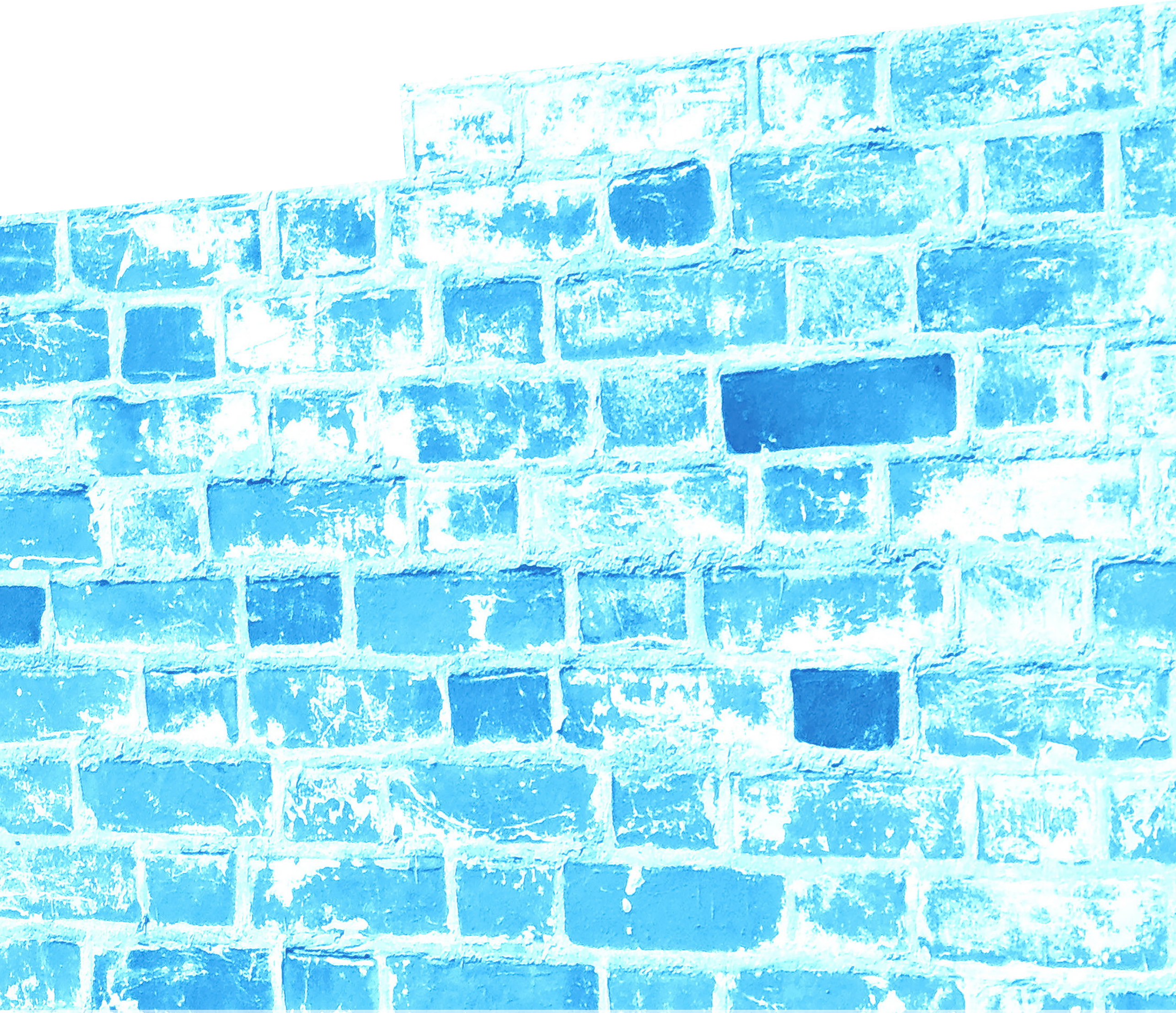

Outcomes in Functional Urology:

Towards a prediction model in pelvic floor disorders

Sarah Reuvers

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COLOFON

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Outcomes in Functional Urology:

Towards a prediction model in pelvic floor disorders

Uitkomsten in de Functionele Urologie:
Richting een predictiemodel in bekkenbodemproblematiek

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Voor mijn vader

Wat had ik je dit graag laten zien

Voor mijn moeder

Wat fijn dat ik je dit kan laten zien

CHAPTER 1

General introduction

Our research group has been dedicated to investigate the field of pelvic floor disorders (PFDs). The focus of our research has been on the validation and value of patient-reported outcome measures (PROMs), quality of life, and therapy outcomes in PFDs. This research line is continued and described in this thesis, and it is put in the context of developing a prediction model to optimize individualized care.

PELVIC FLOOR DISORDERS – URINARY INCONTINENCE

The pelvic floor consists of muscles, bones and fascial components and is involved in both urinary and fecal continence, support of the pelvic organs, and sexual function. Malfunction of any of these components can disrupt the balance and cause PFDs. The most prevalent PFDs are urinary incontinence (UI), fecal incontinence and pelvic organ prolapse. These symptoms often present together.[1, 2] Other PFDs involve pelvic pain syndromes and sexual dysfunction. The occurrence of PFDs has been associated with female gender, increased age, overweight or obesity, and pregnancy and (vaginal) deliveries.[1, 3] PFDs can be considered a common healthcare problem. Although the symptoms are generally not life-threatening, they may have a significant negative impact on the quality of life.

UI is considered a storage symptom of the lower urinary tract, and is defined as the complaint of any involuntary leakage of urine.[4] Two main types are distinguished: urge urinary incontinence (UUI), which is involuntary leakage accompanied by or immediately preceded by a sudden compelling desire to pass urine,[4] and stress urinary incontinence (SUI), which occurs on exertion, effort, sneezing or coughing.[4] These two types of UI often coexist.[5]

UI is highly prevalent all over the world. It is estimated that worldwide about 200 million people experience UI.[5] Depending on the definition used, UI is found in 1-39% of adult men[6] and 13-50% of adult women.[2] The prevalence of UI in the Netherlands was recently studied and it was found that 36.8% of the Dutch adult population had experienced any UI during the past six months.[7] Five percent of the Dutch population experiences UUI and about 5% experiences mixed incontinence, a combination of both UUI and SUI. The occurrence of UI has been associated with female gender, increased age, high BMI, comorbidity, pregnancy, labor, vaginal delivery, hysterectomy, prostatectomy and a positive family history for UI.[6, 8] UI showed to have major impact on a person's quality of life and well-being.[6, 9] Besides the impact on patients' quality of life, the financial impact of UI on the healthcare system is tremendous. It was estimated that the healthcare costs for UI were in 2006 about 32 billion dollar per year in the United States.[10]

PFDs and UI can be of neurological or non-neurological origin. PFDs of neurological origin can occur as a consequence of impaired neurological control of the pelvic floor and lower urinary tract caused by diseases such as spinal cord injury (SCI), multiple sclerosis (MS), and cerebrovascular accidents (CVA). The type of PFD depends on the location and the extent of the neurological lesion.[11-13] For example, UUI is often associated with MS and CVA, SUI is often present in patients with conus-cauda lesions, and bladder emptying problems and high intravesical pressure (often leading to UI and upper urinary tract damage) are often present in patients with high level SCI.

MANAGEMENT OF PELVIC FLOOR DISORDERS – URINARY INCONTINENCE

For the treatment of UI, different treatment modalities are available. Conservative, pharmacological and invasive treatments are typically first, second and third line treatments, respectively.[14, 15] Conservative treatments include pelvic floor muscle training, education and lifestyle interventions, behavioral therapy and bladder training. Of these, pelvic floor muscle training (with or without bladder training) has been studied most extensively and is associated with higher success rates in the treatment of all types of UI than no treatment or other conservative treatment options.[16, 17] Classically, when first line therapy has failed UUI is the domain of pharmacotherapy whereas SUI is the domain of surgical interventions. Pharmacological agents like muscarinic receptorantagonists[17] and a selective beta-3-adrenoceptor-agonist showed to be effective to treat UUI.[18] In case of therapy-resistance for conservative and/or pharmacological treatments, minimal invasive therapeutical options are available to treat UUI, such as Botulinum toxin-A (BTX-A) injections and sacral neuromodulation.[14, 15] Other surgical treatments such as a colposuspension, sling, artificial urinary sphincter (AUS), Adjustable Continence Therapy (ACT or ProACT), and urethral bulking agent showed to be effective to treat SUI.[15]

The treatment of neuro-urological (NU) patients with PFDs can be challenging due to damaged sensory pathways and the possibility of various dysfunctions presenting in parallel.[19] It is important to recognize the neurological origin of a PFD when setting personalized treatment goals so that an essential treatment goal for NU patients, i.e. prevention of deterioration of the upper urinary tract, can be taken into account. Specific guidelines for the treatment of NU patients are developed.[13] Clean intermittent catheterization is a conservative treatment option in patients with bladder emptying problems. Reconstructive surgery, such as the construction of an appendicovesicostomy with or without bladder augmentation and bladder neck surgery, is a treatment option to prevent deterioration of the upper urinary tract (in patients with high intravesical pressure), to regain continence and to solve bladder emptying problems.

OUTCOME MEASURES

Due to new developments such as the introduction of different (continence) devices, minimal invasive techniques, and new pharmaceutical agents, the research field of PFDs has expanded. Unfortunately, in most studies on non-neurogenic PFDs many different outcome parameters and definitions of cure were used.[20, 21] Success in PFDs treatments to promote urinary continence can be defined, for example, as more than 50% reduction in UI episodes, as the patient using no or only one security incontinence pad per day, as satisfaction reported by the patient, or as a certain change in score on a PROM. Failure of a therapy could also be defined in different ways, for example, as the complication rate, as the re-intervention rate (after a surgical therapy), as less than 50% reduction in UI episodes or as dissatisfaction reported by the patient.

Since several years the quality of life has become more and more important as an outcome measure in functional urology. It has been shown that the perceptions of a patient and its physician concerning the impact of PFDs on the quality of life often differ.[22, 23] In order to objectivize this subjective parameter, PROMs have been introduced. PROMs are designed to make the subjective perception of the patient quantifiable and measurable for both patient and physician. PROMs can evaluate symptoms, bother or burden from symptoms, or (health-specific) quality of life.

Various validated PROMs for the use in non-neurological PFDs are available in multiple languages to evaluate distress and bother from urinary complaints including UI (UDI-6 and IIQ-7)[24], sexual function (IIEF-5[25] and PISQ-12[26]), and bowel complaints and fecal incontinence (FIQL and FISI)[27] and a combination of different PFD symptoms (PFDI-20 and PFIQ-7)[28]. In contrast, PROMs for the use in NU patients are not commonly available in different languages. Bother from PFDs experienced by NU patients might differ from bother experienced by non-neurological patients due to the differences in mobility, sensation and other additional symptoms caused by their neurological disease. Therefore it is important to have PROMs specifically designed for NU patients. Only the Actionable[29], a screening questionnaire for neurogenic overactive bladder, is available in Dutch. The European Association of Urology guidelines recommend to implement PROMs, specifically concerning the quality of life, into clinical care for NU patients.[13] In the Netherlands this is presently not possible due to the lack of Dutch translated and validated versions of the most important PROMs.

PREDICTION MODELS

As a consequence of the increasing number of treatment options in the management of PFDs, treatment decision making becomes more important. At present, the choice of treatment is often based on the experience and knowledge of the caregiver and on local treatment availability. This might not always result in the optimal treatment for the individual patient. While some patients respond to a certain type of treatment, others do not. At present, we are not able to identify patients who will and will not respond to a certain PFD therapy beforehand.

Objective multivariate prediction models can be helpful. They showed to be effective to predict the risk of disease and treatment outcome in the individual patient. Prediction models have become popular tools in clinical practice in different areas of medicine and can be helpful in managing patients' expectations, (shared) decision making, and optimization of personalized care.[30] Diagnostic models predict the probability of the presence or absence of a current disease. These models are useful in the diagnostic setting, e.g., to support physicians in their decisions for referral of patients, or to perform further investigations or not. Prognostic prediction models can predict future disease risks or future (treatment) outcomes and can therefore facilitate treatment decision making.[30, 31]

Although not widely used, prediction models in the field of PFDs are not completely new. An example is a prediction model developed by Jelovsek et al.[32] that calculates the future risk to develop PFDs such as UI, pelvic organ prolapse and fecal incontinence for an individual patient after childbirth. It provides the opportunity to perform prevention therapies during pregnancy in high-risk patients, e.g., by deciding to perform a caesarian section instead of a vaginal delivery. Another example is a model that predicts the outcome of one specific pharmacological treatment for UUI (Fesoterodine) that is developed by Darekar et al.[33]

A complete multivariate prediction model that predicts diagnosis and treatment outcome in the field of PFDs that can support (treatment) decision making, is not yet available. Such a prediction model for PFDs would be of great importance for the decision making in the first, the second and the third line of the health care system.

THIS THESIS

The two fundamental research questions of this thesis are:

1) Can we lay the foundations to construct a complete diagnostic and prognostic prediction model in PFDs in the future?

2) Can we construct the first part of this prediction model, a prognostic model that predicts the outcome of UUI treatment?

OUTLINE OF THIS THESIS

In part I of this thesis the focus is on outcome measures used in functional urology and more specifically in the NU patient group. In **chapter 2** the use of different outcome parameters and definitions of cure after surgical treatment for SUI in NU patients is systematically researched. In **chapters 3 and 4** the translation and validation process of the Dutch SF-Qualiveen, a urinary specific quality of life PROM for NU patients, in MS and SCI patients, is described.

The outcomes of different invasive therapies to manage PFDs are described in part II. **Chapter 5** focuses on the mechanism of action of a relatively new minimally invasive continence therapy named ProACT in men with UI after radical prostatectomy. The hypothesis that the ProACT induces changes of the static urethral pressure is studied. In **chapter 6** we describe the outcomes, complications and re-interventions after appendicovesicostomy surgery in children.

In part III, **chapter 7**, the development of a multivariate model for predicting the outcome of UUI treatment based on patient characteristics, patient history and investigations is described.

In **chapter 8** the findings of this thesis will be placed in the context of the present literature. Furthermore, the implications for research and clinical practice and future perspectives will be discussed.

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PART I

OUTCOME MEASURES IN FUNCTIONAL UROLOGY

CHAPTER 2

Heterogeneity in reporting on urinary outcome and cure after surgical interventions for stress urinary incontinence in adult neuro-urological patients: A systematic review.

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ABSTRACT

Aims: To describe all outcome parameters and definitions of cure used to report on outcome of surgical interventions for stress urinary incontinence (SUI) in neuro-urological (NU) patients.

Methods: This systematic review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was registered and published (CRD42016033303; http://www.crd.york.ac.uk/PROSPERO). Medline, Embase, Cochrane controlled trials databases and clinicaltrial.gov were systematically searched for relevant publications until February 2017.

Results: A total of 3168 abstracts were screened. Seventeen studies reporting on SUI surgeries in NU patients were included. Sixteen different outcome parameters and nine definitions of cure were used. Six studies reported on objective outcome parameters mainly derived from urodynamic investigations. All studies reported on one or more subjective outcome parameters. Patient-reported pad use (reported during interview) was the most commonly used outcome parameter. Only three of 17 studies used standardized questionnaires (two on impact of incontinence and one on quality of life). Overall, a high risk of bias was found.

Conclusions: We found a considerable heterogeneity in outcome parameters and definitions of cure used to report on outcome of surgical interventions for SUI in NU patients. The results of this systematic review may begin the dialogue to a future consensus on this topic. Standardization of outcome parameters and definitions of cure would enable researchers and clinicians to consistently compare outcomes of different studies and therapies.

INTRODUCTION

Patients with neurological disease may show various urological symptoms, depending on the type of disease and the neurological location of the lesion.[1, 2] Both storage and voiding problems can considerably reduce patients quality of life.[3] An impaired neurological control of the external sphincter may be the cause of stress urinary incontinence (SUI), defined as urinary incontinence that occurs on exertion, effort, sneezing or coughing.[4] This bothersome condition affects many neuro-urological (NU) patients, typically those with a meningomyelocele or a conus-cauda equina lesion.[1] Owing to the fact that SUI in NU patients often occurs together with other urological dysfunction such as detrusor overactivity and reduced bladder compliance,[1, 3] treatment of SUI in NU patients requires a specific approach. Moreover, NU patients may perceive bother from urinary incontinence differently compared to non-NU patients due to altered sensation and impaired mobility. Therefore, the outcome parameters and the definitions of success or cure used to report on outcome of surgical interventions for SUI in NU patients require specific attention.

To identify the most appropriate therapy, studies on the outcomes of the different therapies used to treat SUI in NU patients should ideally be reported in a standardized way. We performed a systematic review to describe all urinary parameters and definitions of success or cure used to report on outcome of surgical interventions for SUI in NU patients.

MATERIALS AND METHODS

Study registration

The study protocol was registered and published on PROSPERO (CRD42016033303) (http://www.crd.york.ac.uk/PROSPERO). This systematic review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[5] and Cochrane Handbook for Systematic Reviews of Interventions.[6]

Literature search

The Medline, Embase, Cochrane controlled trials databases, and clinicaltrial.gov were systematically searched for all relevant publications until February 2017. The search strategy is available in Supplementary Material S1. Duplicates were removed. No date restrictions were applied. Non-English texts were excluded. Additionally, reference lists of relevant reviews were hand-searched for missed relevant articles.

Study selection

Our aim was to include all publications of original studies that used a predefined urinary outcome parameter or a definition of success or cure to report on outcome of surgical interventions for SUI in adult NU patients. Conference abstracts, reviews and case series with <10 NU patients were excluded. Reviews served only to check the references for eligible extra articles. Studies with both adult NU and non-NU patients or with both children and adult NU patients were included only if adult NU patients were separately reported on or if >90% of the study population were adult NU patients.

Endnote (EndNote X7, Thomson Reuters, 1500 Spring Garden Street, Fourth Floor, Philadelphia, PA 19130, USA) was used to store identified abstracts and to sort the abstracts for inclusion and exclusion. Each title and abstract was reviewed for eligibility by two out of four reviewing authors (BB, JG, JS, SR) independently. Articles of which the abstract met the eligibility criteria were reviewed in full text. Full text selection was performed by two authors independently (JG, SR) using a standardized screening form. Discrepancy between the two authors was resolved by discussion or by consulting a third reviewer (BB). We reported on the literature search and study selection in a PRISMA flow diagram.[5]

Outcomes

All urinary outcome parameters and definitions of cure or success used to report on outcome of surgical interventions for SUI in adult NU patients were summarized. Outcome parameters containing information from questionnaires and patient interviews were considered subjective outcome parameters. Outcome parameters were considered objective when derived from bladder diaries, pad tests, cough stress-tests or urodynamic investigations.

Data extraction and risk of bias assessment

Data on general study characteristics were retrieved by the first author and checked by JG. Two authors (SR and JG) independently extracted predefined data from the included publications using a standardized data extraction form. A risk of bias analysis for included non-randomized comparative studies was performed by using the Cochrane Risk of bias Assessment Tool [7] in combination with an assessment of the main confounders following the recommendations of the Cochrane handbook for non-randomized comparative studies.[6] A list of the main confounders was developed and a priori agreed on with clinical content experts (EAU Neuro-Urology guidelines panel). Identified confounders were age, gender, mixed versus stress incontinence, underlying NU pathology, perineal sensation, previous treatments for SUI, and previous pelvic surgeries. Confounders were determined for the studies during data extraction. The confounding bias was classified as 'high' if the confounder was not considered or described, was imbalanced between the groups or was unadjusted during analysis. The risk of bias in non-comparative studies was determined by assessing the attrition bias (incomplete outcome data), the reporting bias (selective outcome reporting), and availability of an a priori protocol. External validity of these studies was reported by assessing whether participants were selected consecutively. This is a pragmatic approach based on methodological literature.[8, 9] In addition, the main confounders were assessed for these studies. The risk of bias figure was computed in Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Subgroup analyses

Subgroup analyses were intended to be performed if there would be sufficient data. Predefined subgroups were men versus women, SUI versus mixed UI, underlying NU pathology, and no versus one/more former surgeries with potential effect on continence.

RESULTS

Search results

Figure 1 shows the PRISMA flow diagram of the literature search and study selection. After screening of 3168 abstracts, 182 full texts were reviewed. Finally, 17 studies were included in this systematic review.[10-26]

Characteristics of included studies

The included studies were published between 1995 and 2017 and report the results of various SUI surgeries. Table 1 shows the descriptives of the included studies. Most studies had a retrospective single-arm study design. With one exception, all studies were single-center studies. Twelve studies reported on NU patients only. A total of 452 NU patients were included in the studies. Most studies included mixed patient populations regarding underlying NU pathology, detrusor overactivity, mixed urinary incontinence and pure SUI, and patients with and without previous SUI and other pelvic surgeries.

Results on outcome parameters

Table 2 shows the outcome parameters used per study. In total, 16 different outcome parameters were used in the 17 included studies. Furthermore categorization of the outcomes differed (e.g. patient-reported leakage/continence). Eleven studies had applied two or more outcome parameters. Six of the 17 studies reported on both an objective and a subjective outcome parameter.

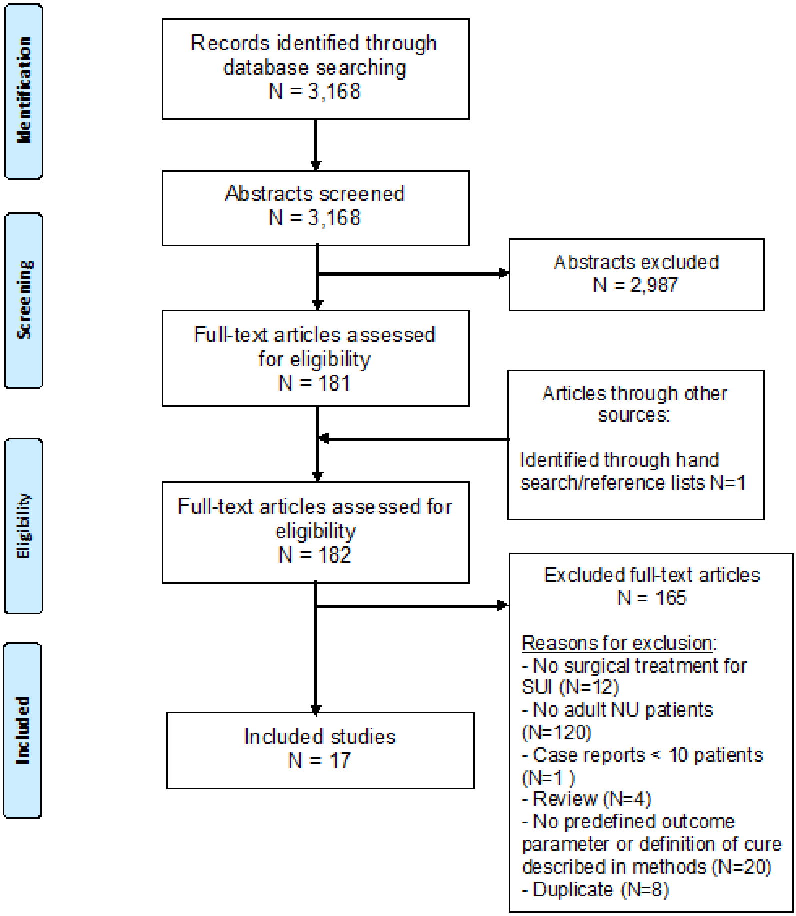

Figure 1. PRISMA flow diagram of identified, excluded and included studies
NU, neuro-urological; SUI, stress urinary incontinence

Table 1. Characteristics of the included studies

Study	Study design	Evaluated intervention	NU patients/ total study population, no.	Type of NU patients	Age of NU patients, yr,	Male/ Female of NU patients, no.	NU patients with mixed urinary incontinence preoperatively, no.	NU patients with DO preoperatively, no.	NU patients with previous SUI surgeries, no.	NU patients with previous pelvic surgeries with potential effect on continence, no.	NU patients with normal perineal sensation, no.
Pannek et al.[10] 2017	Retrospective comparative	Transobturator tape vs. retropubic adjustable system	16/16 (100%)	43.8% thoracic SCI 25.0% lumbar SCI 12.5% cervical SCI 18.7% unknown	Mean 53.5	16/0	NR	0/16 (0%) – DO as an exclusion criterion	NR	5/16	NR
Phé et al.[11] 2017	Retrospective single-arm	Artificial urinary sphincter	26/26 (100%)	12% spina bifida 23% thoracic SCI 65% lumbar SCI	Median 49.2	0/26	NR	16/26 (60.5%)	14/26	11/26	NR
Losco et al.[12] 2015	Retrospective single-arm	Transobturator tape	27/27(100%)	SCI	Mean 56	0/27	NR	6/27 – all patients were successfully treated with Botox	NR	NR	NR
El-Azab et al.[13] 2015	Prospective non-randomized pilot study	Tension-free vaginal tape vs. pubovaginal sling	40/40 (100%)	Sacral spinal pathology	Median 34	0/40	26/40 (65%)	NR	0/40	NR	NR
Costa et al.[14] 2013	Prospective single-arm	Artificial urinary sphincter	54/344 (15.7%)	53.7% spina bifida 33.3% acquired 9.3% posttraumatic 3.7% other congenital	NR (entire study population: mean 57.2)	0/54	NR (entire study population 65/344 mixed incontinence)	NR	NR (entire study population 66% had previous SUI surgeries)	NR	NR
Mehnert et al.[15] 2012	Retrospective single-arm	Adjustable Continence Therapy (ACT/ProACT)	37/37 (100%)	51.4% paraplegia Furthermore: lumbar stenosis, posttraumatic, MS, infectious disease	Mean 46.2	13/24	NR	21/37 (57%)	14/37	NR	NR
Groen et al.[16] 2012	Prospective single-arm pilot study	AdVance male sling	20/20 (100%)	60% MMC 40% lower SCI	Mean 23	20/0	NR	4/20 (20%)	2/20	1/20	10/20
Athanasopoulos et al.[17] 2012	Retrospective single-arm	Autologous fascia rectus sling	33/33 (100%)	63.6% MMC 36.4% SCI	Mean 37	0/33	NR	22/33 (66.7%)	NR	NR	NR
Chartier Kastler et al.[18] 2010	Retrospective single-arm	Artificial urinary sphincter	51/51 (100%)	69% SCI 31% MMC	Mean 35	51/0	NR	20/51 (39%)	NR (11 previous SUI surgeries in this patient group)	NR	NR

Study	Study design	Evaluated intervention	NU patients/ total study population, no.	Type of NU patients	Age of NU patients, yr,	Male/ Female of NU patients, no.	NU patients with mixed urinary incontinence preoperatively, no.	NU patients with DO preoperatively, no.	NU patients with previous SUI surgeries, no.	NU patients with previous pelvic surgeries with potential effect on continence, no.	NU patients with normal perineal sensation, no.
Abdul-Rahman et al.[19] 2010	Retrospective single-arm	Artificial urinary sphincter	12/12 (100%)	50% lumbar disc surgery 25% SCI 25% spinal stenosis	Mean 53	0/12	NR	1/12	4/12	NR	NR
Bersch et al.[20] 2009	Retrospective single-arm	Artificial urinary sphincter	51/51 (100%)	49.0% thoracic SCI 43.2% lumbar SCI 7.8% cervical SCI	Mean 38.7	37/14	NR	NR (only included if DO was sufficiently suppressed)	NR	NR	NR
Ramsay et al.[21] 2007	Retrospective single-arm	Artificial urinary sphincter	11/39 (28%)	54.5% spina bifida 18.2% SCI Furthermore: sacral agenesis, postmeningitis, scoliosis	NR (entire study population: mean 57)	NR (entire study population: 38/1)	NR	NR	11/11	NR (in entire study population 25/39)	NR
Lai et al.[22] 2007	Retrospective single-arm	Artificial urinary sphincter	11/218 (5%)	Including SCI, spina bifida, tethered cord and pelvic fracture	Mean 46.3	11/0	NR	NR	NR (entire study population 25% previous SUI surgery)	NR (in entire study population 176/218)	NR
Hamid et al.[23] 2003	Retrospective single-arm	Polydimethylsiloxane submucosal injections	14/14 (100%)	50% thoracic traumatic SCI 43% lumbar traumatic SCI 7% SCI after surgery	Mean 41	14/0	0/14 (0%) – urge urinary incontinence as an exclusion criterion	NR	NR	NR	NR
Costa et al.[24] 2001	Retrospective single-arm	Artificial urinary sphincter	27/206 (13%)	37.0% spina bifida 18.5% traumatic cauda equina lesion 33.3% SCI 11.1% other	Mean 35.6	0/27	NR	NR	13/27 previous surgery for incontinence (unclear if this was specifically for SUI)	NR	NR
Bennett et al.[25] 1995	Prospective single-arm	Periurethral collagen injection	11/11 (100%)	45% MMC 45% SCI 9% spinal cord tumor	Mean 30.2	9/2	NR	NR	NR	NR	NR
Nataluk et al.[26] 1995	Retrospective single-arm	Periurethral collagen injection	11/45 (24.4%)	NR	NR (entire study population: mean 60)	11/0	NR	NR	NR	NR	NR

DO, detrusor overactivity; MMC, meningomyelocele; MS, Multiple Sclerosis; NR, not reported; NU, neuro-urological; SCI, spinal cord injury; SUI, stress urinary incontinence

Table 2. Used outcome parameters to report on urinary outcome of surgical interventions for SUI in adult NU patients.

