The present study shows that residents can increase or as well as decrease in their level of care dependency. Care dependency may be influenced by individually tailored interventions and this needs further exploration in research. In addition, in view of the association between the CDS score and mortality, it seems relevant to train staff in providing palliative care as well as restorative care.[31]

CONCLUSIONS

The majority of surviving LTCF residents were stable in their care dependency status over two subsequent 6-month periods, even 10% showed improvement and 25% deteriorated in their dependency status. Highly care dependent residents showed an increased mortality risk. Awareness of the natural course of care dependency is essential to residents and their formal and informal caregivers when considering therapeutic and end-of-life care options.

Abbreviations

ADL, Activities of daily living; CDS, Care dependency scale; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; HR, Hazard ratio; IQR, Interquartile range; LTCF, Long-term care facility; NTR, Dutch trial register

Competing interest

All researchers worked independently from the funders. The authors declare that they have no competing interests.

Authors' contributions

MAAC, HJMC and JG contributed to the study concept and design, acquisition of data, analysis and interpretation of the data, drafting of the manuscript and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgments

The authors thank the organisations and members of the University Nursing Home Research Network South Holland (UVN-ZH) and the staff of the LTCFs participating in this study. Their ongoing collaboration enabled us to perform this study.

Funding

A grant was received form ZonMw Doelmatigheid, the Dutch Organization for Health Research, the Netherlands (project no. 170882501).

Role of sponsors

All funding sources were independent and had no influence on the study design, the collection, analysis, and interpretation of our data; the writing of this report; or the decision to submit the manuscript for publication.

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CHAPTER 3

Clinically diagnosed infections predict ADL-disability among the oldest old in the general population. The Leiden 85-plus Study.

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Age and Ageing 2013; 42:482-488

ABSTRACT

Background Ageing is frequently accompanied by a higher incidence of infections and an increase in disability in activities of daily living (ADL).

Objective This study examines whether clinical infections [urinary tract infections (UTI) and lower respiratory tract infections (LRTI)] predict an increase in ADL disability, stratified for the presence of ADL disability at baseline (age 86 years).

Design The Leiden 85-plus Study. A population-based prospective follow-up study.

Setting General population.

Participants A total of 154 men and 319 women aged 86 years.

Methods Information on clinical infections was obtained from the medical records. ADL disability was determined at baseline and annually thereafter during 4 years of follow-up, using the 9 ADL items of the Groningen Activity Restriction Scale.

Results In 86-year-old participants with ADL disability, there were no differences in ADL increase between participants with and without an infection (−0.32 points extra per year; $P = 0.230$). However, participants without ADL disability at age 86 years (n = 194; 41%) had an accelerated increase in ADL disability of 1.07 point extra per year ($P < 0.001$). For UTIs, this was 1.25 points per year ($P < 0.001$) and for LRTIs 0.70 points per year ($P = 0.041$). In this group, an infection between age 85 and 86 years was associated with a higher risk to develop ADL disability from age 86 onwards [HR: 1.63 (95% CI: 1.04–2.55)].

Conclusions Among the oldest-old in the general population, clinically diagnosed infections are predictive for the development of ADL disability in persons without ADL disability. No such association was found for persons with ADL disability.

Keywords ADL disability, infections, oldest-old, general population, older people

INTRODUCTION

The oldest-old are predisposed to infectious diseases as a result of deterioration of the immune system and an increased prevalence of co-morbidity.[1] The incidence of urinary tract infections (UTIs) and lower respiratory tract infections (LRTIs) increase with age[2-6], with an exponential increase in the oldest-old.[5,6]

In vulnerable older persons, the most common bacterial infection is a UTI, with serious adverse health consequences such as delirium, dehydration, urosepsis and hospitalisation.[7,8] Also, UTI has a high mortality rate, especially by hospitalisation.[9] Community acquired pneumonia, also highly prevalent in older persons,[10] is also a frequent cause of hospitalisation and death.[11,12]

Literature on the consequences of infections on the functional decline, also highly prevalent in older persons and increasing with age,[13,14] is limited and mainly describes the impact of infections on the functional status of nursing home residents.[15-17] To our knowledge, there is no information about how infections and activities of daily living (ADL) disability co-occur in the oldest-old in the general population. Therefore, this study examines whether incident clinical infections between age 85 and 86 years contribute to an increase in ADL disability from age 86 onwards, stratified for ADL disability at baseline.

METHODS

Setting and study population

The present study was conducted within the framework of the Leiden 85-plus Study. The Leiden 85-plus Study is an observational population-based prospective study of 85-year-old inhabitants of Leiden, The Netherlands. Between September 1997 and September 1999, all inhabitants of Leiden who reached the age of 85 years (birth cohort 1912–14) were invited to participate in the study. There were no selection criteria concerning health or demographic characteristics. The medical ethics committee of the Leiden University Medical Center approved the study. All participants gave informed consent for the entire study, including the use of data from their medical records for additional analyses, following explanation of the study requirements and assurance of confidentiality and anonymity. For participants with severe cognitive impairment, a guardian gave informed consent.

Participants were visited annually until the age of 90 years. They were visited at their place of residence where face-to-face interviews were conducted, cognitive testing was performed and information on socio-demographic characteristics and disabilities in daily living were obtained. Information on patients' background was obtained annually from the medical records of general practitioners (GPs) and elderly care physicians.

Infections

Information on clinical infections was obtained from the medical records. UTIs were considered present when the treating GP or elderly care physician diagnosed UTI based on signs and symptoms and urine analysis.[18] LRTI was clinically diagnosed by the treating physician based on medical history taking, physical examination and clinical judgment during a consultation with the participant.[10]

ADL disability

ADL disability was measured annually with the nine 'basic activities of daily living' from the Groningen Activity Restriction Scale (GARS),[19] by face-to-face interviews. ADL included the following tasks: getting around the house, getting into and out of bed, standing up from a chair, going to the toilet, dressing oneself, washing hands and face, washing whole body, preparing breakfast and drinking and feeding oneself. Answers ranged from 'fully independently, without any difficulty' (1 point) to 'not fully independently, only with someone's help' (4 points); total score ranged from 9 to 36.[19] Higher scores indicate more ADL disability. ADL disability was considered present when the participant was unable to do at least one of the nine ADL items independently (GARS > 9 points).

Socio-demographic factors

During baseline interviews, a research nurse collected information about the participants' residency, income, level of education and smoking habits.

Mental status

Cognitive function was measured by the Mini-Mental State Examination (MMSE). Scores ranged from 0 to 30, with lower scores indicating impaired cognitive functioning. Severe cognitive impairment was defined as an MMSE score ≤ 19 points.[20] To determine the presence of depressive symptoms, the Geriatric Depression Scale-15 (GDS-15) was conducted. Depressive symptoms were considered present by a GDS-15 score ≥ 4 points,[21-23] but only in those with MMSE ≥ 19 points.

Co-morbidity

Information on participants' medical history was obtained by standardised interviews with their treating GP or elderly care physician, and by examination of the medical records, including data on the presence of myocardial infarction, stroke, diabetes mellitus, and chronic obstructive pulmonary disease (COPD). Information on incontinence and musculoskeletal complaints was collected in face-to-face interviews with the participants.

Statistical analysis

Differences in baseline characteristics at age 86 years, stratified for ADL disability, between the infection and no infection groups, were compared with a Chi-square test or Fisher's exact test when the cells in the 2 × 2 crosstabs were < 10 observed or 5 expected counts, for categorical data. Median scores of the GARS were compared using the Mann–Whitney U test. *P*-values < 0.05 were considered statistically significant.

Short-term effect: retrospective analysis

The short-term effect of infections on ADL disability was studied retrospectively, using 'history of UTI or LRTI between age 85 and 86 years' in relation to ADL disability scores at age 85 and 86 years. The short-term effect of infections on ADL disability was calculated by taking the delta in the ADL score (ADL score at 86 years minus the ADL score at 85 years), stratified for participants with and without ADL disability at age 86 years. The independent t-test was used to test differences in the mean increase in ADL scores between participants with and without infections for both groups.

Long-term effect: prospective analysis

We started the follow-up for 4 years at age 86 years to enable to study the 'history of UTI or LRTI between age 85 and 86 years' as a possible predictor for long-term ADL disability from age 86 years onwards. All analyses were stratified for ADL disability at age 86 years.

Cox regression models were used to analyse whether an infection between age 85 and 86 years was associated with the long-term development of ADL disability from 86 years onwards in those without ADL disability at 86 years.

The relation between infections, between age 85 and 86 years, and changes in ADL disability scores over time (4 years of follow-up) were analysed with linear mixed models (LMM). Each LMM included a term for the baseline difference in the ADL disability score for those with and without infection between age 85 and 86 years, a term for time, and a term for the interaction between infection and time. The effect of time on ADL disability reflects the annual change in ADL disability in those without infection, and is presented as the basic annual change in the ADL disability score (β2). The interaction of infection and time reflects the additional annual change in ADL disability for those with infection and is presented as additional annual change in the ADL disability score (β3).

Cox regression and LMM were adjusted for gender, living situation (independent or long-term care facility) and comorbidity (myocardial infarction, stroke, diabetes mellitus, COPD, musculoskeletal complaints and incontinence).

Analyses were performed with SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Between September 1997 and September 1999, 705 participants were eligible for participation in the Leiden 85-plus Study. Ninety-two participants refused to participate and 14 participants died before enrolment, resulting in a study population of 599 participants at the age of 85 years (response rate 87%). At age 86 years, the baseline of the present study, 551 participants are still alive. A total of 72 participants for whom valid clinical information on infections at the age of 86 years was missing were excluded. For six participants information on ADL disability at 86 years was missing, resulting in a final study population of 473 participants. The 78 participants that were not included in the present study more often had primary school education only, myocardial infarction, COPD and incontinence (data not shown).

Study population

Table 1 presents a comparison of the characteristics of the participants with and without infections between age 85 and 86 years (n = 473), at the age of 86 years stratified for participants with and without ADL disability at the age of 86 years. Almost 70% of the study population was female. In participants without ADL disability at baseline, on all but one there were no significant differences in sociodemographic factors and functioning for both the infection and no-infection group. Only for current smoking, a significant difference between the infection and no-infection group (28 versus 12%; $P = 0.030$) was found. In participants with ADL disability, more participants in the infection group were living in long-term care facilities than in the no-infection group (48 versus 27%, $P = 0.001$). In this group of participants with ADL disability, participants with an infection between 85 and 86 years had a significantly higher median ADL baseline score compared with those without infections (16 versus 13 points; $P < 0.001$). In both strata, there was a higher occurrence of COPD in participants with infections (participants without ADL disability: infection 28% versus no-infection 6%; $P = 0.001$), and in participants with ADL disability: infection 17 versus 7%; $P = 0.009$. In the participants with ADL disability, there was significantly more incontinence among those participants with infection (68 versus 51%; $P = 0.013$).

Short-term consequences: retrospective analysis

Table 2 presents the 1-year increase in ADL disability score from age 85 to 86 years for participants with and without ADL disability at age 86 years. In participants without ADL disability, 32 (16.5%) had at least one infection versus 75 (26.9%) in participants with ADL disability ($P = 0.008$).

In participants with ADL disability at age 86 years, the mean increase in ADL scores was similar in participants with an infection (UTI or LRTI) and without an infection (2.28 versus 2.52 points increase; independent t-test, $P = 0.809$). In participants without ADL disability at

Table 1. Baseline characteristics of the study population at age 86 years (n = 473), stratified for ADL disability at the age of 86 years for the infection or no-infection groups between the ages of 85-86 years.

	No ADL disability at 86 years (GARS = 9)[b]					ADL disability at 86 years (GARS > 9)[b]				
	Infection[a] (n = 32)		No-infection[a] (n = 162)			Infection[a] (n = 75)		No-infection[a] (n = 204)		
	n	%	n	%	*P*-value	n	%	n	%	*P*-value
Socio-demographic factors										
Female	22	68.8	108	66.7	0.819[a]	56	74.7	133	65.2	0.134[*]
Long-term care facility	3	9.4	11	6.8	0.706[b]	36	48.0	55	27.0	0.001[*]
Primary school only	20	62.5	91	56.2	0.509[a]	53	71.6	128	63.1	0.185[*]
Low income	17	53.1	72	44.4	0.384[a]	44	60.3	102	51.0	0.174[*]
Smoking (current)	9	28.1	20	12.3	0.030[b]	10	13.5	31	15.3	0.849[**]
Functioning										
GARS score, median (IQR)[b]	9 (9;9)		9 (9;9)		1.000[c]	16 (12;30)		13(11;18)		<0.001[***]
Severe cognitive impairment (MMSE < 19)	2	6.3	3	1.9	0.191[b]	25	35.2	49	24.1	0.070[*]
Depressive symptoms (GDS-15 > 4)[c]	2	6.7	14	8.8	1.000[b]	8	17.4	32	20.9	0.601[*]
Infections between 85 and 86 years of age										
At least one infection (UTI or LRTI)	32	100.0	NA	NA	NA	75	100.0	NA	NA	NA
UTI	17	53.1	NA	NA	NA	55	73.3	NA	NA	NA
LRTI	15	48.4	NA	NA	NA	30	40.0	NA	NA	NA
Co-morbidities										
Myocardial infarction	3	10.0	12	7.5	0.710[b]	4	5.5	26	12.9	0.123[**]
Stroke	3	9.7	8	5.0	0.391[b]	18	24.0	29	14.3	0.055[*]
Diabetes Mellitus	4	12.9	17	10.5	0.752[b]	9	12.2	30	14.9	0.697[**]
COPD[d]	9	28.1	9	5.6	0.001[b]	13	17.3	14	6.9	0.009[*]
Musculoskeletal complaints	14	43.8	52	32.3	0.212[a]	38	53.5	103	52.9	0.919[*]
Incontinence	11	36.7	49	31.0	0.542[a]	49	68.1	99	51.0	0.013[*]

MMSE, Mini-Mental State Examination; GDS-15, Geriatric Depression Scale with 15 items; ADL, Activities of Daily Living; GARS, Groningen Activity Restriction Scale; SD, standard deviation; UTI, Urinary Tract Infection; LRTI, Lower Respiratory Tract Infection; COPD, Chronic Obstructive Pulmonary Disease; NA, not applicable.

[a]Infection = Urinary tract infection or Lower respiratory tract infection

[b]ADL disability measured with the 9-item Groningen Activity Restriction Scale (9-36)

[c]only administered to participants with MMSE > 19

[d]Chronic Obstructive Pulmonary Disease (COPD) registered at the age of 85 years

[*]Chi-square test

[**]Fisher's exact test

[***]Mann-Whitney U-test

Table 2. Short-term change in ADL score (delta between the ages of 85-86 years) depending on the presence of infections between 85 and 86 years

	No ADL disability at 86 years, n = 194 (GARS = 9)[a]				ADL disability at 86 years, n = 279 (GARS > 9)[a]			
	n	%	Mean ADL-increase (SD) 85-86	*P*-value[b]	n	%	Mean ADL increase (SD) 85-86	*P*-value[b]
No-infection	162	83.5	-0.42 (1.10)		204	73.1	2.52 (8.18)	
At least one infection (UTI or LRTI)	32	16.5	-0.53 (0.98)	0.594	75	26.9	2.28 (5.02)	0.809
UTI	17	8.8	-0.53 (1.07)	0.740	55	19.7	2.53 (5.17)	0.962
LRTI	15	7.7	-0.53 (0.92)	0.715	30	10.8	1.83 (4.62)	0.627

UTI, Urinary Tract Infection; LRTI, Lower Respiratory Tract Infection; SD, standard deviation; ADL, Activities of Daily Living; GARS, Groningen Activity Restriction Scale

[a]ADL disability measured with the 9-item Groningen Activity Restriction Scale (9-36)

[b]Independent t-test; no-infection group compared with infection groups

the age of 86 years, the mean increase in ADL scores was also similar for participants with and without infection (independent t-test, $P = 0.594$).

Long-term consequences: prospective analysis

In participants without ADL disability at baseline (n = 194), an infection (UTI or LRTI) between the ages of 85–86 years was associated with higher risk to develop ADL disability from age 86 onwards [HR: 1.63 (95% CI: 1.04– 2.55)]. After adjustment for gender, living situation and comorbidity this risk remained roughly similar [HR: 1.70 (95% CI: 1.03–2.81)].

For UTI and LRTI, the unadjusted HRs were 1.66 (95% CI: 0.95–2.90) and 1.43 (95% CI: 0.75–2.73), respectively. After adjustment these, HRs remained similar (data not shown).

The changes in ADL disability scores over time for those with and without infection, with and without UTI, and with and without LRTI, are presented in Figure 1, stratified for ADL disability at the age of 86 years. In all groups, ADL disability increased with age.

In participants with ADL disability at baseline, the difference in the ADL score between the infection and no-infection group at baseline was 4.52 points ($P < 0.001$). No accelerated increase was found in this group for those with an infection compared with those without: additional annual change –0.32 points, (95% CI: –0.85–0.21, $P = 0.230$) (Figure 1).

Among the participants without ADL disability at baseline, participants with an infection (UTI or LRTI) between age 85 and 86 years had an accelerated increase in ADL disability (1.07 points extra per year, 95% CI: 0.61–1.53, $P < 0.001$) compared with those without infections (Figure 1). The accelerated increase in ADL disability was 1.25 points extra per year (95% CI: 0.66–1.83, $P < 0.001$) for UTI and 0.70 points extra per year (95% CI: 0.03–1.38, $P = 0.041$) for LRTI. After adjustment for gender, living situation (independent or long-term care facility) and comorbidity, these estimates remained similar, still significant and the conclusions were unchanged (data not shown).

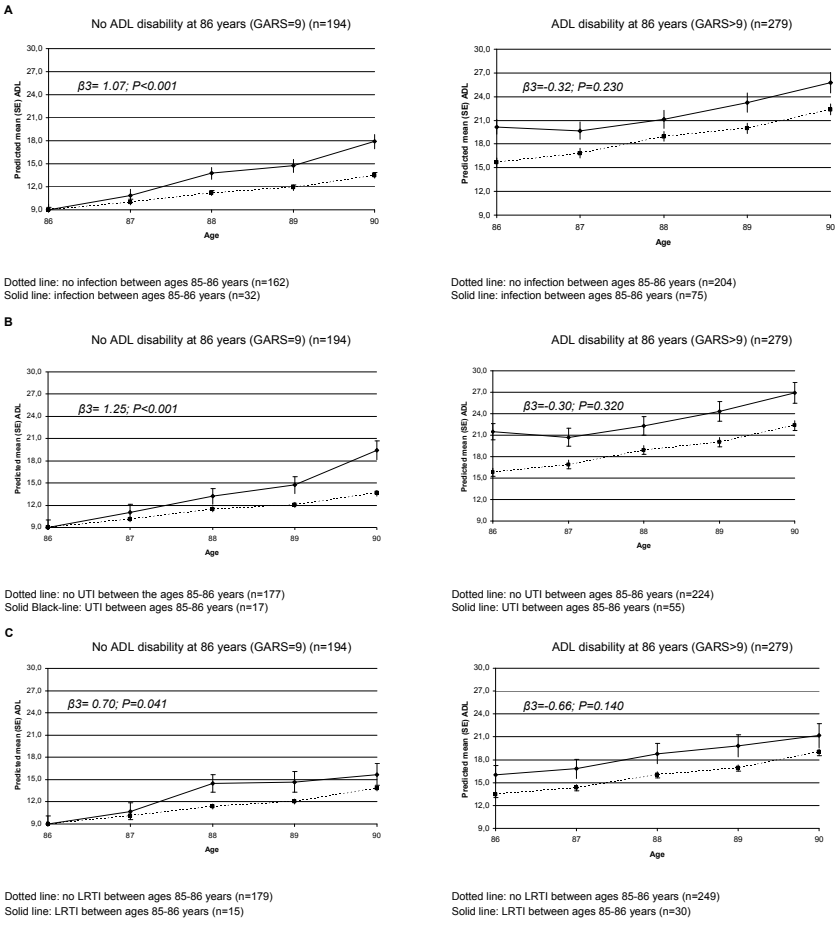

Figure 1. Change in the ADL score over time for those with and without an infection between the ages of 85-86 years (A), with and without UTI (B) and with and without LRTI (C), stratified for ADL disability at age 86 years.
Linear mixed models in which β3 is the additional annual change in ADL disability score for those with infection between ages 85-86 years.

DISCUSSION

The present study shows that, in the general population of the oldest-old, clinically diagnosed infections are predictive for the development of ADL disability for persons without ADL disability at the age of 86 years. Moreover, clinically diagnosed infections contribute to an accelerated increase in ADL disability on the long term. No such association was found for those with ADL disability at baseline.

Our results build on evidence from studies involving patients in selected populations of nursing home residents.[15-17] Bula et al. showed a higher risk of a decline in the functional status in older nursing home residents with an infection (mean age 85.7 years, 76.6% female).[15] Barker et al. found a decrease in functioning in older persons living in long-term care facilities within 3–4 months after an influenza infection.[16] However, in contrast to the previous studies, Loeb et al. found no significant effect in a follow-up period of 3 years on the functional status in nursing home residents, neither for pneumonia nor LRTIs compared with controls (mean age 86.1 years, 75.5% female).[17] Our study is the first to focus on the consequences of infections on ADL disability in the oldest-old in the general population.

Interestingly, in a previous analysis in the Leiden 85-plus Study, we found that chronic multimorbidity predicts an accelerated increase in ADL disability in very old persons with a good cognitive function.[24] This study shows that also an acute illness predicts an accelerated increase in ADL disability in the oldest-old without ADL disability at 86 years.

The present study is based on a unique sample of participants aged ≥ 86 years. The population-based study structure and almost complete follow-up of the participants allow us to generalise our results to the oldest-old in the general population. All infections were clinically diagnosed by GPs and elderly care physicians. This procedure reflects usual care and enables generalisation of our results to daily clinical care for the oldest-old.

