Clinical epidemiological studies of women undergoing surgery for urogynaecological disorders

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THE 4 ORIGINAL PAPERS ARE

I: The Danish Urogynaecological Database – establishment, completeness and validity. Guldberg R, Brostrøm S, Hansen JK, Kærlev L, Gradel KO, Nørgård BM, Kesmodel UK. *International Urogynecology Journal* 2013;24:983-990.

II: Patient reported outcome measures in women undergoing surgery for urinary incontinence and pelvic organ prolapse in Denmark, 2006-2011. Guldberg R, Kesmodel US, Hansen JK, Gradel KO, Brostrøm S, Kærlev L, Nørgård BM. *International Urogynecology Journal* 201;24:1127-1134.

III: Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study. Guldberg R, Brostrøm S, Kesmodel US, Kærlev L, Hansen JK, Hallas J, Nørgård BM. Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study. *BMJ Open* 2013; 19:3(11).

IV: Use of antibiotics for urinary tract infection in women undergoing surgery for urinary incontinence – A cohort study. Guldberg R, Kesmodel US, Brostrøm S, Kærlev L, Hansen JK, Hallas J, Nørgård BM. Submitted for publication at the date of the defence. Following published in a minor revised version, *BMJ Open* 2014;4:4(2).

LIST OF ABBREVIATIONS
(in alphabetical order)
ASA: American Society of Anesthesiologists classification
ATC: Anatomical, Therapeutic and Chemical classification system
CCI: Charlson comorbidity index
CI: Confidence interval
CRN: Civil Registration Number
DugaBase: Danish National Urogynaecological Database
ICD: International Classification of Diseases
MUS: Mid-urethral sling
NPR: Danish National Patient Registry
OPED: Odense University Pharmacoepidemiologic Database
OR: Odds ratio
POP: Pelvic organ prolapse
PROMs: Patient reported outcome measures
toMUS: Trans-obturator mid-urethral sling
SD: Standard deviation
rpMUS: Retropubic mid-urethral sling
UI: Urinary incontinence
UTI: Urinary tract infection
VAS: Visual analogue scale

1. INTRODUCTION

Urinary incontinence (UI) and pelvic organ prolapse (POP) are prevalent disorders in women. None of the disorders are life-threatening, but they certainly affect the quality of life.
The lifetime risk for a woman undergoing surgery for UI or POP, before the age of 80 years, has been estimated at 11% in a U.S. study [1]. Of these 29% will undergo more than one operation. The rates of surgery for both UI and POP is expected to increase substantially (47%) over the next 40 years [2].

Urinary incontinence: clinical end epidemiological aspects
UI is defined as the complaint of involuntary loss of urine [3]. UI can stigmatise women, and affect their psychological and social wellbeing, with associated reductions in quality of life, sexual function, and secondary depression [4,5].
In order to estimate the prevalence of UI accurately several factors need to be taken into account including the symptoms, definition of UI, trial designs, and especially the age groups investigated. Consequently, the prevalence varies greatly across studies [6]. A large review showed a prevalence of UI of 27.6% with increasing prevalence by age [7]. Danish studies have shown a prevalence of 16.1% in 40-60 year old women [8], and 22% in 45-year old women in an average population, as a part of a health survey [9]. The 1-year incidence of UI ranges between 0.9% and 19% [10] and a recent study has shown an incidence of 18.7% in Norwegian women [11].
Several types of UI have been defined, and each with different

treatment options. According to an international joint report on the terminology for female pelvic floor dysfunction from the International Urogynecological Association and the International Continence Society UI can be divided into several subtypes based on symptomatic definitions, signs, and urodynamic studies [3]. Three of the most common symptomatically defined subtypes are:

1. Stress UI - involuntary loss of urine on effort or physical exertion (e.g. sporting activities), or on sneezing or coughing.
2. Urgency UI - involuntary loss of urine associated with urgency (a sudden, compelling desire to pass urine which is difficult to defer).
3. Mixed UI - involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing.

UI is also associated with urinary tract infections (UTIs) [12,13].
A number of risk factors for UI have been identified: age, pregnancy, vaginal delivery, genetic factors (regarding both anatomy and connective tissue), smoking, high body mass index, type 2 diabetes mellitus and race/ethnicity [7,14–17].
The treatment options for UI are conservative (e.g. pelvic floor exercises, bladder training, and lifestyle changes such as weight loss and smoking cessation), pharmacological, mechanical (intravaginal devices) and surgical. Surgery is predominantly used for women with stress UI, and has undergone an improvement during the last decades with the introduction of minimally-invasive sub-urethral sling procedures for stress UI [18–20]. Submucosal intraurethral injections of bulking agents [21] have also been used for stress UI and mixed conditions, and intravesical injections of botulinum toxin have been used for urgency UI [22]. The number of women undergoing surgery for UI has increased in Denmark and other countries in the recent decades [23,24].