Study	Objective outcome parameters				Subjective outcome parameters			
	Bladder diary	**Pad test**	**Cough stress-test**	**Urodynamics**	**Patient-reported pad use**	**Patient-reported urinary leakage**	**Standardized questionnaires**	**Patient satisfaction**
Pannek et al.[10] 2017	NR	NR	NR	Reported: - bladder capacity - compliance - maximum detrusor pressure	Reported: Number of pads per day	NR	NR	NR
Phé et al.[11] 2017	NR	NR	NR	NR	Reported: Number of pads per day	NR	NR	NR
Losco et al.[12] 2015	NR	NR	NR	NR	NR	Reported: - dry - improved - remaining wet	NR	Reported: - satisfied - not satisfied
El-Azab et al.[13] 2015	NR	NR	Reported: leakage at cough/Valsalva at 250ml	Reported: Postvoid residual volume	NR	NR	Reported: UDI-6 and IIQ-7	NR
Costa et al.[14] 2013	NR	NR	NR	NR	NR	Reported: - no leakage - some drops, no pad - use of pads	NR	NR
Mehnert et al.[15] 2012	Reported: Urinary incontinence episodes (number/day)	NR	NR	NR	Reported: Pad use (number/day)	Reported: - complete continence - ≥50% improvement - <50% improvement/failure	NR	NR
Groen et al.[16] 2012	NR	NR	NR	NR	Reported: Number of pads per day	NR	Reported: Visual analog scale for continence and ICIQ male short form	NR
Athanasopoulos et al.[17] 2012	NR	NR	NR	NR	Reported: Mean number of pads per day	NR	NR	Reported: Global assessment question: “Are you satisfied with the outcome of the performed operation?” Yes/No

Study	Objective outcome parameters				Subjective outcome parameters			
	Bladder diary	**Pad test**	**Cough stress-test**	**Urodynamics**	**Patient-reported pad use**	**Patient-reported urinary leakage**	**Standardized questionnaires**	**Patient satisfaction**
Chartier Kastler et al.[18] 2010	NR	NR	NR	NR	NR	Reported: -Dryness at least 4 hours between 2 catheterizations/ micturitions -only nocturnal leakage or need to wear pads or stress leakage -uncontrollable leakage causing discomfort	NR	NR
Abdul-Rahman et al.[19] 2010	NR	NR	NR	NR	Reported: Number of pads per day	NR	Reported: assessment of health related quality of life	NR
Bersch et al.[20] 2009	NR	NR	NR	Reported: - Leakage during VCMG - bladder capacity - compliance	Reported: Number of pads per day	NR	NR	NR
Ramsay et al.[21] 2007	NR	NR	NR	NR	Reported: Number of pads per day	NR	NR	NR
Lai et al.[22] 2007	NR	NR	NR	NR	Reported: Patient-reported post-AUS pad use/ day	NR	NR	NR
Hamid et al.[23] 2003	NR	NR	NR	Reported: Leakage during VCMG	Reported: Number of pads per day	NR	NR	NR
Costa et al.[24] 2001	NR	NR	NR	NR	Reported: Daily pad use *(yes/no)*	Reported: - no leakage - few drops but no pad use - use of pads	NR	NR

Study	Objective outcome parameters				Subjective outcome parameters			
	Bladder diary	**Pad test**	**Cough stress-test**	**Urodynamics**	**Patient-reported pad use**	**Patient-reported urinary leakage**	**Standardized questionnaires**	**Patient satisfaction**
Bennett et al.[25] 1995	NR	NR	NR	Reported: Valsalva leak point pressure	NR	Reported: - no leakage - leakage with brisk exercise/ lifting heavy - leakage with minimal exertion - incontinence in absence of physical exertion, including sleep	NR	NR
Nataluk et al.[26] 1995	NR	NR	NR	NR	NR	Reported: - totally dry - improved - unchanged - worse	NR	NR

NR, not reported; NU, neuro-urological; SUI, stress urinary incontinence; VCMG, Videocystometrogram

Objective outcome parameters

Six of 17 (35.3%) included studies reported on objective outcome parameters. Pad tests were not reported on. In one study patients used a bladder diary to report the number of urinary incontinence episodes per day. One study reported the results of a cough stress-test. Urodynamics was the most used investigation to measure an objective outcome parameter; that is, in five studies. Bladder capacity, compliance, maximum detrusor pressure, postvoid residual volume, leakage during videocystometrogram, and Valsalva leak point pressure were the objective outcome parameters that were derived from urodynamic investigations.

Subjective outcome parameters

Patient-reported pad use (number of pads/24h or yes/no daily pad use reported during an interview) was the most utilized outcome parameter; used in eleven studies. Three studies applied standardized questionnaires. In seven studies patients reported on their urinary leakage status in a post-intervention interview. Two studies reported on patient satisfaction.

Results on definition of success or cure

Table 3 provides an overview of the different definitions for cure or continence used. Fifteen of 17 studies reported on such a definition. In these 15 studies, nine different definitions were used. Only two of five studies that reported on cure, and used an objective and a subjective outcome parameter, used a combination of both outcomes to define cure.

Subgroup analyses

It was not contributive or possible to perform subgroup analyses. First, the number of included studies was small; second, because most studies identified included mixed populations (gender, underlying NU pathology, SUI and mixed UI, former surgeries with potential effect on continence); and finally, subanalyses and information on predefined groups was often missing (Table 1).

Risk of bias assessment

Most of the included studies were assessed as having high or unclear risk of bias (Figure 2). In most retrospective studies, it was unclear if an a priori protocol was available and if there was selective outcome reporting. In one third of these studies, it was unclear if there were incomplete outcome data. Most studies included study participants consecutively. The two comparative studies had a high risk of bias for most assessed factors of the Cochrane Risk of bias Assessment Tool and the confounding factors.

Table 3. Used definitions of cure or continence to report on success of surgical interventions for SUI in adult NU patients.

Study	Cure/ Continence	Definition used
Pannek et al.[10] 2017	Cure	No pads or continence aids used
Phé et al.[11] 2017	Continence	No pad use
Losco et al.[12] 2015	Continent status = dry	If patient reported complete correction of SUI + no pads usage
El-Azab et al.[13] 2015	Cure	Negative cough stress test + no leakage during physical examination
Costa et al.[14] 2013	Fully continent	Patient-reported 'fully continent'
Mehnert et al.[15] 2012	NR	NR
Groen et al.[16] 2012	Cure	Score of 10 on VAS (indicating no incontinence) or using no pads
Athanasopoulos et al.[17] 2012	Cure	No leakage per urethra, 0 pads per day.
Chartier Kastler et al.[18] 2010	Perfect continence	Dryness at least 4 hours between 2 catheterizations/ micturitions
Abdul-Rahman et al.[19] 2010	Cure	Completely dry, no pads.
Bersch et al.[20] 2009	Cure	Subjective cure (no pads or continence aids) + objective cure (continence confirmed during urodynamic investigation)
Ramsay et al.[21] 2007	Socially continent	0 or 1 pads/day
Lai et al.[22] 2007	NR	NR
Hamid et al.[23] 2003	Cure	Cessation of using pads and dry on VCMG
Costa et al.[24] 2001	Continence	Patient reporting no leakage and no use of pads
Bennett et al.[25] 1995	Cure	Patient reporting no leakage
Nataluk et al.[26] 1995	Continent or total continence	Totally dry on postoperative interview

NR, not reported; NU, neuro-urological; SUI, stress urinary incontinence; VCMG, Videocystometrogram

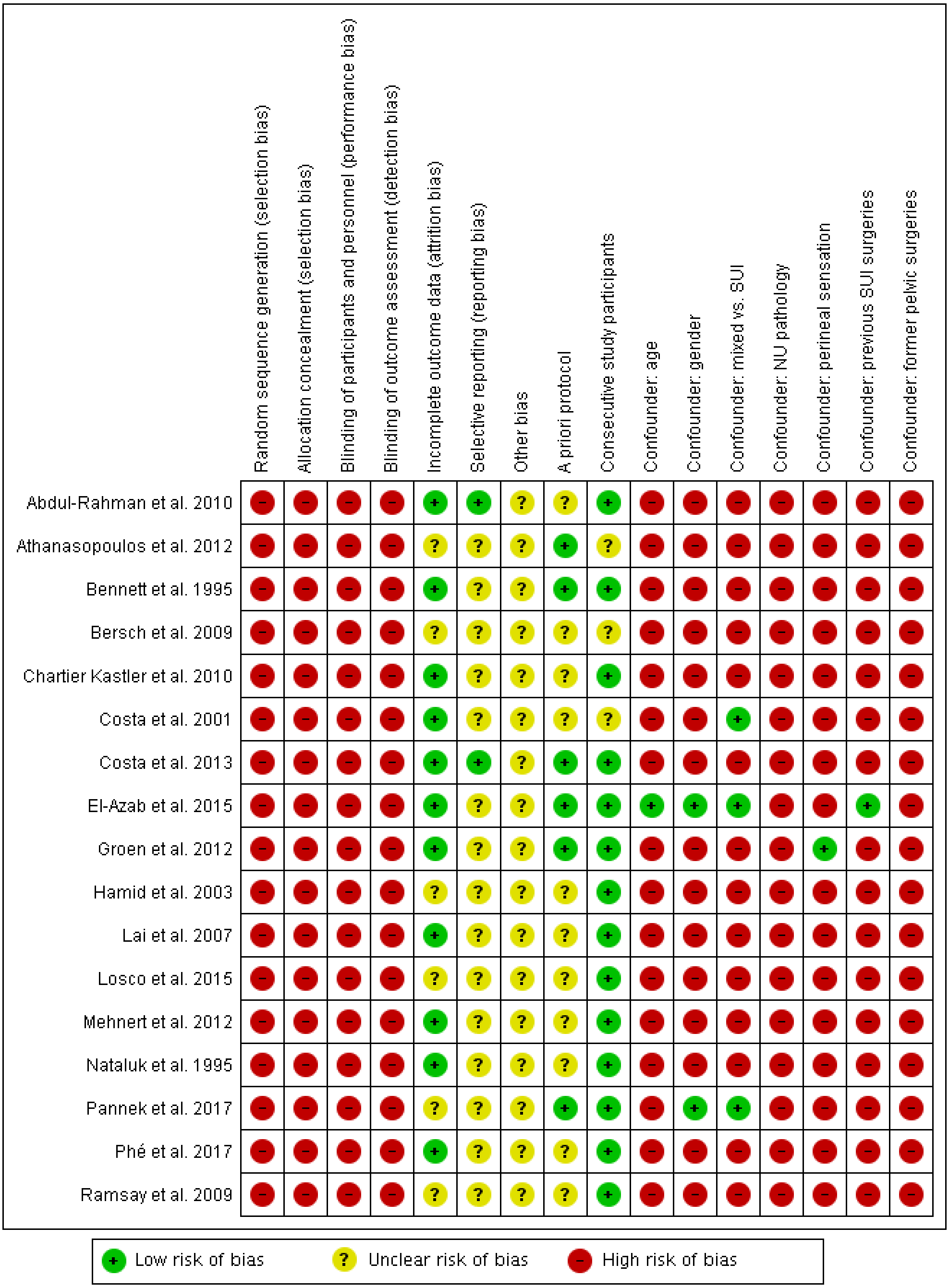

Figure 2. Risk of bias summary.
NU, neuro-urological; SUI, stress urinary incontinence

DISCUSSION

Principal findings

In this systematic review, we have presented all parameters and definitions of cure to report on the outcome of surgical interventions for SUI in adult NU patients. Sixteen different outcome parameters and nine different definitions of cure or continence were used. Most outcomes and definitions of cure were based on non-standardized patient self-assessments (of pad use per day or leakage/continence). A minority of studies made use of objective outcome parameters or validated questionnaires. To the best of our knowledge, this is the first systematic review on this topic in this specific patient group. It is evident that there is a considerable heterogeneity in the urinary outcome parameters and definitions of cure used to report on outcome of surgical interventions for SUI in adult NU patients.

Findings in the context of the existing evidence

The heterogeneity of outcome reporting makes it more difficult to interpret and compare different studies and therapies. The Core Outcome Measures in Effectiveness Trials (COMET) initiative supports the development of standardized sets of outcomes in all fields of health research.[27] In the field of urology such core outcome sets are available for prostate cancer and male sexual dysfunction, but not for UI. The International Continence Society (ICS) and the International Consultation on Incontinence (ICI) recommend using both objective and subjective outcome parameters in UI research.[28, 29] Despite this, these organizations do not provide a definition of cure or make recommendations for the specific outcome parameters to be used.

Specifically in the field of NU patients undergoing SUI surgery there is no consensus on outcome parameters. The ICS does not provide a recommendation on this topic for research in NU patients. The ICI recommends using changes in detrusor leak point pressure for research purposes in NU patients if appropriate.[28] Nevertheless, this parameter was not used in any of the included studies in our systematic review. The EAU guidelines mention prevention of deterioration of the upper urinary tract and optimization of the quality of life as the most important urological treatment goals for NU patients.[30] Therefore, we would expect urodynamic investigations and quality of life measures to be used more often in this patient group. NU patients may have altered sensation and impaired mobility and consequently perceive (UI) complaints different than to non-NU patients. Thus, measuring patients' perception of UI complaints and their health-related quality of life (rather than quantifying symptoms) is important, especially in this patient group. Phé et al.[31] and Castillo et al.[32] reported in their reviews on the commonly used outcome parameters and definitions of cure or treatment success used after SUI surgery (not specifically on NU patients). Phé et al.[31] reviewed publications on all SUI surgeries from 1995 to 2014 and Castillo et al.[32] focused on publications on female SUI from 2005 and 2006. In our systematic review, we found that five out of 17 (29.4%) included studies used outcome parameters derived from urodynamic investigations. Phé et al.[31] and Castillo et al.[32] found that urodynamic investigations were performed in 12 of 54 studies (22.2%) and in 37 of 92 studies (40.2%), respectively. Only two of the 17 (11.8%) studies in our review applied questionnaires on the impact of UI and only one study used quality-of-life assessments. The questionnaires administered were the UDI-6, IIQ-7, visual analog scale for continence, and ICIQ male short form. These are validated questionnaires, but not specifically for NU patients. Although validated (disease-specific) quality of life questionnaires such as the (SF-)Qualiveen[33, 34] have been introduced in the recent past, they have not always been available. In the review by Phé et al.[31] validated questionnaires (including quality of life measures) were used in 55.6% and in the review by Castillo et al.[32] validated questionnaires were used in 40.2% and quality of life measures were used in 60.9% of the studies. So contrary to our expectations, urodynamic investigations and quality of life measures were not used more often in our systematic review in NU patients. For retrospective studies, only available measures from clinical practice can be used. The high number of retrospective studies in our systematic review compared to Phé et al.[31] and Castillo et al.[32] could explain the different findings. On the other hand, one would expect quality of life measures and urodynamic investigations as standard of care in NU patients.

Despite the ICS and ICI recommendations, in only six of 17 (35.3%) included studies in this systematic review both a subjective and an objective outcome parameter was used and only two of these studies used a combination of these parameters to define cure. Compared to the reviews of Phé et al.[31] and Castillo et al.[32] in non-neurological patients, where about half of the studies reported on both a subjective and an objective outcome, this number is low. The high number of retrospective studies could again be an explanation for this finding. Comparable to our results, in the reviews of Phé et al.[31] and Castillo et al.[32] a minority of studies used a combination of subjective and objective outcome parameters to define cure.

Pad use reported by the patient during an interview was the most used outcome parameter in the studies included in our systematic review. Phé et al.[31] reported on this outcome for some studies, but not structurally for all and Castillo et al.[32] did not mention this outcome parameter in their review. In one included study[17] of our review this outcome parameter was chosen because it would reflect the quality of life, referring to a publication by Stoffel et al.[35] that found a correlation between patient-reported pad use and the impact of UI on quality of life. In other publications the reason for choosing this outcome parameter is not clear, but might be the ease of collecting this information (especially for retrospective series) for both patient and researcher; in addition it does not interfere in a patient's "normal daily voiding routine" (as a bladder diary might do). It is questionable if patient-reported pad use during an interview reflects the quantity of urine lost[36] specifically for NU patients with altered sensation in whom the use of incontinence pads is often discouraged to prevent skin problems. Furthermore, it is unknown if patient-reported pad use is comparable to bladder diary reported pad use. As using this outcome parameter may be advantageous, we suggest to further investigate this outcome parameter on psychometric properties, such as test-retest reliability, correlation with bladder diary reported pad use, quantity of urine lost and quality of life.

Implication for research and clinical practice

Farag et al.[37] reported on the success rates of surgical treatments for SUI in both adult and pediatric NU patients in a systematic review. Farag et al.[37] compared the combined success rates of the included studies on urethral bulking agents to urethral sling procedures and artificial urinary sphincters. These studies however used variable definitions of success. A consistent comparison of the outcomes of therapy can only be made after standardization of outcome parameters and definitions of cure or success. We therefore recommend developing a core outcome set for use in UI research with NU patients. It is important that not only medical experts, but also patients and caregivers will be involved in the development of this outcome set, in order to include the various perspectives and also to increase the willingness to implement the outcome set. Until such a set has been developed, we recommend using an objective and a subjective outcome parameter and the combination of both to define cure. Because of the importance of the quality of life, specifically in NU patients, we recommend the use of a disease-specific quality of life questionnaire or a bother questionnaire validated for NU patients such as the (SF-)Qualiveen[33, 34] as a subjective outcome parameter. Implementing such questionnaires in both research and clinical practice places a focus on optimization of the quality of life for these patients and makes it possible to compare outcomes of different studies. A clear recommendation for the use of a specific objective parameter is not feasible because there is insufficient scientific evidence on the psychometric properties of the different objective measures (bladder diaries, urodynamics and pad tests), specifically regarding NU patients.[38]

Strengths and limitations

Performing this systematic review, we followed the recommended Cochrane[6] and PRISMA guidelines[5]. Our study gives a clear overview of all used urinary parameters and definitions of success or cure to report on the outcome of surgical interventions for SUI in NU patients, and will hopefully begin the dialogue to a future consensus on this topic. Unfortunately, the included studies were primarily retrospective and of poor scientific quality. Furthermore, subgroup analyses were not possible due to the limited number of included studies.

CONCLUSIONS

This is the first systematic review that has evaluated the various urinary parameters and definitions of cure to report on outcome after surgery for SUI in adult NU patients. We found a considerable heterogeneity in used outcome parameters and definitions of cure. As it is difficult to interpret and compare the outcomes of different therapies as investigators use different reporting systems of outcomes and definitions of cure, the results of this study will hopefully begin the dialogue to a future consensus on this topic.

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SUPPLEMENTARY MATERIAL S1. LITERATURE SEARCH STRATEGY.

Database: Embase <1974 to 2017 March 09>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials <February 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 8, 2017>
Search Strategy:

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1 exp neurogenic bladder/ or exp Urinary Bladder, Neurogenic/ (16958)
2 (NLUTD or NLUTDs).tw,kw. (146)
3 ((neurogen* or neuropathic or neurologic* or neuro-urological) adj5 (bladder or lower urinary tract or LUTS or LUT or LUTD)).tw,kw. (13866)
4 or/1-3 (22201)
5 exp Urinary Incontinence/ or exp stress incontinence/ or exp mixed incontinence/ (98473)
6 ((urine or urinate or stress or mixed or urinary) adj5 incontinen*).tw,kw. (71029)
7 5 or 6 (114065)
8 (neurogen* or neuropathic or neurologic* or neuro-urological).tw,kw. (758285)
9 Nervous System Diseases/ or cerebrovascular disease/ or Cerebrovascular Disorders/ or cerebrovascular accident/ (421341)
10 spinal cord disease/ or Spinal Cord Diseases/ or Alzheimer Disease/ or meningomyelocele/ or multiple sclerosis/ (437831)
11 Parkinson disease/ or meningomyelocele/ or meningocele/ (202850)
12 diabetes mellitus/ or (diabetes or diabetic).tw,kw. (1425859)
13 ((spina* adj cord) or spina bifida or spina* dysraphism).tw,kw. (293144)
14 (multiple sclerosis or Parkinson* or Alzheimer* or myelitis or multiple systematic atroph*).tw,kw. (651005)
15 (dementia* or progressive supranuclear palsy or corticobasal degeneration or mental retardation or cerebral palsy).tw,kw. (329983)
16 ((cerebral vascular or nervous system or cerebrovascular) adj2 (disease* or disorder* or accident* or insult)).tw,kw. (96766)
17 (meningocele or meningomyelocele or myelomeningocele or myelodysplastic or meningitis).tw,kw. (155314)
18 (Stroke or strokes or poststroke or cerebral tumor* or brain tumor* or trauma*).tw,kw. (1292644)
19 (nerve tube defects or lumbar spine Degenerative disease* or disk prolapse or disk hernia).tw,kw. (1592)

20 (lumbar canal stenosis or cauda syndrome or hydrocephalus or encephalitis).tw,kw. (127425)
21 (Iatrogenic pelvic nerve lesion* or peripheral neuropathy or tethered cord).tw,kw. (43083)
22 or/8-21 (4701030)
23 7 and 22 (20308)
24 4 or 23 (38391)
25 surgical technique/ or General Surgery/ or surgery/ (1085176)
26 (Surgery or surgical or operat* or resect*).tw,kw. (5172826)
27 exp collagen/ or exp dextranomer/ or exp bulking agent/ or exp dimeticone/ (400833)
28 exp hydroxyapatite/ or exp stem cell/ or exp Stem Cells/ or exp Hyaluronic Acid/ or exp Hydrogel/ or exp polyacrylamide gel/ (608868)
29 (bulking agent* or Zuidex or hyaluronic acid or dextranomer or Coaptite or Hydroxylapatite).tw,kw. (42811)
30 (Bulkamid or Polyacrylamide hydrogel or hydroxyapatite or Contigen).tw,kw. (46085)
31 (bovine collagen or Macroplastique or macroparticle* or Durasphere or zirconium oxide beads).tw,kw. (2401)
32 ((injection or injectable*) adj3 ureth*).tw,kw. (881)
33 exp transobturator tape/ or exp suburethral sling/ (9430)
34 (sling or slings or Miniarc or Needleless or Solyx or “Mesh”).tw,kw. (87284)
35 ((tape or tapes) adj4 (vaginal or transobturator or trans-obturator or biological or suburethral or retropubic or mid-urethral)).tw,kw. (5445)
36 (“TVT” or “TOT” or “TVT-O” or Monarc or BioArc or Uratape).tw,kw. (9979)
37 (Fascia* Lata or Rectus fascia* or Raz).tw,kw. (5253)
38 (Synthetic or Dacron or “PTFE-Gore-Tex” or Mersilene).tw,kw. (518282)
39 (suspend or Pelvicol or single incision or one incision or Ajust or Ophira).tw,kw. (11313)
40 (Argus or Saffyre or Remeex or InVance or “AdVance”).tw,kw. (143200)
41 (ACT or ProACT or ProACTTM or Pro-ACT or Pro-ACTTM or adjustable continence).tw,kw. (503042)
42 (colposuspension or Burch or urethropexy or retropubic suspension).tw,kw. (4451)
43 ((artificial adj3 urinary adj3 sphincter) or AMS 800 or AMS800 or AMS792 or AMS 792).tw,kw. (2341)
44 (((adjustable or extraurethral) adj3 balloon*) or (laparoscop* adj3 pelvic adj3 repair)).tw,kw. (207)
45 exp colposuspension/ (1567)
46 or/25-45 (7361424)
47 24 and 46 (11332)

48 (((prostat* or bladder) adj2 (cancer or carcinoma)) not (without or “not” or “non”)).ti. (210154)

49 47 not 48 (11277)

50 ((exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/) not (humans/ or human/)) or ((rats or mice or mouse or cats or dogs or animal* or cell lines) not (human* or men or women)).ti. (10792279)

51 ((child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/) not (adult/ or aged/)) or ((baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*) not (aged or adult* or elder* or senior or men or women)).ti. (4317342)

52 case report/ or case reports/ or case report.ti. (4140401)

53 Conference Abstract.pt. or Congresses as Topic/ (2602269)

54 note/ or editorial/ or letter/ or Comment/ or news/ (3872537)

55 or/50-54 (23357127)

56 49 not 55 (5572)

57 limit 56 to dd=20151230-20170309 use oemezd [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,CCTR,CDSR; records were retained] (125)

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59 limit 56 to yr=”2016 -Current” use cctr (10)

60 limit 56 to yr=”2016 -Current” use coch (23)

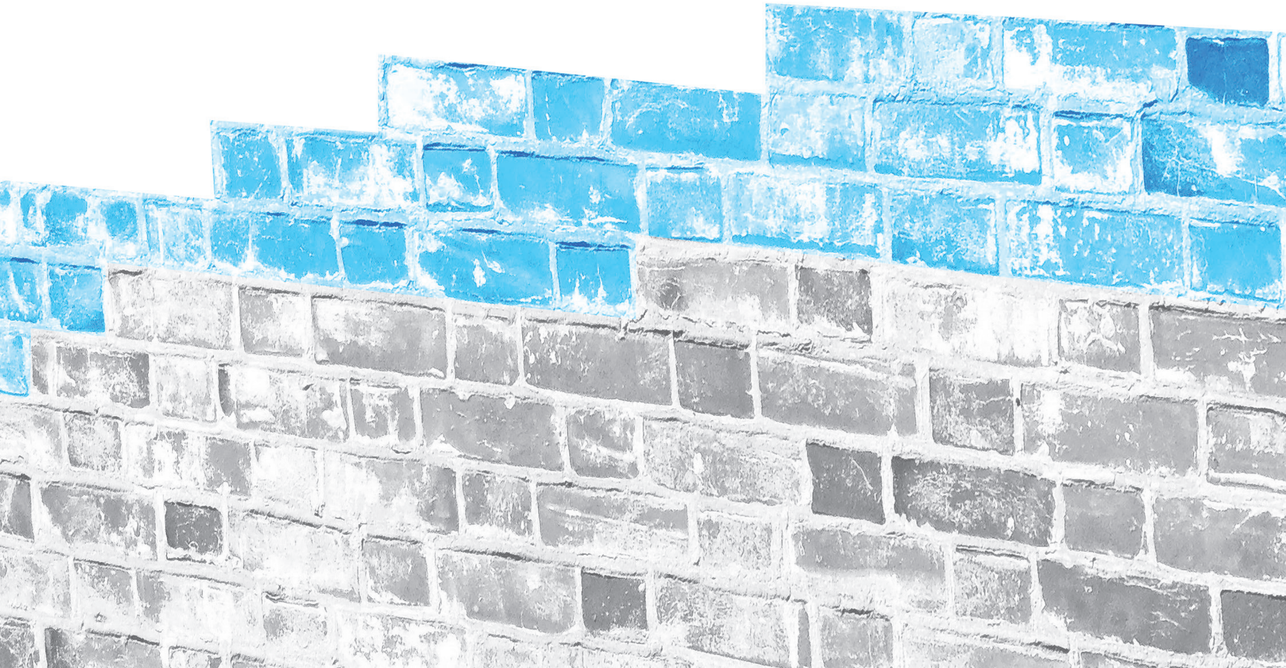
61 (2016* or 2017*).ep. (951360)

62 56 and 61 (75)

63 57 or 58 or 59 or 60 or 62 (338)

64 remove duplicates from 63 (293)

65 limit 64 to english language [Limit not valid in CDSR; records were retained] (276)



CHAPTER 3

The urinary-specific quality of life of multiple sclerosis patients: Dutch translation and validation of the SF-Qualiveen.