A limitation of our study is that we only have information on infections per year and do not know the precise date the infection occurred.

CONCLUSION

This study shows that in older persons without ADL disability at 86 years of age, clinical infections (UTI and LRTI) predict the development of ADL disability from age 86 onwards. These infections may be used in the future as a predictor for ADL disability in the oldest-old who are not yet disabled. The GP or elderly care physician should be vigilant when older persons without ADL disability get infections and may start active functional rehabilitation to maintain independence in ADL. Future studies may also address whether the prevention of infections, a quick recovery after infections and functional rehabilitation are beneficial in the oldest-old in the general population to maintain independence in ADL and to avoid adverse health outcomes.

Key points

- Ageing is frequently accompanied by a higher incidence of infections and an increase in disability in activities of daily living.
- In 86-year-old persons without ADL disability, an infection was associated with a higher risk to develop ADL disability.
- In disabled 86-year-old persons, there were no differences in ADL increase between participants with and without an infection.
- Among the oldest-old in the general population, infections are predictive for the development of ADL disability.

Conflicts of interest

None declared.

Funding

The Leiden 85-plus Study was partly funded by an unrestricted grant from the Dutch Ministry of Health, Welfare and Sports. A grant was received from the Dutch Organisation of Scientific Research (NWO) for Open Access publication of this manuscript.

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CHAPTER 4

Predictive factors of urinary tract infections among the oldest old in the general population. A population based prospective follow-up study

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BMC Medicine 2011, 9:57

ABSTRACT

Background Urinary tract infections (UTI) are common among the oldest old and may lead to a few days of illness, delirium or even to death. We studied the incidence and predictive factors of UTI among the oldest old in the general population.

Methods The Leiden 85-plus Study is a population-based prospective follow-up study of 86-year-old subjects in Leiden, The Netherlands. Information on the diagnosis of UTI was obtained annually during four years of follow-up from the medical records and interviews of treating physicians. A total of 157 men and 322 women aged 86 years participated in the study. Possible predictive factors were collected at baseline, including history of UTI between the age of 85 and 86 years, aspects of functioning (cognitive impairment (Mini-Mental State Examination (MMSE) < 19), presence of depressive symptoms (Geriatric Depression Scale (GDS) > 4), disability in activities of daily living (ADL)), and co-morbidities.

Results The incidence of UTI from age 86 through 90 years was 11.2 (95% confidence interval (CI) 9.4-13.1) per 100 person-years at risk. Multivariate analysis showed that history of UTI between the age of 85 and 86 years (hazard ratio (HR) 3.4 (95% CI 2.4-5.0)), impaired cognitive function (HR 1.9 (95% CI 1.3-2.9)), disability in daily living (HR 1.7 (95% CI 1.1-2.5)) and urine incontinence (HR 1.5 (95% CI 1.0-2.1)) were independent predictors of an increased incidence of UTI from age 86 onwards.

Conclusions Within the oldest old, a history of UTI between the age of 85 and 86 years, cognitive impairment, ADL disability and urine incontinence are independent predictors of developing UTI. These predictive factors could be used to target preventive measures to the oldest old at high risk of UTI.

BACKGROUND

Urinary tract infections (UTIs) are common in the very elderly and account for nearly 25% of all infections.[1,2] The incidence of UTI increases with age in both men and women,[3-5] and increases from 12 to 29 per 100 person-years at risk in community-dwelling elderly populations[5,6] to 44 to 58 per 100 residents per year at risk in long term care facilities.[7,8] These UTI are often complicated, involving the presence of structural or functional abnormalities of the genitourinary tract.[9] Especially in vulnerable older persons living in long term care facilities, UTIs more often have serious consequences such as delirium, dehydration, urosepsis, hospitalisation, or even death.[10,11]

Several strategies to prevent UTI have been developed, such as treatment of those at high risk with low-dose, long-term antibiotics,[12,13] oestrogens[14] and cranberry products.[12,15] These strategies have been shown to be effective in preventing UTI in younger women with recurrent UTI[13-15], but not yet in vulnerable older people. Preventive strategies are best applied to those at risk; however, factors associated with UTI in ambulatory older patients in the community setting have not been described.

Previous studies have shown that increasing age,[4,16] diabetes mellitus,[17,18] stroke,[19] urine incontinence,[1,20,21] prior history of UTI,[1,20] urogenital surgery,[1,20] and impaired functional and cognitive status[16,20] predict the development of UTI among older individuals. However, these studies investigated predictors of UTI in specific patient groups, such as hospitalised patients and patients residing in long-term care facilities and did not include older individuals in the general population. In addition, these studies used different methods to identify UTI. It is generally accepted that diagnosing symptomatic UTI in older persons is complicated due to factors like difficult doctor-patient communication, chronical genito-urinary symptoms, and a high frequency of positive urine cultures due to bacteriuria without complaints.[22]

To target preventive strategies against UTIs in older individuals, those with highest risk to develop UTI have to be identified. The purpose of this study was to determine the incidence and predictive factors of UTI among the oldest old in the general population.

METHODS

Setting and study population

The Leiden 85-plus Study is an observational population-based prospective study of 85-year-old inhabitants of Leiden, The Netherlands. Between September 1997 and September 1999, all inhabitants of Leiden who reached the age of 85 years were invited to participate in the study. There were no selection criteria concerning health or demographic characteristics. The medical ethics committee of the Leiden University Medical Center approved the study. All participants gave informed consent for the whole study including the use of data from their

medical records for additional analysis, following explanation of the study requirements and assurance of confidentiality and anonymity. For participants with severe cognitive impairment, a guardian gave informed consent.

The present study was conducted within the framework of the Leiden 85-plus Study. We started follow-up for four years at age 86 years to allow us to study 'history of UTI between the age of 85 and 86 years' as a possible predictor. In this study, 479 participants aged 86 years were included. Participants were revisited annually until the age of 90 years. All participants were visited at their place of residence where face-to-face interviews were conducted, cognitive testing was performed, information on socio-demographic characteristics and disabilities in daily living was obtained, and a venous blood sample was taken.

Urinary tract infection

The endpoint of this study was the development of the first UTI from age 86 through 90 years. This endpoint was considered present when treating physicians diagnosed UTI based on signs and symptoms and urine analysis.

The endpoint was also reached when a participant during follow-up died from UTI. General practitioners and elderly care physicians were interviewed annually to gather clinical information. Each year data were gathered about the development of clinical diagnosed UTI during the preceding year from clinician interviews and records. Mortality data were obtained from the municipality. Specific data on causes of death were obtained from Statistics Netherlands, according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10), including UTI (ICD-10 code N39.0).[23]

Selection of potentially predictive factors

Through an extensive search of scientific literature, factors that are potentially predictive for UTI in older individuals were identified and selected for the study, within the domains socio-demographic factors, functioning, co-morbidities and renal functioning.

Socio-demographic factors

During baseline interviews, a research nurse collected information about the participants' residency, income, level of education, body mass index and smoking habits.

Functioning

To assess cognitive function, the Mini-Mental State Examination (MMSE) was administered. Severe cognitive impairment was defined as a MMSE score below 19 points.[24,25] The Geriatric Depression Scale-15 (GDS-15) was performed to determine the presence of depressive symptoms. The presence of depressive symptoms was defined as a GDS-15 score above four points. The GDS-15 could only be administered in participants with an MMSE score above 19 points.[26,27] Disability in basic activities of daily living (ADL) was determined using the Gron-

ingen Activity Restriction Scale (GARS)[28] and defined as being unable to do any one of the following nine ADL: independently: walk inside, get out of bed, get into and out of a chair, use the toilet, wash hands and face, wash body, dress and undress, eat and drink, and make breakfast.[29] The GARS-items were dichotomized. Participants were grouped into those who had no difficulty with GARS-items (score 1) and those who had difficulty or were unable to perform the GARS-items independently (score 2, 3 and 4). The total GARS score was calculated by adding the total scores of the nine items of the GARS and than dichotomized into score 9 (independently) and scores > 9 (difficulty or unable to perform independently). All questionnaires were validated in Dutch.

Co-morbidities

Information on participants' medical history was obtained by standardised interviews with their treating general practitioner or elderly care physician and by examination of pharmacy records. We obtained clinical information on the presence of diabetes mellitus, stroke and cancer as well as information on unintentional loss of faeces and/or urine. Diagnosis of incontinence was ascertained by the general practitioner or elderly care physician. For males, complaints of Lower Urinary Tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) were measured with the International Prostate Symptom Score (IPSS). The IPSS is an eight-question written screening tool to rapidly diagnose BPH, track the symptoms of BPH and suggest management of the symptoms of BPH.[30] The severity of urine incontinence was obtained by the PRAFAB-Questionnaire, which combines objective and subjective aspects of the severity of urinary incontinence.[31-33] PRAFAB stands for Protection (the use of pads), Amount of urine loss, Frequency of urine loss, Adjustment of behaviour due to symptoms, and Body (or self) image as a result of the stress urine loss symptoms.

Serum creatinine concentration was measured automatically according to the Jaffe method (Hitachi 747; Hitachi, Tokyo, Japan). Creatinine clearance was calculated from serum creatinine concentration and body weight, using the Cockcroft-Gault formula.[34] Low creatinine clearance was defined as a creatinine clearance below 30 mL/minute. For unknown disease, we measured C-reactive protein (CRP) levels with a fully automated Hitachi 911 analysis system. CRP levels above 5 mg/L were considered elevated CRP levels.[35]

Data analyses

The incidence of UTI from age 86 years onwards was calculated during four years of follow-up (until age 90 years), using the life-table method. The number of first time UTI was assigned to the numerator and the observed person-years at risk were assigned to the denominator. The observed person-years at risk were counted from age 86 to the censor date (age 90 years), to date of death, or to date of first UTI.

The association between predictive factors and the occurrence of UTI in participants from age 86 years onwards was investigated with Cox proportional hazards models. Those factors

predicting UTI in the univariate Cox regression analysis with a *P*-value < 0.10 were included in a multivariate Cox regression analysis. Since the GDS-15 could only be administered to participants without cognitive impairment (MMSE ≥ 19 points, n = 393), the variable 'depressive symptoms' was not included in the multivariate analysis. The relative contribution of the different predictive factors to the occurrence of UTI was determined by calculating the Population Attributable Risk (PAR), which combines the relative risk and the prevalence of the different predictive factors. Data analyses were performed using SPSS for Windows, version 16.0 (SPSS Inc, Chicago, USA).

RESULTS

Study population

Between September 1997 and September 1999, 705 participants were eligible for participation in the Leiden 85-plus Study. Ninety-two participants refused to participate and 14 participants died before enrolment, resulting in a study population of 599 participants (response rate of 87%).[36] For the present study, 72 participants for whom valid clinical information about UTI at age 86 was missing were excluded. Forty-eight participants died before the age of 86, resulting in a study population of 479 persons (response rate of 80.0% of the study population).

Table 1 shows the baseline characteristics of the study population at age 86 years (n = 479). Two-thirds of the population was female and 22% of the participants were institutionalised in long-term care facilities. Restriction in ADL was registered in more than 59% of the participants and 19% had an MMSE-score below 19 points. A total of 44% of the participants reported urine incontinence and in almost 20% of the participants incontinence was diagnosed by the general practitioner or elderly care physician. A total of 15% of the participants had a history of UTI between the age of 85 and 86 years. Additional analysis showed that 8.3% of men and 18.3% of women had a history of UTI between the ages of 85 and 86 years (chi-square 8.3; df = 1; *P* = 0.004).

Incidence of urinary tract infections

In four years of follow-up we observed 140 first episodes of UTI during 1,246 person-years (py) at risk. The overall incidence of UTI was 11.2 (95% CI 9.4-13.1) per 100 py at risk. Ninety-two participants had recurrent UTI (15.6% of the total population and 47.4% of the participants with UTIs). On average 6.5% (per year range 5.7-7.3) of all participants experienced two or more UTIs per year during follow-up, of which 45.6% (per year range 40.0-54.7) had more than one infection per year. A total of 246 participants died during follow-up, of whom seven participants died from UTI according to CBS data. The incidence of UTI was 12.8 (95% CI 10.4-15.2)

Table 1. Risk of UTI from age 86 years onwards depending on socio-demographic, functional and medical baseline characteristics (n = 479)

	Index group N (%)	Incidence in index group, per 100 py (95% CI)	Incidence in reference group*, per 100 py (95% CI)	HR (95%CI)	*P*-value
Socio-demographic factors					
Female	322 (67.2)	12.8 (10.4, 15.2)	7.8 (5.1,10.6)	1.7 (1.1, 2.5)	0.012
Long-term care facility	107 (22.3)	23.5 (16.6, 25.6)	9.1 (7.3, 10.9)	2.4 (1.7, 3.4)	<0.001
Low income	238 (49.7)	11.7 (9.1, 14.4)	10.5 (7.9, 13.1)	1.1 (0.8, 1.6)	0.547
Primary school only	296 (61.8)	12.8 (10.2, 15.3)	8.9 (6.1, 11.3)	1.5 (1.0, 2.1)	0.044
Smoking (current)	70 (14.6)	12.8 (7.3, 18.3)	11.0 (9.0, 12.9)	1.1 (0.7, 1.8)	0.618
Body Mass index ≥2 7	212 (47.2)	11.1 (8.4, 13.9)	9.9 (7.5, 12.4)	1.1 (0.8, 1.6)	0.535
Functioning					
Severe cognitive impairment (MMSE < 19)	90 (19.0)	27.0 (18.6, 35.3)	9.0 (7.2, 10.8)	2.7 (1.9, 3.9)	<0.001
Depressive symptoms (GDS-15 > 4)	58 (14.8)	8.8 (4.0, 13.5)	9.1 (7.2, 10.9)	1.0 (0.5, 1.7)	0.897
Disability in daily living†	283 (59.2)	16.2 (13.0, 19.4)	6.3 (4.3, 8.3)	2.4 (1.6, 3.5)	<0.001
Co-morbidities					
Diabetes mellitus	76 (15.9)	10.6 (5.8, 15.4)	10.4 (8.4, 12.3)	1.0 (0.6, 1.6)	0.963
Stroke	60 (12.6)	20.8 (12.5, 29.1)	10.2 (8.3, 12.0)	1.9 (1.2, 3.0)	0.004
Cancer	97 (20.6)	10.0 (6.0, 14.0)	11.3 (9.2, 13.4)	1.1 (0.7, 1.8)	0.589
Benign Prostatic Hyperplasia (IPSS score ≥ 8)	53 (38.1)	8.4 (3.6, 13.2)	6.3 (3.0, 9.6)	1.4 (0.7, 3.1)	0.376
UTI between the ages of 85 and 86 years	72 (15.0)	37.7 (26.5, 48.8)	8.5 (6.8, 10.2	4.1 (2.9, 5.9)	<0.001
Unintentional loss of faeces	65 (13.6)	32.2 (21.2, 35.6)	9.1 (7.4, 10.9)	3.2 (2.2, 4.8)	<0.001
Self-reported urine incontinence	212 (44.3)	16.1 (12.5, 19.6)	7.5 (5.5, 9.5)	2.0 (1.4, 2.9)	<0.001
Medical diagnosis incontinence	95 (19.8)	16.1 (10.5, 21.7)	10.3 (8.4, 12.3)	1.5 (1.0, 2.2)	0.054
PRAFAB score ≥ 11	100 (81.3)	12.3 (8.0, 16.6)	12.0 (3.1, 21.0)	1.0 (0.4, 2.3)	0.987
PRAFAB: Pad use	91 (74.0)	3.6 (2.5, 5.2)	3.2 (1.7, 6.0)	1.2 (0.6, 2.5)	0.680
Creatinine clearance < 30 mL/min	43 (9.5)	12.1 (5.0, 19.3)	10.6 (8.7, 12.5)	0.9 (0.5, 1.7)	0.794
CRP > 5 mg/L	159 (34.0)	12.9 (9.3, 16.6)	10.1 (8.0, 12.2)	1.2 (0.9, 1.8)	0.222

py = person-years; CI = confidence interval; HR = hazard ratio; CRP = C-reactive protein; GDS-15 = 'Geriatric Depression Scale' with 15 items (only administered to participants with MMSE ≥ 19 (n = 393)); IPSS = 'International Prostate Symptom Score' (only administered to male participants with MMSE-score ≥ 19 (n = 139)); MMSE = Mini-Mental State Examination; PRAFAB = five-item questionnaire score incontinence (only administered to participants with MMSE-score ≥ 19 (n = 123)); UTI = urinary tract infection.

*Definition of reference groups: males, living independently, pension or other extra income, additional education after primary school, not smoking, BMI < 27, MMSE ≥ 19, GDS-15 ≤ 4, no disability in daily living, no diabetes, no stroke, IPSS score < 8, no UTI between the ages of 85 and 86 years, no history of cancer , no unintentional loss of faeces, no urine incontinence, no diagnosis incontinence GP/NP, PRAFAB < 8, creatinine clearance ≥ 30 mL/min, CRP ≤ 5 mg/L.

† Disability in daily living = unable to do any one of the nine basic activities of daily living independently, according to the Groningen Activity Restriction Scale.

per 100 py at risk for women and 7.8 (95% CI 5.1-10.6) per 100 py at risk for men. Women had a 1.7-fold increased risk of developing UTI compared to men (HR 1.7 (95% CI 1.1-2.5); *P* = 0.012).

Predictive factors of urinary tract infections

Table 1 shows the incidences of UTI in various groups for the studied predictive factors with their corresponding hazard ratios (HRs). The occurrence of UTI was univariately associated with (listed highest to lowest HR): a history of UTI between the ages of 85 and 86 years, unintentional loss of faeces, severe cognitive impairment (MMSE <19), institutionalisation, disability in daily living, self-reported urine incontinence, stroke, gender, education, and medical diagnosis of incontinence. UTIs were not associated with income, smoking, body mass index ≥ 27, depressive symptoms, diabetes mellitus, BPH, cancer, severity of urine incontinence, pad use, creatinine clearance < 30 mL/minute and C-reactive protein > 5 mg/L.

Additional analysis showed that all single items of the GARS (walk inside, get out of bed, get into and out of a chair, use the toilet, wash hands and face, wash body, dress and undress, eat and drink, and make breakfast) predicted the risk in developing UTI (Table 2).

After multivariate analysis, severe cognitive impairment (MMSE < 19), disability in daily living, UTI between the ages of 85 and 86 years and self-reported urine incontinence remained independently and significantly predictive for the occurrence of UTI (Table 3).

In both women and men, a UTI between the ages of 85 and 86 years was predictive for developing UTI from age 86 onwards (in women HR 3.8 (95% CI 2.5-5.6); *P* <0.001 and in men

Table 2. Risk of UTI from age 86 years onwards depending on disability (n = 479)

	Index group N (%)	Incidence in Index group, per 100 py (95% CI)	Incidence in reference group*, per 100 py (95% CI)	HR (95%CI)	*P*-value
Going to the toilet	103 (21.5)	5.9 (4.5, 7.7)	2.6 (2.1, 3.2)	3.8 (2.7, 5.4)	<0.001
Drinking and feeding oneself	44 (9.2)	6.0 (4.0, 9.0)	3.0 (2.5, 3.6)	3.5 (2.3, 5.6)	<0.001
Washing hands and face	65 (13.6)	5.6 (4.0, 7.9)	2.9 (2.4, 3.6)	3.3 (2.2, 4.9)	<0.001
Preparing breakfast	80 (16.7)	5.3 (3.8, 7.3)	2.9 (2.4, 3.5)	3.1 (2.1, 4.6)	<0.001
Getting into and out of bed	128 (26.7)	5.1 (3.9, 6.6)	2.7 (2.2, 3.3)	2.6 (1.9, 3.7)	<0.001
Getting around the house	133 (27.8)	4.6 (3.5, 6.0)	2.8 (2.2, 3.4)	2.4 (1.7, 3.3)	<0.001
Washing whole body	204 (42.6)	4.3 (3.5, 5.4)	2.5 (2.0, 3.3)	2.3 (1.7, 3.3)	<0.001
Dressing oneself	183 (38.2)	4.3 (3.4, 5.4)	2.7 (2.1, 3.4)	2.1 (1.5, 3.0)	<0.001
Standing up from a chair	147 (30.7)	4.3 (3.3, 5.6)	2.9 (2.3, 3.5)	2.0 (1.4, 2.8)	<0.001

py = person-years; CI = confidence interval; HR = hazard ratio;

*Definition of reference groups: no disability going to the toilet , no disability drinking and feeding oneself, no disability washing hands and face, no disability preparing breakfast, no disability in getting into and out of bed, no disability in getting around the house, no disability washing whole body, no disability dressing oneself, no disability standing up from chair.

Table 3. Factors predictive for increased risk of developing UTI after age of 86 years onwards by multivariate Cox regression analysis and Population Attributable Risk (PAR) of the occurrence of UTI (n = 479)

	N	HR (95%CI)	PAR (%)
Functioning			
Severe cognitive impairment (MMSE < 19)	88	1.9 (1.3, 2.9)	19.6
Disability in daily living†	275	1.7 (1.1, 2.5)	43.8
Co-morbidities			
UTI between the ages of 85 and 86 years	68	3.4 (2.4, 5.0)	24.1
Self-reported urine incontinence	231	1.5 (1.0, 2.1)	33.0

Variables in multivariate Cox regression model: gender, institutionalisation, education, severe cognitive impairment (MMSE < 19), disability in daily living, UTI between the ages of 85 and 86 years, stroke, unintentional loss of faeces, self-reported urine incontinence and medical diagnosis urine incontinence.

CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination; UTI = urinary tract infection

†Disability in daily living = unable to do any one of the nine basic activities of daily living independently, according to the Groningen Activity Restriction Scale.

HR 4.4 (95% CI 1.8-10.8); *P* = 0.001). Further stratified analysis showed that severe cognitive impairment (MMSE < 19) was associated with a three times higher risk in developing UTI in women (HR 3.0 (95% CI 2.0-4.5); *P* <0.001), but not in men (HR 1.5 (95% CI 0.6-3.9); *P* = 0.41). Moreover, stroke showed significantly higher risk for developing UTI in women (HR 2.0 (95% CI 1.2-3.4); *P* = 0.005), but not in men (HR 1.6 (95% CI 0.6-4.2); *P* = 0.346). Also higher risk was found for CRP > 5 mg/l in women (HR 1.5 (95% CI 1.0-2.2); *P* = 0.049), but not in men (HR 0.8 (95% CI 0.4-1.8); *P* = 0.633). Stratification for living situation (independently or long-term care facility) shows no differences in predictive factors for UTI (Table 4).

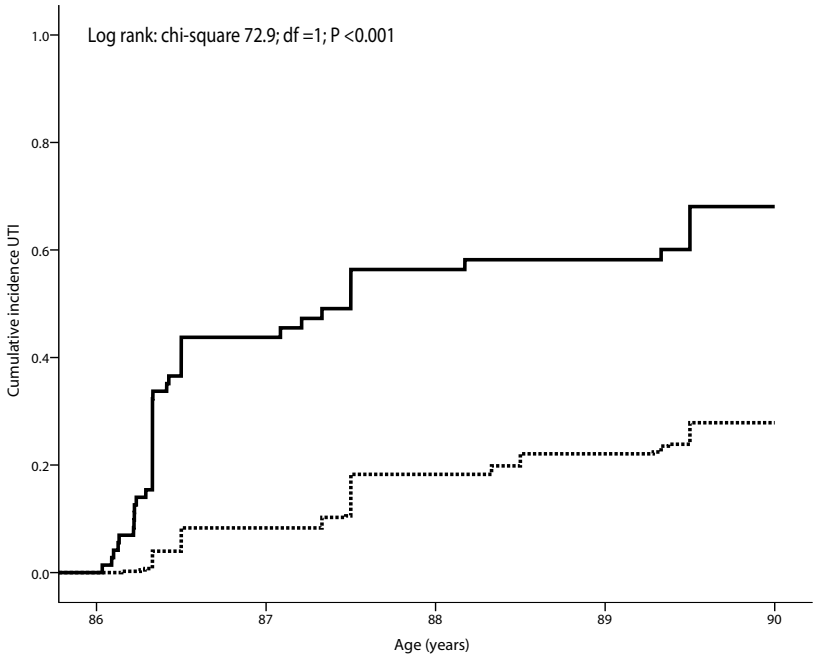
Participants with UTI between the ages of 85 and 86 years had an increased risk of developing UTI during follow-up compared to participants without an episode of UTI between the ages of 85 and 86 years (Figure 1 and Table 1; HR 4.1 (95% CI 2.9-5.9)). The risk of a recurrent UTI was greatest within the first year of follow-up (HR: 6.8 (95% CI 4.1-11.1), HR second to fourth year: 1.8 (95% CI 0.9-3.6)).

Additional analysis showed that among participants without an UTI between the ages of 85 and 86 years, female gender and stroke were predictors of developing UTI (HR 1.5 (95% CI 1.0-2.4); *P* = 0.059 for gender and HR 2.0 (95% CI 1.2-3.2); *P* = 0.011 for stroke, respectively). No further differences in hazard ratios were observed for the other potentially predictive factors between participants who had had a UTI between the ages of 85 and 86 years and participants who had not had an UTI.

Table 4. Predictive factors for UTI stratified for living situation by univariate Cox regression analysis after the age of 86 years

	Independently (n = 372)			Long-term care facility (n = 107)		
	N	**HR (95%CI)**	***P*-value**	**N**	**HR (95%CI)**	***P*-value**
Socio-demographic factors						
Female	242	1.4 (0.9, 2.3)	0.127	80	2.1 (0.9, 4.9)	0.098
Low income	170	1.0 (0.7, 1.5)	0.914	68	0.9 (0.5, 1.6)	0.650
Primary school only	221	1.2 (0.8, 1.9)	0.452	75	2.3 (1.1, 4.9)	0.036
Smoking (current)	55	1.1 (0.6, 1.9)	0.817	15	1.4 (0.6, 3.1)	0.443
Body Mass Index ≥ 27	171	1.2 (0.8, 1.8)	0.329	41	0.9 (0.4, 1.7)	0.655
Functioning						
Severe cognitive impairment (MMSE < 19)	36	1.9 (1.1, 3.4)	0.030	54	2.3 (1.2, 4.4)	0.009
Depressive symptoms (GDS-15 > 4)	46	1.2 (0.6, 2.2)	0.578	12	0.2 (0.0, 1.7)	0.146
Disability in daily living†	191	1.9 (1.3, 2.9)	0.002	92	3.6 (1.1, 11.7)	0.033
Co-morbidities						
Diabetes mellitus	53	0.8 (0.4, 1.5)	0.536	23	1.1 (0.5, 2.6)	0.759
Stroke	31	1.4 (0.8, 2.8)	0.269	29	1.6 (0.9, 3.1)	0.143
Cancer	80	1.1 (0.6, 1.8)	0.845	17	1.0 (0.4, 2.4)	0.963
Benign Prostatic Hyperplasia (IPSS score ≥ 8)	49	1.3 (0.6, 2.9)	0.521	4	NA	NA
UTI between the ages of 85 and 86 years	41	3.3 (2.1, 5.3)	<0.001	31	4.1 (2.2, 7.5)	<0.001
Unintentional loss of faeces	35	2.7 (1.6, 4.8)	<0.001	30	2.5 (1.3, 4.6)	0.004
Self-reported urine incontinence	143	1.7 (1.2, 2.6)	0.007	69	1.9 (0.9, 4.0)	0.071
Medical diagnosis incontinence	69	1.3 (0.8, 2.2)	0.260	26	1.7 (0.9, 3.4)	0.110
PRAFAB score ≥ 11	76	0.7 (0.3, 1.7)	0.462	24	NA	NA
PRAFAB: Pad use	69	1.0 (0.4, 2.2)	0.949	22	1.9 (0.3, 15.1)	0.530
Creatinine clearance < 30 mL/minute	29	0.8 (0.4, 1.6)	0.487	14	1.8 (0.5, 5.8)	0.337
CRP > 5 mg/L	116	1.2 (0.8, 1.8)	0.425	43	1.1 (0.6, 2.1)	0.664

HR = hazard ratio; CI = confidence interval; CRP = C-reactive protein; GDS-15 = 'Geriatric Depression Scale' with 15 items (only administered to participants with MMSE ≥19); IPSS = 'International Prostate Symptom Score' (only administered to male participants with MMSE-score ≥ 19); MMSE = Mini-Mental State Examination; PRAFAB = 5-item questionnaire score incontinence (only administered to participants with MMSE-score ≥ 19); py = person-years; UTI = urinary tract infection.
†Disability in daily living = unable to do any one of the nine basic activities of daily living independently, according to the Groningen Activity Restriction Scale
NA = not applicable



UTI	72	50	43	38	30
No UTI	407	370	319	277	250

Figure 1. Cumulative incidence of UTI from age 86 onwards depending on history of UTI between the age of 85 and 86 years. Black line: participants with episode of UTI between the ages of 85 and 86 years (n=72). Dotted line: participants without episode of UTI between the ages of 85 and 86 years (n=407).

Population Attributable Risk

Table 3 presents the relative contribution of the various predictive factors to the occurrence of UTI from age 86 years onwards, expressed by the Population Attributable Risk (PAR) of each variable that was shown to be predictive of UTI in the multivariate analysis. The highest PARs for the development of UTI were found for disability in daily living (44%), self-reported incontinence (33%), history of UTI between the age of 85 and 86 years (24%) and severe cognitive impairment (20%). After multivariate analysis gender, institutionalisation, education, stroke, unintentional loss of faeces and medical diagnosis urine incontinence were not predictive any more for UTI.

DISCUSSION

In this population-based prospective follow-up study among the oldest old, the incidence of UTI was 11.2 per 100 person years at risk. Severe cognitive impairment, disability in daily living, history of UTI between the age of 85 and 86 years and self-reported urine incontinence were among the strongest predictors for developing UTI from age 86 years onwards. The Population Attributable Risk was highest for disability in daily living (44%).

As in other studies, we found females to have a greater risk of developing UTI than men. However, in the multivariate analysis gender was no longer a predictor of UTI. Possibly, in old age, other predictors play a greater role in predicting UTI than gender per se. In spite of the differences between older persons living independently and older persons living in long-term care facilities; we found the same predictive factors for UTI from the age 86 years onwards in both populations.

It is well known that patients with a history of UTI have a higher rate of UTI than those without a history of UTI.[1,20] In our study a history of UTI between the ages of 85 and 86 years was a strong predictor of recurrent UTI from the age of 86 years onwards. Besides a history of UTI between the age of 85 and 86 years, our study showed that disability in daily living and severe cognitive impairment, both factors reflecting declined functional status, were also predictors of UTI. These findings are in line with other studies.[16,19,20] Since 19% of our population-based sample was severely cognitively impaired and almost 60% had disability in daily activities, declined functional status greatly contributes to the occurrence of UTI in the general oldest old population.

Although diabetes mellitus has been shown to be associated with greater predisposition to UTI in other study populations,[17,18,37-39] we did not find any association between diabetes mellitus and UTI in our study population. Perhaps differences in age, type of diabetes and definition of UTI explain these contradictory findings. On the other hand, previous studies showed that diabetes was no longer associated with cognitive decline and the incidence of lower respiratory tract infections at old age, indicating that the clinical impact of diabetes is possibly diminished in old age.[40,41]

The present study is a unique population-based sample of participants aged 86 years and over, with extensive baseline measurement and almost complete follow-up for morbidity and mortality. To our knowledge, we are the first to examine the incidence and predictive factors of UTI in a large group of unselected very old individuals in a population-based setting. It is important to study predictive factors of UTI in old age specifically, because they are the fastest growing part of the general population and the incidence of UTI increases with age.[3-5] The fact that we only studied 86-year-olds could also be considered a limitation of our study. Since bladder structure and function, and the immune system have been shown to change with age,[3] our results may not be generalized to younger elderly. Another limitation of our study might be that UTIs were diagnosed during clinical practice, not diagnosed by standardised

diagnostic study procedures. In our study, however, all UTIs were diagnosed by general practitioners and elderly care physicians based on signs and symptoms and urine analysis. This procedure reflects usual care and enables generalisation of our results to daily care for the oldest old.

It is generally known that symptomatic UTI is over-diagnosed in elderly populations given the high prevalence of asymptomatic bacteriuria,[5] especially in long-term care facilities with a prevalence of 25 to 50%.[22] Also difficulties in communication, chronic genitourinary symptoms, and the high frequency of positive urine cultures, make ascertainment of symptomatic UTI problematic for the functionally impaired elderly.[22] Also urine cultures are often contaminated and the lack of existence of specific markers of infectious bladder inflammation makes it difficult to diagnose UTI in impaired elderly. In our study, we found an UTI incidence of 11.2 per 100 person years at risk for persons aged 86 years and over. This may be an overestimation due to the presence of bacteriuria. However, the incidence found in this study is comparable with data from the Dutch national GP registration (11.7 for men and 29.4 for women aged 85 years and over)[4] and the fact participants actively visited their treating physician with UTI like symptoms.

Further, it is known that long-term catheterization is a strong risk factor for UTI and bacteriuria in institutionalized older persons.[10] Unfortunately, we did not have any information about long-term catheterization in our study population and could not report on the predicting effect. These is a limitation of our study, but we believe that this may not have affected the results of our study much, since in Dutch nursing homes there is a policy to avoid the use of catheters in situ and it has been so for many years.[42]

CONCLUSIONS

In older populations, UTIs account for nearly 25% of all infections.[1,2] As UTIs are associated with serious negative outcomes, it is important to consider preventive strategies for UTI in older individuals. Our study showed four important predictors for UTI: severe cognitive impairment, disability in ADL, history of UTI between the ages of 85 and 86 years, and self-reported urine incontinence. Remarkably, none of these predictors appear to be modifiable. However, these predictors could still be used in the development of a clinical prediction rule to select for whom apply preventive strategies. Prophylaxis with low-dose, long-term antibiotics,[12,13] oestrogens[14] and cranberry products[12,15] are potential strategies to prevent UTI, but so far none of these strategies have been proven to prevent UTI in the very old. Selection of high risk oldest old is a crucial first step in successful prevention of UTI. Before these preventive strategies may be introduced in the oldest old, their effects and side effects have to be studied in randomised intervention studies.

Abbreviations

ADL = activities of daily living; BMI = body mass index; BPH = prostatic hyperplasia; CI = confidence interval; CRP = C-reactive protein; GARS = Groningen Activity Restriction Scale; GDS = Geriatric Depression Scale; HR = hazard ratio; ICD = international classification of diseases and related disorders; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MMSE = Mini-Mental State Examination; PAR = Population Attributable Risk; py = person-year; UTI = urinary tract infection.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

MC and WE contributed to the analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript and statistical analysis. HC contributed to the interpretation of the data, drafting of the manuscript and critical revision of the manuscript. JG contributed to the study concept and design, acquisition of data, analysis and interpretation of the data, drafting of the manuscript and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgement

The Leiden 85-plus Study is a collaborative project of the Department of Gerontology and Geriatrics (RGJ Westendorp) and the Department of Public Health and Primary Care (J Gussekloo) of the Leiden University Medical Center, Leiden, The Netherlands.

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PART TWO

The CRANBERRY study

CHAPTER 5

Effectiveness of cranberry capsules to prevent urinary tract infections in vulnerable older persons. A double-blind randomized placebo-controlled multi-center trial in long term care facilities

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JAGS 2014; 62:103-110

Trial Registration: www.trialregister.nl; Identifier: NTR1266

ABSTRACT

Objectives To determine whether cranberry capsules prevent urinary tract infection (UTI) in long-term care facility (LTCF) residents.

Design Double-blind randomized placebo-controlled multicenter trial.

Setting Long-term care facilities (LTCFs).

Participants LTCF residents (N = 928; 703 women, median age 84).

Measurements Cranberry and placebo capsules were taken twice daily for 12 months. Participants were stratified according to UTI risk (risk factors included long-term catheterization, diabetes mellitus, ≥ 1 UTI in preceding year). Main outcomes were incidence of UTI according to a clinical definition and a strict definition.

Results In participants with high UTI risk at baseline (n = 516), the incidence of clinically defined UTI was lower with cranberry capsules than with placebo (62.8 vs 84.8 per 100 person-years at risk, $P = 0.04$); the treatment effect was 0.74 (95% confidence interval (CI) = 0.57-0.97). For the strict definition, the treatment effect was 1.02 (95% CI = 0.68-1.55). No difference in UTI incidence between cranberry and placebo was found in participants with low UTI risk (n = 412).

Conclusions In LTCF residents with high UTI risk at baseline, taking cranberry capsules twice daily reduces the incidence of clinically defined UTI, although it does not reduce the incidence of strictly defined UTI. No difference in incidence of UTI was found in residents with low UTI risk.

Key words Geriatrics, long-term care facility, urinary tract infection, prevention, cranberry

INTRODUCTION

Urinary tract infection (UTI) is a common bacterial infection in residents of long-term care facilities (LTCF),[1,2] accounting for nearly 25% of all infections.[3,4] UTI not only causes several days of illness, but may have more-severe consequences such as delirium, dehydration, urosepsis, hospitalization, or even death.[5,6]

Interventions to prevent UTI could reduce these severe consequences,[7] but there are no evidence-based interventions that decrease UTI in institutionalized populations.[1] The use of prophylactic antibiotics is currently controversial because of side-effects and antibiotic resistance.[8,9] Prophylaxis with cranberry is a potential prevention strategy.[10,11] Cranberries contain proanthocyanidins (PACs), which are stable phenolic compounds with anti-adhesion activity against *Escherichia coli*.[12-14] In vitro, antibacterial activity of concentrated cranberry juice against other pathogens such *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Proteus mirabilis* has also been demonstrated.[15,16]

There is aggregated evidence that cranberry juice may lead to a decrease in the incidence of symptomatic UTIs over a 12-month period, particularly in women with recurrent UTIs.[17,18] Another recent systematic review indicates that cranberry-containing products are associated with a protective effect against UTI in different subgroups, albeit with heterogeneity across the included trials.[19] A recent study in children without urological abnormalities showed a 65% reduction of UTI with the use of cranberry.[20]

Two studies reported that cranberry juice may be protective in subgroups of older adults,[21,22] but the effectiveness of cranberry capsules in the protection against UTI in vulnerable older persons in LTCFs has not been studied.

The present study assessed the effectiveness of cranberry capsules in preventing UTI in vulnerable older persons living in LTCFs. Research in an institutionalized population is challenging, and clinical manifestations of UTI may be subtle. [23-25] To be relevant for clinical practice and science, a clinical definition according to international guidelines for LTCF residents and a strict definition according to scientific criteria were both used.

METHODS

Design

This was a double-blind randomized placebo-controlled multicenter trial in two strata, based on baseline UTI risk. Twenty-one LTCF organizations from the University Nursing Home Research Network in South Holland, the Netherlands, participated.

The medical ethics committee of the Leiden University Medical Center approved the study. Written informed consent was obtained from all participants. A guardian provided written

consent for participants incapable of giving informed consent because of cognitive impairment.

Study participants

LTCF residents aged 65 and older were included. Exclusion criteria were use of coumarin and a life expectancy of 1 month or less. Coumarin users were excluded because of a possible interaction between coumarin and cranberry, leading to higher international normalized ratios and bleeding.[26-28]

After informed consent and before randomization, medical records were studied to stratify participants according to baseline UTI risk. Participants with long-term catheterization (> 1 month), diabetes mellitus, or at least one UTI in the preceding year were considered to be at high UTI risk.

Within two strata of UTI risk, participants were randomized into the cranberry or placebo group. Block randomization (blocks of 6) was used, stratified for risk profile and ability to give informed consent, generated using a computer random number generator. Participants, family, nursing staff, physicians, pharmacists, and research nurses were blinded to treatment, and the random numbers were put in sealed envelopes so the research nurse could allocate to the treatment group (cranberry or placebo) directly on the ward. Only the supplier of the capsules knew the codes given to the capsules (cranberry or placebo).

Intervention

Participants were randomly assigned to take cranberry or placebo capsules twice daily for 12 months. Participants already using a cranberry supplement stopped using their own cranberry products before randomization and changed to the study capsule at baseline. The cranberry capsules contain 500 mg of the product, with 1.8% proanthocyanidins (9 mg). The placebo was indistinguishable in color, taste, and appearance, consisting of cellulose microcrystal colored red with azorubin.

The physician prescribed the coded capsules, and the pharmacist added them to the drug-dispensing systems. Nurses distributed the capsules and recorded whether the participant took them on a drug kardex. Adherence was measured over 1 month by counting all capsules that the participants took during the fifth month of intervention and comparing that with the prescribed number of capsules.

Outcome measures

The primary outcome was incidence of UTI. There is no criterion standard in diagnosing UTI in LTCF residents. Most clinical criteria to ascertain UTI are based on consensus.[29-31] A recent study showed that micturition-related signs and symptoms are predictive of UTI.[32]

Because of the absence of a criterion standard in the study population, this study used a clinical definition and a strict UTI definition. The clinical definition of UTI is a broad and practi-

cal definition following clinical practice guidelines for LTCF residents.[24,25] This clinical definition of UTI is based on the presence of a minimum of one of the following characteristics: specific and nonspecific micturition-related symptoms and signs, a positive test (nitrite test, leukocyte esterase test, dipslide, or culture), antibiotic treatment for UTI, or UTI reported in the medical record.

Specific symptoms and signs are pain before, during, or after micturition; increased frequency of micturition; pain in abdomen; hematuria; foul smell; and signs of common sickness (fever > 37.9°C or 1.5°C above baseline temperature, chills, nausea, vomiting). Nonspecific symptoms are anorexia, fatigue and reduced mobility, and signs of delirium (e.g., confusion, deterioration in mental or functional status).

The strict UTI definition is based on a scientific approach, including the presence of micturition-related symptoms and signs confirmed with a positive dipslide or culture. A urine dipslide or culture was considered to be positive when there were 10^5 CFU/mL or more bacteria, with no more than two species of organisms present.

The treating physicians diagnosed the UTI and reported the presence of UTI in the medical record. For this study, they reported the needed study information on a prestructured case report form, including presence of specific and nonspecific micturition-related signs and symptoms, kind of testing and results, and antibiotic treatment. Secondary outcomes were incidence of recurrent UTI, hospitalization, and mortality.

In a companion cost-effectiveness article, whether the effectiveness of cranberry capsule use is attained at reasonable costs was investigated.[33]

At 6 and 12 months, a research nurse visited all participants in their LTCF to check their medical records for the occurrence of UTIs and to verify that all UTIs were collected during the study period. Side effects and reasons for withdrawal from the study were registered.

Additional measurements at baseline

A research nurse interviewed all participants at baseline in their LTCF, where face-to-face interviews were conducted. If participants were not able to answer, their responsible nurse was interviewed. Information on participant sociodemographic characteristics and medical history were obtained at baseline. Care dependency was assessed using the Care Dependency Scale (CDS),[34] which measures 15 items of basic care needs on an aggregate scale from 15 to 75.

Sample size

Sample size was based on an expected incidence of 44 first UTIs per 100 residents per year in the placebo group. To demonstrate a 40% reduction in incidence of UTI with the use of cranberries,[22] 500 residents needed to be included in each stratum (2 strata of 2 groups of 250), 1,000 residents in total (dropout rate 10%, alpha 0.05, power 80%).