Sarah H.M. Reuvers, Ida J. Korfage, Jeroen R. Scheepe, Bertil F.M. Blok

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ABSTRACT

Aims: The SF-Qualiveen is a short questionnaire that measures the impact of urinary symptoms on the quality of life of patients with urological dysfunction due to neurological disorders. The aim of this study is to translate, culturally adapt and validate a Dutch version of the SF-Qualiveen for use in Multiple Sclerosis (MS) patients.

Methods: Cross-cultural adaptation of the original English SF-Qualiveen into Dutch was performed according to standardized guidelines. Adult MS patients with symptomatic urinary disorders who visited the Urology or Rehabilitation outpatient clinic of the Erasmus Medical Center completed the SF-Qualiveen and the Urinary Distress Inventory-6 (UDI-6), that evaluates bother caused by lower urinary tract symptoms and was used as a gold standard, at baseline and 1-2 weeks later. A control group recruited from the Otolaryngology outpatient clinic completed the questionnaires once. Reliability and validity were determined.

Results: Fifty MS patients and 50 controls were included. SF-Qualiveen scores in patients were higher than in controls (on a scale of 0 – 4: 1.73 vs. 0.34; $P < 0.001$). Internal consistency (Cronbach's alpha >0.8) and reproducibility (Intraclass correlation coefficients >0.8) were good for the total SF-Qualiveen. Content validity was adequate and a significant relationship between SF-Qualiveen and UDI-6 (r = 0.510-0.479, $P < 0.001$) confirmed good criterion validity.

Conclusions: The Dutch SF-Qualiveen showed good measurement properties. We recommend its use to measure urinary-specific quality of life in MS patients in research and clinical practice in the Netherlands.

INTRODUCTION

Urological dysfunction is common in patients with multiple sclerosis (MS), with prevalence reported as high as 32% to 97%.[1] This variance is at least partly related to the stage of the progression of the disease. While urinary storage symptoms (urgency, frequency and urinary incontinence) due to overactive contractions of the detrusor muscle often dominate in earlier disease, voiding problems (straining, intermittence, residual urine and retention) due to detrusor-sphincter dyssynergia often arise in addition to the storage symptoms in progressed disease.[1] This bladder dysfunction is associated with an important worsening of the quality of life in patients with MS.[2]

As differences have been noted between doctors' and patients' perceptions of the impact of a chronic disease like MS, there is a need for direct measurements of patients' experiences to be informed about their perception of the impact of the disease on the quality of life.[3] The European Association of Urology (EAU) guidelines on Neuro-Urology highlight quality of life as an import aspect in the management of neuro-urological patients. The Qualiveen[4] and its more practical short form (SF-Qualiveen)[5] are validated questionnaires for patients with MS evaluating the urinary-specific quality of life by assessing the impact of a broad range of bladder problems. The Qualiveen or SF-Qualiveen is recommended by the EAU for the assessment of health related quality of life in this patient group.[6]

The Qualiveen contains 30 questions. It was developed and validated in French for both spinal cord injury and MS patients[4, 7] and underwent successful cross-cultural adaptation into English,[8] German,[9] Italian,[10] Portuguese,[11] and Spanish.[12] The SF-Qualiveen with eight questions proved to have good measurement properties in MS patients and is currently available in French and English.[5] The aim of our study is to translate, culturally adapt and validate a Dutch version of the SF-Qualiveen in MS patients, so as to make the SF-Qualiveen suitable for MS patients in the Netherlands in both research and clinical practice.

MATERIALS AND METHODS

Study design and population

This is a single-center, prospective (cohort) validation study. The local medical research ethics committee reviewed the research proposal with the number MEC-2014-534 and concluded that the rules as stated in the Medical Research Involving Human Subjects Act do not apply. Adult MS patients with urinary symptomatology who visited the Urology outpatient clinic of the Erasmus University Medical Center (Erasmus MC) Rotterdam, the Netherlands, between

October 2015 and April 2016 were invited for the study. MS patients with similar symptoms who visited the Rehabilitation outpatient clinic of the Erasmus MC between February 2016 and April 2016 were invited as well. Patients with Dutch language difficulties, cognitive impairment, active malignant tumors, acute attacks of MS (defined as an acute episode of focal neurological disturbance), symptomatic urinary tract infections, and patients who changed treatment within the test-retest period were excluded. Patients were asked to complete two questionnaires (SF-Qualiveen and UDI-6); during a hospital visit (baseline) and 1-2 weeks later at home. All patients provided written informed consent. Patient and disease characteristics were retrieved from the medical files.
Adult patients who visited the Otolaryngology outpatient clinic between March and May 2016 were invited for the study as well. We considered these patients a proper control group, since Otolaryngology pathology is often limited to the organ and has no relationship with bladder problems. This group completed the questionnaires only once. Exclusion criteria for this group were: neuro-urological dysfunction (patients reporting both bladder symptoms and MS or spinal cord injury), cognitive impairment and Dutch language difficulties.

Questionnaires

The SF-Qualiveen[5] is a validated short version of the Qualiveen-30[4] questionnaire and evaluates urinary-specific quality of life. The SF-Qualiveen consists of eight questions and reports on four domains of two questions each: bother with limitations, fears, feelings and frequency of limitations. Table 1 displays the items of the SF-Qualiveen. Responses are given on a 5-point Likert like scale, where a score of 0 indicates ”no impact” and 4 ”high impact”. The SF-Qualiveen total score is calculated as the mean of the eight responses and the domain scores are calculated as the mean score of the responses per domain.
The Dutch Urinary Distress Inventory (UDI-6) evaluates bother caused by lower urinary tract symptoms.[13] It consists of six questions and reports on three domains: irritative, stress and obstructive/discomfort symptoms. Answers can be given on a 4-point Likert like scale. The questionnaire is validated, but not specifically for neuro-urological patients.

Table 1. Items of the SF-Qualiveen

Domains:	Questions:	
Bother with limitations	1.	In general, do your bladder problems complicate your life?
	2.	Are you bothered by the time spent passing urine or realizing catheterization?
Fears	3.	Do you worry about your bladder problems worsening?
	4.	Do you worry about smelling of urine?
Feeling	5.	Do you feel worried because of your bladder problems?
	6.	Do you feel embarrassed because of your bladder problems?
Frequency of limitations	7.	Is your life regulated by your bladder problems?
	8.	Can you go out without planning anything in advance?

Cross-cultural adaptation

The cross-cultural adaptation of the original English SF-Qualiveen into the Dutch language was performed according to standardized guidelines for linguistic validation.[14] The forward-translation was performed by two professional native Dutch-speaking translators separately, followed by a consensus meeting of these two and the primary investigator (SR). The consensus version was backward translated by a native English speaking translator. During a consensus meeting with the Dutch translators, the English translator and the primary investigator (SR) a few minor adjustments were made. Two urologists (BB and JS) proof-read and agreed on this version of the Dutch SF-Qualiveen. It was then evaluated on content validity,[15] i.e. pre-tested, in face-to-face interviews with patients during August and September 2015. We aimed to include at least 10 MS patients for the face-to-face interviews. These patients were first asked to complete the questionnaire. Thereafter, content and wording of the questions were discussed with the patients and suggestions for improvement were solicited.

Validation – reliability

Internal consistency

This is the intercorrelation of the questions of a questionnaire and demonstrates if the questions measure the same underlying concept. The correlation between the questions of the SF-Qualiveen for the total score and for the separate domains were measured by determination of the Cronbach's alpha. If Cronbach's alpha was between 0.7 and 0.95, internal consistency was considered good.[15]

Reproducibility

The intraclass correlation coefficients (ICC) for agreement were calculated for the overall SF-Qualiveen score and for the four domains to test the test-retest reliability. A score of 0.7 or higher was considered good.[15]

Limits of agreement

The limits of agreement (LOA) were calculated as the mean change in scores of repeated measurements ± 1.96 x SD of the changes. Provided differences within the LOA could be interpreted as measurement error and would not be clinically important. [16]

Validation – validity

Content validity

During the cross-cultural adaptation process, content validity was assessed by patient interviews.

Construct validity:
Predefined hypotheses about the relation of the SF-Qualiveen to other measures were tested:

- "Patients with higher SF-Qualiveen scores (indicating higher impact on urinary-related quality of life) will have higher scores on the UDI-6 (indicating more bother of urinary symptoms)." The association between the SF-Qualiveen and UDI-6 scores will be assessed using the Pearson's correlation coefficient in case of a linear association.

- "The SF-Qualiveen scores in the patient group will be higher than the reference group." The Student's *t*-test will be used to assess the differences between groups.

Criterion validity
For the SF-Qualiveen no perfect gold standard exists. In the absence of a perfect gold standard the UDI-6 is used as a gold standard to determine criterion validity. The correlation of the SF-Qualiveen to the UDI-6 is determined by using the Pearson correlation coefficient in case of a linear association.

Floor and ceiling effects
If more than 15% of respondents achieved the highest or lowest possible score, floor or ceiling effects are presumed to be present. We calculated the percentages of patients with the highest or lowest possible score.

Further statistical methods
We aimed at a sample size of 50 MS patients and 50 control persons based on guidelines for validation of questionnaires.[15] SPSS version 21 was used to perform the statistical analyses in this study. Mean ± standard deviations were used to present descriptive results for continuous data and counts and percentages for discrete data. Differences between groups were tested with Chi-Square tests for categorical variables and with Student's *t*-tests for continuous variables. *P*-values of less than 0.05 were considered to reflect statistical significance.

RESULTS

Fifty-six MS patients with symptomatic urinary disorders were initially included in the study. Patients signed informed consent and filled in the baseline questionnaire. Six patients were excluded afterwards for the following reasons: four patients did not return the second questionnaire for unknown reasons, one refused to fill in the second questionnaire and one changed treatment within the test-retest period. Eventually the data of 50 MS patients could be used for analyses. The mean time between completing the first and second questionnaire was 15.7 ± 10.6 days.

Fifty persons who visited the Otolaryngology outpatient clinic of the Erasmus MC between March and May 2016 completed the questionnaires once as a control group. Table 2 displays the characteristics of the included MS patients and controls. The MS patient group was significantly older ($P = 0.013$) and had more females ($P = 0.002$) than the control group. Most patients had relapsing-remitting MS (60%), were limited in walking (46%), voided without catheterization (72%) and experienced both storage and voiding urinary symptoms (70%).

Table 2. Patient and clinical characteristics

		Patients	Controls	*P*-value
Characteristics				
n		50	50	
Age at examination (years)		50.3 ± 11.7	42.3 ± 14.2	0.013
Gender	Male	11 (22.0%)	26 (52.0%)	0.002
	Female	39 (78.0%)	24 (48.0%)	
MS characteristics				
Duration of MS since diagnosis (years)		13.3 ± 9.0		
MS course	Relapsing-remitting	30 (60.0%)		
	Primary progressive	5 (10.0%)		
	Secondary progressive	11 (22.0%)		
	Missing	4 (8.0%)		
Mobility	Fully ambulatory	16 (32.0%)		
	Limited walking	23 (46.0%)		
	Wheelchair bound	10 (20.0%)		
	Missing	1 (2.0%)		
Urinary symptoms				
Duration of urinary symptoms (years)		7.6 ± 5.5		
Urinary symptoms	Storage	7 (14.0%)		
	Voiding	8 (16.0%)		
	Storage + voiding	35 (70.0%)		
Manner of bladder emptying	(normal) voiding	36 (72.0%)		
	Intermittent catheterization	10 (20.0%)		
	Indwelling catheter	4 (8.0%)		

Validation – reliability

Internal consistency

With Cronbach's alpha's of >0.8, the internal consistency for the total SF-Qualiveen can be considered good. (Table 3) With a Cronbach's alpha of >0.7 the domains "bother with limitations" and "feeling" showed a good internal consistency as well. The domain "frequency of limitations" showed moderate internal consistency and the domain "fears" showed weak internal consistency.

Table 3. Internal consistency – Cronbach's alpha (*n* = 50 MS patients)

	Test	Re-test
SF-Qualiveen total	0.84	0.85
SF-Qualiveen subscales:		
Bother with limitations	0.72	0.78
Fears	0.26	0.40
Feeling	0.77	0.75
Frequency of limitations	0.43	0.66

Reproducibility

The ICCs for agreement for the total SF-Qualiveen and the four domains were all higher than 0.7, indicating good reproducibility (Table 4).

Table 4. Reproducibility of SF-Qualiveen

	Test (mean ± SD)	Re-test (mean ± SD)	Mean change (mean ± SD)	ICC	LOA
SF-Qualiveen total score	1.73 ± 0.84	1.73 ± 0.84	0.00 ± 0.39	0.90	-0.76 to 0.76
Bother with limitations	1.67 ± 1.10	1.70 ± 1.06	0.03 ± 0.61	0.84	-1.17 to 1.23
Fears	1.59 ± 0.98	1.58 ± 0.96	-0.01 ± 0.53	0.85	-1.05 to 1.03
Feeling	1.56 ± 1.09	1.50 ± 1.09	-0.06 ± 0.73	0.78	-1.50 to 1.38
Frequency of limitations	2.09 ± 0.95	2.13 ± 1.02	0.00 ± 0.39	0.72	-0.76 to 0.76

SD, standard deviation; ICC, intraclass correlation coefficient; LOA, limits of agreement

Limits of agreement

The LOA ranges of the total SF-Qualiveen and the domains are presented in Table 4. A change of less than 0.76 in the total SF-Qualiveen score could be interpreted as measurement error.

Validation – validity

Content validity

This was evaluated in face-to-face interviews with 11 MS patients and 12 other neuro-urological patients. The importance of all questions, to assess the broad range of bladder problems patients experience, was confirmed by the majority of patients. The Dutch-version questionnaire was found generally accessible, clear, easy to understand, and fast to complete and it was not necessary to make adjustments.

Construct validity

Both predefined hypotheses about the relation of the SF-Qualiveen score to other measures were confirmed:

- We found a significant linear correlation between the total score of SF-Qualiveen and total score of UDI-6 in the patient group (T0: $r = 0.510$ and $P < 0.001$; T1: $r = 0.479$ and $P < 0.001$). This confirmed the hypothesis "patients with higher SF-Qualiveen scores have higher UDI-6 scores".

- The mean of the total score of the SF-Qualiveen differed between patient and the control group (1.73 vs. 0.34; P < 0.001). The hypothesis "SF-Qualiveen scores in the patient group are higher than in the control group" is hereby confirmed.

Criterion validity

A significant relationship was found between the UDI-6 total score, and the SF-Qualiveen total score in both MS patient group (T0: $r = 0.510$ and $P < 0.001$; T1: $r = 0.479$ and $P < 0.001$) and the control group ($r = 0.632$ and $P < 0.001$).

Floor and ceiling effects

In the patient group no floor or ceiling effects were found in total or domain scores. Two percent of patients had the lowest possible total score and no patients had the highest possible score. Four to ten percent of the patients reported the lowest possible scores for the separate domains. Zero to four percent of the patients reported the highest possible scores for the separate domains.

In the control group, floor effects were found in all domains and in the total score. (domains: 58-86% and total score: 50%). No ceiling effects were found in the control group.

DISCUSSION

We translated the SF-Qualiveen into Dutch, and culturally adapted and validated it for use in MS patients. The measurement properties demonstrated the Dutch version of the SF-Qualiveen to be valid, reliable and consistent. This enables the use of the SF-Qualiveen for future research and clinical practice in the Netherlands.

For chronic diseases like MS, quality of life is an important aspect of healthcare. The urinary symptoms that are often described in patients with MS can diminish the quality of life.[2] This study makes it possible for Dutch-speaking MS patients to directly measure the impact of urinary symptoms on the quality of life with the SF-Qualiveen. We chose to translate and validate the short form because this is more practical, easier to implement into research and clinical practice, and causes less patient burden to complete. In validation studies of the Qualiveen the length of the questionnaire has been mentioned as a limitation.[11, 12] The Dutch SF-Qualiveen can be a valuable addition to diagnostics, so as the EAU guidelines recommends its use.[6]

The Cronbach's alpha of >0.8 indicates good internal consistency for the entire SF-Qualiveen questionnaire. For the development of the SF-Qualiveen Bonniaud et al.[5] selected two questions per domain of the Qualiveen-30, based on the most responsive items to represent that domain. The authors did not address the internal consistency of the SF-Qualiveen, neither for the total score, nor for the domain scores. The internal consistency of a questionnaire is dependent upon the number of items in a scale.[15] In a short questionnaire like the 8-item SF-Qualiveen categorization into 4 domains might therefore be questioned. In our study, the domains "bother with limitations" and "feeling" showed good internal consistency and the domain "frequency of limitations" showed moderate internal consistency. The domain "fears" showed weak internal consistency. Although its two questions (see Table 1) are both important (as was confirmed during cross-cultural adaptation), the answers to these questions do not necessarily have to be associated. It is doubtful if the two questions measure the same underlying construct of "fears". A potential explanation for the moderate internal consistency of the questions within the domain "frequency of limitations" (Table 1) is that patients' answers to the last question might not be exclusively related to their bladder problems. The question arising from our study results on the internal consistency of the separate domains and that each consists of only a small number of questions, is whether the domains of the SF-Qualiveen can still be considered as actual domains. Therefore, we investigated this issue by performing a factor analysis of the eight questions of the SF-Qualiveen. This resulted in the identification of two components within the questionnaire. The first component is represented by the first seven questions and the second component by question 8. This indicates that the four Qualiveen domains can no longer be identified in the SF-Qualiveen and that question 8 might assess a different construct than the other questions. This reasoning is confirmed by the Cronbach's alpha rising from 0.835 to 0.855 at baseline and from 0.851 to 0.871 at re-test when excluding question 8 from the analysis. Therefore, exclusion of question 8 from the questionnaire can be considered. In view of the good internal consistency of the total SF-Qualiveen, the lack of identification of four domains in the SF-Qualiveen, the patients agreement on the importance of all 8 questions of the questionnaire (content validity), and to support consistent (international) usage of the SF-Qualiveen we recommend to use the entire SF-Qualiveen questionnaire and not the separate domains.

The ICCs showed a good reproducibility of the Dutch SF-Qualiveen. These ICCs are lower than reported in the original Qualiveen-30 questionnaire,[4] but are comparable to those found in the French and English validation study of the SF-Qualiveen.[5] The lower ICCs for the SF-Qualiveen are probably to the result of the shortening. We believe that the advantages of the short SF-Qualiveen (more practical, less patient burden and easier to implement into practice) outweigh this minor disadvantage.

The Dutch SF-Qualiveen showed good validity. Predefined hypotheses to test construct validity could be confirmed. Patients' scores on the SF-Qualiveen were significantly higher than those of controls, which demonstrates good discriminative ability of the SF-Qualiveen. Furthermore, a correlation was found between the UDI-6 as a gold standard and the SF-Qualiveen. This confirmed good criterion validity. In the patient group no floor or ceiling effects were found. As expected, a floor-effect was found in the control group (no urological patients).

One of the strengths of our study is that we followed all proposed quality criteria for the validation of a questionnaire of Terwee et al.[15] Furthermore, we included a very homogeneous study population of only MS patients. Therefore we conclude that the SF-Qualiveen can be used to measure the urinary-specific quality of life for MS patients with symptomatic functional urologic disorders. Further research is needed to validate the questionnaire for other neurological diseases such as spinal cord injury.

A limitation of this study is that we were no yet able to measure the responsiveness of the SF-Qualiveen. Another limitation is that the exact response rate cannot be established. We aimed at including all consecutive eligible patients. Study inclusions were performed by selected urologists and a rehabilitation specialist specialized in the treatment of MS patients. We were not able to establish whether indeed all eligible patients were approached by these physicians and how many patients declined to participate. We could also have missed a small number of eligible patients who visited other (non-specifically MS specialized) urologists or rehabilitation specialists at our hospital during the inclusion period. Furthermore, there was no perfect gold standard questionnaire available. A perfect gold standard would be a questionnaire that is available in Dutch, commonly used, measures the urinary-specific quality of life and is validated in neuro-urological patients. In the absence of a perfect gold standard we chose the UDI-6, a commonly used questionnaire, which evaluates bother by lower urinary tract symptoms to function as the gold standard. Finally, due to the single-center design of the study in a referral center, the generalizability of the questionnaire is questionable. On the other hand, the SF-Qualiveen showed good measurement properties in the original validation multicenter study.[5]

CONCLUSIONS

In conclusion, the Dutch version of the SF-Qualiveen showed good measurement properties. We recommend using the entire Dutch version of the short and practical SF-Qualiveen to measure urinary-specific quality of life experienced by MS patients in both research and clinical practice in the Netherlands. SF-Qualiveen outcomes can support healthcare professionals in treatment decision making to optimize patients' quality of life.

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CHAPTER 4

The validation of the Dutch SF-Qualiveen, a questionnaire on urinary-specific quality of life, in spinal cord injury patients.

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ABSTRACT

Background: Optimizing the patients' quality of life is one of the main goals in the urological management of spinal cord injury (SCI) patients. In this study we validated the Dutch SF-Qualiveen, a short questionnaire that measures the urinary-specific quality of life, in SCI patients. No such measure is yet available for this patient group.

Methods: In 2015-2016 SCI patients with urinary symptomatology who visited the outpatient clinics of Urology at the Erasmus Medical Centre and Rehabilitation at Rijndam Revalidation completed the SF-Qualiveen and UDI-6 during the visit and 1-2 weeks later. The UDI-6, a urinary tract symptom inventory, served as gold standard. Controls, recruited from the Otolaryngology outpatient clinic, completed the questionnaires once. Content-, construct-, and criterion validity and reliability (internal consistency and reproducibility) of the SF-Qualiveen were determined.

Results: 57 SCI patients and 50 controls were included. 12 SCI patients asserted that the SF-Qualiveen covered their bladder problems (good content validity). Patients' SF-Qualiveen scores being positively associated with severity of urinary symptoms and patients' scores being higher than those of controls indicated good construct validity. The positive association that was found between SF-Qualiveen and UDI-6 in patients (r = 0.66-0.67, P < 0.001) and controls (r = 0.63, P < 0.001) confirmed good criterion validity. Internal consistency (Cronbach's alpha 0.89–0.92) and reproducibility (intraclass correlation coefficient 0.94) of the SF-Qualiveen were good.

Conclusions: The Dutch SF-Qualiveen is a valid and reliable tool to measure the urinary-specific quality of life in SCI patients.

Trial registration: No trial registration (no clinical trial – no health-related intervention)

BACKGROUND

Spinal cord injury (SCI) causes urological dysfunction in 70 - 84% of patients.[1] The type of detrusor and/or sphincter dysfunction depends on the localization of the SCI and the damage to the spinal cord. Clinical presentation can vary from urinary incontinence to inability to empty the bladder.[2]

More than two thirds of SCI patients in the Netherlands reported bladder regulation problems as one of their most frequent health problems.[3] Bladder problems were perceived as a major secondary impairment and as having the greatest impact on social life.[3] Bladder problems in patients with SCI were found to be associated with a lower quality of life.[4] Optimizing the quality of life is considered one of the most important aspects in the urological management of patients with neuro-urological dysfunction due to SCI.[5]

Currently, there is no validated measure available in the Netherlands to evaluate the urinary-specific quality of life in SCI patients. The Qualiveen-30[6] and its short version, the SF-Qualiveen,[7] are measures that evaluate urinary-specific quality of life in patients with neurological disorders. The Qualiveen-30 has been validated in both multiple sclerosis (MS) and SCI patients,[6, 8] but is not available in Dutch. Based on data of MS patients only, the eight most responsive items of the Qualiveen-30 were used to create the SF-Qualiveen.[7] The SF-Qualiveen has been validated in English[7], French[7] and Dutch[9] for MS patients, but not yet for SCI patients. Although the neuro-urological dysfunction in MS and SCI patients is similar in some aspects, its clinical presentation and the influence on the quality of life might differ due to dissimilarities between the two diseases (e.g. the onset of disease is acute in SCI vs. progressive in MS; SCI often entails a total loss of sensation of the lower body, while MS entails an altered sensibility, but often no total loss of sensibility). For this reason, it is essential to evaluate the validity and reliability of the SF-Qualiveen in SCI patients before its use can be recommended as a measurement tool in the management of Dutch SCI patients to optimize their quality of life.

METHODS

Design and subjects

The research protocol (MEC-2014-534) was reviewed by the local medical research ethics committee, which concluded that the rules as stated in the Dutch Medical Research Involving Human Subjects Act did not apply to this study. The study was conducted at the Urology outpatient clinic of the Erasmus University Medical Center (Erasmus MC), Rotterdam,

the Netherlands and at the Rehabilitation outpatient clinic at Rijndam Rehabilitation, Rotterdam, the Netherlands. In August and September 2015 face-to-face interviews were conducted with SCI patients with urinary symptomatology to assess content-validity of the Dutch translated version of the SF-Qualiveen. Between late September 2015 and May 2016 adult patients with SCI and urinary symptomatology were included. We intended to invite all eligible consecutive patients who visited the outpatients clinics to participate. Exclusion criteria were cognitive impairment, Dutch language difficulties, recent malignant tumors, symptomatic urinary tract infections, and (foreseen) change of (bladder-specific) treatment within the test-retest period. After having provided written informed consent, participants completed the SF-Qualiveen and the Urinary Distress Inventory-6 (UDI-6) at the outpatient clinic (test) and 1 to 2 weeks later at home (re-test). Clinical characteristics of included patients were retrieved from their medical charts.
We used earlier collected data of a control group, that was recruited at the Otolaryngology outpatient clinic in 2016.[9] Exclusion criteria for this group were cognitive impairment, Dutch language difficulties and neuro-urological dysfunction. The control patients had provided written informed consent and completed the measures once.

Measures
The SF-Qualiveen is a measure that evaluates the urinary-specific quality of life in neuro-urological patients. Table 1 shows the eight questions of the questionnaire. Each item is scored on an ordinal Likert scale ranging from 0 (no impact) to 4 (high impact). The total score is the mean of the eight separate scores[7]. The SF-Qualiveen consists of four domains, each containing two questions: bother with limitations (question 1 and 2), fears (question 3 and 4), feelings (question 5 and 6) and frequency of limitations (question 7 and 8).

Table 1. Questions of the SF-Qualiveen

1.	**In general, do your bladder problems complicate your life?**
2.	**Are you bothered by the time spent passing urine or realizing catheterization?**
3.	**Do you worry about your bladder problems worsening?**
4.	**Do you worry about smelling of urine?**
5.	**Do you feel worried because of your bladder problems?**
6.	**Do you feel embarrassed because of your bladder problems?**
7.	**Is your life regulated by your bladder problems?**
8.	**Can you go out without planning anything in advance?**

The Dutch UDI-6 is a validated Dutch measure,[10] but has not been specifically validated in a neuro-urological patient group. The questionnaire (six questions) assesses the severity of urinary tract symptoms. It consists of three domains: irritative, stress and obstructive/discomfort urinary symptoms.[11] We chose this measure as a gold standard in the absence of a perfect gold standard for this patient group.

Validation process

The cross-cultural adaptation of the SF-Qualiveen into Dutch by our group was previously described.[9] In short; two forward-translations of the SF-Qualiveen from English to Dutch, and one backward translation were followed by consensus meetings between translators and clinicians. Standardized guidelines for linguistic validation were followed.[12] *Content validity* was assessed by face-to-face interviews with SCI and MS patients.[13] The goal of these interviews was to confirm that the translated version of the SF-Qualiveen used clear wording and that it was a complete measure.

In the current study, predefined hypotheses on *construct validity* were assessed:

1. We hypothesized that SF-Qualiveen scores of patients would be positively associated with the severity of urinary symptoms (UDI-6 domains irritative, stress and obstructive/discomfort urinary symptoms and total score).

2. We hypothesized that scores of the SF-Qualiveen in the patient group would be higher than scores in the control group.

Criterion validity was determined by assessing the relationship between the SF-Qualiveen and the UDI-6 as a gold standard. *Floor and ceiling effects* were presumed to be present if more than 15% of respondents achieved the highest or lowest possible score. Therefore, percentages of respondents with the highest and lowest possible score were calculated. A floor effect was to be expected in the control group.

The *internal consistency* of the SF-Qualiveen questions, i.e. whether the questions measure the same underlying construct, was determined by calculating Cronbach's alpha. The *reproducibility* of the SF-Qualiveen was determined by calculating the intraclass correlation coefficient (ICC) for agreement of the repeated measurements. The *limits of agreement* (LOA) were determined. In general, differences in scores within the LOA can be interpreted as measurement error.[14]

A post hoc subgroup analysis was performed to investigate construct- and criterion validity, internal consistency and reproducibility of the Dutch SF-Qualiveen in different subgroups based on level of SCI, ASIA (American Spinal Injury Association) Impairment Scale and manner of bladder emptying.