Statistical analysis

Differences in baseline characteristics between treatment groups were compared using the Student t-test for continuous variables and chi-square for categorical variables. The incidence of UTI was calculated using the life-table method. The number of first UTIs was assigned to the numerator and the number of observed person-years at risk was assigned to the denominator. The observed person-years at risk were counted from randomization to end of study, to date of death, or to date of first UTI. The cumulative incidence of UTI for cranberry and placebo was calculated accounting for mortality as competing risk.[35] The difference in the cumulative incidence of UTI in residents between cranberry and placebo was tested using the log-rank test. The treatment effect of cranberry with respect to placebo was investigated using Cox proportional hazards models, expressed as hazard ratios (HRs).

The number needed to treat (NNT) was calculated over 1 year of follow-up, based on the difference in proportion of being event free in the placebo and cranberry group.[36,37] The difference in NNT between treatment groups was tested using a z-test; $P = 0.05$ was considered significant.

To investigate possible heterogeneity in UTI rates between individuals, a gamma-frailty model was fitted,[38] a random effect model for time-to-event data in which the random effect (frailty) has a multiplicative effect on baseline hazard function. Analyses were performed based on intention to treat using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL) and R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between November 2008 and August 2009, all 2,086 eligible residents were invited to participate in a letter, and then a research nurse orally invited them. The study stopped in June 2011. Twenty-seven of the 955 residents who gave written informed consent died before randomization, resulting in a study population of 928 participants (Figure 1). A nonresponder analysis for giving informed consent showed no difference between nonresponders and responders in age, sex, or UTI risk profile. None of the participants had end-stage renal disease.

Four hundred twelve low-UTI-risk and 516 high-UTI risk-participants were included. There were no baseline differences within the UTI risk groups between the cranberry and placebo groups (Table 1). Mean capsule intake was 97% (95% confidence interval (CI) = 96.6-97.6%) and was similar between the randomization groups and between the risk groups.

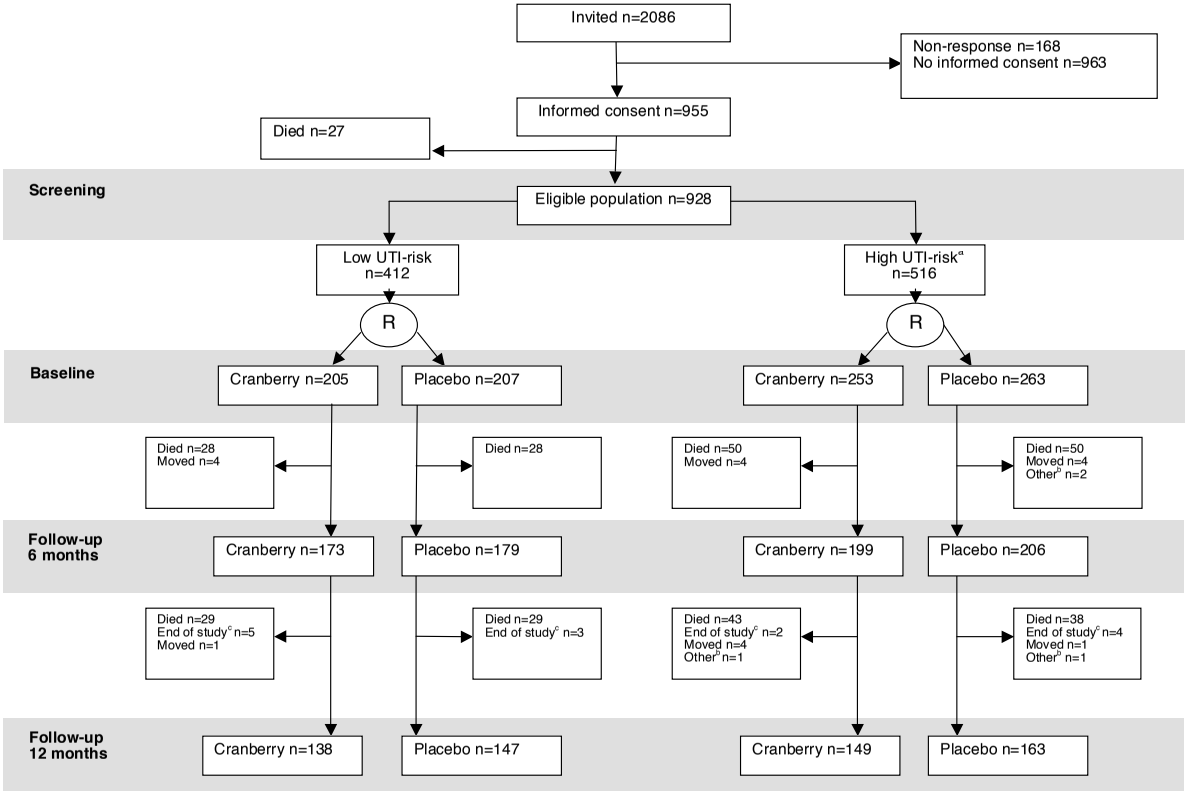

Figure 1. Participant recruitment and follow-up.

[a] Diabetes mellitus or urinary catheter or treated urinary tract infection in past 12 months. [b] No adherence, withdrawn by elderly care physician or family. [c] Intervention stopped because of end of study period.

UTI = urinary tract infection.

Table 1. Baseline characteristics of the study population at randomization (intention-to-treat analysis)

	Low UTI-risk (n = 412)				High UTI-risk (n = 516)[a]			
	Cranberry (n = 205)		Placebo (n = 207)		Cranberry (n = 253)		Placebo (n = 263)	
	n	n (%)	n	n (%)	n	n (%)	n	n (%)
Socio-demographic								
Female	205	143 (69.8)	207	159 (76.8)	253	188 (74.3)	263	213 (81.0)
Age in years: median (IQR)	205	84.0 (78.5-88.5)	207	83.0 (79.0-88.0)	253	85.0 (79.0-89.0)	263	84.0 (79.0-88.0)
Length of stay: months, median (IQR)	204	18.0 (4.0-42.0)	205	19.0 (4.0-39.0)	251	17.0 (6.0-41.0)	263	19.0 (6.0-39.0)
Family informed consent	205	180 (87.8)	207	185 (89.4)	253	205 (81.0)	263	212 (80.6)
Functioning								
15-item Care Dependency Scale score (range 15-75), median (IQR)	199	42.0 (30.0-56.0)	197	45.0 (30.5-55.0)	244	44.0 (31.0-56.0)	250	43.0 (30.0-56.0)
Cranberry use before start of study	196	3 (1.5)	202	6 (3.0)	248	18 (7.3)	253	22 (8.7)
Urine incontinence	198	138 (69.7)	199	136 (68.3)	247	152 (61.5)	246	157 (63.8)
Urine catheter	205	0 (0.0)	207	0 (0.0)	253	49 (19.4)	263	47 (17.9)
Infections in the past 12 months								
Urinary tract infection	205	0 (0.0)	207	0 (0.0)	253	203 (80.2)	263	200 (76.0)
Number of UTI past 12 months: median (IQR)	--	--	--	--	202	1.0 (1.0-2.0)	199	2.0 (1.0-2.0)
Antibiotics for UTI suppression	196	0 (0.0)	202	1 (0.5)	248	3 (1.2)	253	5 (2.0)
Lower respiratory tract infection	200	35 (17.5)	204	35 (17.2)	249	47 (18.9)	259	54 (20.8)
Other infection	200	21 (10.5)	204	24 (11.8)	248	38 (15.3)	255	33 (12.9)
Comorbidities								
Renal dysfunction	201	20 (10.0)	206	16 (7.8)	252	37 (14.7)	262	34 (13.0)
Urogenital surgery	200	40 (20.0)	203	45 (22.2)	253	50 (19.8)	262	66 (25.2)
Myocardial infarction	203	14 (6.9)	205	17 (8.3)	252	25 (9.9)	262	25 (9.5)
Stroke	204	38 (18.6)	205	33 (16.1)	251	64 (25.5)	261	76 (29.1)
Cancer	202	38 (18.8)	203	42 (20.7)	252	42 (16.7)	259	48 (18.5)
Diabetes mellitus	205	0 (0.0)	207	0 (0.0)	253	79 (31.2)	263	103 (39.2)
COPD	203	36 (17.7)	199	26 (13.1)	250	40 (16.0)	256	32 (12.5)
Dementia	199	162 (81.4)	207	177 (85.5)	250	174 (69.6)	261	187 (71.6)

IQR = interquartile range; UTI = Urinary tract infection

[a]Diabetes mellitus or urine catheter or treated urinary tract infection in past 12 months

Incidence of UTI

In the high-UTI-risk group, the curve of cumulative incidence of clinically defined UTI showed a positive treatment effect from 2 months of follow-up onward ($P = 0.03$). No such effect was found for strictly defined UTI ($P = 0.91$). There was no difference between cranberry and placebo in the low-UTI-risk group (Figure 2).

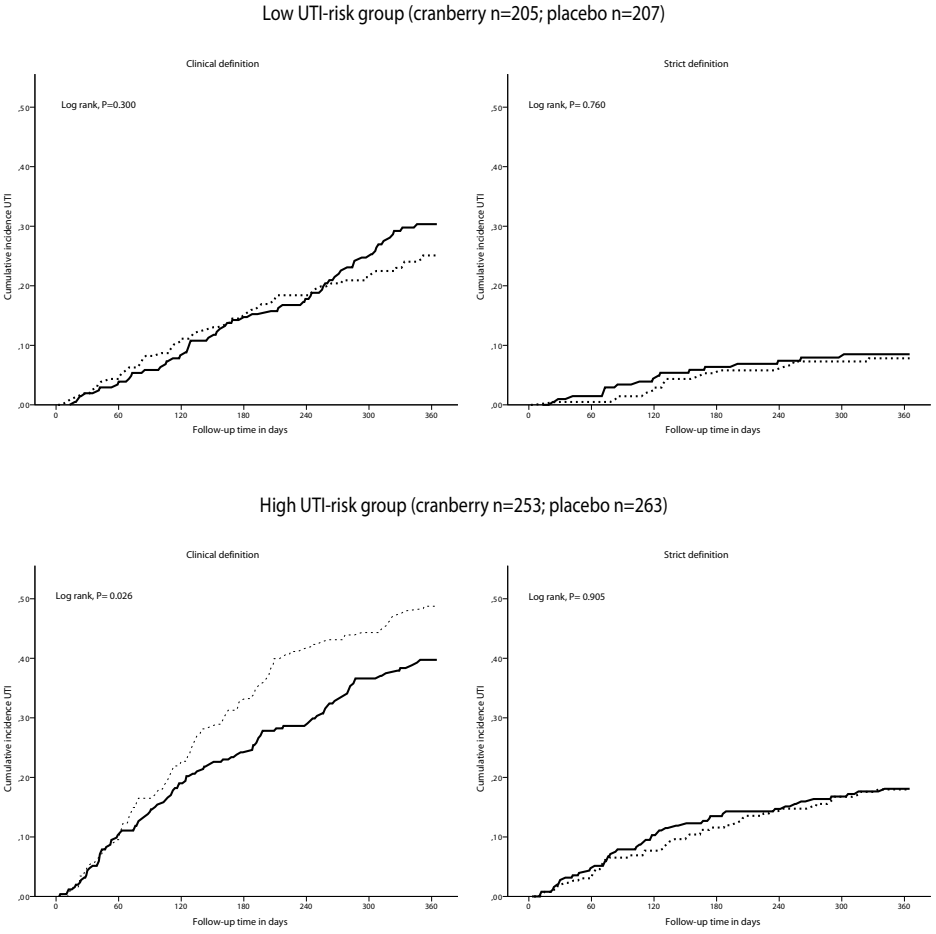

Figure 2. Cumulative incidence of urinary tract infection (UTI) within 1 year of follow-up depending on treatment (cranberry or placebo) stratified for those at low and high UTI-risk, accounting for mortality as competing risk.
Solid line: cranberry group; dotted line: placebo group. Clinical definition: symptom or positive testing (nitrite test, leukocyte esterase test, dipslide or culture) or antibiotic treatment or UTI reported in the medical record. Strict definition: symptom and positive dipslide or culture.

Table 2. Incidence of urinary tract infections (UTI), according to two definitions, depending on treatment with cranberry for different definitions and UTI-risk during 12 months of follow-up.

	Events, n		Person days at risk		Incidence per 100 person years at risk (95%CI)				
UTI risk	**Cranberry**	**Placebo**	**Cranberry**	**Placebo**	**Cranberry**	**Placebo**	**Risk Difference (95%CI)**	**Treatment effect, Hazard ratio (95% CI)**	***P*-value**
Low[a]									
Clinical[b]	59	51	53498	55806	40.3 (30.0-50.5)	33.4 (24.2-42.5)	6.9 (-6.9 - 20.7)	1.22 (0.84-1.77)	0.301
Strict[c]	17	16	58888	61812	10.5 (5.5-15.5)	9.4 (4.8-14.1)	1.1 (-5.7 - 7.9)	1.11 (0.56-2.20)	0.760
High[d]									
Clinical	98	125	56989	53783	62.8 (50.3-75.2)	84.8 (70.0-99.7)	-22.0 (-41.4 - -2.7)	0.74 (0.57-0.97)	0.026
Strict	45	46	64888	68248	25.3 (17.9-32.7)	24.6 (17.5-31.7)	0.7 (-9.5 – 11.0)	1.02 (0.68-1.55)	0.905
High UTI-risk without long-term catheter[e]									
Clinical	71	99	47569	44382	54.5 (41.8-67.2)	81.4 (65.4-97.5)	-26.9 (-47.4 - -6.5)	0.67 (0.49-0.91)	0.010
Strict	31	39	53585	55775	21.1 (13.7-28.5)	25.5 (17.5-33.5)	-4.4 (-15.3 – 6.5)	0.83 (0.52-1.33)	0.429

CI = confidence interval

[a]Cranberry, n = 205; placebo, n = 207

[b]Symptom or positive testing (nitrite test, leukocyte esterase test, dipslide or culture) or AB treatment or UTI reported in the medical record

[c] Symptom and positive dipslide or culture

[d]Cranberry, n = 253; placebo, n = 263

[e]Cranberry, n = 204; placebo, n = 216

In the high-UTI-risk group, the incidence of UTI according to the clinical definition was 62.8 per 100 person-years at risk (95% CI = 50.3-75.2) for cranberry and 84.8 per 100 person-years at risk (95% CI = 70.0-99.7) for placebo ($P = 0.04$). The treatment effect in those at high UTI risk was 0.74 (95% CI = 0.57-0.97). The incidence for UTI following the strict definition was not different in those using cranberry and placebo. The treatment effect was 1.02 (95% CI = 0.68-1.55; Table 2). A subanalysis in participants without long-term catheters in the high-UTI-risk group (n = 420) showed a larger treatment effect of cranberry capsules than of placebo for clinically defined UTI (Table 2). According to the clinical definition, five high-risk residents need to be treated with cranberry for 1 year to prevent one resident free of UTI for 1 year ($P = 0.01$).

In the low-UTI-risk group, the incidence of UTI according to the clinical definition was 40.3 per 100 person-years at risk (95% CI = 30.0-50.5) for cranberry and 33.4 per 100 person-years at risk (95% CI = 24.2-42.5) for placebo ($P = 0.30$).

Recurrent UTI

In a gamma-frailty model (a random effect model) using all recurrent clinical UTIs, cranberry did not significantly reduce the UTI rate in the high-UTI-risk group (HR = 0.92, 95% CI = 0.71-1.17, frailty variance 0.62, $P < 0.001$). In the low-UTI-risk group, the HR of cranberry versus placebo was 1.14 (95% CI = 0.78-1.68, frailty variance 1.50, $P < 0.001$).

Hospitalization and mortality

Five participants (0.5%), all from the high-UTI-risk group, were hospitalized during follow-up for UTI, with no difference between cranberry and placebo ($P = 0.62$). In the low-UTI-risk group, 114 (27.7%) participants died during follow-up, of whom three died from UTI (cranberry vs placebo $P = 0.56$). In the high-UTI-risk group, 181 participants (35.1%) died during follow-up, of whom 14 (7.7%) died from UTI, with no difference between cranberry and placebo (7 vs 7 $P = 0.91$).

DISCUSSION

This double-blind randomized placebo-controlled multicenter trial investigated the effectiveness of cranberry capsules to prevent UTI in older LTCF residents. In participants with high UTI risk, twice-daily intake of cranberry capsules resulted in a 26% lower incidence of clinically defined UTI than placebo, but no difference was found in UTI incidence of strictly defined UTI. In residents with low UTI risk, twice-daily intake of cranberry capsules did not result in a lower incidence of UTI than with placebo.

Effectiveness

A systematic review showed that cranberry-containing products were associated with a protective effect against UTI in certain populations.[19] A Cochrane review reported a UTI reduction of 35% (95% CI = 10-54%).[17] In the recent update of this Cochrane review in 2012, the authors performed a meta-analysis based on two studies evaluating cranberry in elderly adults (N = 413).[18] Cranberry did not significantly reduce UTI in this population (risk ratio = 0.75, 95% CI = 0.39-1.44).[18] In contrast with this last review, the current study found a positive effect of treatment with cranberry capsules on the incidence of clinically diagnosed UTI in 516 older persons with high UTI risk. A possible explanation for this difference could be the product used (juice vs capsules), study population (hospitalized vs institutionalized), and sample size. Another study comparing cranberry with low-dose trimethoprim (follow-up 6 months) showed no difference between cranberry and low-dose antibiotics but did not include a placebo arm.[39]

It could have been expected that the beneficial effect of cranberry capsules would be fairly prompt after starting treatment, but the current study showed a beneficial effect of cranberry capsules in the high-UTI-risk group starting from 2 months of treatment on for clinically defined UTI. This was shown in an earlier study that found a reduction that started between 1 and 2 months after initiating cranberry juice and remained stable throughout the 6 months of follow-up.[21] Cranberries with PAC were expected to have an effect by different mechanisms, because they influence the adhesive capacity of fimbriae of bacteria and build a biofilm on the surface, preventing adhesion. Nevertheless, bacteria could be persistent (chronic bacteriuria), and the types of bacteria could vary over time. So cranberry protects against UTI, but it takes some time to have an effect.

Because the effect of preventive care depends on the incidence of the disease, a preplanned stratification was made at baseline on baseline UTI risk. Based on the literature, LTCF residents with diabetes mellitus,[40-42] long-term catheterization,[24,43,44] or UTI in the preceding year[3,42,45,46] were considered to be at high risk. Although a group of LTCF residents with a high incidence were selected using these criteria, it might be that other criteria would have selected a group with even higher risks or more preventable UTIs.

Strengths and limitations

This is the first large study of the effectiveness of cranberry capsules in preventing UTI in LTCF residents. These residents represent a vulnerable older population, with a median age of 85 and older, severely dependent on care, high infection rates, high levels of comorbidity, and 1-year mortality of 35%,[47] a population in which clinical manifestations of UTI may be subtle.[23]

The current study was performed in Dutch LTCFs , intramural care settings where elderly care physicians provided medical care.[48-50] Medication prescription and distribution are well organized. The study capsules were added to the existing drug-dispensing system. Medication distribution by nurses is routine in Dutch LTCFs, and participants rarely missed taking

any capsule, which was reflected in a high adherence rate, although adherence was assessed only in the fifth month, which might not be generalizable to the other months. This high and similar level of adherence in both treatment groups also suggests that capsules were well tolerated, side-effects were negligible, and blinding remained adequate during the study.

A technical assessment of blinding was not performed, although the research nurses did not receive information about deblinding during the study visits. In addition, the distribution and adherence of participants in the cranberry and placebo groups were similar.

The clinical definition for UTI is based on a broad definition of UTI (symptoms and signs, positive test, antibiotic treatment, or reported in the medical record) and relies on the clinical judgment of the elderly care physician, in accordance with international clinical guidelines for UTIs in LTCFs.[24,25] Although this UTI definition is different from the strict definition, it reflects clinical care in LTCFs and adds knowledge to practice guidelines to assist physicians in making decisions.

The strict definition of UTI is based on a scientific approach, including micturition-related symptoms and signs confirmed according to a positive culture or dipslide, and could be used for comparisons with studies in other populations but is difficult to generalize to clinical practice in LTCFs. It is generally accepted that diagnosing UTI in vulnerable older persons, especially in long-term care, is complicated. A recent study in nursing home residents with advanced dementia showed that symptoms and signs of UTI are frequently not present in older persons with dementia.[51] In the current study, for example, most participants had dementia (76%) or incontinence (64%). Therefore, a clean catch urine sample for culturing is often not available, making it impossible to diagnose UTI according to the strictest criteria.[52] The current study was doubleblinded, so the randomization itself cannot have influenced the clinical definition. Despite the large study sample, no treatment effect was shown in those at high UTI risk using the strict definition. The study may have been slightly underpowered for the rarer strictly defined UTIs.

The optimum dosage of cranberries is not clear, and a well-designed dose-finding study is needed. An in vitro study suggests that the administration of 72 mg of PAC daily may offer some protection against bacterial adhesion in the bladder.[53] The daily use of 18 mg of PAC (two capsules) in this study may not have been high enough.

These results are not automatically generalizable to vulnerable older persons living at home. Differences not only in vulnerability and infection rates, but also in adherence and hospitalization rates were expected.

CONCLUSIONS

In LTCF residents with high UTI risk, taking cranberry capsules twice daily results in a 26% lower incidence of clinically defined UTI than with placebo, although no difference was found

in UTI incidence according to a strict definition. Cranberry capsules may offer an opportunity to decrease the incidence of this common infection in high-UTI-risk LTCF residents by using a well-tolerated treatment.

Acknowledgements

The authors thank the organizations and members of the University Nursing Home Research Network South Holland and the staff of the LTCFs participating in this study. Their ongoing collaboration enabled us to perform this study.

Conflict of Interest

The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

A grant was received from ZonMw Doelmatigheid, the Dutch Organization for Health Research, the Netherlands (Project 170882501). Springfield Nutraceuticals B.V., Oud-Beijerland, the Netherlands, supplied the cranberry and placebo capsules. A grant was received from the Dutch Organization of Scientific Research (NWO) for Open Access publication of this paper.

Author Contributions

Jacobijn Gussekloo had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Caljouw, van den Hout, Cools, Gussekloo. Analysis and interpretation of data: Caljouw, van den Hout, Putter, Achterberg, Cools, Gussekloo. Drafting of the manuscript: Caljouw. Critical revision of the manuscript for important intellectual content: Caljouw, van den Hout, Putter, Achterberg, Cools, Gussekloo.

Sponsor's Role

All funding sources and suppliers were independent and had no influence on study design; collection, analyses, and interpretation of data; writing the report; or the decision to submit the manuscript for publication.

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CHAPTER 6

Costs-effectiveness of cranberry capsules to prevent urinary tract infections in long-term care facilities: economic evaluation with a randomized controlled trial

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JAGS 2014; 62:111-116

ABSTRACT

Objectives To investigate whether the preventive use of cranberry capsules in long-term care facility (LTCF) residents is cost-effective depending on urinary tract infection (UTI) risk.

Design Economic evaluation with a randomized controlled trial.

Setting Long-term care facilities.

Participants LTCF residents (N = 928, 703 female, median age 84), stratified according to UTI risk.

Measurements UTI incidence (clinically or strictly defined), survival, quality of life, quality-adjusted life years (QALYs), and costs.

Results In the weeks after a clinical UTI, participants showed a significant but moderate deterioration in quality of life, survival, care dependency, and costs. In high-UTI-risk participants, cranberry costs were estimated at €439 per year (1.00 euro = 1.37 U.S. dollar), which is €3,800 per prevented clinically defined UTI (95% confidence interval = €1,300-infinity). Using the strict UTI definition, the use of cranberry increased costs without preventing UTIs. Taking cranberry capsules had a 22% probability of being cost-effective compared with placebo (at a willingness to pay of €40,000 per QALY). In low-UTI-risk participants, use of cranberry capsules was only 3% likely to be cost-effective.

Conclusion In high-UTI-risk residents, taking cranberry capsules may be effective in preventing UTIs but is not likely to be cost-effective in the investigated dosage, frequency, and setting. In low-UTI-risk LTCF residents, taking cranberry capsules twice daily is neither effective nor cost-effective.

Key words Economic evaluation, geriatrics, long-term care facility, urinary tract infection, prevention, cranberry

INTRODUCTION

Urinary tract infection (UTI) is a common bacterial infection in residents of long-term care facilities (LTCFs).[1-4] The effectiveness of the use of cranberry capsules to prevent UTIs was assessed in a randomized controlled trial.[5] In residents with high UTI risk, taking cranberry capsules twice daily reduced the incidence of clinically defined UTI by 26%. No reduction was found for strictly defined UTI or in residents with low UTI risk. The current brief report investigates the effect of UTI on health and costs and whether the preventive use of cranberry capsules in LTCFs is cost-effective.

METHODS

This economic evaluation was part of a double-blind randomized placebo-controlled multicenter trial.[5] Residents from LTCFs (N = 928, median age 84, 703 female) were randomized to receive cranberry or placebo capsules twice daily for 12 months. The cranberry capsules contained 500 mg of the product with 1.8% proanthocyanidins (9 mg). Participants were stratified according to UTI risk (including long-term catheterization, diabetes mellitus, ≥ 1 UTIs in the preceding year). Main outcomes of the trial were incidence of UTI according to a clinical definition (following clinical practice guidelines for residents in LTCFs) and a strict definition (with confirmation by a positive dipslide or culture).[5]

Cost-effectiveness and cost-utility analysis

The economic evaluation consisted of a cost-effectiveness analysis (CEA) from a narrow perspective and a cost-utility analysis (CUA) from a lifelong societal perspective for high- and for low-UTI-risk participants.

The CEA from a narrow perspective was based directly on the trial data during follow-up, to prevent modeling assumptions. Effectiveness was measured according to the number of clinically defined and strictly defined UTIs (first and recurrent). Costs included only cranberry use.

The CUA was performed from a lifelong societal perspective. Costs, survival and quality-adjusted life years (QALYs) were estimated using a non-Markovian state-transition model, with parameters estimated from the trial data. In this model, the cranberry and placebo groups differed in their clinically defined UTI infection rate but not in the consequences per UTI. Thus, it was implicitly assumed that prevented UTIs are comparable with non-prevented UTIs and that cranberry use has no relevant effects other than cranberry costs and UTI prevention. These modeling assumptions were made beforehand because it was clear that the study would have insufficient power for a direct randomized economic comparison.

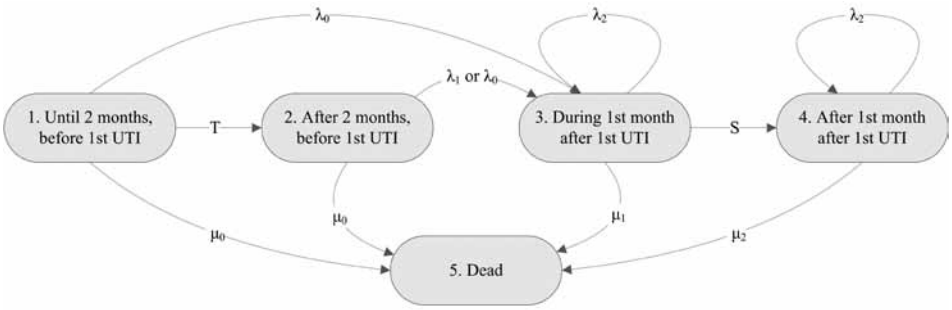

Figure 1. The state-transition model used in the economic evaluation.
UTI = urinary tract infection.

In the CUA model (Figure 1), participant time was categorized into five model states: during the initial 2 months and before the first UTI, after the initial 2 months and before the first UTI, during the first month after the first UTI, after the first month after the first UTI, and death.

UTI infection rate and mortality

Three separate annual UTI infection rates were estimated in a combined Poisson regression analysis. Infection rates in the cranberry and placebo groups were different after the first 2 months and before the first UTI (State 2). No effect of cranberry use was seen in the initial 2 months (State 1) or after the first UTI (States 3 and 4). Occurrence of a first UTI was associated with greater mortality during the subsequent month (State 3) and after the subsequent month (State 4). Annual mortality was estimated in a combined Poisson regression analysis.

Utilities

Utilities represent the valuation of the quality of life of the participants on a scale anchored at 1 (perfect health) and 0 (as bad as being dead). Utility was measured using the EQ-5D classification system, which is a brief questionnaire with five domains (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), each with three levels (no, some, or extreme problems).[6] Utility values were assigned to the EQ-5D using the Dutch tariff.[7]

Valuations were also obtained using a visual analog scale (VAS) ranging from 100 (perfect health) to 0 (worst imaginable health), which was transformed to a utility scale using a power transformation.[8] EQ-5D and VAS measurements were obtained from the participants (11%) or from well-informed nurses or caregivers (89%).

Utility before and after the first UTI (parameters U_0 and U_2) was estimated from EQ-5D and VAS measurements obtained at baseline and after 6 and 12 months (correcting for time). In addition, UTIs were assumed to have a short-term effect on utility for 2 weeks. Additional EQ-5D and VAS measurements were obtained in 123 participants with a clinically defined UTI (from 17 different LTCFs) every 3 days over 3 weeks after the UTI to estimate this effect. The utility decrement during the UTI was estimated as the difference between the average over

the first 2 weeks and the average over the third week (parameter ΔU, attributed to State 3 with parameter $U_1 = U_2 - \Delta U \times 14/30$).

Costs

The economic model included two types of costs. The first was the costs of cranberry use (parameter c_1). These costs were estimated at €439 annually (€0.62 per intake) based on one capsule twice a day, a market price of €44 for 180 capsules, on average 45 seconds of nursing time per capsule (estimated using time registrations), nursing time valued at €30 per hour,[9] and 97% adherence (1.00 euro = 1.37 U.S. dollar).

The second type of costs were the costs associated with each UTI (parameter c_2, Table 1), including costs of UTI diagnostics and antibiotic treatment, additional care by the elderly-care physician, additional nursing care, and hospitalizations. Costs of UTI diagnostics and antibiotic treatment per UTI were calculated from actual costs in patient records for each UTI (n = 548). Additional care by the elderly-care physician was estimated at on average €25 per UTI (10-30 minutes of time, valued at €111 per hour[9,10]). Additional nursing costs during the 2 weeks after a UTI were estimated in proportion to the Care Dependency Scale,[11] which measures 15 items of basic care needs, each rated on a 5-point scale (1 = completely dependent; 5 = completely independent). Hospitalizations costs were recorded for six UTIs (1% of n = 548), all in high-UTI-risk participants. Costs per hospitalization ranged from €3,000 (for 6 days of normal hospital care) to €15,000 (for 7 days of normal care and 5 days of intensive care).[9]

Costs were presented in euros, at 2013 prices (updated if necessary using the general Dutch consumer price index).[12] Included costs were all medical costs, which for this trial population coincided with the societal perspective.

Lifelong Outcomes The model shown in Figure 1 and Table 1 was used to extrapolate the trial period to lifelong outcomes. Life expectancy was calculated as the expected total time spent in States 1 to 4. QALYs were calculated by weighing the time in each state with the appropriate utility value, discounted at $\delta = 4\%$.[13] Using this approach, the following formula for the difference in discounted QALYs between the cranberry and the placebo groups was derived:

$$\Delta\text{QALY} = (\lambda_0 - \lambda_1)\frac{(\mu_0 + \delta)}{(\lambda_0 + \mu_0 + \delta)(\lambda_1 + \mu_0 + \delta)}\exp\left(-(\lambda_0 + \mu_0 + \delta)T\right) \times \left[\left(\frac{U_0}{\mu_0 + \delta} - \frac{U_1}{\mu_1 + \delta}\right) - \left(\frac{U_2}{\mu_2 + \delta} - \frac{U_1}{\mu_1 + \delta}\right)\exp\left(-(\mu_1 + \delta)S\right)\right],$$

where T denotes the initial 2 months and S denotes the 1 month after the first UTI. A similar formula was derived for the discounted costs. The models for the cranberry and placebo

Table 1. Parameters for the health-economic model, estimated from the trial data

Parameters	Estimated value	(95%CI)
UTI infection rates[b] among low UTI-risk participants		
Rate before the first UTI, during the first two months (λ_0)	0.32	(0.23 – 0.395)
Hazard ratio before first UTI, after first two months (λ_1/λ_0)[a,c]	1.41	(0.77 – 1.857)
Hazard ratio after the first UTI (λ_2/λ_0)[c]	4.02	(2.11 – 5.288)
UTI infection rates[b] among high UTI-risk participants		
Rate before the first UTI, during the first two months (λ_0)	0.81	(0.68 – 0.94)
Hazard ratio before first UTI, after first two months (λ_1/λ_0)[a,c]	0.75	(0.52 – 0.94)
Hazard ratio after the first UTI (λ_2/λ_0)[c]	1.81	(1.35 – 2.18)
Mortality rates[b]		
Rate before the first UTI (μ_0)	0.33	(0.29 – 0.38)
Hazard ratio during the first month after first UTI (μ_1/μ_0)[c]	3.57	(2.00 – 4.81)
Hazard ratio after the first month after first UTI (μ_2/μ_0)[c]	1.32	(0.87 – 1.67)
Utilities[d] based on EQ-5D		
Before the first UTI (U_0)	0.37	(0.36 – 0.38)
Decrement after the first UTI ($U_2 - U_0$)[c]	0.02	(-0.01 – 0.05)
Decrement during first two weeks after first UTI (ΔU)[c]	0.04	(0.01 – 0.07)
Utilities[d] based on VAS		
Before the first UTI (U_0)	0.73	(0.72 – 0.74)
Decrement after the first UTI ($U_2 - U_0$)	0.00	(-0.02 – 0.02)
Decrement during first two weeks after first UTI (ΔU)	0.03	(0.00 – 0.05)
Annual costs (€)		
Annual costs of cranberry use (c_1)[a]	439	–
Costs per UTI (€)		
Costs of diagnostics	8	(6 – 10)
Costs of antibiotic treatment	3	(2 – 4)
Costs of elderly care physician	25	(22 – 28)
Costs of additional nursing care	120	(49 – 194)
Costs of hospitalizations	40	(-8 – 74)
Total costs per (prevented or non-prevented) UTI (c_2)	196	(111 – 278)

[a]Only in the cranberry group

[b]Annual event rate

[c]Relative or absolute change during the specified period, compared with the base value

[d]The valuation of quality of life of the participants, on a scale anchored at 1 (perfect health) and 0 (as bad as dead)

UTI = urinary tract infection

groups only differ in their value for the infection rate (λ_1 and λ_0, respectively) and in their value for the annual cranberry costs (c_1 and 0, respectively).

Statistical analysis

Uncertainty due to sampling error for the estimated lifelong outcomes was assessed using bootstrap analysis (using B = 10,000 bootstrap samples). For each bootstrap sample, all model parameters (Table 1) were re-estimated, and the lifelong formulae were used to estimate outcome. The 95% confidence intervals (CIs) for the parameters and outcomes were assessed from the 2.5 and 97.5 percentiles among the bootstrap samples.[10] Statistical analyses for the economic evaluation were performed in R version 2.13.0 (Vienna, Austria).

Depending on the willingness to pay (WTP) for obtained effectiveness, cranberry use is estimated to be cost-effective if it has a better net benefit (NB = WTP x effectiveness - costs) than placebo. Cost-effectiveness acceptability curves were used to plot the probability that cranberry use is more cost-effective than placebo as a function of WTP (estimated as the percentage of bootstrap samples in which cranberry use had a better estimated NB). Confidence intervals for the cost-effectiveness ratio were calculated as WTP values for which the difference in net benefit was not significantly different.[14] The base-case CUA compared total societal costs with QALYs calculated from the Dutch tariff for the EQ-5D at a WTP of €40,000 per QALY.

RESULTS

Effect of UTIs on mortality, utility, and costs

Quality of life was significantly but moderately worse during a UTI; comparing the first 2 weeks after a UTI with the third week, averages were 0.341 versus 0.379 for the EQ-5D (difference 0.038, P = 0.02) and 0.727 versus 0.753 for the VAS (difference 0.026, P = 0.03).

Mortality in the month after a first UTI was 3.6 times as great as in residents without a UTI (Table 1). After more than a month, the difference was not statistically significant.

The Care Dependency Scale was also significantly but moderately worse during a UTI (40.7 vs 42.0; difference 1.2; P = 0.01), with an estimated 4% increase in nursing costs in the 2 weeks after a UTI. Total healthcare costs associated with (prevented) UTIs were estimated at €196, primarily consisting of the additional nursing care (61%), followed by hospitalization costs (20%), care by the elderly-care physician (13%), diagnostics (4%), and antibiotic treatment (2%).

High-UTI-risk participants

Cranberry use on average prevented 0.09 clinically defined UTIs (0.69 vs 0.78, P = 0.32) during the trial follow-up (of 289 vs 289 days, P = 0.99). The associated costs were estimated at

€3,800 per prevented UTI (95% CI = €1,300-infinity). Cranberry use did not prevent strictly defined UTIs during follow-up (0.28 vs 0.22, $P = 0.30$). From a lifetime societal perspective, the reduced clinical UTI infection rate resulted in improvements in other health outcomes and costs, although not significantly (Table 2). Life expectancy was estimated to be approximately 2 weeks longer (0.044 years, 95% CI = -0.023-0.091). The savings on costs associated with UTIs were much smaller than the cranberry costs, use of cranberry capsules increased lifelong total costs by €941 (95% CI = €779-1,055). Whether this cost difference is economically acceptable depends on how much one is willing to pay for the health improvement in terms of QALYs (Figure 2). For relatively low willingness to pay up to €20,000 per QALY, the probability that cranberry use is more cost-effective than placebo was estimated at less than 1% (in the base-case analysis using the EQ-5D). At €40,000 per QALY, the probability that cranberry use is cost-effective was estimated at 22%. When the VAS was used instead of the EQ-5D, more value was assigned to quality of life during the added life expectancy. As a result, the estimated probability that cranberry use is more cost-effective than placebo at a willingness to pay of €20,000 and €40,000 per QALY was 16% and 53%, respectively (Figure 2).

The economic assessment would be more favorable to cranberry use if the costs of cranberry use were lower or the savings per prevented UTI were higher. The costs of cranberry

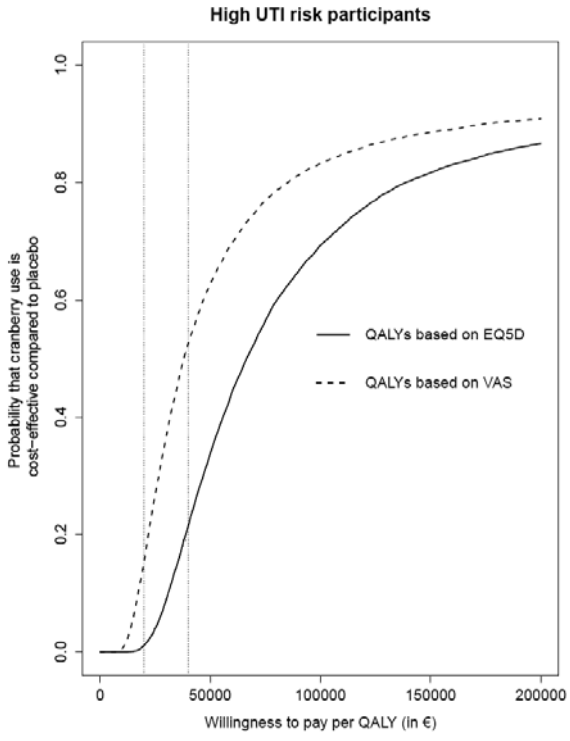

Figure 2. Cost-effectiveness acceptability curves, for high-urinary tract infection (UTI)-risk participants (the probability that cranberry use is more cost-effective than placebo, depending on how much one is willing to pay for a quality-adjusted life year (QALY), based on utility measured using EQ-5D or visual analog scale (VAS)).

Table 2. Mean lifelong health-economic outcomes of treatment with or without cranberry, estimated from the health-economic model.

Outcome	Cranberry	Placebo	Difference	(95%CI)
Low UTI-risk				
Number of UTI[a,b]	2.13	1.84	0.29	(-0.06 – 0.60)
Life expectancy [a] (years)	2.53	2.59	-0.06	(-0.14 – 0.05)
QALYs based on EQ-5D[c]	0.83	0.85	-0.02	(-0.05 – 0.01)
QALYs based on VAS[c]	1.69	1.73	-0.04	(-0.09 – 0.03)
Costs of cranberry use (€)	1012	0	1012	(863 – 1120)
Costs of diagnostics (€)	15	13	2	(-1 – 5)
Costs of antibiotic treatment (€)	5	4	1	(-1 – 2)
Costs of elderly-care physician (€)	47	40	7	(-2 – 15)
Costs of additional nursing care (€)	228	196	32	(-22 – 68)
Costs of hospitalizations (€)	76	65	11	(-13 – 23)
Total UTI costs (€)	1383	318	1065	(889 – 1183)
High UTI-risk				
Number of UTI[a,b]	2.75	2.96	0.21	(-0.42 – 0.04)
Life expectancy [a] (years)	2.45	2.40	0.05	(-0.02 – 0.09)
QALYs based on EQ-5D[c]	0.81	0.79	0.02	(-0.01 – 0.03)
QALYs based on VAS[c]	1.64	1.61	0.03	(-0.01 – 0.06)
Costs of cranberry use (€)	982	0	982	(814 – 1099)
Costs of diagnostics (€)	20	22	-2	(-4 – 1)
Costs of antibiotic treatment (€)	7	8	-1	(-2 – 1)
Costs of elderly-care physician (€)	61	66	-5	(-10 – 1)
Costs of additional nursing care (€)	298	323	-25	(-49 – 13)
Costs of hospitalizations (€)	99	107	-8	(-17 – 9)
Total UTI costs (€)	1467	526	941	(779 – 1055)

[a]Undiscounted

[b]Lifelong, both first and other urinary tract infections (UTIs), using the clinical definition

[c]Quality adjusted life years (QALYs; life expectancy weighed by utility for quality of life

VAS = Visual Anolog Scale

use would need to decrease from €439 to €300 to make cranberry and placebo equally cost-effective. Similarly, the savings per prevented clinical UTI would need to increase from €196 to €1,704 to make cranberry and placebo equally cost-effective.

Low-UTI-risk participants

In the low-UTI-risk participants, because no effect of cranberry use on UTI infection rate was found, there was also no difference in the other health outcomes. The only difference was the estimated lifelong costs of €1,012 for cranberry use. As a result, it is highly unlikely that use of cranberry capsules is cost-effective in low-UTI-risk residents (probability < 3%, regardless of willingness to pay per QALY).