Statistical analyses

We aimed to include at least 50 patients and 50 controls to comply with the guidelines for validation of questionnaires.[13] For the face-to-face interviews we aimed to include at least 10 SCI patients.

For the statistical analyses we used SPSS version 21. Descriptive results are presented as mean ± standard deviations for continuous data and counts and percentages for discrete data. Student's T-tests were used to assess differences between groups for continuous variables and Chi-Square tests for categorical variables. Associations between variables were assessed using the Pearson's correlation coefficient in case of a linear association. Cronbach's alpha's were calculated to determine the internal consistency. Cronbach's alpha's between 0.7 and 0.95 were considered good.[13] The LOA were calculated as the mean change in scores of repeated measurements ± 1.96 x standard deviation (SD) of the changes.[14] ICCs of 0.7 or higher were considered to represent good reproducibility.[13] Statistical significance was assumed at a p-value of less than 0.05.

RESULTS

66 SCI patients completed the questionnaires at baseline ('test'). Seven patients did not return the second questionnaires while one declined further participation. The mean SF-Qualiveen score (test) of these patients was 1.81 ± 0.65. One patient was diagnosed with a malignant tumor and excluded. In total, 57 SCI patients completed the second questionnaires (retest) on average 12.7 (± 9.0) days after the first questionnaires and were included in the analyses. Characteristics of the study groups are displayed in Table 2. Most patients had a thoracic SCI, required a wheelchair for mobility and were dependent upon catheterization (intermittent or indwelling) to empty their bladder. The 50 controls were significantly younger than the SCI patients. The proportion of males and females was similar in both groups.

Table 2. Clinical characteristics

		Patients	Controls	P-value
N		57	50	
Age at examination		53.2 ± 14.6	42.3 ± 14.2	<0.001
Sex	Male	37 (64.9%)	26 (52.0%)	0.176
	Female	20 (35.1%)	24 (48.0%)	
Years after SCI		13.1 ± 12.8		
Level of SCI	Cervical	15 (26.3%)		
	Thoracic	31 (54.4%)		
	Lumbar	11 (19.3%)		
ASIA Impairment Scale	A	23 (40.3%)		
	B	5 (8.8%)		
	C	7 (12.3%)		
	D	20 (35.1%)		
		Missing: 2 (3.5%)		
Mobility	Fully ambulatory	4 (7.0%)		
	Limited walking	16 (28.1%)		
	Wheelchair only	35 (61.4%)		
		Missing: 2 (3.5%)		
Manner of bladder emptying	(normal) voiding	5 (8.8%)		
	Abdominal pressure	1 (1.8%)		
	Total incontinence	1 (1.8%)		
	Intermittent catheterization	27 (47.4%)		
	Indwelling catheter	22 (38.6%)		
		Missing: 1 (1.8%)		

Results are presented as mean ± standard deviations for continuous data and counts and percentages for discrete data. ASIA Impairment Scale, American Spinal Injury Association Impairment Scale (A: Complete, B: Sensory incomplete, C: Motor incomplete - half of key muscle functions below the neurological level of injury have a muscle grade less than 3, D: Motor incomplete - at least half of key muscle functions below the neurological level of injury have a muscle grade > 3)[15]; SCI, Spinal Cord Injury

Validation process

Following the translation of the SF-Qualiveen into Dutch, 12 SCI patients and 11 MS patients were interviewed to assess c*ontent validity*. The translated SF-Qualiveen was distributed to the patients. Thereafter, patients were asked whether the questions covered all the bladder problems that affected their quality of life. Both patient groups agreed on the importance of the questions and found it a complete measure that covered the broad range of bladder problems that they experienced. Furthermore, patients found the Dutch version clear and easy to complete.

The predefined hypotheses on *construct validity* were confirmed:

1. Positive significant associations were found between both the total UDI-6 and the different domains of the UDI-6 which measure the severity of irritative, stress and obstructive/discomfort urinary symptoms and the total SF-Qualiveen scores in the patient group. (Table 3) The hypothesis that SF-Qualiveen scores of patients would be positively associated with the severity of urinary symptoms was confirmed.

2. The mean of the total scores of the SF-Qualiveen for the patient group was 1.81 ± 0.99 for the test and 1.80 ± 1.08 for the re-test while the control group reported a mean score of 0.34 ± 0.59 (P < 0.001). In an older subgroup of controls >40 years (n = 27, mean age 53.9 years) the mean total SF-Qualiveen score was 0.51. A significant difference in mean SF-Qualiveen scores between the patient group and the control group >40 years was found (P < 0.001).

A significant positive association between the SF-Qualiveen and the UDI-6 was found in both the patient (Table 3) and control group (r = 0.632 and P < 0.001). *Criterion validity* was hereby found to be good. *Floor and ceiling effects* were not found in the patient group for the total SF-Qualiveen score (Test: no patients had the lowest or highest possible score. Re-test: 2% of the patients had the lowest and 2% had the highest possible score). As expected, a floor effect was found in the control group for the total SF-Qualiveen score: 50% of the controls had the lowest possible score. No ceiling effect was found in the control group (none had the highest possible score).

Table 3. Correlations between severity of urinary symptoms (UDI-6 domain scores) – and SF-Qualiveen total scores in patient group

	Test	Re-test
UDI-6 – total score	r = 0.663 and P < 0.001	r = 0.673 and P < 0.001
Severity of irritative urinary symptoms	r = 0.596 and P < 0.001	r = 0.543 and P < 0.001
Severity of stress urinary symptoms	r = 0.451 and P < 0.001	r = 0.424 and P = 0.001
Severity of obstructive/discomfort urinary symptoms	r = 0.521 and P < 0.001	r = 0.630 and P < 0.001

Pearson's correlation coefficients were determined to assess the relationship between variables. UDI-6, Urinary Distress Inventory-6.

Cronbach's alpha's of 0.89 (test) and 0.92 (re-test) indicated good *internal consistency* for the total SF-Qualiveen. (Table 4) The domains 'bother with limitations' and 'feeling' showed good internal consistency as well. Internal consistency of the domains 'fears' and 'frequency of limitations' was moderate. The ICCs for the repeated measurements of the test and re-test for the SF-Qualiveen total score and domain scores showed good *reproducibility* (Table

5). Table 5 shows the *limits of agreement* (LOA) as well. Differences between -0.72 and 0.70 can be interpreted as not clinically important.

Table 4. Internal consistency – Cronbach's alpha (*n* = 57 SCI patients)

	Test	Re-test
SF-Qualiveen total score	0.89	0.92
SF-Qualiveen domains:		
Bother with limitations	0.87	0.90
Fears	0.53	0.73
Feeling	0.80	0.84
Frequency of limitations	0.55	0.75

SCI, Spinal Cord Injury

Table 5. Reproducibility of SF-Qualiveen

	ICC	LOA
SF-Qualiveen total score	0.94	-0.72 to 0.70
Bother with limitations	0.90	-1.12 to 1.00
Fears	0.92	-0.97 to 0.99
Feeling	0.87	-1.27 to 1.23
Frequency of limitations	0.79	-0.72 to 0.70

ICC, Intraclass Correlation Coefficient; LOA, Limits of Agreement

In Table 6 the results of the post hoc subgroup analyses based on level of SCI, ASIA Impairment Scale and manner of bladder emptying are shown. Most subgroups showed a positive significant association between the SF-Qualiveen total scores and the UDI-6 score and a significant difference in mean SF-Qualiveen scores compared to the control group, indicating good criterion and construct validity. Cronbach's alpha's of >0.79 and ICCs >0.86 confirmed good internal consistency and reproducibility for the different subgroups.

Table 6. Subgroup analyses

		Patient numbers	Mean total SF-Qualiveen scores	Cronbach's alpha	ICC	Correlation between SF-Qualiveen scores and UDI-6 scores	Patients' SF-Qualiveen scores compared to controls
Level of SCI	Cervical	15 (26%)	1.68-1.68	0.93-0.96	0.95	$r = 0.853$, $p < 0.001$ $r = 0.788$, $p < 0.001$	$p < 0.001$
	Thoracic	31 (55%)	1.77-1.75	0.88-0.91	0.95	$r = 0.552$, $p = 0.001$ $r = 0.547$, $p = 0.001$	$p < 0.001$
	Lumbar	11 (19%)	2.11-2.15	0.79-0.80	0.89	$r = 0.686$, $p = 0.02$ $r = 0.769$, $p = 0.006$	$p < 0.001$
ASIA Impairment Scale	A	23 (40.3%)	1.58-1.50	0.88-0.92	0.94	$r = 0.585$, $p = 0.003$ $r = 0.650$, $p = 0.001$	$p < 0.001$
	B	5 (8.8%)	2.18-2.48	0.80-0.88	0.92	$r = 0.895$, $p = 0.040$ $r = 0.597$, $p = 0.287$	$p < 0.001$
	C	7 (12.3%)	1.70-1.57	0.83-0.82	0.86	$r = 0.715$, $p = 0.071$ $r = 0.677$, $p = 0.095$	$p < 0.001$
	D	20 (35.1%)	2.04-2.11	0.90-0.92	0.96	$r = 0.706$, $p < 0.001$ $r = 0.709$, $p < 0.001$	$p < 0.001$
		Missing: 2					
Manner of bladder emptying	No catheter use	7 (12%)	1.36-1.21	0.87-0.91	0.94	$r = 0.707$, $p = 0.076$ $r = 0.817$, $p = 0.025$	$p < 0.001$
	Intermittent catheterization	27 (47%)	2.19-2.20	0.89-0.88	0.92	$r = 0.571$, $p = 0.002$ $r = 0.518$, $p = 0.006$	$p < 0.001$
	Indwelling catheter	22 (39%)	1.47-1.48	0.85-0.93	0.95	$r = 0.743$, $p < 0.001$ $r = 0.768$, $p < 0.001$	$p < 0.001$
		Missing: 1					

ASIA Impairment Scale, American Spinal Injury Association Impairment Scale; ICC, Intraclass Correlation Coefficient

DISCUSSION

In this study we introduced the SF-Qualiveen in a SCI patient group. We showed good content-, construct- and criterion validity, internal consistency and reproducibility of the SF-Qualiveen in this patient group. We conclude that the SF-Qualiveen can be used in the Netherlands to evaluate the urinary-specific quality of life in SCI patients.

The ICCs of the repeated measurements in this study (ranging from 0.79 to 0.94) showed good reproducibility for the total SF-Qualiveen and the separate domains, although they were somewhat lower than the ICCs found in the French and English SF-Qualiveen validation study in MS patients (0.88 to 0.94).[7] The ICCs as found in the present study are comparable to the Dutch validation study of the SF-Qualiveen in MS patients (0.72 to 0.90).[9] The Dutch SF-Qualiveen showed to be a reliable instrument for SCI patients.

Internal consistency for the total SF-Qualiveen was good. Cronbach's alpha's of 0.53 to 0.75 for the separate domains 'fears' and 'frequency of limitations' showed moderate internal consistency. This is consistent with results from the Dutch validation study of the SF-Qualiveen in MS patients.[9] Internal consistency was not described in the French and English validation study of the SF-Qualiveen. These study results indicate that the four domains of the Qualiveen-30 cannot be confirmed in the SF-Qualiveen, probably due to the small number of questions (two) in every domain. This strengthens the previous recommendation of Reuvers et al.[9] to not use the separate domains of the SF-Qualiveen, but only the total SF-Qualiveen.

The results of the subgroup analyses suggest that the Dutch SF-Qualiveen has equal measurement properties for SCI patients with different levels of SCI, ASIA Impairment statuses and manners of bladder emptying. Not finding a statistical significant correlation between the SF-Qualiveen scores and UDI-6 scores in the ASIA group B (*n* = 5) and C (*n* = 7) and the group without catheter usage (*n* = 7) could be explained by the lack of statistical power in the small patient groups due to the post hoc analysis.

Most SCI patients experience bladder problems as a consequence of damage to the spinal cord.[1, 3] These bladder problems have a negative effect on patients' quality of life.[4] In the urological management of SCI patients optimization of the quality of life is an important aspect as mentioned in the EAU guidelines.[5] Therefore, it is essential for healthcare professionals to be informed about a patients' present urinary-specific quality of life. The SF-Qualiveen is now available to objectively assess this topic in the Dutch SCI population. Only after being informed about present urinary-specific quality of life, an optimal treatment plan can be defined.

For the future we suggest that urology and rehabilitation departments in the Netherlands implement the Dutch-version SF-Qualiveen in the urological management of SCI patients. The Dutch SF-Qualiveen is now available as a measurement tool. Further research should be aimed at determining its responsiveness to treatment. Once this has been established as sufficient, the Dutch SF-Qualiveen may be used to evaluate the effect of treatments on the urinary-specific quality of life in clinical and research settings.

A question that arises is if we can recommend the use of the SF-Qualiveen in all neuro-urological patients. D'Ancona et al.[16] included, next to 33 SCI and eight MS patients, 10 patients with meningomyelocele (MMC) in the validation study of the Portuguese Qualiveen-30. Results of the different patient groups were not separately described. The authors state that MMC patients would have the same concerns regarding urinary-specific quality of life as SCI and MS patients. However, there might be a difference in the experience of patients with congenital neurological diseases such as MMC compared to patients with acquired diseases like SCI and MS. Therefore, it would be valuable to study the usefulness of the SF-Qualiveen in congenital neurological patients.

It is questionable if our Dutch version SF-Qualiveen validated in the Netherlands can be used in other Dutch speaking countries such as Belgium and South-Africa. Although the language is technically the same, wording and expressions can be different as well as cultural habits. Therefore, we recommend a new validation process before introducing the Dutch SF-Qualiveen in other Dutch language countries.

A strength of this study was the homogeneous patient group of SCI patients. Study results therefore provide a clear view of the validity and reliability of the SF-Qualiveen in this patient group. Furthermore, as this study was conducted at the outpatient clinics of urology of a general hospital and rehabilitation clinic, the SF-Qualiveen may be considered suitable for the use in both settings.

A limitation of the study was that eight of 66 patients (12.1%) were excluded because they did not complete the second questionnaire. This may have introduced a selection bias. However, the SF-Qualiveen scores (test) of these patients were similar to those of the included patients. Therefore, the selection bias may not be an important issue. Another limitation is that no other validated urinary-specific quality of life measure for neuro-urological patients is available to serve as a perfect gold standard to determine the criterion validity of the SF-Qualiveen. In the absence of a perfect gold standard, we chose the UDI-6, a urinary tract symptom inventory, which may have been suboptimal. In addition, criticism could be raised on the age difference between the patient and control group. To investigate one of the hypotheses on construct validity, we used data of a control group. We hypothesized that scores of the SF-Qualiveen in the patient group would be higher than scores in the control group. As a consequence of using earlier collected data, the age of the patient and control group were not matched and we found a statistical significant age difference between the groups. However, we did not expect this age difference to influence outcomes. We assumed that non-neuro-urological patients of the control group, regardless of their age, would have lower scores on a measure that evaluates the urinary-specific quality of life (developed for the use in neuro-urological patients) than the neuro-urological patient group. This expectation was strengthened by the fact that we also found a statistical significant difference in SF-Qualiveen scores between the patient group and the older control group (>40 years).

CONCLUSIONS

From this study we can conclude that the Dutch SF-Qualiveen is valid and reliable to measure the urinary-specific quality of life in SCI patients. This short questionnaire, which is easy to complete, can be a valuable instrument. We suggest to use the total Dutch SF-Qualiveen for evaluation of the urinary-specific quality of life in SCI patients.

List of abbreviations

Erasmus MC: Erasmus University Medical Center
ICC: intraclass correlation coefficient
LOA: limits of agreement
MMC: meningomyelocele
MS: multiple sclerosis
NU: neuro-urological
SCI: spinal cord injury
SUI: stress urinary incontinence
SD: standard deviation
UI: urinary incontinence

Declarations

Ethics approval and consent to participate

The research protocol (MEC-2014-534) was reviewed by the local medical research ethics committee of the Erasmus MC, which concluded that the rules as stated in the Dutch Medical Research Involving Human Subjects Act did not apply to this study.

Consent for publication

Not applicable

Availability of data and materials' statement

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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Authors contributions

SR concept and design, data acquisition, data analysis and interpretation, drafting of the manuscript. IK concept and design, data analysis and interpretation, revision of the manuscript. JS concept and design, data acquisition, revision of the manuscript. LH concept and design, revision of the manuscript. TS data acquisition, revision of the manuscript. BB concept and design, data acquisition, revision of the manuscript. All authors read and approved the final manuscript.

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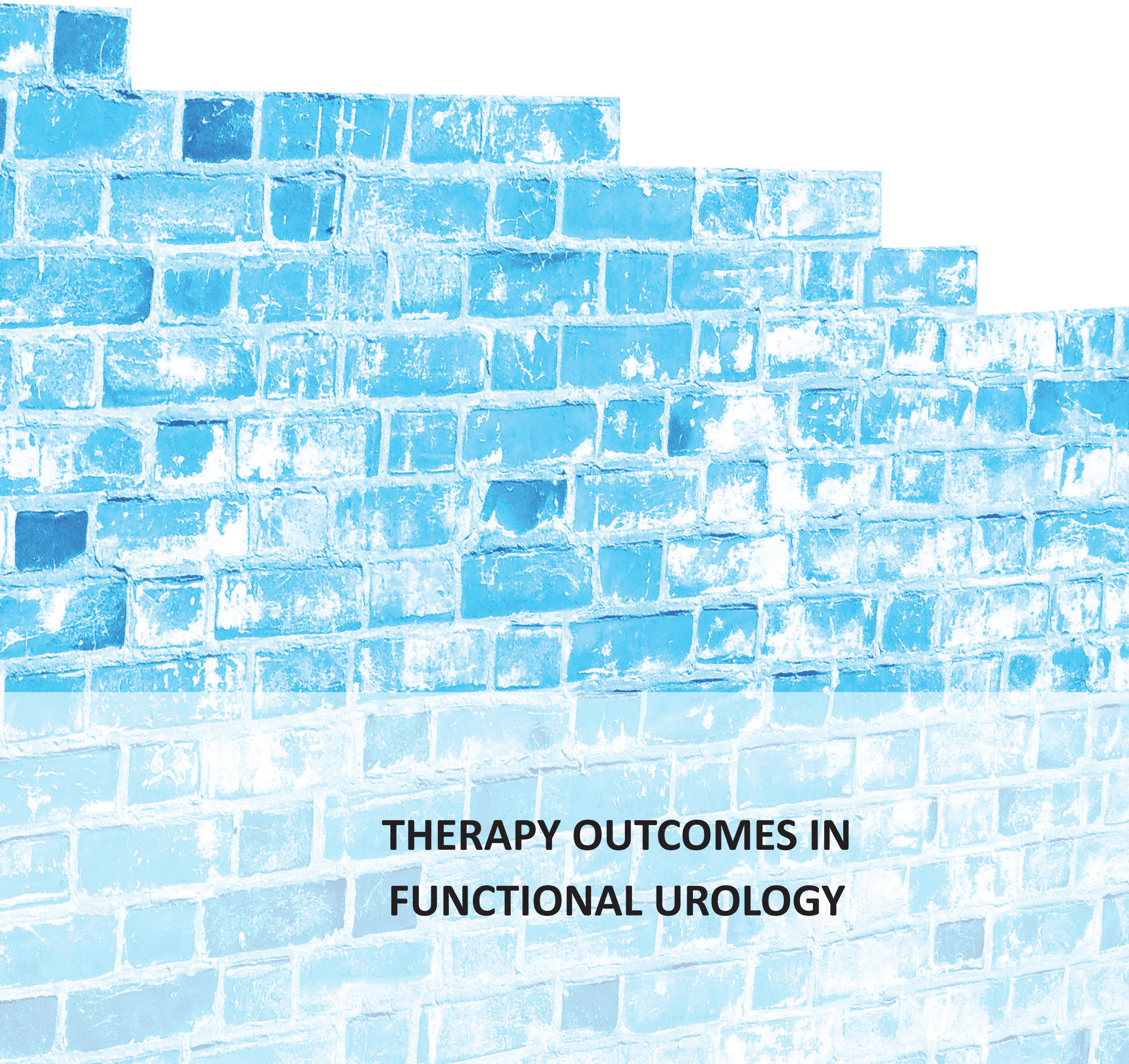
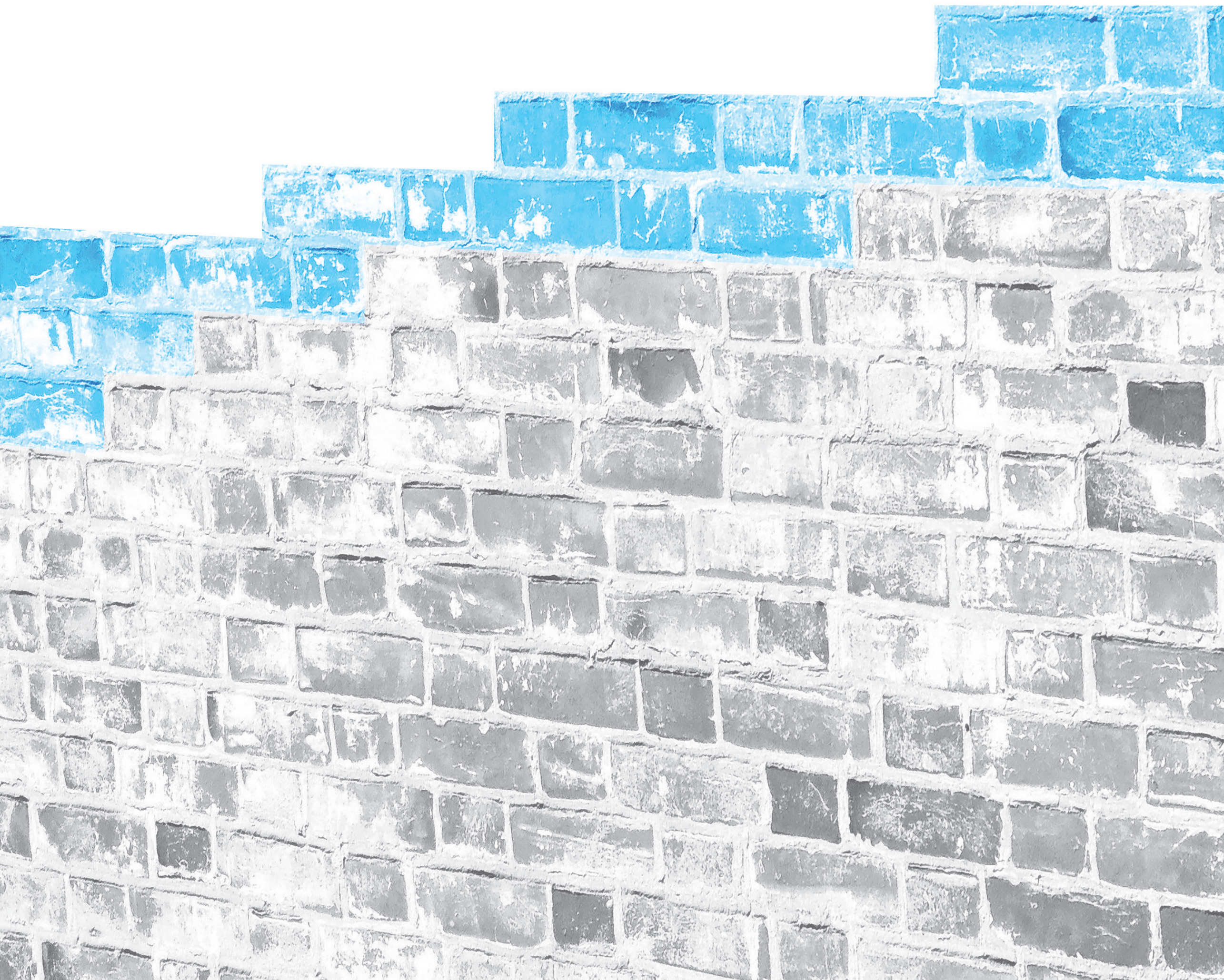
PART II



THERAPY OUTCOMES IN FUNCTIONAL UROLOGY



CHAPTER 5

Maximum urethral closure pressure increases after successful adjustable continence therapy (ProACT) for stress urinary incontinence after radical prostatectomy

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ABSTRACT

Objective: To evaluate changes of the urethral pressure profile (UPP) after implantation of adjustable continence therapy (ProACT), a minimally invasive procedure in which 2 volume-adjustable balloons are placed periurethrally for treatment of male stress urinary incontinence. The working mechanism of the ProACT to achieve continence has not been fully understood. We hypothesized that successful treatment with ProACT improves urinary continence by inducing a significant increase in static urethral pressure.

Materials and methods: We included patients who underwent UPP before and after ProACT implantation. UPPs were initially performed with the Brown-Wickham water perfusion method and later with the T-DOC Air-Charged catheter method. Pre- and postoperative UPPs and International Prostate Symptom Scores were evaluated. UPP measurements of successfully (no or 1 precautionary pad per day) and unsuccessfully treated patients were compared.

Results: Twenty-seven patients were included in the study; 23 patients were successfully and 4 patients were unsuccessfully treated. Maximum urethral closure pressure (MUCP) increased significantly from median 58.0 to 79.0 cm H2O in the successfully treated group ($P = .001$). Within the subgroup of unsuccessfully treated patients, MUCP did not change significantly ($P = .715$). The change in MUCP was statistically significantly different between the successful and unsuccessful group ($P = 0.034$). Total score of the International Prostate Symptom Scores did not change significantly after ProACT implantation ($P = .097$).

Conclusions: Successful treatment with ProACT is associated with a significant increase of MUCP. This implies that increased static urethral pressure contributes to the working mechanism of the ProACT device to achieve continence.

INTRODUCTION

Postprostatectomy incontinence (PPI) is a common complication after radical prostatectomy (RP) that can cause great distress.[1] One year after RP, the incidence of urinary incontinence is 9%-16% depending on the definition used and surgical technique.[2, 3] Most of the PPI patients suffer primarily from stress urinary incontinence (SUI). The maximum urethral closure pressure (MUCP) and functional profile length (FPL) are decreased after RP, presumably caused by the loss of forces normally generated by the prostate and sphincter, and are associated with regaining continence.[4, 5] Although implantation of an artificial urinary sphincter is still the gold standard treatment for moderate to severe SUI after RP, less invasive techniques have become more available.[6]

One such technique is the Adjustable Continence Therapy (ProACT, Uromedica, Minneapolis, MN). This implies implantation of a device consisting of 2 periurethrally placed volume-adjustable balloons. ProACT implantation achieved continence (defined as the use of no or 1 precautionary pad) in 60%-80% of patients[7-11] and quality of life index scores for urinary incontinence improved by 31-48 points (score range 1-100).[8-10, 12]

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The working mechanism of the ProACT has not been fully understood. Other continence devices like the male sling[13-15] elevate the MUCP after (successful) treatment. Utomo et al. [16] demonstrated that the urethral resistance during voiding had increased in men who were successfully treated with ProACT for SUI after RP. We hypothesized that the ProACT induces changes of the static urethral pressure profilometry (UPP), especially an increase of MUCP, and that this mechanism contributes to regaining continence. The objective of this study was to evaluate the UPP and International Prostate Symptom Score (IPSS) measures before and after ProACT implantation in patients with SUI after RP.

MATERIALS AND METHODS

Subjects

We reviewed the medical charts of patients who had undergone ProACT implantation for SUI after RP at our institution. We included patients for whom a pre- and postoperative UPP was available. Patients who underwent urinary tract surgery between the pre- and postoperative measurements were excluded. This study was approved by the local ethic committee.

Intervention

The first ProACT implantation at our institution was performed on May 2007. Since then, all implantations were done by one surgeon (BFMB). The procedure was performed as firstly described by Hubner and Schlarp[11]. In the first cohort of patients, a rigid 19F cystoscope was used, and in the second cohort from April 2014, a flexible cystoscope was used. Patients initially visited the department of Urology every 3-4 weeks after implantation. Balloon volume adjustments were made by percutaneous scrotal needle puncture with a maximum of 1 mL on each side if patients reported persistent SUI. Adjustments were made until continence was achieved, until the balloons were filled with a maximum of 8 mL or until there was any other reason to stop filling the balloons (eg, symptoms of obstructed voiding, infection, dislocation of the balloons).