DISCUSSION

This study investigated whether the use of cranberry capsules is more cost-effective than placebo based on data from a randomized controlled trial.[5] In participants with low UTI risk, the use of cranberry capsules did not prevent UTIs, and consequently, their use is not cost-effective. In high-UTI-risk participants, there were fewer clinically defined UTIs. Moreover, there was a significant, but moderate, short-term effect of those UTIs on quality of life and care dependency. Most of the QALY gain was due to the prevented UTI mortality, resulting in a gain in life expectancy of approximately 2 weeks. This relative 1.5% improvement in life expectancy is consistent with the estimated mortality attributable to UTI (7.7%) combined with the 26% treatment effect.[5]

Savings on prevented UTIs partly compensate for the costs of the cranberry capsules, but using a lifelong perspective, those savings added up to approximately €50. As a result, the overall cost difference is about equal to the costs of the cranberry capsules, estimated at €439 per year or at €3,800 per prevented clinically defined UTI. The health gain in terms of QALYs was small in comparison with the costs, so use of cranberry capsules was not likely to be cost-effective (22% for a WTP threshold of €40,000 per QALY).

Options to improve cost-effectiveness

Cranberry use does not constitute a low-cost strategy to prevent UTIs.[15] The estimated price for the capsules was lower than the price estimated previously (€0.24 vs CAN $0.73 ≈ €0.61),[16] but the overall costs per capsule were somewhat similar because of the added nursing time in the current study. The previous study estimated the costs per prevented UTI at CAN$1,890, which was acknowledged as quite high.[16] That study suggested that cranberry use could be cost-effective if the strength or size of the cranberry product could be reduced without reducing effectiveness. In the current study, a preventive effect was seen with the cranberry capsules after 2 months. It is unknown whether lowering the frequency after those 2 months would change not only the costs, but also the effect.

Second, the cost-effectiveness of cranberry use would also be more favorable in settings in which the savings per prevented UTI were higher. In the current study, these savings would need to be eight times as high to make cranberry and placebo equally cost-effective. This seems unrealistic for the Dutch LTCF setting, although in other healthcare systems, residents with UTIs may more frequently be referred to a hospital than the 1% in the current study population. Similarly, in noninstitutionalized vulnerable older persons, the savings associated with prevented UTIs may be higher because of the need for additional formal and informal care during and after a UTI.

Third, the high-UTI-risk criteria included diabetes mellitus, long-term catheterization, and UTI in the preceding year. Better identification of older persons at high UTI risk may also improve cost-effectiveness.

Limitations

There are several complicating factors in analyzing cost-effectiveness in vulnerable older persons in LTCFs. The first is how to value the residents' health. According to the EQ-5D, health during the 2-week life expectancy gain was valued at approximately 40%, whereas according to the VAS, this gain would be valued at approximately 70%. In accordance with the study protocol, the EQ-5D was considered to be more appropriate than the VAS because the EQ-5D provides a societal valuation and because the descriptions it requires are less subjective than the valuations that the VAS requires.[17] Consistent with the high percentage of participants with dementia (76%) and the high percentage of participants for whom family provided informed consent (84%),[5] nurses mostly provided the utility measures (89%), and little is known about the validity of proxy VAS valuations in a LTCF context. Considering the often poor health of LTCF residents, the VAS valuations appear high.

Another factor is the high costs of standard LTCF care, amounting to approximately €80,000 annually in the Netherlands.[9,18] Including these high costs in the analysis would make any life-prolonging treatment too expensive, even if the treatment itself was cost free. In the analysis, the 2-week life expectancy gain would add approximately €1,500 to the costs associated with cranberry use, confirming the conclusion that use of cranberry capsules is not likely to be cost-effective. Dutch guidelines for economic evaluations in health care recommend including costs associated with additional life time only if they are related to the primary intervention, which was not the case in the current analysis.

Third, it was decided beforehand that the economic state/transition model would be based on the clinical definition, because it was expected that it would be more predictive of outcome. Had the strict UTI definition been used for the model, the estimated effectiveness and cost-effectiveness would have been less favorable to the use of cranberry capsules, confirming the conclusion that use of cranberry capsules is not likely to be cost-effective.

Finally, this study was performed in Dutch LTCFs, where elderly-care physicians provide medical care.[19-21] The results are not automatically generalizable to vulnerable older persons living at home. In LTCFs, medication prescription and distribution are well organized. Because the study capsules were added to the existing drug-dispensing system, participants rarely missed taking a capsule, reflected in a high adherence rate. For other settings, not only differences in vulnerability and infection rates are expected, but also in adherence. Moreover, at home, cranberry capsules can be taken without the help of nurses, which would halve the costs of cranberry use.

CONCLUSIONS

In high-UTI-risk residents, taking cranberry capsules may be effective in preventing UTIs but is not likely to be cost-effective in the investigated dosage, frequency, and setting. In low-UTI-risk LTCF residents, taking cranberry capsules twice daily is neither effective nor cost-effective.

Acknowledgements

The authors thank the organizations and members of the University Nursing Home Research Network South Holland, Parnassia, and the staff of the LTCFs participating in this study. Their ongoing collaboration enabled us to perform this study.

Conflict of Interest

All researchers worked independently from the funders. The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

A grant was received from ZonMw Doelmatigheid, the Dutch Organization for Health Research, the Netherlands (Project 170882501). Springfield Nutraceuticals B.V., Oud-Beijerland, the Netherlands, supplied the cranberry and placebo capsules.

Author Contributions

Dr. Jacobijn Gussekloo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Caljouw, van den Hout, Cools, Gussekloo. Analysis and interpretation of data: van den Hout, Caljouw, Putter, Cools, Gussekloo. Drafting of the manuscript: van den Hout. Critical revision of the manuscript for important intellectual content: van den Hout, Caljouw, Putter, Cools, Gussekloo.

Sponsor's Role

All funding sources and suppliers were independent and had no influence on the study design; collection, analyses, and interpretation of data; writing of the report; or the decision to submit the manuscript for publication.

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CHAPTER 7

General discussion

The overall aim of this thesis was to explore the possibilities for and effects of prevention of clinical urinary tract infections (UTI) in vulnerable very old persons.

The first part of this thesis investigates the effects of infections on functioning and examines which very old persons would benefit most from UTI prevention. Firstly, we focused on the most vulnerable very old persons, often with (advanced) dementia and with high and complex care dependency, in long-term care facilities (LTCF). For this, we studied changes in the natural course of care dependency in LTCF residents. The conclusions drawn from this prospective follow-up study are that the majority of surviving LTCF residents were stable in their care dependency status over two subsequent 6-month periods and that residents who are most highly dependent on care have an increased risk of mortality (Chapter 2).

Secondly, within the Leiden 85-plus Study, we examined whether clinical UTI predict an increase in disability of the activities of daily living (ADL) among the oldest-old in the general population (Chapter 3). The general population was studied to unravel how infections and disability co-occur. This study showed that in 86-year-old persons without ADL disability, a clinical UTI is associated with a higher risk to develop ADL disability from age 86 years onwards. However, no such association was found for persons who already had disabilities related to ADL (Chapter 3).

Thirdly, we investigated which factors are predictive of clinical UTI among the oldest-old in the general population. This study showed that cognitive impairment, ADL disability, self-reported urine incontinence, and a one-year history of clinical UTI, are independent predictive factors of an increased incidence of clinical UTI from age 86 onwards (Chapter 4). These predictive factors can be used to target preventive measures to the oldest-old at high risk of clinical UTI.

In summary, the first three studies presented in this thesis show that the majority of LTCF residents remained stable in their care dependency status, that clinical UTI are frequently present in vulnerable very old persons, and that these clinical UTI have consequences for daily functioning. Furthermore, there are factors that can be used to identify older persons at risk for developing clinical UTI. Thus, prevention of clinical UTI is important and it is possible to identify vulnerable very old persons at risk for developing clinical UTI. Therefore, we searched for preventive strategies which are suitable for the prevention of UTI in this specific population.

Until now, there are no evidence-based interventions that show a decrease in clinical UTI in institutionalized populations;[1] however, there is increasing evidence that cranberry products may lead to a decrease in the incidence of clinical UTI over a 12-month period, particularly in women with recurrent UTI.[2-4] Although two studies reported that cranberry juice may be protective in older adults,[5;6] the effectiveness of cranberry capsules in the protection against UTI in vulnerable older persons in LTCF had not yet been studied. Therefore, we designed the CRANBERRY study to assess the effectiveness and costs of cranberry capsule use to prevent

clinical UTI in LTCF residents, stratified for UTI risk at baseline. The results of the CRANBERRY study are described in the second part of this thesis.

The CRANBERRY study (Chapter 5) shows that taking cranberry capsules twice daily results in a 26% lower incidence of clinically defined UTI compared to placebo in residents at high risk of UTI, but that cranberry use is unlikely to be cost-effective in the investigated dosage, frequency and setting (Chapter 6). In other words, although cranberry capsules reduce the number of clinical UTI in vulnerable very old persons living in LTCF, the capsules cost more than they save in relation to the costs of regular treatment of clinical UTI.

This chapter places the preventive care for vulnerable very old persons in a broader perspective and discusses the challenges and barriers of research in long-term care. The chapter ends by discussing the clinical impact of our findings for daily practice in long-term care and makes some recommendations for future research.

PREVENTIVE CARE IN VULNERABLE VERY OLD PERSONS

Within preventive care for vulnerable older persons, the traditional prevention goals (such as preventing diseases and mortality) should be extended by goals such as preventing loss of quality of life and self-reliance[7], and the prevention of discomfort. This will enable older persons to be as independent and healthy as possible, in relation to their care needs and health problems.

The most vulnerable older persons generally live in LTCF. These older persons with multimorbidity, functional decline and a high prevalence of cognitive impairment, are dependent on care. In this population, preventive care focuses particularly on loss of quality of life, minimization of the impact of a disease, and reduction of the burden of this disease in the prevention of complications, comorbidity and disability. In addition, preventive measures to achieve a dignified end-of-life are part of the preventive tasks (e.g. mouth care, and prevention of pressure ulcers, urinary retention and constipation) of professional caregivers in long-term care.

Depending on the goals, a well-considered choice has to be made in the selection of a preventive measure in LTCF. When considering preventive strategies to prevent clinical UTI in long-term care, several topics need to be addressed:

1. Care dependency and the resident's ADL status
2. Expected impact of clinical UTI prevention
3. Selection of residents at high risk for developing clinical UTI
4. Challenge of diagnosing clinical UTI
5. Selection of appropriate preventive treatment
6. Cost-effectiveness of clinical UTI prevention

These six points will be discussed in detail below.

1. Care dependency and the resident's ADL status

In this thesis, changes in the natural course of care dependency were examined to shed light on how to manage and provide better tailored care (including prevention) for individual LTCF residents (Chapter 2). Awareness of the natural course of care dependency is essential for residents, as well as for their formal and informal caregivers, when considering therapeutic and end-of-life care options, as well as preventive measures. With this in mind, research among the oldest-old needs to include an assessment of the impact of a disease on an individual's functional capacity and on maintaining their independence.[8]

Since aging is often accompanied by a higher incidence of infections and an increase in ADL disability, it is important to establish whether there is a relation between infections and ADL disability. In addition, prevention of infections may also prevent a decline in ADL. But how do infections and disability in ADL co-occur? It is known that disability in ADL is independently associated with the onset of nosocomial infections in hospitalized older persons,[9] and is a risk factor for infections in LTCF.[10,11] However, it is also known that, amongst the oldest-old in the general population, clinically diagnosed infections are predictive for the development of ADL disability in those without onset of ADL disability (Chapter 3). ADL disability can be considered as a risk factor for an infectious disease, but also as an outcome itself.[8,9,11]

A decline in ADL in older persons has to be placed in a proper perspective. Other non-infectious illnesses and chronic diseases, such as cardiopulmonary, neurological and musculoskeletal diseases, can also lead to ADL disability. In addition, under-nutrition and incontinence can contribute to a decline in ADL.[12-14] A severe decline in ADL can even lead to a higher mortality rate,[10] more care dependency, and a higher risk of being admitted to a LTCF.[15]

2. Expected impact of clinical UTI prevention

In general, infections contribute to higher morbidity and mortality, infection outbreaks, increased antimicrobial medication use, and additional costs in LTCF.[16,17] In addition, the frequent use of antibiotics contributes to more pathogens becoming multi-resistant to antibiotic treatment;[18] moreover, prophylactic antibiotic use is controversial because of side-effects.

Clinical UTI are common and account for 25% to 40% of all bacterial infections in LTCF.[19-21] They place a considerable burden on daily care and have serious consequences for vulnerable older persons living in LTCF. Clinical UTI not only cause several days of illness, but may have more severe consequences such as delirium, dehydration, urosepsis, hospitalization or even death[22,23] and also lead to a deterioration in daily functioning, even when the infection is over (Chapter 3). Considering the impact of clinical UTI in LTCF residents, it seems important to prevent clinical UTI in these vulnerable older persons.

In this thesis, several studies illustrate the high incidence of clinical UTI. Although the study in Chapter 3 shows a decline in ADL in the oldest-old who are not yet disabled, in the CRAN-

BERRY study we were able to reduce the incidence of clinical UTI but were unable to show a reduction in functional decline or mortality. Because LTCF residents represent a vulnerable population, often with (advanced) dementia and high care dependency, the expected impact of clinical UTI in this population may be limited to mainly temporary discomfort, but can lead to higher care dependency, complications, and even mortality.

3. Selection of residents at high risk for developing clinical UTI

Since preventive strategies are best applied to those persons at risk for developing UTI, it is important to know which factors predict clinical UTI in older persons. Within the oldest-old in the general population, a history of UTI, cognitive impairment, ADL disability and urine incontinence, are independent predictive factors for developing UTI (Chapter 4). These predictive factors could be used to target preventive measures to the oldest-old at high risk of UTI. Despite that none of these predictive factors appear to be modifiable, they can be used to select individuals who will most benefit from preventive strategies. Selection of high-risk residents is a crucial first step in successful prevention of clinical UTI.

Following the results of the 85-plus Study (Chapter 4), the CRANBERRY study showed that through selection of residents at low and high risk of UTI, it is possible to distinguish groups of LTCF residents with varying risks of clinical UTI. For example, in the CRANBERRY study, residents with long-term catheterization, diabetes mellitus, or at least one UTI in the preceding year, were considered to be at high risk. Although our high-risk residents were selected using these criteria, it is possible that the use of other criteria might have selected a group at even higher risk or with even more preventable UTI. Prediction rules to select residents at risk for UTI need further study in order to make a more efficient and effective prediction of the UTI risk in this specific population. Improved identification of older persons at high risk of UTI may also improve cost-effectiveness.

Another point to be taken into consideration is that a UTI risk assessment should be evaluated regularly, because the risk for developing UTI can change over time. Moreover, a preventive measure should not necessarily be applied 'forever'. Additional research is required to develop rules related to 'stopping' because, for example, the preventive action of cranberry capsules can cease when a person has been one year free of UTI, and when no other risk factors are present.

4. Challenge of diagnosing clinical UTI

According to clinical guidelines (and also for many studies) the appropriate gold standard for diagnosing UTI is detection of the pathogen in the presence of inflammatory signs and clinical symptoms of micturition.[24,25] A less rigorous definition can easily lead to over-diagnosis and false conclusions.[26] Although clinical UTI is a common bacterial infection in LTCF residents,[1,27] diagnosing UTI in these vulnerable older persons remains a challenge. Factors such as impaired communication because of dementia, a high prevalence of incontinence, chronic

genitourinary symptoms, and a high frequency of positive urine cultures due to bacteriuria without complaints,[28-30] make the diagnosis of UTI difficult. In addition, clinical symptoms of UTI are frequently absent[31] and differentiating between asymptomatic and symptomatic UTI in this population is complicated.[28,32] The use of the gold standard for diagnosing clinical UTI is not suitable for LTCF residents and would lead to substantial under-diagnosis. Thus, no unambiguous criterion standard for diagnosing UTI is available for LTCF populations and most of the clinical criteria applied to ascertain UTI in these vulnerable residents are based on consensus.[33-36]

Generally, these consensus guidelines define a clinical UTI as the presence of specific and non-specific symptoms and signs of UTI, such as dysuria, change in the character of urine, and change in mental status, confirmed with a urinalysis to evaluate for evidence of the presence of nitrite and leukocyte esterase. A positive nitrite and leukocyte esterase test may indicate the presence of clinical UTI, and treatment with antibiotics may then start. Although UTI are often treated empirically,[18] a urine culture may be necessary in LTCF residents with recurrent UTI to confirm the diagnosis and guide antibiotic treatment. In addition, the treatment of clinical UTI in LTCF residents is similar to that of older patients in the community, but with more emphasis on individualized and tailored antimicrobial therapy.[24,36]

Because the confirmation of clinical UTI in LTCF residents remains difficult, in the CRANBERRY study two definitions for UTI were used, i.e. a clinical one and a 'strict' UTI definition (Chapter 5). The strict UTI definition is based on a scientific approach and includes the presence of micturition-related signs and symptoms, confirmed with a positive culture or dipslide. Using only this strict UTI definition probably leads to under-estimation of the true incidence of UTI in LTCF residents and could be less sensitive for our LTCF population.

To make research possible in a 'real world' LTCF population, besides the strict definition, a clinical UTI definition was used. This clinical definition is a broad and practical definition, follows the clinical practice guidelines for LTCF residents,[25,37] and is based on the experience of elderly care physicians and nursing staff. Experienced staff can achieve an even higher diagnostic precision than that acquired with a urine culture.[38] There is also evidence that micturition-related signs and symptoms are predictive for UTI.[28] Although use of the clinical definition can lead to an over-estimation of UTI, it closely reflects clinical care in LTCF and adds knowledge to the practice guidelines to assist physicians in their decision-making. Because the beneficial effect of cranberry capsule use was only found when using our clinical UTI definition, the presence of false-positive clinical UTI is limited. Furthermore, the cost-effectiveness analysis described in this thesis (Chapter 6), also illustrates the relevance of the clinical definition, as clinical UTIs were followed by a significant deterioration in quality-of-life and survival, and an increase in care dependency and costs.

5. Selection of appropriate preventive treatment

As very old people can differ considerably from one another with respect to their health, and functional and cognitive status, instead of a 'one size fits all' approach a personalized preventive care approach is needed. In addition, it is recommended to incorporate 'lag time to benefit' in the preventive care decisions for older populations.[39] Lag time to benefit is defined as the period between an intervention and the moment that improved health outcome is observed.[40] Incorporating lag time estimates into preventive care for vulnerable older persons will encourage a more explicit consideration of the risks and benefits of prevention.[41]

In this thesis, cranberry use for the prevention of clinical UTI showed a positive treatment effect from 2 months of follow-up onward, with a risk reduction of 22% in high UTI-risk residents during the 12-month follow-up (Chapter 5). This level of risk reduction seems to be meaningful in this specific population in which clinical UTI are frequently present.

The CRANBERRY study showed positive effects of cranberry capsule use for UTI in LTCF residents; other benefits of cranberry capsules may also be considered. For example, in daily practice, cranberry use may also reduce antibiotic prescription, including inappropriate prescriptions. In other words prevention with cranberry may lead to even less antibiotic resistance in long-term care. Also, less clincial UTI will lead to a reduction in the burden of UTI symptoms and to less discomfort.

It is important to realize that many preventive measures have not yet been tested in LTCF populations. More research is needed in this specific population to achieve an optimal, personalized and tailored prevention strategy, in which prevention is focused on increased quality of life, minimization of the impact of disease, reduction of the burden of disease in the prevention of complications, comorbidity and disability, and a dignified end-of-life.

Thus, prevention in LTCF needs to be examined in contexts other than the traditional prevention approach which has the prevention of disease and mortality as its ultimate goal. A new framework for preventive care in LTCF needs to be developed which involves both the older person and their informal caregiver(s). Within the individualized preventive care for vulnerable very old persons, the practical feasibility of interventions needs to be taken into account, as well as an effective implementation in daily care which includes education, knowledge and professional development, regulations, and financial considerations.

6. Cost-effectiveness of clinical UTI prevention

Justifying the implementation of new prevention strategies not only requires evaluation of its effectiveness, but also requires economic evaluation. For an economic evaluation in long-term care the impact of clinical UTI on the resident's health is relevant, and the resident's quality of life plays an important role in the societal valuation. The ultimate goal in long-term care is not simply adding 'years to life' but adding 'quality of life to years'. Therefore, the costs and benefits of interventions to prevent clinical UTI in LTCF populations need to be carefully weighed.

The CRANBERRY study shows that it is unlikely that cranberry capsule use will be cost-effective in the investigated dosage, frequency and setting (Chapter 6). However, cranberry capsules can be 'efficient' from the perspective of the individual resident with a high risk of UTI, resulting in a lower incidence of clinical UTI, less impact of UTI on the resident's health (e.g. less disability in ADL, care dependency and less discomfort), and a better quality of life. Also, less antibiotic use and (probably) less antibiotic resistance is likely to lower the costs. The costs attributed to antibiotic resistance were not discounted in the CRANBERRY study.