Design

Relevant data were retrospectively retrieved from the patients' medical files, including the IPSS.[17] Urinary incontinence was classified as mild (1 or 2 pads per day), moderate (3 or 4 pads per day), or severe (5 or more pads per day or use of condom catheter). The treatment was defined as 'successful' when patients used no or 1 precautionary pad per day after balloon adjustments.

Methods of measurement

UPPs were performed by one physician (JG) pre- and postoperatively after the balloon volume adjustments were completed.

Two UPP techniques were used. In a first cohort of patients, we used the Brown-Wickham water perfusion method.[18, 19] Two consecutive UPPs were performed. A side-hole 9F water perfusion catheter oriented at the 12 o'clock position was inserted into the bladder and withdrawn through the urethra (withdrawal rate 1 mm/s and perfusion rate 1 mL/min). Rectal pressure was monitored with an 8F tube. From 2011, the T-DOC Air-Charged 7F catheter (Laborie, Mississauga, Canada) method[20] was used. One UPP was performed in every patient pre- and postoperatively. After inserting the catheter into the bladder, the catheter balloons were inflated. The catheter was withdrawn at a speed of 1 mm/s. In each patient, the pre- and postoperative measurements were performed using the same technique. The measurements were done at a bladder volume of 100 mL. The FPL and MUCP were derived from the UPPs.

AUDACT software version 7.11 (Andromeda Medizinische Systeme GmbH, Taufkirchen, Germany) was used to measure and analyze UPP data.

Analysis

Statistical analyses were performed with the statistical package SPSS 21 version. A *P* value of < 0.05 was considered to reflect statistical significance. Descriptive results are presented as median and interquartile range for continuous data, and as counts and percentages for discrete data. We used the Wilcoxon signed-rank test for continuous variables to compare preoperative and postoperative data within groups. The Mann-Whitney U test for continuous variables and Pearson's Chi-Square test for discrete variables were used to compare variables between groups. Spearman rank correlation was used to test the association between 2 variables.

RESULTS

At our institution, 29 patients underwent UPP before and after ProACT implantation between December 2008 and March 2015. Two patients underwent urinary tract surgery between the preoperative and postoperative UPP and were excluded. Basic characteristics of the included men are displayed in Table 1. We compared the patient characteristics between the group with a successful clinical outcome (n = 23) and the group with an unsuccessful outcome (n = 4). The successful group had a significantly lower number of balloon volume adjustments than patients in the unsuccessful group (P = .001). We found no further statistically significant differences between the groups.

Table 1. Patient characteristics

	Complete group	Successful group	Unsuccessful group
N	27	23	4
Age	65.0 (62.0-71.0)	65.0 (62.0-71.0)	66.0 (60.5-75.3)
Body weight (kg)	85.0 (83.0-92.0)	85.0 (83.0-92.0)	87.5 (78.5-93.5)
Balloon volume adjustments (number)	3.0 (1.0-5.0)	3.0 (1.0-4.0)	7.5 (5.5-8.0)
Interval prostatectomy – ProACT (months)	29.0 (20.0-74.0)	33.0 (20.0-74.0)	25.0 (17.3-151.3)
Interval ProACT – UPP postoperatively (months)	7.0 (5.0-10.0)	6.0 (4.0-9.0)	10.0 (7.0-17.5)
Incontinence severity before ProACT			
- Mild: 1-2 pads/24h	- 8 (29.6%)	- 8 (34.8%)	- 0 (0%)
- Moderate: 3-4 pads/24h	- 13 (48.1%)	- 11 (47.8%)	- 2 (50.0%)
- Severe: > 4 pads/24h	- 6 (22.2%)	- 4 (17.4%)	- 2 (50.0%)
UPP measurement method			
-Brown-Wickham	- 11 (40.7%)	- 10 (43.5%)	- 1 (25.0%)
-T-DOC air charged catheter	- 16 (59.3%)	- 13 (56.5%)	- 3 (75.0%)

ProACT, adjustable continence therapy; UPP, urethral pressure profile.

Changes of the UPP After ProACT Implantation

The MUCP and FPL increased significantly after successful treatment with ProACT (Table 2). In contrast, both parameters did not significantly change within the subgroup of unsuccessfully treated patients. The change in MUCP, from preoperative to postoperative, was median 13.0 cm H2O in the successfully treated group and 4.5 cm H2O in the unsuccessfully treated group. This increase was statistically significantly different between the groups (P = .034). The change in FPL was not significantly different between the groups (P = .576). A typical example of a UPP after successful treatment with ProACT is shown in figure 1.

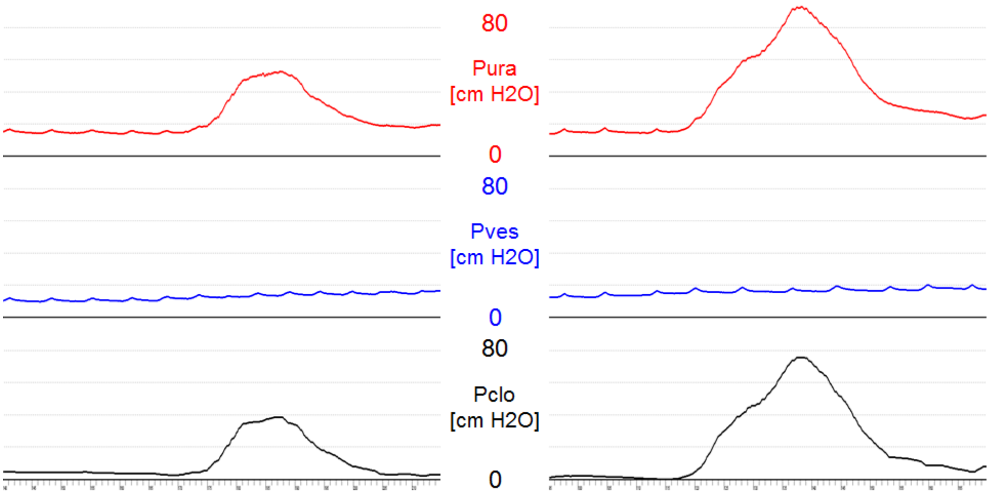

Figure 1. Typical example of a UPP before and after successful treatment with ProACT. Pclo, urethral closure pressure; ProACT, adjustable continence therapy; Pura, urethral pressure; Pves, intravesical pressure; UPP, urethral pressure profile.

The UPP measurements were compared between the 2 measurement methods. MUCP increased significantly after ProACT in both groups. (Table S1) No significant differences were found in baseline MUCP (P = .544), postoperative MUCP (P = .716), and change in MUCP (P = .610) between the 2 measurement methods. FPL increased significantly after ProACT in the Brown-Wickham group, whereas it did not change significantly in the T-DOC subgroup. (Table S1) Although a significant difference was found in the postoperative FPL (P = .017), the preoperative FPL (P = .071) and the change in FPL (P = .645) were not significantly different between the Brown-Wickham water perfusion and the T-DOC air charged catheter subgroup.

Table 2. UPP parameters before and after ProACT implantation

	Complete group			Successful group			Unsuccessful group		
	Preoperative	Postoperative	P*	Preoperative	Postoperative	P*	Preoperative	Postoperative	P*
MUCP (cmH2O)	58.0 47.0-78.0	76.0 56.0-134.0	**.002**	58.0 47.0-71.0	79.0 56.0-136.0	**.001**	65.5 41.8-81.8	60.0 47.5-77.0	.715
FPL (mm)	29.7 24.3-52.3	43.1 32.3-55.0	**.013**	29.8 24.3-52.3	43.1 32.3-50.6	**.043**	27.5 22.5-50.1	48.2 24.5-61.9	.144

FPL, functional profile length; MUCP = maximum urethral closure pressure. Data are displayed as median and interquartile range. * P values resulting from Wilcoxon signed-rank test comparing parameter values before and after ProACT implantation. Bold values indicate a statistically significant correlation with a P-value of < 0.05.

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IPSS

IPSS total score and IPSS questions 5 and 6 scores (which are assumed to reflect voiding problems) did not change after ProACT implantation (table 3).

Table 3. IPSS scores before and after ProACT implantation.

	Preoperative	Postoperative	P*
IPSS - total score	11.0 (5.5 - 15.5) Missing: 10	7.0 (4.0 – 11.0) Missing: 0	.097
IPSS - question 5	0.5 (0 – 3.0) Missing: 9	1.5 (0 – 3.3) Missing: 1	.298
IPSS - question 6	0 (0 – 1.0) Missing: 9	0 (0 – 2.0) Missing: 1	.277
IPSS – QoL question 8	4.0 (4.0 – 5.0) Missing: 7	1.0 (1.0 – 2.0) Missing: 0	**< .001**

IPSS, International Prostate Symptom Score. Data are displayed as median (Interquartile Range). The number of missing values per item is displayed. IPSS question 5: How often have you had a weak urinary stream? IPSS question 6: How often have you had to strain to start urination? IPSS – QoL question 8: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? * P, Wilcoxon signed-rank test to assess changes in outcomes before and after ProACT implantation. Bold values indicate a statistically significant correlation with a P-value of < 0.05.

No statistically significant correlations were found between the postoperative IPSS total score and postoperative MUCP (rho = -0.086 and P = .670) and FPL (rho = 0.004 and P = .984). In addition, no correlations were found between the postoperative IPSS question 5 score and the postoperative MUCP (rho = -0.303 and P = .133) and FPL (rho = -0.040 and P = -.847), nor between postoperative IPSS question 6 score and postoperative MUCP (rho = 0.163 and P = 0.426) and FPL (rho = 0.310 and P = 0.124).

IPSS question 8, a quality of life due to urinary symptoms question, increased significantly from median 4 (mostly dissatisfied) preoperatively to 1 (pleased) postoperatively (table 3).

COMMENT

In this study it was found that static UPP values had increased after ProACT implantation in men who suffered from SUI after RP. MUCP significantly increased in the successfully treated group, whereas it did not in the unsuccessfully treated patients. In addition, the change in MUCP was statistically different between the groups. This suggests that the increase in static urethral pressure is an important factor to regain continence. Although FPL significantly increased postoperatively in the successfully treated group and did not reach the significance level in the unsuccessfully treated group, the change in FPL was not statistically different between the groups.

No other studies have analyzed the effect of ProACT implantation on UPP. However, UPP changes have been studied in the context of other male continence devices, such as slings[13-15]. Horstmann et al.[13] investigated urodynamic findings in patients before and after bulbourethral composite suspension. They included 10 successfully treated patients and performed UPP by the air-charged catheter method. An increase in MUCP from 40 to 58 cmH2O and an increase in FPL from 31 to 40 mm was found. When comparing the successfully treated group in our study with the patients in Horstmann et al's study, pre- as well as postoperative MUCP values were higher in our study (they changed from 58 cm H2O preoperatively to 79 cm H2O postoperatively). Also in the T-DOC subgroup in our study, MUCP values were higher. The FPL measurements and changes in the Horstmann et al. study are comparable to the results we found in our study, where FPL changed from 30 mm to 43 mm in the successfully treated group. The different outcomes between these two studies can be explained by the used definitions of success. Horstmann et al. defined success as a > 50% reduction in pad use. Our definition of success (dry or 1 pad for precaution) is more strict.

Wadie[14] described UPP changes (using the water perfusion measurement method) in 40 male patients after retropubic bulbourethral sling placement. Successfully (in this study defined as no pad use and a negative stress test) and unsuccessfully treated patients were included. MUCP changed from 57 cmH2O preoperatively to 100 cmH2O postoperatively, and FPL changed from 21 mm to 52 mm. Although these changes seem numerically relevant, they did not reach statistical significance.

Rehder and Gozzi[15] reported on the outcome of 20 patients treated by transobturator sling suspension. UPPs were performed in 5 patients. It is unclear if the patients who underwent UPPs were successfully or unsuccessfully treated and which measurement method was used. Although it is hypothesized that the transobturator sling does not compromise the urethra, MUCP changed from 13 cmH2O preoperatively to 86 cmH2O postoperatively. FPL changed from 3 mm to 17 mm. Baseline MUCP and FPL in our study were higher than in the patients studied by Rehder and Gozzi. It is difficult to compare the results because the outcome of treatment in these patients and the used measurement method are unknown.

The urethral pressure is derived from the distensibility of the urethra, the forces of the surrounding tissues (eg, the prostate and the sphincter) and the cross-sectional area of the urethra.[5] It is known that the MUCP is decreased postprostatectomy and that MUCP values are higher in men who regain continence than in men who remain incontinent.[4] We found an increase in MUCP after successful treatment with the ProACT device. Bilateral compression of the urethra by the balloons might be responsible for this increase and could partially replace the forces normally generated by the prostate and sphincter. This implies that an increase in the static urethral pressure contributes to the working mechanism of ProACT.

The regain of continence may not be fully explained by the increase of MUCP, because such an increase did not occur in all successfully treated patients. An additional factor that might contribute to the continence mechanism is the displacement of the urethra toward the pubic bone by the balloons. This mechanism has been described after placement of a transobturator sling with minimal tension in male cadavers (presumably not postprostatectomy).[15] However, periurethral fibrotic tissue after prostatectomy makes displacement at the level of the balloons toward the pubic bone less probable. It could be hypothesized that the ProACT induces a displacement of the urethra, but this seems less important than the direct compressive effect on the urethra.

The role of FPL in the working mechanism of ProACT remains unclear. The observed increase of FPL in the small group of unsuccessfully treated men (although not significant), the insignificant difference in change in FPL between the successful and unsuccessful groups, and the difference in values obtained with the 2 techniques hamper a straightforward interpretation of results.

We evaluated the IPSS, a patient-reported outcome measure, with special interest in the questions reflecting obstructive voiding symptoms and patient satisfaction. IPSS did not significantly change after ProACT implantation. This suggests that ProACT is not associated with the occurrence of obstructive voiding symptoms. This is of clinical importance for future use of the ProACT. The occurrence of voiding symptoms did not correlate with postoperative MUCP and FPL. Patients' satisfaction with their urinary condition (IPSS question 8) changed from mostly dissatisfied preoperatively to pleased postoperatively. This indicates that the most important treatment goal, patient satisfaction, was realized in most patients.

This is the first study that describes UPP changes after ProACT implantation and it thus contributes to the understanding of the working mechanism of ProACT. This is of relevance for the development of future devices and it could contribute to understanding the mechanism of PPI as well.

A limitation of our study is the use of 2 different UPP measurement techniques. Although both the Brown-Wickham water perfusion catheter method[18, 19, 21] and the T-DOC air-charged catheter method[20] have been separately proven to accurately measure the UPP, it is unknown if they can be used interchangeably. No comparing trials between the 2 used techniques are available. Comparing the results obtained with the 2 techniques in our study, we only found a statistically significant difference in the postoperative FPL values. We used the same technique pre- and postoperatively in each patient. Intrapatient comparisons are therefore reliable. Another limitation of the study is that the IPSS is not validated in this study population. The IPSS is validated in patients with benign prostate hypertrophy. The reason for using the IPSS in our practice during and after balloon adjustments of the ProACT is that it informs us on the occurrence of obstructive voiding complaints. No such questionnaire is validated for this specific patient group. Other limitations of the study are its retrospective design and the relatively small study group.

CONCLUSIONS

We conclude that successful treatment with ProACT is associated with a considerable and significant increase of MUCP. This implies that increased static urethral pressure contributes to the working mechanism of the ProACT device to achieve continence.

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SUPPLEMENTARY MATERIAL S1

Supplementary material S1. UPP parameters before and after ProACT implantation. Brown-Wickham water perfusion method vs. T-DOC Air-Charged catheter method.

	Brown-Wickham subgroup (Successful N = 10, Unsuccessful N = 1)			**T-DOC subgroup** (Successful N = 13 Unsuccessful N = 3)		
	Preoperative	Postoperative	P*	Preoperative	Postoperative	P*
MUCP (cmH2O)	58.0 47.0-85	79.0 56.0-166.5	**0.041**	60.0 45.5-76.0	75.0 51.0-104.3	**0.021**
FPL (mm)	24.9 21.4-37.5	32.3 20.9-45.5	**0.013**	30.0 26.1-54.4	45.4 36.1-59.6	0.121

Data are displayed as median and Inter Quartile Range. MUCP = Maximum Urethral Closure Pressure, FPL = Functional Profile Length. P* = Wilcoxon signed rank test to assess changes in outcomes before and after ProACT implantation.

CHAPTER 6

20 years experience with appendicovesicostomy in paediatric patients: complications and their re-interventions

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ABSTRACT

Aims: To evaluate the long-term outcome of appendicovesicostomies and to present the frequency and timing of complications needing re-intervention.

Methods: In this retrospective study we included patients in whom an appendicovesicostomy was created at our institution between 1993 and 2011. Patients with a follow-up less than 1 year were excluded. Patient characteristics and conduit-related complications requiring re-intervention were collected.

Results: One hundred and twenty-eight patients were included with mean age at initial surgery of 10.1 ± 3.9 years. Two thirds of the children had underlying neurogenic disease. The mean follow-up was 10.1 ± 4.8 years. All but one patient continued to use the catheterizable channel. Re-intervention for conduit-related complications was necessary in 32.0% of the patients. A second, third and fourth re-intervention was required in respectively 10.9%, 2.3% and 1.6%. The commonest complications were cutaneous/fascial stenosis in 14.8%, stenosis at conduit-bladder level in 9.4%, and stomal incontinence in 6.3% of the patients. The most performed re-interventions were stoma revision (in 16.4% of the patients), conduit revision (10.2%), and dilatation of a stenotic tract (4.7%). 63.3% of the re-interventions was superficial and/or endoscopic. The peak incidence of re-interventions was in the 1st year after conduit construction and decreased yearly.

Conclusions: Our study gives an overview of patients and their conduits developing from prepubertal children to young adults. During a mean follow-up of 10.1 years, roughly one third of the patients needed a re-intervention. We conclude that an appendicovesicostomy is an effective and durable treatment for whom transurethral clean intermittent catheterization is not feasible.

INTRODUCTION

For children with irreversible lower urinary tract dysfunction, for whom transurethral clean intermittent catheterization (CIC) is not feasible, a continent catheterizable conduit can be a solution for bladder drainage. Mitrofanoff appendicovesicostomy[1] and Monti ileovesicostomy[2] are the most common created continent catheterizable channels.

Although short-term outcomes, complications and re-interventions after continent catheterizable conduit construction are commonly reported,[3-10] the long-term follow-up and thereby the durability of conduits is still under-documented.[11-14] Previous long-term follow-up studies included small study populations,[11, 13] heterogenic study populations,[13] and a mean follow-up of less than 10 years.[12-14] The long-term follow-up of paediatric patients after continent catheterizable conduit construction is of particular interest, because of their long life expectancy.

For this reason we evaluated the long-term outcome of continent catheterizable conduits. We present the frequency and time of occurrence of complications needing re-intervention in a group of 128 paediatric patients with a mean follow-up of 10 years after appendicovesicostomy construction.

MATERIALS AND METHODS

We reviewed the medical charts of all paediatric patients who had undergone surgical construction of a continent catheterizable conduit using appendix at our institution between 1993 and 2011. Patients with a minimum follow-up of 1 year after initial surgery were included in our study.

Surgical procedures were performed as described by Mitrofanoff to create an appendicovesicostomy.[1] If, for a concurrent procedure, it was necessary to open the bladder (i.e. augmentation), a submucosal tunnel was created. In patients with no concurrent procedure the detrusor tunnel was created according to the Lich-Gregoire technique.[15] In the majority of cases, stomas were constructed umbilical by using a V-shaped skin flap.

Patients were initially followed up every 3 months. If a conduits' condition was stable, the frequency of visits was lowered. CIC was started 4-6 weeks postoperatively, using disposable catheters 12-14 Fr. Antegrade colonic enema (ACE) stoppers (a silicone plug) were not routinely prescribed.

Information about demographics, underlying diagnosis, surgical procedure, conduit related complications and their re-interventions (performed under general anaesthesia) and follow-up duration was retrospectively retrieved from the medical files.

Statistical analyses were performed with the statistical package SPSS 21 version. A *P*-value of < 0.05 was considered to reflect statistical significance. Descriptive results are presented as mean ± standard deviation for continuous data and as counts and percentages for discrete data. The Chi-Square test was used to compare the frequency of re-interventions between groups for categorical variables. Kaplan-Meier curves were generated to display the time to re-interventions and the re-intervention free survival.

RESULTS

At our institution 131 paediatric patients underwent surgery to construct an appendicovesicostomy between 1993 and 2011. Three patients had a follow-up of < 1 year and were excluded. We included all other 128 patients for as long as they were under treatment at our hospital. The mean follow-up was 10.1 ± 4.8 years and ranged from minimum 1.9 to maximum 21.8 years. After 5, 10 and 15 years respectively 111, 59 and 26 patients were still in follow-up. At the end of follow-up the mean age was 20.7 ± 6.3 years and ranged from minimum 8.1 to maximum 35.8 years. Currently, 93/128 patients (72.6%) are still in follow-up at our institution. 2/128 (1.6%) died of unrelated diseases, care for 27/128 patients (21.1%) was transferred to another hospital (most at the time of transition from paediatric to adult care) and 6/128 patients (4.7%) were lost to follow-up due to unknown reasons. Mean follow-up of the 35 patients who were lost to follow-up was quite long: 7.7 ± 3.5 years and the mean age at the final follow-up visit was 18.3 ± 5.7 years.

Patient characteristics are displayed in table I. The gender distribution was almost equal. The underlying diagnosis was neurogenic bladder dysfunction in 85 (66.4%) and non-neurogenic bladder dysfunction in 43 (33.6%). In the neurogenic group myelomeningocele was the commonest diagnosis (75.3%), followed by tethered cord, spinal cord injury and spastic tetraplegia. Bladder exstrophy was the most common non-neurogenic diagnosis (55.8%), followed by cloacal malformation, epispadias, Prune belly syndrome and traumatic lesions of the lower urinary tract. Bladder neck surgery was performed as a concurrent procedure in 57.1% of the patients and bladder augmentation in 69.5%. In all patients the aim of treatment was to create a high-volume, low-pressure reservoir. Other concurrent procedures were reimplantation of a ureter, urethral reconstruction and Botulinum toxin injections in the bladder.

Table I. Patient characteristics of 128 patients.

Age at conduit creation		10.1 ± 3.9 years
Gender	Male	68 (53.1%)
	Female	60 (46.9%)
Underlying diagnosis	Neurogenic	85 (66.4%)
	Non-neurogenic	43 (33.6%)
Concurrent procedures	None	18 (14.1%)
	Augmentation (alone)	34 (26.6%)
	Augmentation + bladder neck surgery	55 (43.0%)
	Bladder neck surgery (alone)	18 (14.1%)
	Other	3 (2.3%)
Stoma location	Umbilical	107 (83.6%)
	Lower abdominal quadrant	21 (16.4%)

Mean ± standard deviation and number (percentage), are given where appropriate.

One hundred and twenty-seven of 128 patients (99.2%) continued to use their catheterizable channel for bladder emptying. In one patient the conduit could not be preserved due to postoperative bowel strangulation around the stoma resulting in ischemia of the channel.

Forty-one of 128 patients (32.0%) underwent a re-intervention for conduit-related complications. A second, third or fourth re-intervention was necessary in respectively 10.9%, 2.3% and 1.6% of patients. The commonest conduit-related complications requiring re-intervention were cutaneous/fascial stenosis in 14.8%, stenosis at conduit-bladder level in 9.4% and stomal incontinence in 6.3% of the patients. In total 60 re-interventions were performed for conduit related complications in 41 patients (table II).

The mean age at re-intervention was 14.9 ± 5.4 years. The most performed re-interventions were stoma revision (in 16.4% of the patients), conduit revision (including re-implantation of the conduit into the bladder) (10.2%), dilatation of a stenotic tract (4.7%), and replacement of the conduit (3.9%). Other re-interventions were excision of the conduit and drainage of a parastomal abscess.

Three of the six patients who underwent dilatation of a stenosis needed a second surgical re-intervention to treat the stenosis.

Thirty-eight of the 60 (63.3%) re-interventions were superficial and/or endoscopic: stoma revisions, dilatations, excision of polyps, bulking agent for stomal incontinence and endoscopic placement of an indwelling catheter.

Table II. Re-interventions and their indications.

Re-interventions	Number
Stoma revision Indication: - cutaneous/fascial stenosis (20) - fascial defect (2) - mucosal prolapse (1) - other (1)	24
Revision conduit Indication: - incontinence (8) - stenosis conduit-bladder (6)	14
Dilatation of stenosis Indication: - cutaneous/fascial stenosis (3) - stenosis conduit-bladder (3)	6
Replacement conduit Indication: - stenosis conduit-bladder (4) - other (1)	5
Bulking agent conduit Indication: stomal incontinence (3)	3
Endoscopic placement of an indwelling catheter Indication: other catheterization problems (3)	3
Excision polyps Indication: polyps (2)	2
Other	3
TOTAL	**60 re-interventions in 41 patients**

Figure 1 displays the occurrence and timing of the first re-intervention. After 1 year the risk of having had a re-intervention is 12.5%. After 5, 10 and 15 years, the cumulative risk of having had a re-intervention respectively is 22.9%, 32.7% and 36.5%. Fourteen patients needed a second, three patients needed a third and two patients needed a fourth re-intervention during follow-up. Three of 19 second, third and fourth re-interventions (15.8%) were performed in the 1st year after appendicovesicostomy construction. Ten of 19 of these re-interventions (52.6%) were performed between the 2nd and 5th year of follow-up and 6 of 19 (31.6%) re-interventions were performed after 5 years. Considering all 60 performed re-interventions, the peak incidence was in the first year after conduit formation, i.e., 31.7% of all re-interventions, and decreased thereafter. With 102 of 128 patients (79.7%) in follow-up, only 12/60 (20.0%) re-interventions were performed after 6 years. Conduit-bladder stenosis was the commonest late (after 6 years) complication (41.7%), followed by cutaneous/fascial stenosis (16.7%) and stomal incontinence (16.7%). The most performed re-interventions after 6 years were conduit revision (41.7%) and stoma revision (25.0%).

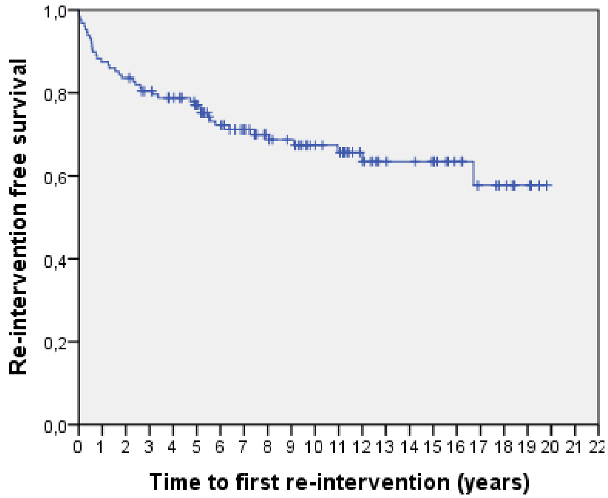

Figure 1. Timing of re-interventions
Kaplan-Meier curves represent data on the re-intervention free survival distribution.

Analysis revealed no significant differences in complication rate between male and female patients, neurogenic versus non-neurogenic underlying diagnosis, patients with or without augmentation and between the various stoma locations (Table III).

Table III. Number of patients needing re-intervention in different groups

Male 23/68 (33.8%)	vs	Female 18/60 (30.0%)	P = 0.644
Neurogenic 28/85 (32.9%)	vs	Non-neurogenic 13/43 (30.2%)	P = 0.756
Augmentation 26/89 (29.2%)	vs	No augmentation 15/39 (38.5%)	P = 0.302
Umbilical stoma 35/107 (32.7%)	vs	Lower abdominal quadrant stoma 6/21 (28.6%)	P = 0.710

Statistical significances of different variables were explored using Chi-Square Tests.

DISCUSSION

During a mean follow-up of 10.1 years, roughly one third of the children with an appendicovesicostomy required a re-intervention. The commonest complications were cutaneous/fascial stenosis, stenosis at conduit-bladder level, and stomal incontinence. The most frequent re-interventions were stoma revision, conduit revision and dilatation of a stenosis. In 63.3% of cases, the re-interventions were superficial and/or endoscopic. After conduit-replacement in five patients in the study group, all but one patient continued to catheterize the conduit. The peak incidence of re-interventions was in the 1st year after conduit formation and decreased yearly.

About 32.0% of the patients required a re-intervention after a mean follow-up of 10.1 years. This is in line with the literature with a long-term follow-up. In a study by Rubenwolf et al.[13] with a median follow-up of 7.3 years, 39% of the patients required a re-intervention for stoma-related complications after initial surgery (continent urinary diversion and enterocystoplasty). Leslie et al.[12] reported a re-intervention rate of 39% after a follow-up of 5.8 years in a study population of 169 children with a continent catheterizable channel (Mitrofanoff or Monti). Liard et al. [11] reported conduit-related complications which required re-intervention in 11 of 22 patients (50%) during 20 years' follow-up after appendicovesicostomy construction. In other relatively large series with follow-up between 28 months and 4 years, conduit related re-interventions were reported in 16-55% of patients.[3-10]

In our series, 63.3% of the re-interventions was superficial and/or endoscopic. We assume that hospitalization is shorter and recovery is faster after superficial and/or endoscopic re-interventions in comparison to more extensive re-interventions. Nowadays in our institution we perform endoscopic re-interventions regularly in day surgery. Due to missing data as a result of the retrospective study design, we were not able to report on hospitalization after re-interventions in our patient group. Although most series do not specifically report on the extent of the re-intervention, our results are in line with the literature. Welk et al.[6] reported that 82% of the re-interventions in their study population of 67 patients with a median follow-up of 28 months were endoscopic or superficial. Rubenwolf et al.[13] reported on 44 children after continent urinary diversion or enterocystoplasty with a follow-up of 7.3 years. In 54% of the re-interventions (including stoma-related complications, ureteric stenosis, stone formation and adhesive small bowel ileus) only minor revisions were required.

Like in comparable studies, cutaneous or fascial stenosis was the most prevalent complication which needed re-intervention in our study (in 14.8% of the patients). Reporting rates of comparable series vary between 6% and 39% of the patients.[3-8, 10-12, 14] The second and third most common reasons to perform a re-intervention were stenosis at conduit-bladder level in 9.4%, and stomal incontinence in 6.3% of patients. This is consistent with previous series which report on stenosis at conduit-bladder level in 6-16%[4, 6, 12] and on channel incontinence in 1-10% of the patients.[6, 9, 12, 14]

The outcome of dilatation of a stenotic tract was successful in three of six patients. In general in our hospital, dilatation is not the first choice treatment to treat a stenosis. Low success rates are described in literature. Suzer et al.[8] reported an unsuccessful outcome of dilatation of a stenosis in 11 of 14 patients, Thomas et al.[5] in 8 of 16 patients and McAndrew et al.[7] in 18 of 35 patients. There might be a bias in the patient selection for dilatation. Patients with a mild stenosis might be more likely to be treated by dilatation than people with severe stenosis. Due to the small number of patients who underwent dilatation and the possible selection bias, no conclusions can be drawn from this study to this specific topic.

Some patients in our series used an ACE stopper to ensure the stoma open if necessary. The ACE stopper was not routinely prescribed. Due to the retrospective design of the study, we were not able to retrieve the exact number of patients using the ACE stopper. Our clinical experience with the ACE stopper is variable and some patients express discomfort during use. One report on the effectiveness of the ACE stopper in preventing stomal stenosis in the urinary tract has been published. Subramaniam et al.[16] reported that 6/19 (32%) patients needed a revision after construction of a catheterizable channel without ACE stopper (follow-up 47 months) and no one out of 14 patients needed a revision after using an ACE stopper for 3-6 months postoperatively (follow-up 22 months). Some patients experienced minimal discomfort while using the ACE stopper. Two reports on the effectiveness of the ACE stopper in preventing stomal stenosis after construction of an ACE show nil stomal stenosis after a follow-up of 12 months[17] and 8% after a mean follow-up of 2.6 years.[18] The results of these studies seem promising for prevention of stomal stenosis with an ACE stopper, and therefore routine use of an ACE stopper can be considered.

In our series we found a re-intervention peak in the 1st year after conduit construction and yearly decreasing incidence of re-interventions thereafter. This initial peak might be explained by the initial postoperative healing process and patients' unfamiliarity with handling the channel. We found no specifically late-onset complications or re-interventions. Previous studies on conduit construction also reported an initial re-intervention peak in the first year.[5, 6, 8, 12, 14] Only two previous studies have reported particularly on the timing of re-interventions during long-term follow-up. Leslie et al.[12], reporting on 169 paediatric patients with a median follow-up of 5.8 years, showed declining revision rates over the years, but the authors recommended continuous monitoring to detect late problems. Szymanski et al.[14] reported on an appendicovesicostomy group (median follow-up 5.7 years) and a Monti ileovesicostomy group (median follow-up 7.7 years) and showed a decrease in revision risk after 5 years, but concluded that channel complications continue over the channel's lifetime. Considering results of previous studies and our results, we may conclude that late re-interventions are rare and that it is safe to lower the frequency of follow-up visits after 1 year (provided the underlying diagnosis allows this).

With a mean follow-up of 10.1 years, mean age at conduit creation of 10.1 years and a mean age at the end of follow-up of 20.7 years, our study gives an overview of patients and their conduits developing from prepubertal children to young adults. All but one patient continued to use the catheterizable channel for bladder drainage. In this one exceptional case, the conduit could not be preserved due to ischemia of the channel and transurethral CIC was restarted. In only 3.9% of the study population the conduit needed to be replaced. These results demonstrate a good durability of the conduits during the progression of children to adulthood. The construction of a continent catheterizable channel is a good alternative for transurethral CIC in a paediatric patient group with irreversible lower urinary tract dysfunction.

Thirty-five of one hundred and seven (32.7%) patients with an umbilical stoma and 6 of 21 (28.6%) patients with a lower abdominal quadrant stoma underwent a re-intervention in our study population. No statistical significant difference in re-intervention rate between the different stomal sites was found. These results reconfirm the results of the long-term follow-up studies of Leslie et al.[12] and Szymanski et al.[14] Leslie et al.[12] reported no differences in surgical revision free survival and Szymanski et al.[14] found no overall difference in subfascial (not stomal revision) re-intervention rate between the different stomal sites (umbilical vs. non-umbilical/lower quadrant). No significant relations were found between re-intervention rate and augmentation status, gender nor underlying diagnosis in our study population.

A limitation of our study is the retrospective design. Missing data, (selection) bias and patient loss during follow-up are generally more common in retrospective studies. In addition, in this study we focused on re-interventions performed under general anaesthesia. We did not include complications which were conservatively managed or performed without general anaesthesia. Therefore we probably underestimated the overall complication rate. Despite these limitations, this study adds reliable information about the long-term outcome of continent catheterizable conduits in view of its large sample size and long follow-up (mean 10.1 years). All previous studies had a shorter follow-up or a smaller study population. Especially in a patient group with mostly prepubertal children, monitoring the function of the conduit during their progression to adulthood is of interest. For patient counselling it is valuable to create awareness in patients and their parents about what to expect after reconstruction of a continent catheterizable conduit.

CONCLUSIONS

We present a series of 128 paediatric patients with a mean follow-up of 10.1 years after appendicovesicostomy creation. Our study gives an overview of patients and their conduits developing from prepubertal children to young adults. After construction of an appendicovesicostomy 32.0% of the patients needed a re-intervention. 63.3% of the re-interventions was superficial and/or endoscopic. After an initial peak incidence of re-interventions in the 1st year after conduit construction, the incidence of re-interventions decreased yearly. We conclude that creation of a continent catheterizable conduit is an effective and durable treatment for paediatric patients for whom transurethral CIC is not feasible. This information is of relevance for patient counselling and managing of expectations for patients and their parents.

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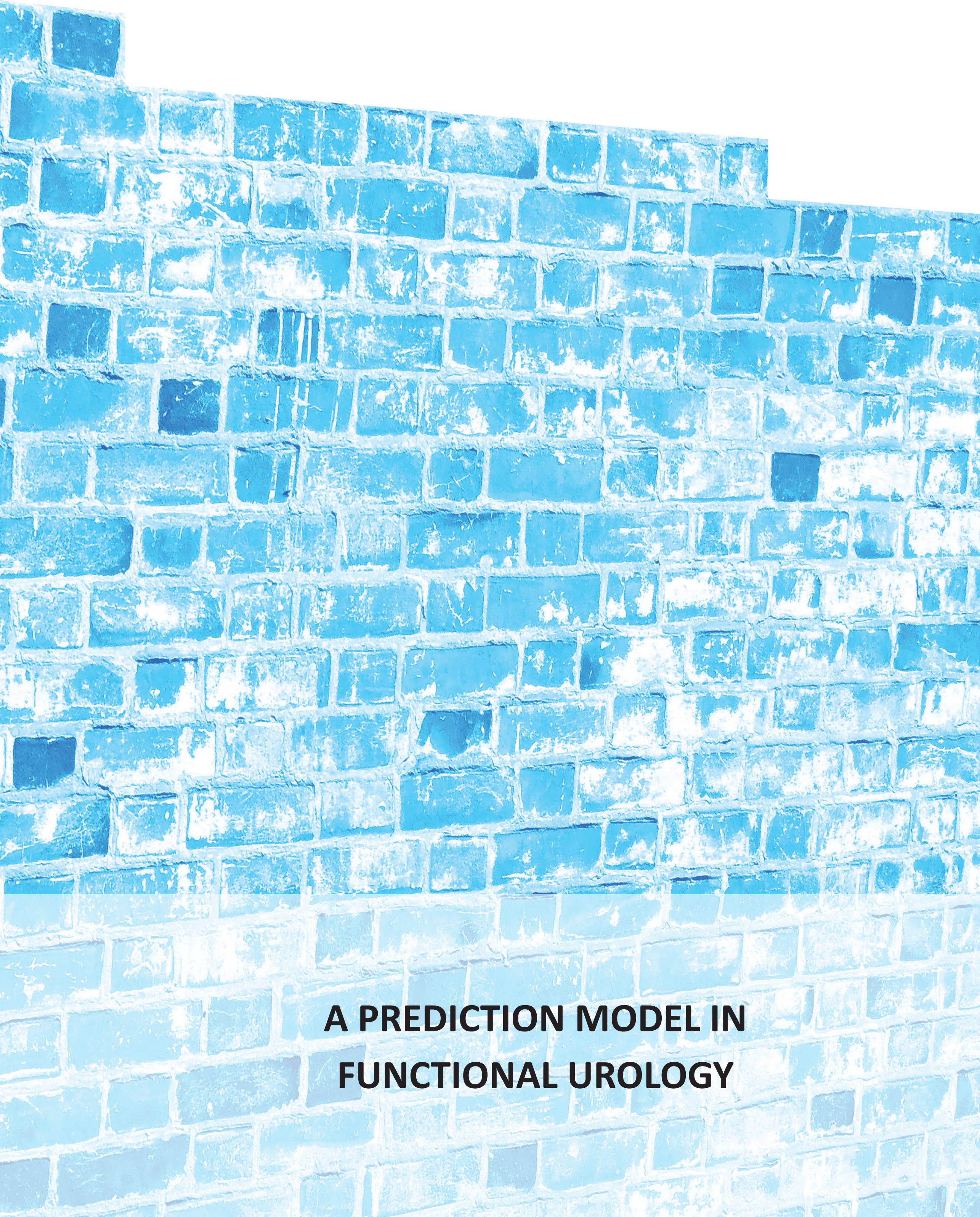
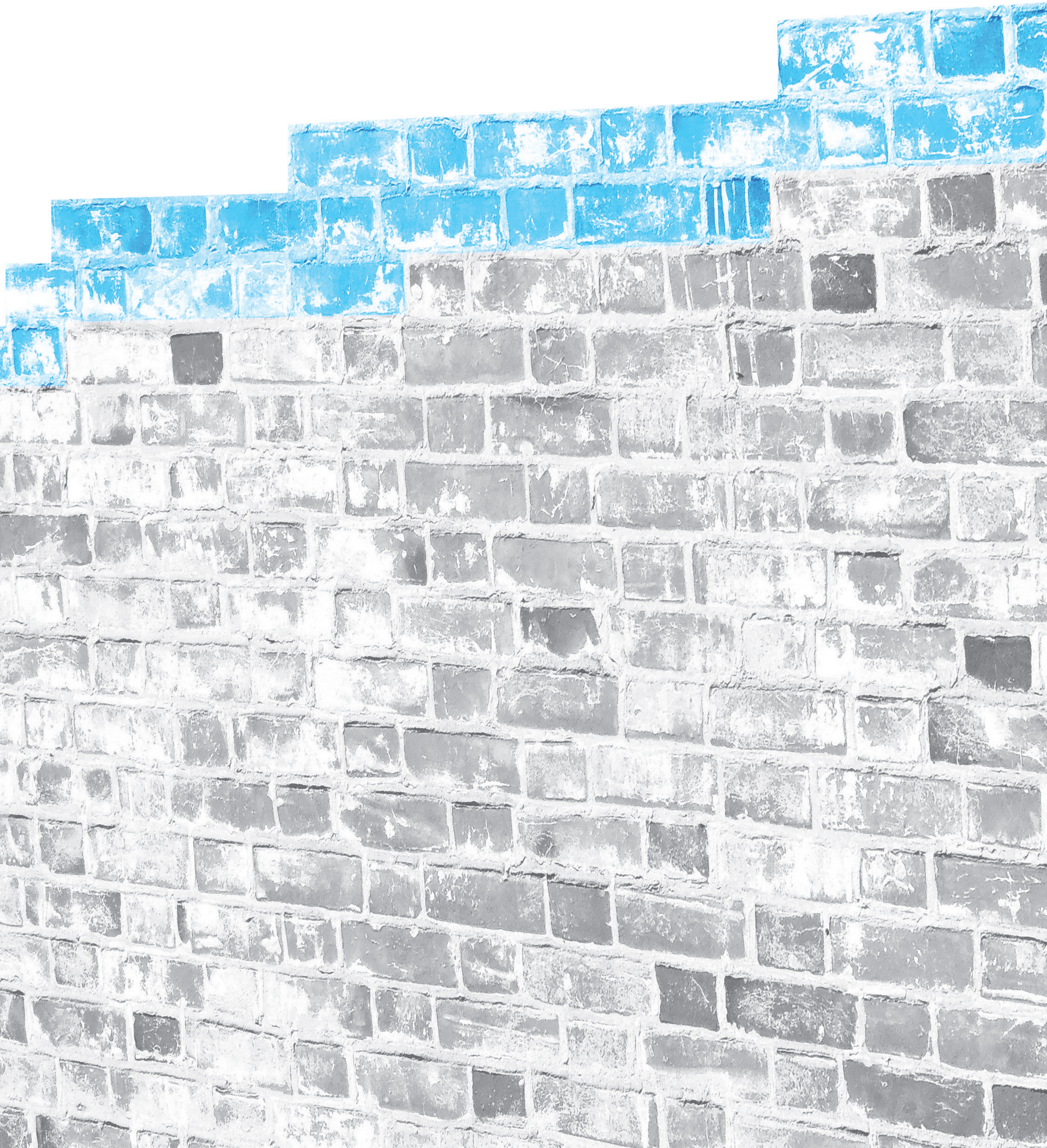
PART III



A PREDICTION MODEL IN FUNCTIONAL UROLOGY



CHAPTER 7

Development of a prediction model in female urge urinary incontinence

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ABSTRACT

Background: Present approach of pelvic floor disorders (PFDs) depends on the knowledge and preference of the caregiver/patient and might result in suboptimal patient outcomes.

Objective: To predict the treatment outcome of urge urinary incontinence (UUI) in women.

Design, setting and participants: Data on patient characteristics, history and investigations of 512 consecutive women treated for UUI in three hospitals in the Netherlands were retrospectively collected and evaluated as potential predictors of treatment outcome.

Intervention: -

Outcome measurements and statistical analyses: The predicted outcome was the short-term subjective continence outcome, defined as patient-reported continence three months after treatment. The outcome is categorized as cure (no urinary leakage), improvement (any degree of improvement of urinary leakage) and failure (no improvement or worsening of urinary leakage). Multivariable ordinal regression with backward stepwise selection was applied to analyze association between treatment benefit and patient's characteristics. Discrimination ability was assessed after internal validation with c-statistic with ordinal outcome.

Results and limitation: Conservative treatment was applied in 12% of the patients, pharmacological 62%, and invasive 26%. Subjective continence outcome was cure, improvement and failure in 20.3%, 48.8%, and 30.9%, respectively. Incontinence episodes/24h, voiding frequency during the day, subjective quantity of UI, coexistence of SUI, night incontinence, and bladder capacity were included in the model. Type of treatment interacted with predictors and resulted in individual estimates of treatment benefit. After internal validation the c-statistic was 0.683 for the ordinal interaction model.

Conclusions: Six variables can be used to predict UUI treatment outcome in women. Further development into a complete model for the use in various PFDs and treatments is recommended to optimize individualized care. This model requires external validation before implementation.

Patient summary: Based on information of patients treated for UUI in the past, we developed a model that predicts the probability of improvement and cure after a UUI treatment for each individual female patient. In the future it could be used to personalize treatment choices.

INTRODUCTION

Pelvic floor disorders (PFDs) such as urinary incontinence (UI) are highly prevalent.[1] Prevalence of UI varies between 13-50% for women[1] and between 1-39% for men[2]. UI has major impact on patients' quality of life[3] and has great economic impact, with high costs for treatment and absorbent products.[1] Urge urinary incontinence (UUI), urinary leakage accompanied by a sudden compelling desire to pass urine[4], is one of the main types of UI.[1] Treatment options vary from conservative (pelvic floor muscle training, PFMT) to invasive therapy like neuromodulation.[5, 6]

Diagnosis and treatment decision making in patients with PFDs is a complex and often subjective process, depending on the knowledge and preference of the caregiver and patient. This might result in suboptimal patient outcomes. A prediction model could therefore provide support in the process of decision making.

A prediction model calculating the probability of the type of UI the patient suffers and at the same time providing the optimal choice of treatment does not yet exist. Such a model will, if implemented into daily clinical practice contribute to individualised care. A successful multivariable prediction model is the Prostate Cancer Risk Calculator.[7] This multiple externally validated prediction tool has shown to be able to reduce unnecessary testing in men with low risk of harbouring a life threatening prostate cancer.[7, 8]

Such tools, combining diagnostics and prognostics are currently lacking in the field of PFDs. As a first step we aim to develop a multivariable model to predict the effect on continence outcome of different UUI treatments. It could aid in shared decision making when choosing UUI treatment in female patients.

PATIENTS AND METHODS

Study design and subjects

The study was conducted at the departments of urology in one academic hospital (Erasmus MC) and two non-academic hospitals (Amphia Hospital and Haven Hospital) in the Netherlands. Data of female adult consecutive patients treated for UUI from 2010 (Erasmus MC), from 2013 (Amphia Hospital), or from 2015 (Haven Hospital) to 2016 were retrospectively included. These starting years coincided with the institutions' implementation of electronic patient files. Eligible patients were identified based on 'diagnosis treatment combination codes' used for reimbursement of health care costs in the Netherlands. Only data on the first UUI treatment during the inclusion period were evaluated based on the intention-to-treat principle. Patients with bladder stones, bladder cancer, urinary tract infections, urinary catheters, (congenital) anatomical abnormalities of the urinary tract, neuro-urological dysfunction, symptomatic pelvic organ prolapse and pregnant women were excluded. The medical ethics review board of the Erasmus MC reviewed the study protocol (MEC-2016-103). All data were collected from the electronic patient files. For quality control, 5% of all data entered into the study database was cross-checked with the patient file (JS, TN, IG).

Predicted outcome parameter

The predicted outcome parameter was the short-term subjective continence outcome reported three months after initiation of UUI treatment, and was categorized as cure (no urinary leakage), improvement (any degree of improvement of urinary leakage), or failure (no improvement or worsening of urinary leakage). A time range between one week and six months was accepted depending on the evaluated treatment. An outcome of percutaneous needle evaluation after one week was considered acceptable while, e.g., an outcome one week after initiation of PFMT was not.

Predictive variables

Table 1 shows the variables that were considered potential predictors for treatment outcome. Other previous invasive treatments with influence on the continence status included therapies such as a hysterectomy or prolapse surgery. For variables derived from bladder diaries, the mean values for two days were used if available. Detrusor overactivity (DO) was defined as any involuntary detrusor muscle contraction during filling cystometry.[4] The cystometric bladder capacity was defined as maximum filling during urodynamic studies (UDS). Cough-stress-tests were considered positive in case of any urinary leakage during coughing or Valsalva maneuver.

The type of UUI treatment was categorized as conservative, pharmacological or invasive. Conservative treatment was defined as any treatment for UUI without the use of invasive or drug therapy, such as PFMT. Invasive treatment was defined as any treatment involving incision or puncture of the skin, such as sacral neuromodulation (SNM) or Botulinum toxin-A (BTX-A) injections in the detrusor muscle.

Table 1. Baseline patient characteristics – evaluated as potential predictors

Characteristics	
Age (y)	60.8 (50.0-70.9)
Missing	0
Length	1.65 (1.60-1.70)
Missing	124 (24)
Weight (kg)	75.0 (66.0-90.0)
Missing	125 (24)
BMI, kg/m²	28.0 (24.5-32.1)
Missing	127 (25)
Patient history	
Coexistence of SUI	
Yes	270 (52)
No	196 (38)
Missing	46 (9)
In case of coexistence of SUI: predominant type of UI	
UUI	211 (41)
SUI	19 (4)
Equal	3 (1)
No coexistence	196 (38)
Missing	83 (16)
Voiding frequency/24h	13 (10-17)
Missing	226 (44)
Voiding frequency during the day	10 (8-13)
Missing	209 (41)
Voiding frequency during the night	3 (1-4)
Missing	193 (38)
Incontinence pad use/24h	3 (2-5)
Missing	121 (24)
UI during night	
Yes	142 (28)
No	82 (16)
Missing	288 (56)
Vaginal deliveries	
0	90 (18)
1	68 (13)
More than 1	273 (53)
Missing	81 (16)
Episiotomies or spontaneous lacerations (during vaginal deliveries)	
0	128 (25)
1	83 (16)
More than 1	66 (13)
Missing	235 (46)
Comorbidities	
DM	
Yes	69 (13)
No	443 (87)
Missing	0

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Cardiovascular disease	
Yes	225 (44)
No	287 (56)
Missing	0
COPD	
Yes	34 (7)
No	476 (93)
Missing	2 (0)
Psychiatric disorders and/or sexual abuse	
Yes	96 (19)
No	69 (13)
Missing	347 (68)
Previous treatments	
Previous treatments for UUI	
None	183 (36)
Conservative	114 (22)
Pharmacological	152 (30)
Invasive	63 (12)
Missing	0
Previous surgical treatments for SUI	
Yes	73 (14)
No	438 (86)
Missing	1 (0)
Previous other invasive therapies with influence on continence status	
Yes	184 (36)
No	326 (64)
Missing	1 (0)
Current treatment	
Type of UUI treatment	
Conservative	64 (12)
Pharmacological	317 (62)
Invasive	131 (26)
Missing	0
Bladder diary	
Number of UI episodes/24h	5 (2-8)
Missing	220 (43)
Subjective quantity of UI	
None	20 (4)
Drops	62 (12)
A splash	103 (20)
A lot	156 (31)
Missing	171 (33)
Number of incontinence pad use/24h	3 (2-5)
Missing	121 (24)

Voiding frequency/24h	11 (9-114)
Missing	118 (23)
Voiding frequency during the day	9 (7-12)
Missing	118 (23)
Voiding frequency during the night	2 (1-3)
Missing	118 (23)
Maximum portion of urine	350 (250-500)
Missing	135 (26)
Mean volume of a portion of urine	166 (121-210)
Missing	135 (26)
Total voided volume/24h	1800 (1273-2363)
Missing	138 (27)
Fluid intake/24h	1725 (1350-2150)
Missing	281 (55)
Urodynamic study	
DO	
Yes	169 (33)
No	93 (18)
Missing	250 (49)
In case of DO: (n = 169) DO from mL filling	166 (80-268)
Missing	14 (8)
In case of DO: (n = 169) leakage during DO	
Yes	93 (55)
No	66 (39)
Missing	10 (6)
Bladder capacity	350 (210-480)
Missing	253 (49)
Cough-stress test	
Positive	64 (12)
Negative	187 (37)
Missing	261 (51)
Other investigations	
Cough-stress test (separate test)	
Positive	96 (19)
Negative	158 (31)
Missing	258 (50)

BD, bladder diary; BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DO, detrusoroveractivity, IQR, inter quartile range; kg, kilogram; mL, milliliter; PH, Patient History; SUI, stress urinary incontinence; UI, urinary incontinence; UUI, urge urinary incontinence; y, year. Data are displayed as n (%) or median (interquartile range). Numbers do not add up to 512 patients due to missing data.

Analyses

Descriptive statistics were used to summarize data. For all variables except age, diabetes mellitus (DM), cardiovascular disease, and type of UUI treatment, data were missing. These missing data (1%-68%) were imputed using multiple imputation with the chained equations.[9] Due to high percentage of missing values we did not include the variable 'in case of DO: from mL filling' and 'leakage during DO' in further analyses.
Ordinal logistic regression was used to evaluate the association between each prognostic factor and the three outcomes: dry, improvement, failure. As a first step, predictors were entered into univariate regression model, taking into account the multiple imputed datasets. Significant predictors form the univariate regression were entered into the ordinal regression model with a backward stepwise selection procedure using the Wald selection criterion ($p<0.157$).[10] Subsequently, the main effect model was augmented with interaction of the three treatment options. Statistical significance of interactions in main model was quantified by the p-value of the overall likelihood ratio test statistic.[11]

The overall model performance predicting the absolute treatment benefit was assessed with the ordinal c-statistic.[12] The model was internally validated using bootstrapping with 200 samples. Predictor effects were shrunken using the calibration slope at internal validation as heuristic shrinkage factor. Due to the treatment interaction, the predictive value of a single predictor cannot easily be interpreted. The predictive value i.e. logit is visualized with a Logit plot for every predictor. All statistical analyses were performed using R version 3.4.2 (R Foundation, Vienna, Austria) with package 'rms' and mice.[9, 13]

RESULTS

Based on 'diagnosis treatment combination codes', 1395 consecutive female adult patients with UUI were identified. Twenty-five percent of these patients was not treated (for UUI) or treatment was not adjusted and 33% was excluded based on one or more of the exclusion criteria. In total, 598 female patients met the inclusion criteria. Data of 86/598 (14.4%) were excluded because no short-term subjective continence outcome could be determined from the patient file. Of the 512 remaining patients, 235 (45.9%) were recruited from the Erasmus MC, 204 (39.8%) from the Amphia Hospital, and 73 (14.3%) from the Haven Hospital.

Table 2. Subjective continence outcome categorized by treatment groups

	Conservative (N = 64)	Pharmacological (N = 317)	Invasive (N = 131)	Total
Cure	7 (10.9%)	51 (16.1%)	46 (35.1%)	104 (20.3%)
Improvement	30 (46.9%)	165 (52.0%)	55 (42.0%)	250 (48.8%)
Failure	27 (42.2%)	101 (31.9%)	30 (22.9%)	158 (30.9%)

In univariate analyses, number of UI episodes/24h, voiding frequency during the day based on patient history, coexistence of SUI based on patient history, predominant type of UI, UI during night, bladder capacity and subjective quantity of UI were found significant (Table 3). Predominant type of UI was manually removed, due to limited cases in the conservative and invasive treatment groups. All other predictors were still individually significant after the backward selection procedure. Addition of treatment interaction resulted in an increase in predictive capability (LR ratio test: Chisq: 39.5 $p < 0.001$ with 14 degrees of freedom). The ordinal c-statistic for the complete model was 0.710 and after internal validation 0.683.

Figure 1, based on the average patient in our cohort, displays the predictors on the X-as and the predictive ability (Logit) on the Y-axis, where a higher Logit indicates a higher probability of improvement or cure. In general, a larger bladder capacity, higher voiding frequency during the day, and UI during the night increase the probability of a successful treatment while the subjective quantity of UI ranked as ‘a lot’, the coexistence of SUI and an increased number of UI episodes/24h decrease the probability of a successful treatment. The predicted outcome of UUI treatment for the several factors is also illustrated in two fictive patients in Table 4.