Economic evaluations usually express the effects of the intervention in the number of life-years gained and in health-related quality of life.[42] Preferably, a cost-utility analysis is performed for economic evaluations, whereby the effectiveness of the intervention in terms of quality-adjusted life years (QALYs) is expressed in a cost-utility ratio per QALY. This ratio is defined as the amount of money the society is willing to pay to gain one QALY.[43;44] The CRANBERRY study shows that the health gain in terms of QALYs was small in comparison with the costs. Most of this gain was due to the prevented clinical UTI mortality, i.e. a QALY gain in life expectancy of two weeks (Chapter 6). Although two weeks seems relatively small, in a vulnerable LTCF population with a life expectancy of around 1.5 years after admission to a LTCF, this is relatively large. The six-month mortality rate in LTCF residents with advanced dementia ranges from 18% to 37%,[45,46] and the overall 2-year mortality rate after institutionalization is 57%.[47]

Usually the QALYs are based on health-related quality of life, measured using the European Quality of Life utility measure (EQ-5D); this is a generic preference-based measure using a health state classification system with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[48] Although use of the EQ-5D allows to compare economic evaluations internationally, it is less suitable for use in the LTCF setting.[49-51] Normally, quality of life measurements require the resident's self-assesment of their fulfilment and impairment in daily life;[50] however, because the most vulnerable people, often with (advanced) dementia, live in LTCF, the proxy (e.g. the responsible nurse, or relative) generally provides the utility measure. However, there is evidence that the rating of quality of life by proxy is influenced by the personal and/or professional characteristics of the proxy, the nature of the relationship, the time spent with the resident, the stage of dementia, and also the caregiver burden.[49,50] Thus, there is often a discrepancy between the quality of life rating acquired from the residents themselves and that of their proxy, although the viewpoint of the proxy appears to be important when rating the EQ-5D.[52] Despite that, the responsible nurse is well acquainted with the residents, it is difficult to rate the resident's pain/discomfort and anxiety/depression, especially in residents suffering from dementia. The EQ-5D is too narrowly focused and does not cover the domains relevant to the quality of life of persons with dementia. In the CRANBERRY study the EQ-5D had to be filled in by a professional proxy because 76% of the participants had dementia. A recently developed prototype of the Dementia Quality of life Instrument (DQI) seems more suitable, but has not yet been tested in a large LTCF population.[49]

Another aspect related to economic evaluations in LTCF needs to be adressed, i.e. how do we measure the additional nursing care for LTCF residents who already have continous care? Until now, there is no standard for measuring the costs of additional nursing care in LTCF residents who are already highly care dependent. Therefore, we calculated the additional nursing costs during the two weeks following a clinical UTI, by estimating the proportion of change on the Care Dependency Scale (Chapter 6).[53] Although this method was suitable for our study, additional research is required to validate this method.

In the light of all these difficulties related to economic evaluations in long-term care, there is an urgent need for a more suitable instrument to conduct economic evaluations, because the present methods may never demonstrate cost-effectiveness.

RESEARCH IN LONG-TERM CARE FACILITIES: CHALLENGES AND BARRIERS

The above mentioned substantive and methodological points show that research in LTCF populations is challenging and needs specific knowledge and a specific infrastructure. This section discusses the challenges and barriers to research in LTCF populations.

The proportion of older people is steadily rising worldwide; moreover, they live longer and manage their daily activities for longer than ever before.[54] However, these people also have a higher risk of higher care dependency, institutionalization and mortality.[55,56] Admission to a LTCF is usually the result of a complex interaction of problems in many domains, in which care and treatment are insufficient to handle all the needs that the individual resident has. Especially behavioral problems (e.g. wandering, aggression, delusions), as well as depression and anxiety, apathy, resistance to care, functional impairment, incontinence, and informal caregiver burden, are reasons for institutionalization.[57,58] Therefore, in the future, LTCF will probably admit only the most problematic and vulnerable persons, often with (advanced) dementia. Prevention of loss of quality of life and self-reliance is challenging in this vulnerable population. However, an even greater challenge is to minimize the impact of a disease, and reduce the burden of this disease in the prevention of complications, comorbidity and disability; all this requires specific insight and solid evidence. Therefore, research is needed in LTCF populations to generate specific knowledge that also takes into account implementation of this new knowledge into daily practice.

LTCF residents are often excluded from participation in research, sometimes due to the high prevalence of cognitive impairments (e.g. dementia) and sometimes due to medico-ethical considerations.[59] Also, difficulty in acquiring informed consent for study participation from representatives is often a reason for not conducting research in this population. In addition, various methodological issues may form a barrier to research in an LTCF population: for example, difficulties in formulating clear research outcomes or clinical endpoints, problems in defining a clear and unambiguous diagnosis of the disease, the high mortality rate in this

population, and the related high level of drop-out during a study. Moreover, some logistic challenges in performing research in LTCF are present, such as obtaining permission from the directors for their organization(s) to participate in the research project and the geographical distance between the participating organizations; often, this distance makes data collection and monitoring of the research project both difficult and costly.

Most research in LTCF is pragmatic and will take place in a 'real world' LTCF population. Therefore, research in LTCF requires a specific infrastructure as well as a considerable effort to enable research in this population. In 2003 the formation of academic nursing home research networks was started in the Netherlands. Currently, in 2014, there are five networks (located in Amsterdam, Groningen, Leiden, Maastricht, and Nijmegen) that have expertise related to performing research in complex care among vulnerable persons living in LTCF. The mission of an academic nursing home research network includes the development of an infrastructure for research.[60,61] Care professionals collaborate with scientists of a university medical center to develop, implement, and test initiatives to improve quality of care.[60] Within this structure, university and practice are closely linked. Research outcomes will be directly implemented in daily practice and in the education/training of care professionals; hopefully, all this will serve to improve directly patient care.

CLINICAL IMPACT AND RECOMMENDATIONS FOR FUTURE RESEARCH

Based on the work presented in this thesis, the following conclusions can be drawn:

1. The natural course of care dependency is a dynamic process. LTCF residents can either improve or deteriorate in their care dependency status during their stay in a LTCF. Regular and simple assessment of the care dependency status is important, since this allows nursing staff to become more aware of the variability in the care dependency status of their residents, manage care, anticipate residents' care needs, and provide better tailored care for individual residents. Awareness of the course of care dependency is essential for residents, as well as for their formal and informal caregivers, when considering therapeutic, palliative, and end-of-life care options. Although care dependency can be influenced by individually-tailored interventions, these types of interventions need additional research.

2. In older persons without ADL disability at 86 year of age, clinical infections predict the development of disability in ADL from age 86 years onwards. These infections may be used as a predictor for ADL disability in the oldest-old who are not yet disabled. General practitioners and elderly care physicians should be vigilant when older persons without ADL disability have an infection. Besides treatment, they may start active functional rehabilitation to maintain independence in ADL. Future studies need to address whether the prevention of infections, a quick recovery after infections, and functional rehabilitation, are beneficial in the oldest-

old in the general population to maintain independence in ADL and to avoid adverse health outcomes.

3. Diagnosing clinical UTI is challenging in vulnerable very old persons. Although several guidelines are available to assist physicians in the diagnosis of clinical UTI in this population, there is no unambigous definition of clinical UTI. The current guidelines are not optimal for clinical decision-making, or for a 100% confirmation of clinical UTI. Additional studies are required to further refine these consensus guidelines and to establish how to optimally diagnose clinical UTI in vulnerable very old persons.

4. It is possible to select vulnerable very old persons at high risk for developing UTI. LTCF residents with long-term catheterization, diabetes mellitus, or at least one UTI in the preceding year, are considered to be at high risk of UTI. It is possible that the use of other criteria would have selected a group with even higher risks or even more preventable UTI. Therefore, prediction rules to select residents at risk for UTI need to be studied to enable a more efficient prediction of the UTI risk in this specific population. In addition, it is recommended to evaluate UTI risk on a regular basis, because the risk for developing UTI can change over time.

5. The use of cranberry capsules (twice daily) is effective in the prevention of clinical UTI in LTCF residents at high risk of UTI. The capsules reduce the incidence of clinical UTI and thereby reduce the days of illness and the negative consequences of UTI, e.g. a reduction of the burden of the symptoms of UTI and less discomfort. The use of the capsules was shown not to be cost-effective; nevertheless, for reasons of effectiveness, it is still recommended to give residents at high risk of UTI preventive treatment with cranberry capsules.

Finally, additional studies are required to investigate whether, for example, clinical UTI prevention with cranberry capsules is effective in providing improvement in care from the perspective of the resident. In this case, the care improvement should focus mainly on quality of life, minimization of the impact of a disease, and a reduction in the burden of this disease in the prevention of complications, comorbidity and disability. To stratify residents and to make a well-considered choice for the indicated preventive interventions, assessment of the impact of the disease on an individual's functional capacity and their ability to maintain independence, is recommended.

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CHAPTER 8

Summary

Urinary tract infections (UTI) are among the most frequently reported infections among older persons. Annually, 20% of all older persons visit their general practitioner for a UTI and about 50% of the residents in long-term care facilities (LTCF) get a UTI. This type of infection not only causes several days of illness but may have more severe consequences for older persons, such as a decline in functioning, as well as delirium, dehydration, urosepsis, hospitalization, or even death. It is generally assumed that infections also lead to a general decline in functioning, which is often irreversible and can cause a cascade of general deterioration, more care dependency, and a higher mortality risk. In addition, it is known that disability in activities of daily living (ADL) is independently associated with the development of infections. Considering this negative impact of UTI, we were particularly interested in how to prevent UTI in vulnerable very old persons.

To avoid the possible negative effects of UTI in vulnerable older persons, interventions are needed. To more efficiently prevent UTI and their subsequent negative consequences it is important to identify older persons at risk for UTI. Among vulnerable older persons, an increasing age, diabetes mellitus, stroke, urine incontinence, prior history of UTI, and impaired functional and cognitive status are predictive for the development of UTI. A first step towards effective prevention of UTI in older persons is to gain insight into whether these factors also play a role in the occurrence of UTI in the oldest old. If these factors are known, it should be easier to detect the group of oldest old with an increased risk of UTI.

The use of prophylactic antibiotics in older persons at risk remains controversial because of the associated side-effects as well as antibiotic resistance. In addition, no other evidence-based interventions are known to decrease UTI in institutionalized populations. However, prophylaxis with cranberry is a potential prevention strategy. Cranberries contain proanthocyanidins, which are stable compounds with anti-adhesion activity against, for example, *Escherichia coli*. Although two studies have reported that cranberry juice may be protective in older adults, the effectiveness of cranberry capsules in the protection against UTI in vulnerable very old persons in LTCF has not yet been studied.

The general aim of this thesis is to study the possibilities for and the effects of the prevention of UTI in vulnerable very old persons.

PART ONE: CORRELATES OF URINARY TRACT INFECTIONS

Chapter 2 focuses on the care dependency of the most vulnerable very old persons in LTCF, often with (advanced) dementia and with high and complex care dependency. In a prospective follow-up study in 21 Dutch LTCFs, changes in care dependency were examined over two 6-month periods, and the possible predictive factors of change and the effect of care dependency on mortality were explored. The changes in care dependency were examined to shed light on how to manage care and provide better tailored care for individual LTCF residents. A

total of 890 LTCF residents with a median age of 84 years participated. At baseline, and at 6 and 12 months, the care dependency status was assessed by the nursing staff using the Care Dependency Scale (CDS). The CDS comprises 15 items measuring basic care needs of LTCF residents.

The conclusions drawn from this study are that the majority of surviving LTCF residents were stable in their care dependency status over two subsequent 6-month periods, and that residents who are most highly dependent on care have an increased mortality risk. A 1-point decrease in CDS score between 0 and 6 months was related to an increased mortality risk of 4%. In addition, gender, age, urine incontinence, dementia, cancer and baseline care dependency status predict an increase in care dependency over time. The results of this study indicate that residents, and their formal and informal caregivers, need to be aware of the natural course of care dependency when considering therapeutic and end-of-life care options, as well as preventive measures, in long-term care.

Because infections are more common in vulnerable older persons and these infections may also have negative consequences for their (ADL), the study in Chapter 3 examined whether UTI or lower respiratory tract infections predict an increase in disability of ADL among the oldest old in the general population. This study used data from the Leiden 85-plus Study (a population-based prospective follow-up study) and was performed to establish whether infections at old age predict an increase in ADL disability, stratified for the presence of ADL disability. A total of 473 persons aged 86 years participated. ADL disability was determined at baseline and annually thereafter during 4 years of follow-up, using the 9 ADL items of the Groningen Activity Restriction Scale.

The study showed that in persons without disability in ADL between age 85 and 86 years, infections are associated with a 1.6 times higher risk to develop ADL disability from age 86 years onwards compared with older persons without infections. However, no such association was found for persons who already had disabilities related to ADL. In addition to treatment, active functional rehabilitation may be important to restore independence in ADL.

In order to take effective preventive measures against UTI, especially older persons who are at increased risk to develop UTI should be selected. Therefore, the study in Chapter 4 determined which predictive factors of UTI among the oldest old in the general population were predictive for UTI. This population-based prospective follow-up study (also based on data from the Leiden 85-plus Study) showed that cognitive impairment, ADL disability, self-reported urine incontinence and a one-year history of UTI, are independent predictive factors of an increased incidence of UTI from age 86 onwards. These predictive factors can be used for the development of a clinical prediction rule to select the most appropriate persons for preventive strategies.

PART TWO: THE CRANBERRY STUDY

Until now, apart from general hygienic precautions, adequate hydration, regularly toilet visits and sufficient urination (bladder emptying), there are no evidence-based non-antibiotic interventions that show a decrease in clinical UTI in institutionalized populations. However, there is increasing evidence that cranberry products may lead to a decrease in the incidence of clinical UTI over a 12-month period. Although two studies have reported that cranberry juice may be protective in older adults, the effectiveness of cranberry capsules to protect against UTI in vulnerable older persons in LTCF had not yet been studied; therefore, we designed the CRANBERRY study.

The CRANBERRY study is a double-blind randomized placebo-controlled multi-center trial, in which a total of 21 LTCF from the University Network for the Care sector in South-Holland (UNC-ZH) participated. The CRANBERRY study assesses the effectiveness and costs of cranberry capsule use to prevent clinical UTI in vulnerable older persons living in LTCF, stratified for UTI risk at baseline. Participants were stratified according to UTI risk at the start of the study. Participants with long-term catheterization, diabetes mellitus, and at least one UTI in the preceding year, were considered to be at high risk for UTI. In total, 928 residents (225 men and 703 women) aged over 65 years of age were randomized in two groups: one group received cranberry capsules and the other group a placebo. Cranberry and placebo capsules were provided twice daily for 12 months.

The primary outcome was the incidence of UTI. However, because diagnosing UTI in vulnerable older persons is difficult, the CRANBERRY study not only used the prevailing scientific gold standard (strict definition), but also used the clinical diagnosis made for each individual resident (clinical definition). The strict definition is based on a scientific approach, which always involves the presence of clinical symptoms and the presence of bacteria in the urine. In contrast, the clinical definition varies between residents and is therefore a broad and practical definition, following current clinical practice guidelines and based on clinical agreement of 'elderly care' physicians and the nursing staff.

The study in Chapter 5 investigates the effectiveness of cranberry capsule use in the prevention of UTI in vulnerable older persons living in LTCF. The CRANBERRY study shows that the use of cranberry capsules reduced the number of clinical UTI by 26% in LTCF residents with a high UTI risk; this treatment effect occurs after 2 months of capsule use. Also, more than 20% of the residents no longer developed any UTI at all. No difference in incidence was found in residents with low UTI risk. For UTI defined according to the strict definition, no difference was found in UTI incidence between residents who used cranberry or placebo capsules.

The use of cranberry capsules requires not only evaluation of its clinical effectiveness but also an examination of its cost-effectiveness. Therefore, the economic evaluation presented in Chapter 6 investigated the effect of clinical UTI on health and costs and examined whether the preventive use of cranberry capsules in LTCFs is cost-effective. This study concluded that,

in high UTI risk residents, taking cranberry capsules is unlikely to be cost-effective in the investigated dosage, frequency and setting. In other words, although cranberry capsules reduce the number of clinical UTI in vulnerable very old persons living in LTCF, the capsules cost more than they save in relation to the costs of regular treatment of clinical UTI.

Finally, Chapter 7 presents a general discussion on the main findings of the work presented in this thesis. The chapter also reflects on the difficulties in diagnosing UTI in vulnerable older persons with dementia, considers the clinical implications of our findings for daily practice in long-term care, and makes some recommendations for future research. The preventive care for vulnerable very old persons is placed in a broader perspective and the challenges and barriers of research in long-term care are discussed.

The first three studies presented in this thesis show that clinical UTI are frequently present in vulnerable very old persons and that these clinical UTI can have consequences for the daily functioning of the oldest old who are not yet disabled. In addition, the majority of LTCF residents remained relatively stable in their care dependency status. Furthermore, it was established that some factors can be used to identify older persons at risk for developing clinical UTI. Thus, prevention of clinical UTI is important and it is possible to identify vulnerable very old persons at risk for developing clinical UTI.

The results of the CRANBERRY study allow to conclude that the use of cranberry capsules (twice daily) is effective in the prevention of clinical UTI in LTCF residents at high risk of UTI. The capsules reduce the incidence of clinical UTI and thereby reduce the days of illness and the negative consequences of UTI, e.g. reducing the burden of the symptoms of UTI and less discomfort. Although the use of the capsules was not cost-effective, for reasons of effectiveness it is still recommended to give residents at high risk of UTI preventive treatment with cranberry capsules.

Because the confirmation of clinical UTI in LTCF residents remains difficult, in the CRANBERRY study two definitions for UTI were used, i.e. a clinical one and a strict UTI definition. The appropriate scientific 'gold standard' for diagnosing UTI is detection of the pathogen in the presence of inflammatory signs and clinical symptoms of micturition. However, factors such as impaired communication due to dementia, high prevalence of incontinence, chronic genitourinary symptoms and a high frequency of positive urine cultures due to bacteriuria, without being clear whether these bacteria are from the urine bladder or from the environment after urination, makes the diagnosis of UTI even more difficult. The use of the 'gold standard' for diagnosing clinical UTI is not suitable for LTCF residents and will probably lead to substantial underdiagnosis. As a result, no unambiguous criterion standard is available for diagnosing UTI in LTCF populations; most clinical criteria to ascertain UTI in these vulnerable residents are based on consensus about grouped clinical manifestations, as presented in clinical guidelines. Currently, these guidelines define a clinical UTI as the presence of specific and non-specific symptoms and signs of UTI, such as dysuria, change in the character of urine, and change in mental status, confirmed with a urinalysis to evaluate the evidence of the presence of nitrite

and leukocyte esterase. UTI are often treated empirically, but a urine culture may be necessary in LTCF residents with recurrent UTI to confirm the diagnosis and guide antibiotic treatment.

Although several guidelines are available to assist physicians in the diagnosis of clinical UTI in this population, no unambiguous definition of clinical UTI is available. The current guidelines are not optimal for clinical decision-making or for a 100% confirmation of clinical UTI. Additional studies are required to further refine these consensus guidelines and to establish how to optimally diagnose clinical UTI in vulnerable very old persons.

Within the preventive care for vulnerable older persons, the traditional prevention goals (such as preventing diseases and mortality) could be extended by goals such as preventing loss of quality-of-life and self-reliance, and the prevention of discomfort. Because the most vulnerable older persons generally live in LTCF a well-considered choice has to be made in the selection of a preventive measure in this population. Additional studies are required to investigate whether prevention is effective in providing improvement in care from the perspective of the resident. Care improvement in LTCF needs to focus mainly on quality-of-life, minimization of the impact of a disease, and a reduction in the burden of this disease in the prevention of complications, comorbidity and disability. All this requires specific insight and solid evidence. Therefore, research in LTCF populations needs specific knowledge that also takes into account the implementation of this new knowledge into daily practice and a specific infrastructure.

Future research in LTCF can best be performed within an academic nursing home research network, such as the UNC-ZH. An academic nursing home network has expertise related to performing studies in complex care among vulnerable older persons living in LTCF. Within this network, care professionals collaborate with scientists of a university medical center to develop, implement, and test initiatives to improve quality of care. Within this structure, university and practice are closely linked and research outcomes can be directly implemented in the daily practice and education of care professionals.

CHAPTER 9

Samenvatting

Urineweginfecties zijn veel voorkomende infecties bij ouderen. Jaarlijks meldt 20% van de ouderen zich bij de huisarts met een urineweginfectie en krijgt ongeveer 50% van de ouderen in het verpleeghuis een urineweginfectie. Urineweginfecties veroorzaken niet alleen specifieke klachten en enkele dagen van algemeen ziek zijn, maar kunnen ook meer ernstige gevolgen hebben voor de oudste ouderen, zoals het optreden van verwardheid (delirium), uitdroging (dehydratie), urosepsis (bloedvergiftiging door een urineweginfectie) en zelfs leiden tot een ziekenhuisopname of overlijden. Over het algemeen wordt aangenomen dat infecties een algemene achteruitgang in het dagelijks functioneren kunnen veroorzaken. Deze achteruitgang kan mogelijk leiden tot meer zorgafhankelijkheid en een hoger risico op overlijden. Daarnaast is bekend dat een beperking in het dagelijks functioneren in verband kan worden gebracht met het ontstaan van nieuwe infecties. De kans op deze complicaties is groter bij kwetsbare ouderen. Het is dus belangrijk om urineweginfecties bij vooral kwetsbare oudste ouderen te voorkomen.

Om de mogelijke negatieve gevolgen van urineweginfecties bij kwetsbare oudste ouderen met een verhoogd risico te voorkomen, zijn preventieve interventies nodig. Uit de literatuur blijkt dat een toenemende leeftijd, diabetes mellitus, hersenbloeding, urine incontinentie, een eerder doorgemaakte urineweginfectie en een verminderd dagelijks en cognitief functioneren voorspellende factoren van een urineweginfectie zijn. Een eerste stap naar een doelmatige preventie van urineweginfecties bij ouderen, is het inzicht krijgen of deze factoren ook een rol spelen bij het ontstaan van een urineweginfectie bij oudste ouderen. Als deze factoren bekend zijn kunnen ouderen met een verhoogd risico op urineweginfecties makkelijker opgespoord worden.

Het preventief gebruik van antibiotica bij ouderen is werkzaam, maar omstreden door onder andere bijwerkingen en de afgenomen gevoeligheid van bacteriën voor antibiotica. Daarnaast zijn er tot op heden geen andere wetenschappelijk onderbouwde interventies bekend die urineweginfecties bij verpleeghuisbewoners kunnen voorkomen. Een goed alternatief kan het gebruik van cranberry's (veenbessen) zijn. Cranberry's bevatten proanthocyanidine, dat er onder meer voor zorgt dat bacteriën, waaronder *Escherichia coli,* zich niet aan de blaaswand kunnen hechten en daardoor geen infectie meer kunnen veroorzaken. Er zijn tot nu toe twee onderzoeken bekend die aantonen dat cranberrysap mogelijk beschermend kan werken bij ouderen, maar de effectiviteit van het gebruik van cranberry capsules om urineweginfecties bij kwetsbare oudste ouderen in verpleeghuizen te voorkomen, is nog niet eerder onderzocht.

Het doel van dit proefschrift is om de mogelijkheden voor, en de gevolgen van preventie van urineweginfecties te onderzoeken bij verpleeghuisbewoners.

DEEL 1: FACTOREN DIE SAMENHANGEN MET URINEWEGINFECTIES

In hoofdstuk 2 wordt de zorgafhankelijkheid van verpleeghuisbewoners belicht, de meest kwetsbare groep oudste ouderen. In een prospectieve follow-up studie in 21 Nederlandse verpleeghuizen is de verandering in zorgafhankelijkheid bestudeerd gedurende twee aansluitende perioden van ieder 6 maanden. De mogelijke voorspellende factoren van zorgafhankelijkheid en het effect op sterfte zijn in kaart gebracht. In totaal hebben 890 verpleeghuisbewoners met een mediane leeftijd van 84 jaar, aan de studie meegedaan. Bij de start van de studie en na 6 en 12 maanden is de mate van zorgafhankelijkheid door de verzorgende gemeten met de Care Dependency Scale (CDS). De CDS bestaat uit 15 items, die betrekking hebben op de basiszorgbehoeften van verpleeghuisbewoners.

Tijdens de studie bleek de zorgafhankelijkheid van de meerderheid van de verpleeghuisbewoners over een periode van 6 maanden stabiel. Echter, de meest zorgafhankelijke verpleeghuisbewoners hadden een toegenomen risico op overlijden. Eén punt minder op de CDS in de eerste 6 maanden bleek gerelateerd aan een toegenomen risico op overlijden van 4% in de daarop volgende 6 maanden. Daarnaast waren geslacht, leeftijd, urine incontinentie, dementie, kanker en de zorgafhankelijkheid bij de start van de studie onafhankelijke voorspellers voor een toename van zorgafhankelijkheid over de tijd. Deze resultaten kunnen verpleeghuisbewoners, hun mantelzorgers en professionele zorgverleners meer bewust maken van het verloop van zorgafhankelijkheid en het kiezen van op de individuele bewoner afgestemde, behandeling, preventie en palliatieve zorg.

Omdat infecties vaker voor komen bij kwetsbare ouderen en daardoor mogelijk ook negatieve gevolgen kunnen hebben voor het dagelijks functioneren van deze ouderen, is in hoofdstuk 3 onderzocht of infecties van de urinewegen en lage luchtwegen op oudere leeftijd een toename van beperkingen in activiteiten van het dagelijks leven (ADL) voorspellen. Deze studie was onderdeel van de Leiden 85-plus Studie, een observationele prospectieve cohort studie in de algemene bevolking. Van de 473 deelnemers van 86 jaar werden aan het begin van de studie en daarna jaarlijks gedurende 4 jaar follow-up, met behulp van de 9 ADL items van de Groningen Activity Restriction Scale beperkingen in ADL vastgesteld.

De studie toonde aan dat oudste ouderen die een infectie tussen het 85^{e} en 86^{e} jaar hadden, een 1,6 keer hoger risico hebben om een ADL beperking te ontwikkelen in vergelijking met ouderen die geen infectie doormaakten. Dit gold alleen voor ouderen die nog geen ADL beperkingen hadden. Er werd echter geen verschil gevonden voor 86-jarigen die al wel een ADL beperking hadden. Naast goede behandeling van infecties, is ook actieve aandacht voor het herstel van functioneren wellicht belangrijk om beperkingen in ADL te herstellen.

Om effectieve preventieve maatregelen tegen infecties te kunnen nemen, moeten echter vooral die ouderen worden geselecteerd die een verhoogd risico lopen op een urineweginfectie. Daarom werd in hoofdstuk 4 onderzocht welke voorspellende factoren van een urineweginfectie bij de oudste ouderen in de algemene bevolking bestaan. Deze studie maakte

ook gebruik van gegevens uit de Leiden 85-plus Studie. De studie toonde aan dat vanaf de leeftijd van 86 jaar, cognitieve stoornissen, ADL beperkingen, zelf gerapporteerde urine incontinentie en een urineweginfectie in het voorgaande jaar onafhankelijke voorspellende factoren zijn van een toename van het aantal urineweginfecties. Deze voorspellers kunnen worden gebruikt voor de ontwikkeling van een klinische predictieregel om ouderen te selecteren die baat kunnen hebben bij preventieve maatregelen.

DEEL 2: DE CRANBERRY STUDIE

Tot nu toe zijn er, naast algemene hygiënische maatregelen, voldoende inname van vocht, regelmatig toiletbezoek en het voldoende ledigen van de blaas, geen niet-antibiotische interventies bekend die een afname van urineweginfecties bij verpleeghuisbewoners laten zien. Er is echter toenemend bewijs dat het gebruik van cranberry producten kan leiden tot een vermindering van het aantal urineweginfecties over een periode van 12 maanden. Ondanks dat twee studies aangeven dat cranberrysap beschermend kan werken bij ouderen, is de effectiviteit van het gebruik van cranberry capsules ter preventie van urineweginfecties bij verpleeghuisbewoners nog niet eerder onderzocht. Daarom is de CRANBERRY studie opgezet.

De CRANBERRY studie is een dubbelblinde gerandomiseerde placebo-gecontroleerde studie die plaats heeft gevonden in 21 verpleeghuizen van het Universitair Netwerk voor de Caresector in Zuid-Holland (UNC-ZH). Om te bepalen of het gebruik van cranberry capsules een doelmatige interventie is ter preventie van urineweginfecties, zijn in de CRANBERRY studie zowel de effectiviteit als de kosten van het gebruik van cranberry capsules onderzocht.

In totaal hebben 928 verpleeghuisbewoners (225 mannen en 703 vrouwen) ouder dan 65 jaar aan de CRANBERRY studie meegedaan. De deelnemers werden bij aanvang van de studie ingedeeld op het risico van het krijgen van een urineweginfectie. Verondersteld werd dat verpleeghuisbewoners met langdurige blaaskatheterisatie, diabetes mellitus, en het gehad hebben van ten minste één urineweginfectie in het jaar voorafgaande aan de studie, een hoog risico hebben op een urineweginfectie. Alle andere verpleeghuisbewoners behoorden tot de laag risico groep.

Door loting zijn de deelnemers ingedeeld in twee groepen. Een groep kreeg cranberry capsules, de andere groep een niet te onderscheiden placebo capsule (dat is een capsule met niet-werkzame bestanddelen). De deelnemers kregen twee keer per dag een cranberry of placebo capsule voor een periode van 12 maanden.

De primaire uitkomstmaat in de studie was de incidentie van urineweginfecties. Omdat het vaststellen van een urineweginfectie bij verpleeghuisbewoners lastig is, gebruikte de CRANBERRY studie niet alleen de geldende wetenschappelijke gouden standaard (strikte definitie), maar ook de bij iedere individuele patiënt klinisch gebruikte diagnose (klinische definitie). De strikte definitie is gebaseerd op een wetenschappelijke benadering, waarbij altijd sprake is

van de aanwezigheid van klinische symptomen en de aanwezigheid van bacteriën in de urine. De klinische definitie varieert per patiënt en is daardoor een brede en praktische definitie die bestaande richtlijnen volgt, die gebaseerd zijn op klinische overeenstemming tussen professionals, voor het vaststellen van een urineweginfectie bij verpleeghuisbewoners.

In hoofdstuk 5 wordt de werkzaamheid van cranberry capsules ter preventie van urineweginfecties bij verpleeghuisbewoners beschreven. Uit de CRANBERRY studie blijkt dat door het gebruik van cranberry capsules het aantal klinische urineweginfecties met 26% vermindert bij verpleeghuisbewoners met een hoog risico op een urineweginfectie. Dit behandeleffect treedt op na 2 maanden capsule gebruik. Bij meer dan 20% van de bewoners ontwikkelen zich helemaal geen urineweginfecties meer. Er is geen verschil gevonden bij verpleeghuisbewoners met een laag risico. Voor urineweginfecties die gedefinieerd zijn volgens de strikte definitie wordt geen verschil gevonden in het aantal urineweginfecties tussen bewoners die cranberry of placebo capsules hebben gebruikt.

Een onderzoek naar het gebruik van cranberry capsules vereist naast een evaluatie van de werkzaamheid ook onderzoek naar de kosteneffectiviteit. Daarom is in een economische evaluatie in hoofdstuk 6 beschreven wat de effecten zijn van klinische urineweginfecties op de gezondheid en kosten, en of het preventief gebruik van cranberry capsules in verpleeghuizen kosteneffectief is. Deze studie laat zien dat het gebruik van cranberry capsules door verpleeghuisbewoners met een hoog risico, in de huidige dosering en frequentie waarschijnlijk niet kosteneffectief is. Met andere woorden, het gebruik van cranberry capsules vermindert wel het aantal klinische urineweginfecties bij verpleeghuisbewoners, maar kost meer dan de reguliere behandeling van klinische urineweginfecties.

Hoofdstuk 7 presenteert een algemene discussie over de belangrijkste bevindingen uit de studies die beschreven zijn in dit proefschrift. Verder wordt gereflecteerd op het stellen van de diagnose urineweginfectie in kwetsbare ouderen met dementie. Ook worden klinische implicaties van de bevindingen voor de dagelijkse praktijk in de verpleeghuiszorg gegeven en aanbevelingen gedaan voor toekomstig onderzoek. Tenslotte wordt de preventieve zorg voor de kwetsbare oudste ouderen in een breder perspectief geplaatst en de uitdagingen en barrières van onderzoek in de verpleeghuiszorg besproken.

Uit de eerste drie studies die in dit proefschrift beschreven zijn, blijkt dat klinische urineweginfecties vaak voorkomen bij oudste ouderen en dat deze infecties nadelige gevolgen kunnen hebben voor het dagelijks functioneren van oudste ouderen die nog niet beperkt zijn hun functioneren. Daarnaast blijkt dat de meerderheid van de verpleeghuisbewoners relatief stabiel blijven in hun zorgafhankelijkheid. Het is belangrijk om oudste ouderen met een verhoogd risico op het ontwikkelen van een klinische urineweginfectie op te sporen. Dat blijkt ook mogelijk te zijn.

Uit de CRANBERRY studie blijkt dat het gebruik van cranberry capsules (tweemaal daags) effectief is in het voorkomen van klinische urineweginfecties bij verpleeghuisbewoners met een hoog risico op het ontwikkelen van urineweginfecties. Als er minder urineweginfecties

zijn, worden daarmee ook ziektedagen en de negatieve gevolgen van een urineweginfectie voorkomen. Dat betekent voor de verpleeghuisbewoner minder ongemak. Het gebruik van de cranberry capsules bleek echter niet kosteneffectief te zijn. Niettemin, om redenen van effectiviteit is het nog steeds aan te raden om verpleeghuisbewoners met een hoog risico op urineweginfecties, preventief te behandelen met cranberry capsules.

Omdat de diagnostiek van urineweginfecties bij ouderen met dementie lastig is, gebruikte de CRANBERRY studie niet alleen de geldende wetenschappelijke gouden standaard, maar ook een klinisch diagnose. De wetenschappelijke 'gouden standaard' voor de diagnose van een urineweginfectie bestaat uit het vaststellen van de aanwezigheid van klinische symptomen van een urineweginfectie, het opsporen van de veroorzakende bacterie en onderzoek naar de aanwezigheid van kenmerken van een ontsteking. Factoren zoals een moeilijke patiënt-dokter communicatie door (gevorderde) dementie, het vaak voorkomen van incontinentie, chronische klachten van de urinewegen en vaak positieve urinekweken (bacteriurie) zonder dat duidelijk is of deze bacteriën uit de blaas of na urinelozing uit de omgeving afkomstig zijn, maakt het vaststellen van een urineweginfectie in deze groep kwetsbare oudste ouderen moeilijk. De geldende wetenschappelijke gouden standaard blijkt hierdoor minder goed bruikbaar en kan leiden tot onjuiste maar ook gemiste diagnoses. Daarom zijn de meeste richtlijnen voor het vaststellen van een urineweginfectie bij kwetsbare ouderen gebaseerd op overeenstemming over gegroepeerde verschijnselen. Een klinische urineweginfectie wordt omschreven als de aanwezigheid van specifieke en niet-specifieke klachten en symptomen, zoals onder andere pijn bij het plassen (dysurie), verandering in het karakter van urine, en veranderingen in de mentale toestand. Met urineonderzoek wordt vervolgens de aanwezigheid van nitriet en leukocyten vastgesteld, wat kan duiden op een urineweginfectie. Eventueel kan met een urinekweek worden vastgesteld welke bacterie de urineweginfectie veroorzaakt en voor welke antibiotica deze bacterie gevoelig is, zodat de behandelend arts weet welk antibioticum aan de bewoner kan worden gegeven.

Hoewel er verschillende klinische richtlijnen beschikbaar zijn om artsen te helpen bij het stellen van de diagnose van een klinische urineweginfectie bij verpleeghuisbewoners, is er geen eenduidige definitie beschikbaar. De huidige richtlijnen zijn niet optimaal voor de klinische besluitvorming en voor een 100% bevestiging van een klinische urineweginfectie. Verder onderzoek is nodig om de richtlijnen te verbeteren waarmee klinische urineweginfecties bij kwetsbare oudste ouderen beter vastgesteld kunnen worden.

De zorg in verpleeghuizen richt zich vooral op verbetering van kwaliteit van leven, het verminderen van de gevolgen van ziekte, en het beperken van ziektelast door het voorkomen van complicaties, comorbiditeit (het tegelijk voorkomen van verschillende aandoeningen) en beperkingen in het dagelijks functioneren. De preventieve zorg voor de kwetsbare oudste ouderen zal zich daarom vooral moeten richten op het voorkomen van verlies van kwaliteit van leven en zelfredzaamheid in plaats van op het voorkomen van ziekte en sterfte. Daarnaast is het voorkomen van ongemak veroorzaakt door ziekte en beperkingen in het functioneren

een ander belangrijk preventiedoel. Omdat de meest kwetsbare oudste ouderen over het algemeen in verpleeghuizen wonen en deze groep ouderen heterogeen van samenstelling is, zal altijd een weloverwogen keuze gemaakt moeten worden voor preventie maatregelen. Dit betekent dat per individuele verpleeghuisbewoner bekeken moet worden welke preventieve maatregelen geschikt zijn. Hierbij zal ook rekening gehouden moeten worden met de wensen en voorkeuren van individuele verpleeghuisbewoners zodat gericht en bij het individu passende preventie aangeboden kan worden. Dit alles vraagt om specifieke inzichten en solide bewijs. Er is daarom aanvullend onderzoek nodig om te onderzoeken of individueel gerichte preventie inderdaad effectief is in het voorkomen van verlies van kwaliteit van leven en zelfredzaamheid.

Onderzoek in verpleeghuizen vraagt om specifieke kennis en een specifieke infrastructuur. Toekomstig onderzoek in verpleeghuizen zou daarom het beste uitgevoerd kunnen worden binnen een academisch onderzoeksnetwerk. Binnen een academisch onderzoeksnetwerk, zoals het Universitair Netwerk voor de Caresector Zuid-Holland (UNC-ZH), werken zorgprofessionals samen met wetenschappers. Zij ontwikkelen, implementeren en testen initiatieven om de kwaliteit van zorg te verbeteren. Binnen de netwerkstructuur zijn de universiteit en de praktijk nauw met elkaar verbonden en daardoor hebben zij expertise ontwikkeld met betrekking tot het uitvoeren van onderzoek in de complexe zorg voor kwetsbare ouderen in verpleeghuizen. Een ander belangrijk voordeel van het netwerk is dat door deze samenwerking de onderzoeksresultaten direct in de dagelijkse verpleeghuispraktijk en de opleiding van zorgprofessionals kan worden toegepast.

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Dankwoord

Onderzoek doe je niet alleen, het is het werk van velen. Daarom wil ik iedereen bedanken die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift.

In het bijzonder gaat mijn dank uit naar alle zorgprofessionals van de 21 verpleeghuizen uit het Universitair Netwerk voor de Caresector (UNC-ZH), zonder hen was dit onderzoek nooit mogelijk geweest. Ik dank de vele bewoners en hun vertegenwoordigers, dat zij toestemming hebben gegeven om aan dit onderzoek mee te doen. Zonder hun bereidwilligheid is een onderzoek als dit niet mogelijk.

Ook zonder de onderzoeksmedewerkers Astrid Cock, Els de Haas, Inge Mooyekind en Olga Weeda, onderzoek secretaresse Anita Pannekoek en datamanager Henk de Jong was de dataverzameling van dit onderzoek niet mogelijk geweest. Dank voor al jullie inzet, ook al was het soms lastig om alle gegevens boven water te krijgen. Dank ook aan diverse studenten die via hun wetenschapsstage hieraan een bijdrage hebben geleverd.

Jacobijn, dank voor de gedegen, positief kritische en motiverende manier waarop je me hebt begeleid. Ook op de momenten dat het even moeilijker ging, was er altijd een bemoedigend woord.

Herman, dank voor je kritische blik en welgemeende adviezen, waarbij je nooit de verpleeghuispraktijk uit het oog verloor. Nu 15 jaar na het ontstaan van jouw eerste ideeën voor de CRANBERRY studie, is de klus geklaard.

Collega's van de afdeling Public Health en Eerstelijnsgeneeskunde (PHEG), dank voor alle prettige en leerzame uitwisselingen tijdens de wetenschapsbesprekingen, maar ook voor de informele praatjes in de wandelgangen en tijdens de lunchpauzes. Speciaal wil ik Wendy den Elzen noemen, ik heb veel van je geleerd. Dank daarvoor.

Ook Wilbert van den Hout, van de afdeling Medische Besliskunde, bedankt dat je me wegwijs hebt gemaakt in de materie van economische evaluaties.

In het bijzonder wil ik Wilco Achterberg bedanken voor zijn reflecties op mijn onderzoek en de betekenis daarvan voor de verpleeghuissector. Fijn dat we samen verder kunnen bouwen aan wetenschappelijke evidentie om de zorg aan de kwetsbaarste groep oudste ouderen te verbeteren.

Yvonne, in de jaren dat we samen een kamer mochten delen op PHEG was je niet alleen een collega met wie ik inspirerende gesprekken kon voeren over ons onderzoek, maar ook een fijn mens. Ruim een jaar geleden mocht ik jouw paranimf zijn. Ik vind het fijn dat jij nu ook naast mij mag staan op deze bijzondere dag.

Familie en vrienden dank voor jullie interesse in de vorderingen en de resultaten van mijn onderzoek.

Lieve Simone, ik ben erg blij en trots met jou als zus. Dank voor je steun en vertrouwen. Ik verheug me op jouw aanwezigheid als paranimf tijdens mijn promotie.

Lieve mam, fijn dat je me altijd de ruimte hebt gegeven om mijn eigen weg te gaan. De 'keukentafel' gesprekken en je onvoorwaardelijke steun en belangstelling waardeer ik zeer.

Dank zij jou heb ik dit kunnen bereiken. En pap, jij ook bedankt voor het meeleven en je interesse in mijn werk.

Tot slot natuurlijk Eric. Ik ben heel gelukkig dat ik jou heb leren kennen, dat we er voor elkaar zijn en dat je me de ruimte geeft om mijn ambities waar te maken. Dank je wel!

Curriculum vitae

Monique Caljouw was born on 22 November 1967 in Middelburg, the Netherlands. In 1987, after graduating secondary school at the 'Stedelijke Scholengemeenschap' in Middelburg, she started her nursing study (HBO-V) at the 'Hogeschool West-Brabant' in Breda and obtained her Bachelor degree in 1991. She then started her Master's degree in Health Sciences (main subject Nursing Science) at University Maastricht where she graduated in 1995. During that same period, she worked as a nurse in Amphia Hospital (formerly 'Hospital De Baronie') in Breda for seven years and, thereafter, as staff member clinical care in the same hospital.

Then, in 1999, she started working as a research nurse at the department of Hematology at Erasmus Medical Center Rotterdam. Thereafter, in April 2001, she started working as a researcher at the department of Nursing Science at the Leiden University Medical Center. During that period she worked on several research studies in cooperation with the departments of Gynaecology, Neonatology, Rheumatology, and the Intensive Care and Operating Theatre Center. These collaborations resulted in several scientific publications.

In addition to her regular work, she had several related professional activities. For five years she was chair of the Professional Advisory board of the HBO-V of Hogeschool West-Brabant, Sector Healthcare Education. Subsequently, she was board member of the Dutch Association of Research Nurses and founded the Journal of this association, i.e. the Research Bulletin for Research Professionals, of which she was chief editor for five years. Finally, she was member of Group 7: 'Research' of the General Assembly of Nurses.

In February 2008, Monique moved to a research position at the department of Public Health and Primary Care of the Leiden University Medical Center. She started working on the CRANBERRY study that is described in this thesis. At the same time she started as a coordinator of the University Network for the Care sector South Holland (UNC-ZH), a collaborative network between care organizations in the region of South Holland (the Netherlands) and the department of Public Health and Primary Care.

At present, she is continuing her studies in the research program 'Geriatrics in Primary Care', at the department of Public Health and Primary Care. The aim of this research program is to improve medical care for all older persons outside the hospital, by building up scientific knowledge and related evidence. Monique has a special interest in research in vulnerable older persons in long-term care facilities and focuses her studies on 'Geriatric Rehabilitation' and 'Quality of life in dementia'. She also supervises several PhD students within these research topics and continues her activities as scientific coordinator of the UNC-ZH.