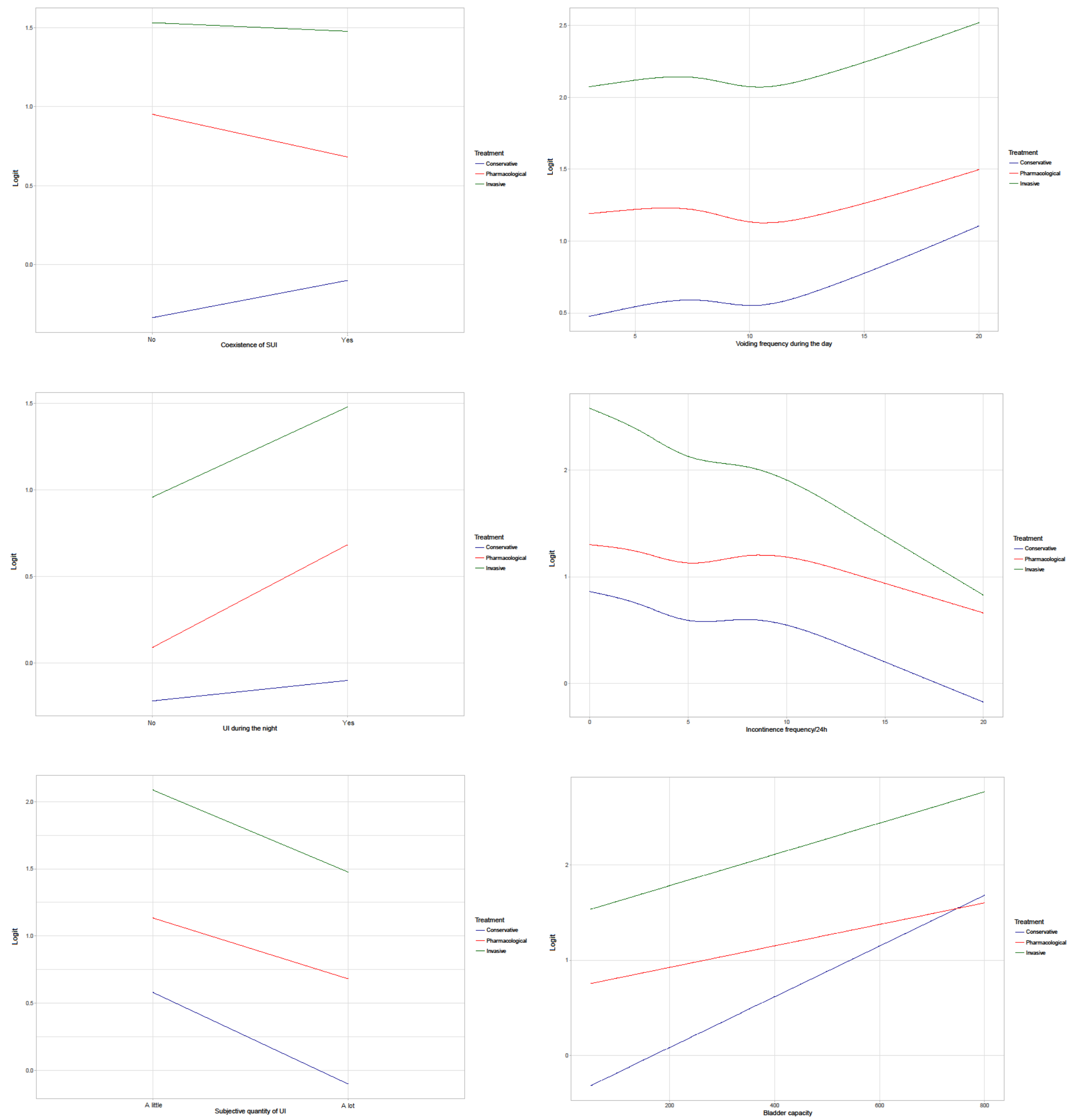

Figure 1. Predictive value of the six predictors with respect to improvement or cure of incontinence in the average patient (defined as Coexistence of SUI (yes), Voiding frequency during the day (10), UI during night (yes), Number of UI episodes/24h (5), Subjective quantity of UI (a lot), Bladder Capacity (350)) visualized with Logit plots, stratified to treatment option. A higher Logit indicates a higher probability of improvement or cure.

Table 3. Univariate analysis

Variable	Odd Ratio (95% CI)
Characteristics	
Age	0.92 (0.74-1.14)
Length	0.94 (0.72-1.22)
Weight	1.10 (0.87-1.39)
BMI	1.12 (0.88-1.43)
Patient history	
Coexistence of SUI (Yes)	0.69 (0.50-0.96)*
In case of coexistence of SUI: predominant type of UI (SUI vs. UUI & no coexistence)	0.24 (0.09-0.62)*
Voiding frequency/24h	1.15 (0.92-1.43)
Voiding frequency during the day	1.18 (0.97-1.43)*
Voiding frequency during the night	0.89 (0.70-1.14)
Incontinence pad use/24h	1.00 (0.84-1.17)
UI during night (Yes)	1.44 (0.89-2.32)*
Vaginal deliveries (1 or more vs. No)	1.08 (0.64-1.82)
Episiotomies or spontaneous lacerations (1 or more vs. No)	0.91 (0.58-1.44)
Comorbidities	
Comorbidity, any (Yes)	0.96 (0.69-1.33)
Sexual and/or physical abuse (Yes)	1.54 (0.68-3.47)
Psychiatric diagnosis (Yes)	1.23 (0.61-2.49)
Previous treatments	
Previous treatments for UUI	
None	Ref
Conservative	0.83 (0.53-1.29)
Pharmacological	0.77 (0.51-1.15)
Invasive	1.20 (0.70-2.07)
Previous surgical treatments for SUI (Yes)	1.31 (0.81-2.11)
Previous other invasive therapies with influence on continence status (Yes)	1.17 (0.83-1.65)
Current treatment	
Conservative	Ref
Pharmacological	1.53 (0.92-2.53)*
Invasive	3.30 (1.85-5.87)*
Bladder diary	
Number of UI episodes/24h	0.77 (0.59-0.99)*
Subjective quantity of UI (a lot vs. a little)	0.70 (0.49-0.99)*
Number of incontinence pad use/24h	0.92 (0.78-1.09)
Voiding frequency/24h	0.96 (0.78-1.18)
Voiding frequency during the day	1.01 (0.81-1.26)
Voiding frequency during the night	0.87 (0.73-1.06)
Maximum portion of urine	0.92 (0.66-1.29)
Mean volume of a portion of urine	0.91 (0.73-1.15)
Total voided volume/24h	1.03 (0.66-1.60)
Fluid intake/24h	0.99 (0.77-1.26)
Urodynamic study	
DO (Yes)	0.90 (0.58-1.38)
DO from mL filling	0.86 (0.54-1.35)
leakage during DO	0.84 (0.46-1.51)
Bladder capacity	1.41 (1.10-1.83)*
Cough-stress test (Positive)	1.37 (0.93-2.04)
Other investigations	
Cough-stress test (Positive)	1.10 (0.58-2.08)

Odds ratio (OR) for continuous variables are calculated between first and third quartile. OR>1 indicates improved cure rate. BMI, Body Mass Index; SUI, stress urinary incontinence; UI, urinary incontinence; UUI, urge urinary incontinence. Comorbidity is positive in presence of cardiovascular disease, chronic obstructive pulmonary disease or diabetes mellitus disease. * Significant with p<0.157

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Table 4. The predicted short-term subjective continence outcome for two fictive patients based on our multivariate prediction model

A) Female patient, six urinary incontinence episode/24h, 11 voiding frequency during the day, coexistence of SUI, no extensive subjective quantity of UI, UI during the night, and a bladder capacity of 400cc

Patient information – model predictors		Predicted short-term subjective continence outcome
Type of treatment:	Conservative	Probability of CURE: 12% Probability of IMPROVEMENT: 52% Probability of FAILURE: 36%
Type of treatment:	Pharmacological	Probability of CURE: 20% Probability of IMPROVEMENT: 56% Probability of FAILURE: 24%
Type of treatment:	Invasive	Probability of CURE: 38% Probability of IMPROVEMENT: 51% Probability of FAILURE: 11%

B) Female patient, 15 urinary incontinence episode/24h, 11 voiding frequency during the day, coexistence of SUI, extensive subjective quantity of UI, no UI during the night, and a bladder capacity of 300cc

Patient information – model predictors		Predicted short-term subjective continence outcome
Type of treatment:	Conservative	Probability of CURE: 3% Probability of IMPROVEMENT: 27% Probability of FAILURE: 70%
Type of treatment:	Pharmacological	Probability of CURE: 6% Probability of IMPROVEMENT: 39% Probability of FAILURE: 55%
Type of treatment:	Invasive	Probability of CURE: 8% Probability of IMPROVEMENT: 45% Probability of FAILURE: 47%

DISCUSSION

We developed a multivariable model to predict the effect of UUI treatment in female patients. The model, providing estimates of treatment outcome, includes information from bladder diaries, patient history, and urodynamic studies and might, after being externally validated, be a promising aid in shared decision making for the use in daily practice.

Other prediction models in the field of PFDs and functional urology are, for example, a model that predicts the future risk of PFDs.[14] It provides the opportunity of prevention during pregnancy in high-risk patients. More specific to our area of work, Darekar et al.[15] reported on the development of a model to predict the outcome of UUI treatment with fesoterodine. In both our study and that of Darekar et al.[15] a lower number of UI episodes/24h was found to be a positive predictor for being dry after treatment. Herschorn et al.[16] also acknowledged this variable as a predictor for being dry after antimuscarinic treatment. Although using other outcome parameters (reduction in UI episodes or symptoms), Yazdany et al.[17] and Richter et al.[18] also found associations between the number of UI episodes/24h and outcome of UUI therapies (BTX-A and SNM). Hence, the number of UI episodes can be interpreted as a measure of the severity of incontinence. Furthermore, the quantity of UI can be interpreted as a measure of the severity of incontinence. It is shown in this study that the quantity of UI ranked as ‘a lot’ rather than ‘none or a little’ decreases the probability of a successful outcome. We can conclude from these two predictors that, in general, patients with more severe UI are more difficult to treat.

The presence of UUI is often a symptom of the overactive bladder syndrome, defined as a complex of symptoms including urinary urgency, with or without UUI, usually with voiding frequency and nycturia.[4] Patients with this syndrome often present clinically with high voiding frequency and small portions of urine. We had expected that a higher probability of cure after UUI treatment, would be associated with a lower voiding frequency and a higher bladder capacity, reflecting a lower severity overactive bladder syndrome. For example, a higher therapeutic efficacy of BTX-A was described to be associated with lower baseline score of overactive bladder symptoms.[19] In line with this, in our study we found that a positive treatment outcome was associated with a higher bladder capacity. Contrary and unexpectedly, we found that a positive treatment outcome was associated with a higher voiding frequency during the day. No explanation could be found for this result. Future research should focus on this topic.

The coexistence of SUI and UUI is associated with worse outcomes in incontinence treatments such as PFMT and surgical treatments for SUI.[20] In our study the coexistence of

SUI (based on patient history) was found to be a predicting factor for failure of treatments, especially in patients with predominant SUI. A possible explanation is that by treating the UUI component, the SUI component remains untreated and might even worsen due to the increased bladder capacity after UUI treatment.

Additionally, we found that patients who experienced UI during the night had a higher probability of cure and improvement. The presence of UI during the night might be representative for pure UUI and therefore better outcomes of UUI treatment.

The type of treatment as interaction improved the prediction of individual treatment benefit in terms of the subjective continence outcome. Our study showed that that conservative, pharmacological and invasive therapy have increasing cure rates, which is in line with the previous published literature.[5, 6, 21, 22]

Variables concerning DO derived from urodynamics were not found to be predictive for the outcome of UUI treatment. This is in concordance with findings from a systematic review of Rachaneni et al.[23] that concluded that the presence of DO seems not to influence the effectiveness of invasive UUI treatments.

In the present study, comorbidities and previous treatments were not found as predictors for outcome of treatment. The scarce evidence on this topic is contradictory. While Darekar et al.[15] also did not find prior pharmacological UUI treatment and DM as predictors for pharmacological treatment outcome, Herschorn et al.[16] did find previous UUI treatments to be predictive. Khan et al.[24] found that depression or anxiety might influence the outcome of PFMT; Marcelissen et al.[25] found that psychological factors could not predict success in SNM. If future research confirms our findings, this is interesting information for clinical decision making. In current clinical practice, comorbidities and previous treatments are often a reason to refrain from further (invasive) treatments in these patients to avoid burdensome procedures.

Other bladder diary and patient history derived parameters, such as the number of incontinence pad use/24h, portions of urine and voiding frequency during the night were not found as predictors. We had expected that especially pad use would have predictive value, based on the idea that this reflects the severity of UUI. On the other hand, Dylewski et al.[26] showed that the number of pad use is not associated with the quantity of urine lost.

The strength of present study lies in the model that predicts the improvement or cure not only of a single treatment, but of three UUI treatment outcomes based on multicenter data.

This makes it possible to compare between the three treatment options and aids in shared decision making. This study represents the first step, of developing a comprehensive set of prediction models for PFDs. However, several limitations of our study need to be addressed. First, confounding could have been introduced due to the retrospective study design and treatment decisions being based on the judgement of the treating physician. The interaction modeling strategy to explore treatment benefit would be most optimal in a randomized (collaborative) setting with increased sample size and prospectively collected data.[27] Second, due to small numbers for specific treatments (e.g. BTX-A, SNM), treatment benefit could only be categorized as conservative, pharmacological or invasive. It might well be that the predicting factors differ per specific treatment. When more patient data have become available, sub-analyses per specific treatment could be performed. Third, only internal validation could be performed and external validation is still required to confirm the model's performance.[28] Fourth, there was a high number of missing data, which were imputated, however, we cannot rule out that variables entering the main model were selected or rejected based on chance. Finally, the choice of the outcome parameter 'subjective continence outcome' could be criticized. We chose however to include this outcome parameter, since it is commonly used in clinical care. Disadvantages are the subjectivity of the measure, the lack of standardization, and the wide range of patients categorized under 'improvement'. Ideally a validated questionnaire, with a previously determined minimally important change, should serve as an outcome parameter. In contrast, from a clinical point of view, treatment for UI is based on patient-reporting and the subjective continence outcome is easy recognizable for patients in shared decision making.

CONCLUSION

We identified six independent predictors for the short-term subjective continence outcome of UUI treatments in women and developed a multivariable prognostic prediction model. The model has the potential to be used as an aid in decision making for patients and physicians in the future. This study represents a first step in developing prediction models for use in various pelvic floor disorders. Before implementation of the prediction model in practice external validation is required.

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Take home message

We present a prognostic prediction model for short-term subjective continence outcome of urge urinary incontinence treatments in women with the potential to be used as an aid in decision making for patients and physicians in the future.

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CHAPTER 8

General discussion

In this general discussion, the main findings of the studies are presented and put in the context of the present literature. The fundamental research questions of this thesis are answered:

1) Can we lay the foundations to construct a complete diagnostic and prognostic prediction model in pelvic floor disorders (PFDs) in the future?

2) Can we construct the first part of this prediction model, a prognostic model that predicts the outcome of urge urinary incontinence (UUI) treatment?

Furthermore, the potential implications for research and clinical practice (for the future) are discussed. Finally, the overall conclusion of this thesis is given.

STANDARDIZATION

In **chapter 2** a systematic review was described, which summarized all outcome parameters and definitions of cure used to describe outcome of surgical treatments for stress urinary incontinence (SUI) in neuro-urological (NU) patients. A great heterogeneity in outcome reporting was found: sixteen different outcome parameters and nine different definitions of cure or success were used in the seventeen included studies. The most commonly used outcome parameter was patient-reported pad use, reported during an interview. Only three studies used a standardized patient-reported outcome measure (PROM). This heterogeneity makes it difficult to compare outcomes of different studies and therapies. This systematic review was performed to delineate the extent of this problem.

The heterogeneity in outcome reporting in healthcare was earlier described for outcome reporting in PFDs of non-neurological origin.[1, 2] Outcome reporting in the specific group of NU patients did not differ from that in other patient groups according to the heterogeneity found in our study (**chapter 2**). As a consequence of the use of various outcome parameters and definitions of cure it is difficult to validly compare outcomes of studies or interventions. For example, when considering two treatment options: a study on the one presents outcomes by the number of patients who report to be satisfied after treatment, while a study on the other describes outcome by reporting the number of patients whose urinary incontinence (UI) episodes were reduced by 50% or more after treatment. It is impossible to compare, based on this information, the differences in efficacy between the two treatment options. Furthermore, subjective and objective outcome parameters, PROMs and traditional outcome measures are used interchangeably within and between studies. An important question is: what is most appropriate outcome parameter to describe efficacy of a treatment? This issue concerns both the research field and clinical practice.

Systematic reviews on treatment efficacy are aimed to build robust evidence by combining outcomes of different studies. Guidelines are often based on the outcomes of systematic reviews. When outcome parameters and definitions of cure in included studies of systematic reviews differ, meta-analyses cannot be performed and outcomes on efficacy of different therapies are inconclusive.

The COMET-initiative tries to reach consensus among different healthcare specialties on outcome parameters for research purposes.[3] The intention is to develop core outcome sets, standardized sets of outcomes, per specific healthcare field for use in research. Important issues here are described as: identifying the scope for the outcomes, inventorying the existing knowledge on outcome sets in the specific areas, the involvement of different key stakeholders such as patients, clinicians, and researchers, and methods of reaching consensus.[4] Reviews of previous trials can reveal need for a core outcome set and identify a potential list of outcomes.[4] For this purpose, our systematic review (**chapter 2**) is an appropriate review; it describes the heterogeneity in outcome reporting in the specific field of SUI in NU patients and it summarizes all used outcome parameters and definitions of cure or success. Therefore, it might lie on the basis of a future consensus on this topic.

The use of outcome parameters and definitions of cure is a complex issue specifically in the field of PFDs and functional urology, because it is not immediately clear what outcome parameter should be used for this patient group. In other areas of health care such as cancer or cardiovascular disease it is often more obvious; e.g., survival as a clear outcome. Furthermore, the patient's quality of life and subjective perception or satisfaction are the most important goals of therapy in functional urology. Therefore, it would also be very important to have patients participate in the discussion on what outcome parameters to use. It is difficult, however, to measure a patient's subjective perception, such as the impact of disease on the quality of life. It is often based on the patient history and hard to quantify. This is the reason why PROMs have been introduced. Surprisingly, in our systematic review (**chapter 2**) only three of the seventeen studies used a PROM as an outcome measure. This shows that PROMs are not yet fully implemented into the research field of PFDs. The use of PROMs in daily healthcare practice is virtually absent.

PATIENT REPORTED OUTCOME MEASURES (PROMS)

For evaluation of PFDs such as UI, which can have major impact on the quality of life[5], PROMs are very important. When only using objective outcome parameters, the impact of symptoms on the patient's life is often not taken into account. PROMs can make the subjective perception of a patients measurable and available in a standardized way. PROMs can be valuable at different points in the care trajectory. They can be used as a diagnostic tool or as a baseline measurement to assess a patient's perception and impact of symptoms on his or her daily life. The impact of symptoms on the quality of life measured by PROMs can also guide the decision whether or not to start (invasive) treatments and thereby enhance patient-centered care. In addition, PROMs may serve as an outcome measure for treatment evaluation in a research setting, and also for this purpose in clinical practice. Symptom burden or health-related quality of life over time can be measured.

The implementation of PROMs into standard care showed to increase patient satisfaction with health care[6] and to improve diagnostic procedures and communication between physician and patient.[7] Due to improved communication and physicians being informed about patient's perception, it is imaginable that the use of PROMs could also influence treatment decisions and eventually (treatment) outcome, but this is not yet clear. Recognition of the importance of implementation of PROMs is upcoming, and the use of PROMs has already been recommended by several national and international guidelines on PFDs.[8-11]

At present, both the availability of PROMs and the general implementation of the PROMs into research and clinical care are challenging issues. Several PROMs for the use in PFDs have recently been translated into Dutch and validated for use in the Netherlands.[12-16] There is still a lack of validated PROMs for assessment of patients' perception in NU patients in the Netherlands. For example, a PROM for the use in patients with bowel complaints and fecal incontinence such as the neurogenic bowel dysfunction score[17] and a sexual PROM such as the MSISQ-15[18, 19] for the use in neurogenic PFDs patients are not yet available in a Dutch validated version. Until recently, a PROM focusing on the quality of life in NU patients with urinary symptoms was also not available.

To improve the availability of PROMs for the use in NU patients in the Netherlands, the SF-Qualiveen was translated into Dutch and validated in the Netherlands. The Qualiveen is a measure that consists of 30 questions to assess NU patients' urinary-specific quality of life.[20, 21] It was originally developed for spinal cord injury (SCI) patients and later on also validated for the use in multiple sclerosis (MS) patients. The SF-Qualiveen is a short version of the Qualiveen.[22] Both the English Qualiveen and the SF-Qualiveen proved to have good measurement properties.[20-22] In Dutch the Qualiveen, SF-Qualiveen, or a similar PROM has not been available. In **chapters 3 and 4** the translation and validation process of the SF-Qualiveen into Dutch for the use in MS and SCI patients in the Netherlands was described. We chose to translate and validate the SF-Qualiveen, the short version questionnaire, for the ease-of-use of patients and physicians. In general, after translation of a validated questionnaire into another language, validation of that language version is necessary to account for any cross-cultural differences. The proposed guidelines for translation and validation were adhered to in our study.[23] The Dutch SF-Qualiveen scores correlated with the scores on the reference standard, UDI-6[14], that showed good criterion validity. Construct validity was confirmed by predefined hypotheses that were met: patient scores were significantly higher than control scores and patients with higher scores on the SF-Qualiveen reported more bother from urinary symptoms. By comparing the SF-Qualiveen scores between baseline and 1-2 weeks later, the Dutch SF-Qualiveen showed good reproducibility. Additionally, it was found that the different items of the SF-Qualiveen were measuring the same concept, i.e. items were correlated, which confirmed good internal consistency. As an unexpected observation, the domains that were present in the Qualiveen were not found in the short version SF-Qualiveen and therefore we recommend to only use the entire SF-Qualiveen and not the separate domains. All outcomes were found comparable for the use in MS (**chapter 3**) and SCI (**chapter 4**) patients. These studies confirm that the SF-Qualiveen can be validly used in the Netherlands.

After making PROMs available for use, their structural implementation into clinical care is another challenge. Black et al.[24] speculated on how to implement PROMs into clinical care. The use of new technologies to provide PROMs (web based entry systems or apps) could make implementation easier. On the other hand, physicians and patients could find it very time-consuming to complete and interpret the PROMs. Routine use could be supported by making PROMs short, easy to understand and with scores that can easily be interpreted. To increase the ease of interpretation of PROMs, it can be useful to determine cut-off values for PROMs, e.g., to distinguish a 'normal score' from an 'abnormal score'. An example is the International Prostate Symptom Score, IPSS, a symptom assessment tool for patients with benign prostate hypertrophy[25] that categorizes scores into mild, moderate and severe complaints. Additionally, determination of the minimally important change, defined as 'the minimal change in score that patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management[26] can increase the ease of interpretation of PROM scores.

THERAPY OUTCOMES

In part II of this thesis, interventional therapies to regain urinary continence are evaluated using more traditional outcome measures. Outcomes derived from urodynamics, pad tests, bladder diaries, and cough-stress tests can be seen as traditional outcome measures, and these differ from PROMs in that they do not specifically take the perspective of the patient into account.

UI remains a common complication after radical prostatectomy.[27] The artificial urinary sphincter is still the gold standard treatment for moderate to severe post prostatectomy SUI, but minimal invasive techniques such as ProACT (Prostate Adjustable Continence Therapy), have become more available and earned their place in the treatment of male SUI.[28] **Chapter 5** focuses on the mechanism of action of the ProACT in men with UI after radical prostatectomy. The ProACT is a system that comprises two volume adjustable balloons that are placed paraurethrally. These balloons are attached to a port inserted into the scrotum. Via this port the balloons can be separately adjusted until continence is achieved.[29] The maximum urethral closure pressure (MUCP) decreases after prostatectomy, probably as a consequence of the loss of forces previously generated by the prostate and urethral sphincter. In men who regain continence after prostatectomy, MUCP values are higher compared to men who remain incontinent.[30] The hypothesis that the ProACT induces changes of the static urethral pressure is researched in **chapter 5**. Included patients underwent a urethral pressure profilometry before and after ProACT insertion. A statistically significant increase in urethral pressure was found in the patients with a successful clinical outcome (defined as the use of no or one precautionary incontinence pad per day) when comparing the pre- versus the postoperative MUCP. In the unsuccessful outcome group this increase was not found. Furthermore, a statistically significant difference was found between the increase in MUCP in the successful versus the unsuccessful outcome groups. These findings suggest that increased urethral pressure contributes to achieving continence and give insight to the mechanism of action of the ProACT. This knowledge can also be used in the development of future continence devices.

In **chapter 6** we describe the long-term outcomes of appendicovesicostomy (AVS) surgery in children. In case of irreversible lower urinary tract dysfunction and the inability to perform clean intermittent catheterization through the urethra, constructing an AVS can be a solution for catheterization of the bladder and improvement of continence. Literature on the long-term follow-up after AVS placement, especially with a focus on the durability of treatment, complications and re-interventions, is scarce. In this study we found that, after a mean follow-up of 10 years, all but one of 128 included patients continued to use their AVS for bladder drainage. Roughly one third of the patients needed a re-intervention during this period. No variables were identified that could predict the need for re-intervention.

Utomo et al.[31] searched for urodynamic predictors for the success or failure of a ProACT therapy and found that a longer duration of UI, more severe UI and a smaller cystometric bladder capacity were predictors for failure. Although the study described in **chapter 5** was not designed to find predictors for treatment outcome, it is imaginable that in the future urethral pressure profilometry could be used in predicting successful outcome as well. In **chapter 6** various variables were evaluated as potential predictors for the need for a re-intervention, but none was found to be a significant predictor.

The identification of variables that predict the outcome of treatment can help to identify patients that will or will not respond to a certain treatment. If beforehand it is likely that outcome of a specific therapy will not be successful in an individual patient, another treatment could be initiated as first treatment. To accurately predict treatment outcome, different predictors should be combined in a multivariate model.

A PREDICTION MODEL IN PELVIC FLOOR DISORDERS

In part III, **chapter 7**, the development is described of a multivariate prognostic model that aimed at prediction of the outcome of UUI treatment in female patients based on patient characteristics, patient history and investigations. The model consists of six predictors (number of UI episodes/24h, voiding frequency during the day, subjective quantity of UI, coexistence of SUI, UI during the night, and bladder capacity) and has the potential to be implemented into clinical care after external validation in the future. Although our model has a moderate predictive power and some limitations, it shows great promise to be able to develop a model in this patient group to predict the outcome of treatment in PFDs.

In this thesis, we are working towards the development of a comprehensive prediction model in PFDs in the future: a combined diagnostic and prognostic (treatment outcome) prediction model. The diagnostic part of the model can predict the risk of disease in present time and the prognostic part can predict both treatment outcome and the risk of disease development in the future. Our focus is first on the prognostic treatment outcome part of the model. Important requirements for the development of such a complete prediction model and its potential implications are discussed below.

Requirements for developing a prediction model

Preferably, a prediction model is based on data of large cohorts representative for the patient population and followed prospectively. A prospective study design will achieve high quality data with missing data kept to a minimum. Another optional study design is a randomised trial, which will minimize the bias of treatment indication.[32] Variables that predict the outcome of interest should be selected. Predictors are preferably standardized, clearly defined and reproducible. As a single predictor can often not give an adequate prognosis, different predictors should be combined in a multivariable prediction model. This strategy will probably lead to the best prediction.[32] Furthermore, to build a prognostic model predicting treatment outcomes, the outcomes of different therapies need to be available. The predicted outcome measures should be standardized, clearly defined, available for use and, moreover, clinically relevant for patients, with the perception of the patient taken into account.[32] When developing a prediction model in PFDs, several types of health care practitioners should preferably be involved, such as urologists, gynaecologists, rehabilitation specialists, general practitioners, surgeons, gastroenterologists, physiotherapists and nurses, because the treatment of PFDs is multidisciplinary. Moreover, all other participants in the health care chain, like patients, health insurers, relevant governmental bodies and industry representatives, should also be involved.

Potential implications and impact of prediction models

Physicians can use a prediction model in clinical care as an aid in decision making in addition to the physician's expertise and guidelines.[32] A diagnostic prediction model can give guidance in the choice of referral of a patient or in the choice to perform further investigations. The prognostic treatment outcome model can give an accurate estimate of outcome probabilities and can help to select the optimal treatment for the individual patient. Ideally, the possibility of treatment response or non-response is established beforehand so that every single patient will get the optimal personal management. In spite of the recent spate of publications about multivariate prediction models in health care, studies that investigate the actual impact of using a prediction model in clinical practice are scarce.[33] In the field of cardiovascular disease it is shown that cardiovascular prognostic risk assessments can change physician's decision making, e.g., by prescription of medication in high-risk patients, and that it can influence patient's outcomes in a positive way.[34]

Furthermore, a prognostic model gives accurate probabilities on (treatment) outcome which can be used to manage patients' expectations. This information can be used in shared decision making, which encounters a partnership between patient and health care professional in making healthcare choices.[35] One of the key elements in shared decision making is adequately informing the patient on expected (treatment) outcomes.

Multivariable prediction models can also be used to investigate the added predictive value of a single variable, e.g., an additional investigation.[32] For example, to investigate whether a urodynamic study, which is relatively expensive and might give complications in the patient, adds extra predictive value for the prognosis.

Prediction models in urology

The Rotterdam Prostate Cancer Risk Calculator[36], developed on the basis of data derived from the European Randomized Study of Screening for Prostate Cancer (ERSPC)[37], is a successful multivariate prediction model that serves as an example for the development and implementation of our prediction model in PFDs. It has been found a useful tool in predicting the prostate cancer risk and in avoiding unnecessary testing.[36, 38] It is an internet-based model which is also available as an app. Its availability for patients, general practitioners and physicians and for use at different time points makes it a very usable tool.

Prediction models are relatively new in managing PFDs and represent a new way of looking at PFDs. For example, a recently published multivariate prediction model in PFDs predicts the risk of occurrence of UI, fecal incontinence and pelvic organ prolapse in women 12 and 20 years after childbirth.[39] Another recently published model predicts bladder outcomes one year after traumatic SCI.[40] Both models showed adequate predictive accuracy and were externally validated. The clinical impact of implementation of the models is not (yet) described. Additionally, some models in the field of PFDs on treatment outcome are available. Darekar et al.[41] developed a model that predicts the outcome of fesoterodine treatment in the management of UUI. Other models predict cystocele recurrence after surgical treatment[42] or adverse events and continued UI after sling surgery.[43] Note that these models predict the outcome of one specific treatment.

The Rotterdam Pelvic Floor Outcome Calculator - PREFOCUS®

In parts I and II of this thesis, the foundations are laid for a prediction model in PFDs in the future, that is by evaluating treatment outcomes (**chapters 5 and 6**) and potential predictors (**chapter 6**), making the first step to standardization of outcomes (**chapter 2**) and making (patient reported) outcome measures available (**chapters 3 and 4**). In part III, **chapter 7**, it is shown that we are able to develop a multivariate model in the group of PFD patients that predicts outcome of UUI treatment. This could be seen as the first part of the construction of a complete prediction model in PFDs. The fundamental research questions of this thesis are hereby answered.

Our future objective is to develop the Rotterdam Pelvic Floor Outcome Calculator, the PREFOCUS®, a complete diagnostic, prognostic disease risk and prognostic treatment outcome prediction model in PFDs. The focus of the PREFOCUS® will be on the treatment outcome part. This part will include all available therapies per specific PFD and will give a complete outcome prediction for all therapies. After the development of the total PREFOCUS® and its implementation into clinical care, it can aid (shared) decision making and also optimize individualized care. The Rotterdam Prostate Cancer Risk Calculator[36] and other described published prediction models in PFDs may serve as examples for the design and implementation into clinical care in the future.

FUTURE PERSPECTIVES

A great heterogeneity in outcome reporting in SUI in NU patients was found in our systematic review described in this thesis. We hope that findings from this study will start the dialogue on this topic and will eventually lead to consensus on what outcome parameter or set of outcome parameters to use in the future in this specific patient group.

We pursue widespread availability and implementation of PROMs in health care and specifically for the use in patients with PFDs in the Netherlands. The next steps of our research group will be the translation and validation of PROMs for neurogenic PFD patients, e.g. the MSISQ-15[18], which was identified as best quality PROM for evaluating sexuality in neurogenic patients[19], and the neurogenic bowel dysfunction score.[17] In this research field, further improvement in the ease of interpretation of PROMs can be accomplished by determining the minimally important change in available Dutch validated PROMs, e.g. for the SF-Qualiveen.

Especially for the ProACT, as a new minimally invasive therapy, further research on long-term outcomes and identification of the perfect patient group to treat, would add valuable information to treatment decision making. Furthermore, outcomes on the quality of life after both ProACT placement and AVS construction (in both pediatric and adult patients) would add valuable information to existing literature. The identification and further evaluation of available therapies in PFDs in combination with identifying outcome predictors could eventually lead to a reliable prediction model.

Our research group will continue this research line, and extension of the PREFOCUS® is foreseen. Extension for use in other types of UI and other PFDs, for use by patients, and first, second and third line of health care practitioners is intended. External validation[44] and impact studies[33] should be performed before implementation of the model into practice. Furthermore, more predictors will be searched for to improve the model's predictive value and PROMs might be used in the model as an outcome parameter or as a predictor. In addition, separate models for the use in different patient groups, such as children and NU patients will be created. Developing an internet-based model with availability of an app is aimed for. These plans could be realized after initiation of a large prospective multicentre study in patients with PFDs. The value of the model will drastically increase after extension. After the development of the complete PREFOCUS® and the implementation into clinical care, it can be used as an aid in (shared) decision making, managing patients' expectations and it can promote individualized care.

EPILOGUE

In this thesis, our fundamental research questions on the feasibility of constructing prediction models in PFDs have been answered and we can conclude that the foundations are laid to develop a complete prediction model in PFDs, the Rotterdam Pelvic Floor Calculator - the PREFOCUS®, in the future. As a first step, a multivariate model that predicts UUI treatment outcome was developed. An objective multivariate prediction model such as the PREFOCUS® has the potential to be used as an aid in decision making in treatment of PFD patients in the future and to promote individualized care. It could mean an important health care improvement in the future, as the PFD patient population is large[45], decision making in PFD is complex, and PFDs have major influence on the quality of life.[5]

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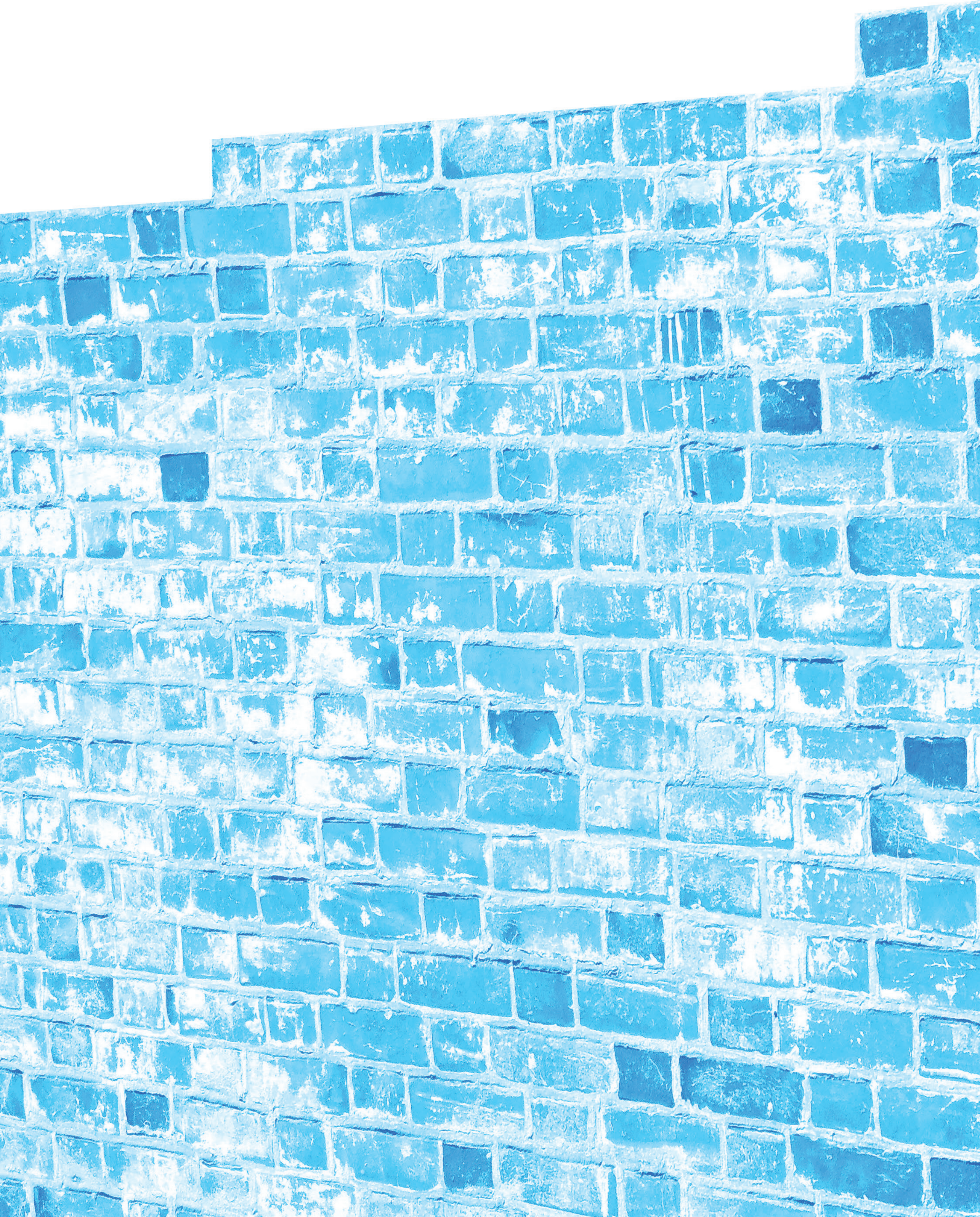

APPENDICES

SUMMARY

Pelvic floor disorders (PFDs) such as urinary incontinence (UI) are highly prevalent and have great negative impact on the quality of life of a patient. **Chapter 1**, the general introduction of this thesis, introduces the background of PFDs, the use of different outcome measures in PFDs and prediction models. Due to various new treatment options in the management of PFDs, treatment decision making becomes more important. Objective multivariable prediction models can be useful in (shared) decision making and optimization of personalized care. A prognostic treatment outcome model can help to identify patients who will and will not respond to a certain PFD therapy beforehand. The aim of this thesis is to lay the foundations for the development of a complete diagnostic and prognostic prediction model in PFDs with the goal of optimizing individualized care.

The first part of this thesis is about outcome measures: the use of different outcome parameters and definitions of cure is studied (**chapter 2**) and the translation and validation of a patient-reported outcome measure (PROM) for the use in the Netherlands is described (**chapter 3 and 4**).

A systematic review was described in **chapter 2**. All used outcome parameters and definitions of cure used to describe outcome of surgical treatments for stress urinary incontinence in neuro-urological (NU) patients were summarized. A great heterogeneity in outcome reporting was found. Sixteen different outcome parameters and nine different definitions of cure were used in seventeen included studies. This heterogeneity in outcome reporting makes it difficult to validly compare outcomes of studies or interventions. We hope that the results of this study will begin the dialogue on this issue and will finally lead to a consensus on which outcome parameters and definitions of cure to use in this specific patient group in the future.

Especially for the NU patient group, there is a lack of validated questionnaires for the use in the Netherlands. In **chapter 3 and 4** the translation and the validation of the Dutch SF-Qualiveen, a urinary-specific quality of life PROM for NU patients, is described in multiple sclerosis patients (**chapter 3**) and spinal cord injury patients (**chapter 4**). Guidelines for translation and validation of questionnaires were adhered to. In the test-phase of the Dutch SF-Qualiveen, we found good content validity. Good construct validity was showed by the predefined hypotheses that were met: SF-Qualiveen scores in patients were higher than in controls and patients with higher SF-Qualiveen scores had a higher burden of urinary symptoms. A significant correlation was found between the Dutch SF-Qualiveen scores and the reference standard (UDI-6) scores, confirming good criterion validity. The intraclass

correlation coefficient for agreement of the repeated SF-Qualiveen measurements (baseline and 1-2 week later) represents good reproducibility. Internal consistency was confirmed by finding that the different items of the SF-Qualiveen were intercorrelated. Unexpectedly, we found that the domains of the Qualiveen (the long version of the SF-Qualiveen) were not present in the SF-Qualiveen. Therefore, we recommend to only use the total SF-Qualiveen and not the separate domains. These validation studies confirm that the Dutch SF-Qualiveen can be reliably and validly used in both multiple sclerosis and spinal cord injury patients in the Netherlands.

In part II of this thesis, the outcomes of different interventional therapies to regain urinary continence are described.

In **chapter 5**, the hypothesis that the relatively new minimally invasive therapy ProACT, Prostate Adjustable Continence Therapy, induces changes of the static urethral pressure is researched. Patients who were included in this study suffered from UI after radical prostatectomy and underwent urethral pressure profilometries before and after ProACT placement. It was found that the maximum urethral closure pressure (MUCP) significantly increased in the group with successful clinical outcome (the use of no or one precautionary incontinence pad per day). In the group with non-successful clinical outcome, no significant increase in MUCP was found. When comparing the increase in MUCP between the group with successful and non-successful clinical outcome, a statistically significant difference was found. In conclusion, successful treatment with ProACT is associated with a significant increase of the urethral pressure. This implies that increased urethral pressure contributes to the mechanism of action of the ProACT.

Chapter 6 describes the use, complications, and re-interventions after appendicovesicostomy (AVS) placement in children. Indications for placement of an AVS were irreversible lower urinary tract dysfunction due to neurological or non-neurological disorders and the inability to perform clean intermittent catheterization through the urethra. After AVS construction, 32% of the patients needed a re-intervention during a mean follow-up of 10 years. The most common complications were cutaneous/fascial stenosis, stenosis at conduit-bladder level and stomal incontinence. Roughly two thirds of the re-interventions were performed superficially and/or endoscopically and the peak incidence of re-interventions was in the first year after conduit construction. No variables were identified that could predict the need for re-intervention. After the mean follow-up of 10 years, 99% of the patients continued to use their conduit for clean intermittent catheterization.

In part III, **chapter 7**, of this thesis, the development of a multivariable model that predicts the short-term outcome of urge urinary incontinence treatment in women based on patient characteristics, patient history and investigations, is described. The model includes six predictors; number of UI episodes/24h, voiding frequency during the day, subjective quantity of UI, coexistence of stress urinary incontinence, UI during the night, and bladder capacity. The model has a moderate predictive power and some limitations, but it has the potential to be used in practice in the future after external validation. The development of this model can be seen as the first step in the development of a complete diagnostic and prognostic prediction model in PFDs.

In the general discussion, **chapter 8**, the need for standardization of outcomes, the use of PROMs and traditional outcome measures, the development and use of prediction models and finally our future perspectives are discussed. By evaluating treatment outcomes and potential predictors, making the first step to standardization of outcomes and making PROMs available, all chapters of this thesis contribute to the development of a complete diagnostic and prognostic (treatment) outcome prediction model in PFDs in the future, the Rotterdam Pelvic Floor Outcome Calculator – the PREFOCUS®. It is shown that we are able to develop a first model in this patient group to predict the outcome of treatment of PFDs. The PRECOCUS® has the potential to be used as an aid in decision making for PFD patients in the future and to promote individualized care.

SAMENVATTING

Bekkenbodemproblemen (BBP) zoals urine-incontinentie (UI) hebben een hoge prevalentie en kunnen een grote negatieve invloed hebben op de kwaliteit van leven van een patiënt. **Hoofdstuk 1**, de introductie van dit proefschrift, introduceert het onderwerp van BBP, het gebruik van uitkomstmaten bij BBP en het gebruik van voorspelmodellen. Nu er verschillende nieuwe behandelingsmogelijkheden zijn ontwikkeld voor BBP, wordt de keuze van een behandeling belangrijker. Objectieve multivariabele voorspelmodellen kunnen gebruikt worden als hulpmiddel bij (gezamenlijke) besluitvorming en kunnen bijdragen aan optimalisatie van gepersonaliseerde zorg. Een prognostisch model om de uitkomst van een behandeling te voorspellen, kan gebruikt worden om voorafgaand aan een behandeling te identificeren welke patiënten wel en niet baat zullen hebben bij therapie. Het doel van dit proefschrift is om de fundering te leggen voor de ontwikkeling van een compleet diagnostisch en prognostisch voorspelmodel voor BBP dat de geïndividualiseerde zorg kan optimaliseren.

Het eerste deel van dit proefschrift gaat over uitkomstmaten: het gebruik van verschillende uitkomstparameters en definities van genezing wordt onderzocht (**hoofdstuk 2**) en de vertaling en validatie van een patiënt-gerapporteerde uitkomstmaat (PROM) wordt beschreven voor gebruik in Nederland (**hoofdstuk 3 en 4**).

Een systematische review wordt beschreven in **hoofdstuk 2**. Alle gebruikte uitkomstparameters en definities van genezing die gebruikt werden om de uitkomst van chirurgische behandeling van stress urine-incontinentie bij neuro-urologische (NU) patiënten te beschrijven, worden opgesomd. Een grote heterogeniteit in uitkomstrapportage werd gevonden. Zestien verschillende uitkomstparameters en negen verschillende definities van genezing werden gebruikt in zeventien geïncludeerde studies. Deze heterogeniteit in uitkomstrapportage maakt het moeilijk om betrouwbaar de uitkomsten van studies of interventies met elkaar te vergelijken. Wij hopen dat de resultaten van deze studie de discussie over dit onderwerp op gang zal brengen en dat dit uiteindelijk zal leiden tot een consensus over welke uitkomstparameters of definities van genezing in de toekomst gebruikt dienen te worden in deze specifieke patiëntengroep.

Er is een tekort aan gevalideerde vragenlijsten voor gebruik in Nederland, in het bijzonder voor NU patiënten. In **hoofdstuk 3 en 4** wordt de vertaling en validatie van de Nederlandse SF-Qualiveen, een blaas-specifieke kwaliteit van leven PROM voor NU patiënten, beschreven voor multiple sclerosis (**hoofdstuk 3**) en dwarslaesie patiënten (**hoofdstuk 4**). De richtlijnen voor vertaling en validatie van vragenlijsten werden gevolgd. In de testfase van de Nederlandse

SF-Qualiveen, vonden wij goede ‘content’ validiteit. Goede ‘construct’ validiteit werd getoond doordat vooraf gedefinieerde hypotheses werden bevestigd: SF-Qualiveen scores waren hoger bij patiënten dan bij controle personen en patiënten met hogere SF-Qualiveen scores gaven aan meer hinder te ervaren van hun blaasklachten. Een significante correlatie tussen de SF-Qualiveen scores en de referentiemaat (UDI-6) bevestigde een goede ‘criterion’ validiteit. We vonden een overeenkomst tussen eerste meting van de SF-Qualiveen scores (test) en scores 1-2 weken later (re-test), wat een goede reproduceerbaarheid aantoont. Interne consistentie werd bevestigd doordat de verschillende items van de SF-Qualiveen met elkaar in verband stonden. Onverwachts vonden wij dat de domeinen van de Qualiveen (de lange versie van de SF-Qualiveen) niet konden worden aangetoond in de Nederlandse SF-Qualiveen. Daarom adviseren wij alleen de gehele SF-Qualiveen te gebruiken en niet de aparte domeinen. De validatiestudies bevestigen dat de Nederlandse SF-Qualiveen betrouwbaar en valide gebruik kan worden in multiple sclerosis en dwarslaesie patiënten in Nederland.

In deel II van dit proefschrift, worden de uitkomsten van verschillende invasieve continentie behandelingen beschreven.

In **hoofdstuk 5** wordt onderzocht of de relatief nieuwe minimaal invasieve therapie ProACT, Prostaat Aanpasbare Continentie Therapie, veranderingen in de statische urethrale druk veroorzaakt. Geïncludeerde patiënten hadden klachten van UI na radicale prostatectomie en ondergingen urethrale druk profilometrie voor en na ProACT plaatsing. De maximale urethrale sluitingsdruk (MUCP) was significant verhoogd na ProACT plaatsing in de groep met een succesvolle klinische uitkomst: het gebruik van geen of één incontinentie pad per dag uit voorzorg. In de groep met een onsuccesvolle klinische uitkomst werd geen significante verhoging van de MUCP gevonden na ProACT plaatsing. Wanneer de verhoging in MUCP tussen de groepen met een succesvolle en een onsuccesvolle klinische uitkomst werd vergeleken, werd een statistisch significant verschil gevonden. Concluderend is een succesvolle behandeling met ProACT geassocieerd met een significante verhoging van de urethrale druk. Dit impliceert dat verhoging van de urethrale druk bijdraagt aan het werkingsmechanisme van de ProACT.

Hoofdstuk 6 beschrijft het gebruik, de complicaties en de re-interventies na appendicovesicostomie (AVS) plaatsing bij kinderen. Indicatie voor plaatsing van een AVS was irreversibele lage urineweg dysfunctie met neurologisch of niet-neurologisch onderliggend lijden en onvermogen om intermitterende katheterisatie via de urethra te verrichten. Na AVS constructie had 32% van de patiënten een re-interventie nodig gedurende een gemiddelde follow-up van 10 jaar. De meest voorkomende complicaties waren cutane/fasciale stenose,

stenose op de overgang conduit-blaas en stoma-incontinentie. Ongeveer twee-derde van de re-interventies werd oppervlakkig en/of endoscopisch uitgevoerd en de piekincidentie van re-interventies was in het eerste jaar na conduit-constructie. Er konden geen variabelen worden geïdentificeerd die de noodzaak voor een re-interventie konden voorspellen. Na een gemiddelde follow-up van 10 jaar gebruikte 99% van de patiënten de conduit nog voor het verrichten van intermitterende katheterisatie.

In deel III, **hoofdstuk 7**, van dit proefschrift wordt de ontwikkeling beschreven van een multivariabel model dat de korte-termijn uitkomst van urge urine-incontinentie behandelingen bij vrouwen voorspelt op basis van patiëntkarakteristieken, anamnese en aanvullend onderzoek. Het model bestaat uit zes predictoren; aantal UI episoden/24h, mictiefrequentie gedurende de dag, co-existentie van stress urine incontinentie, UI gedurende de nacht, subjectieve hoeveelheid UI, en blaascapaciteit. Het model heeft een matig voorspellende waarde en een aantal limitaties, maar het toont grote potentie gebruikt te worden in de praktijk in de toekomst na externe validatie. De ontwikkeling van dit model kan gezien worden als de eerste stap in de ontwikkeling van een compleet diagnostisch en prognostisch voorspelmodel bij BBP.

In de algemene discussie, **hoofdstuk 8**, worden de noodzaak voor standaardisatie van uitkomsten, het gebruik van PROMs en traditionele uitkomstmaten, de ontwikkeling en het gebruik van predictiemodellen en uiteindelijk onze toekomstige perspectieven bediscussieerd. Door (de uitkomsten van) behandelingen en potentiële predictoren te evalueren, door de eerste stap richting standaardisatie van uitkomsten te zetten en door PROMs beschikbaar te maken, dragen alle hoofdstukken van dit proefschrift bij aan de ontwikkeling van een compleet diagnostisch en prognostisch (behandelings-) uitkomst predictiemodel voor BBP in de toekomst, de Rotterdam bekkenbodem uitkomst calculator, de PREFOCUS®. Er is aangetoond dat wij in staat zijn een eerste model te ontwikkelen dat de uitkomst van behandeling bij BBP voorspelt. De PREFOCUS® kan in de toekomst gebruikt worden als een hulpmiddel bij het maken van keuzes in de behandeling van BBP patiënten en voor het optimaliseren van geïndividualiseerde zorg.

ABOUT THE AUTHOR

Sarah Reuvers was born in Leiderdorp, the Netherlands, on the 24th of April, 1986. She graduated from her high school, Stedelijk Gymnasium Leiden, in 2004. After high school, she went to Ghana for six months as a volunteer to work in an orphanage, teach at a school and help establishing a new school. She moved to Groningen in 2005 and she started her study Medicine at the University of Groningen. In 2012 she obtained her medical degree. From Groningen, via Deventer and The Hague, she moved to Amsterdam and enjoyed living there together with her boyfriend Marijn. She started working as a 'resident not in training' in October 2012 at the department of urology of the Spaarneziekenhuis. In 2014 she worked at the department of travellers vaccinations at the 'Gemeentelijke Gezondheids Dienst' in Amsterdam for six months. In 2015 she started working on her PhD thesis at the department of urology of the Erasmus Medical Center, in combination with working as a 'resident not in training' at the paediatric urology department of the Sophia's children's hospital in Rotterdam. She worked fulltime on her research project to complete her PhD thesis in 2016 and 2017. She still lives together with Marijn Verhoef in Amsterdam, who meanwhile became her husband. As of January 2018 Sarah Reuvers works as a 'resident not in training' at a nursing home at Cordaan in Amsterdam and the future is there to discover!

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Reuvers S, Zonneveld W, Meiland-van Bakel M, Putter H, Nicolai M, Pelger R, Elzevier H. *Indwelling Urinary Catheter-Related Problems After Laparoscopic Radical Prostatectomy.* J Wound Ostomy Continence Nurs. 2016 Jul-Aug;43(4):420-4. doi: 10.1097/WON.0000000000000241.

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Reuvers SHM, Roobol MJ, Verbeek JF, Scheepe JR, Wolterbeek JH, van der Schoot DKE, Nieboer D, ’t Hoen LA, Blok BFM. *Development of a prediction model in female urge urinary incontinence.* (Manuscript in preparation)

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De wereld ligt aan onze voeten!

PHD PORTFOLIO

Name PhD student: Sarah Reuvers Erasmus MC Department: Urology	PhD period: January 2015 – May 2018 Promotor(s): prof. dr. C.H. Bangma Supervisor: dr. J.R. Scheepe, dr. B.F.M. Blok	
1. PhD training		
	Year	**Workload (Hours/ECTS)**
General courses		
- Research Integrity, January 2015	2015	0.3 ECTS
- Biomedical English Writing Course, March – May 2015	2015	2.0 ECTS
- BROK ‘Basiscursus Regelgeving Klinisch Onderzoek’, e-learning course, September 2015	2015	1.5 ECTS
- Basic Introduction Course on SPSS, November 2015	2015	1.0 ECTS
- Course on NCBI, Pubmed, April 2016	2016	0.7 ECTS
- Survival Analysis course, June 2016	2016	1.0 ECTS
- Microsoft Excel 2010 course, April 2017	2017	0.3 ECTS
- ZorgSamenEvent, April 2017	2017	0.3 ECTS
- VVAA Workshop ‘Loopbaanontwikkeling’, May 2017	2017	0.2 ECTS
Specific courses (e.g. Research school, Medical Training)		
- Systematic Review Course, Amsterdam, EAU guidelines office, February 2015	2015	1.0 ECTS
Seminars and workshops		
- Department Journal Club	2015 - 2017	3.0 ECTS
- Department educational program ‘Onderwijsuur’	2015 - 2017	1.0 ECTS
- Department educational program ‘Refereeravonden’	2015 - 2017	1.0 ECTS
Presentations		
- Oral presentation ‘UPPs after ProACT’, NVU, November 2015	2015	1.0 ECTS
- Presentation ‘New studies in neuro-urology’, dept of Urology education Erasmus MC, February 2016	2016	0.3 ECTS
- Oral presentation ’20 years appendicovesicostomy’, educational programme (Refereeravond) Erasmus MC, March 2016	2016	1.0 ECTS
- Oral presentation ‘Validation of the Dutch SF-Qualiveen’ NVU, May 2017		
- Oral presentation ‘alphablockers in female patients with MS’, NVU, May 2017	2017	1.0 ECTS
- Poster presentation ‘Validation of the Dutch SF-Qualiveen’, ICS, September 2017	2017	1.0 ECTS
- Poster presentation ‘Heterogeneity in reporting on outcome’, ICS, September 2017	2017	1.0 ECTS
	2017	1.0 ECTS
(Inter)national conferences		
- NVU Nieuwegein, November 2015	2015	1.0 ECTS
- EAU Munich, March 2016	2016	1.0 ECTS
- NVU, May 2016	2016	1.0 ECTS
- EAU London, March 2017	2017	1.5 ECTS
- NVU, May 2017	2017	1.0 ECTS
- ICS Florence, September 2017	2017	1.0 ECTS

Other - Associate member of Neuro-Urology EAU guidelines panel	2016 - 2017	2.0 ECTS
2. Teaching		
	Year	**Workload (Hours/ECTS)**
- Coaching bachelor students - Course on coaching bachelor students, February 2016 - Intervision on coaching, May 2016	2015 – 2017 2016 2016	1.5 ECTS 0.2 ECTS 0.2 ECTS
Supervising interns - During clinical hours at the paediatric urology department	2015	1.0 ECTS

Total **31.0 ECTS**