Pelvic organ prolapse: clinical and epidemiological aspects

POP has been defined as the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy) [3].
The prevalence of POP in the general population is 37% [25], with higher proportion (50%) in parous women [26], and correlated with increasing age [27]. The mean age of women undergoing surgery for POP is 60 years [1], and the lifetime risk of surgery for POP has been reported to be 11-19% [1,28,29]. Only few studies have reported incidence rates of POP. The incidence rates for POP surgery have been estimated at 1.0-1.8 surgical procedures per 1,000 women per year [2,30,31] and many will undergo repeat surgery.
Most often, the sign of POP is correlated with a sensation of a vaginal bulge or heaviness, when the level of the measurable descent is at the level of the hymen or beyond. Symptoms are generally worse when gravity is inclined to make the prolapse worse (e.g. after long periods of standing or exercise), and better when gravity is not a factor e.g. lying supine. Prolapse may be more prominent at times of abdominal straining, e.g. defecation. Symptomatology and symptom intensity vary. Besides a sensation of vaginal "bulge" heaviness, women with POP can have different levels of urinary urgency and UI, voiding disorder, residual urine, and recurrent UTIs. There are often discrepancies between the 'objective' measurement of descent of the vaginal walls or apex and the women's own report of prolapse symptoms [32] and not all women with measurable descent have symptoms, and vice versa. Frequently, POP is associated with splinting or digitation, which is the need to digitally replace the prolapse or apply pressure to the vagina, perineum or rectum to assist voiding or defecation. Sexual dysfunction is frequently a complicating factor [33,34].
POP can be treated conservatively using intravaginal devices or by surgery. The choice of treatment depends on symptoms, severity of prolapse, as well as patient and doctor preferences [34].
Previous studies have shown significant improvement in anatomical measures and quality of life after surgery for POP [35–37]. A 5-year follow-up study showed a poor correlation between anatomic and symptomatic recurrence after surgery for POP [38]. The treatment success varies widely depending on the definition of the treatment success used (anatomic, symptomatic, or re-treatment) [39]. There are no studies of similar Danish data.

Quality assessment after urogynaecological surgery

The Danish Urogynaecological Database (DugaBase) was established in 2006 as a nationwide clinical database, with the aim of monitoring and improving the quality of urogynaecological surgery in Denmark. The DugaBase includes data on performed surgical procedures, patient reported outcome measures (PROMs), as well as pre- and postoperative examinations for both UI and POP. The reporting of clinical data to national clinical databases such as the DugaBase is mandatory by law in Denmark for both public and private hospitals. The DugaBase has so far been used to monitor the performed urogynaecological surgeries, and annual reports have been published (http://www.dugabase.dk/wm186305). The DugaBase has not previously been validated or used for research.
In assessment of the outcome of surgery, PROMs are highly relevant, because physicians tend to underestimate the extent to which patients are affected by their symptoms by 25-37% [40]. The importance of the patient's perspective on disease impact has been increasingly recognised, leading to the development of PROMs [41] as well as routine measurements of quality of life [42]. Thus, the DugaBase contains information from patient questionnaires including questions based on the validated International Consultation on Incontinence Questionnaire (ICIQ) on symptoms and disease-specific quality of life (ICIQ-UI and ICIQ-VS), which have been translated into Danish. Since PROMs are included in the DugaBase, it is possible to assess the change in symptoms and quality of life after UI or POP surgery in a population-based setting.

Pharmacoepidemiology in urinary incontinence

Different types of drugs have been used to treat UI, including antimuscarinic drugs for urgency UI and overactive bladder, and a serotonin-norepinephrine reuptake inhibitor (duloxetine) used for stress-predominant UI. Studies on drug use after abdominal surgery have shown that the consumption of symptomatic drugs, e.g. proton pump inhibitors was not reduced, as should be expected after laparoscopic surgery for reflux [43,44]. Similar conditions might be true for patients with UI, but only three small studies (n=84/98/162) have been published, showing that nearly 40% of preoperative antimuscarinic users continued the use after surgery for UI.
Antibiotics for UTI are commonly used in relation to surgery for UI. UI is associated with UTI [12,13], and UTI has been regarded as a comorbid condition in women with UI [45]. UTI is also well known as a complication to UI surgery, and the risk has been estimated at 2-32% in a systematic review based on 36 studies [46]. Surgery related infections usually occur within 2 months

after surgery (short term). To our knowledge, there is only little evidence on the frequency of UTI in a more long term perspective after UI surgery [47].
Analysis of drug use before and after surgery for UI is both interesting i) from an economic point of view, ii) according to the preoperative counseling of women, and iii) from the patients' point of view in relation to potential side effects and expectations. Such analyses can also be used to elicit potential indicators for monitoring surgical outcome.

Aims
The overall aim of the thesis was to examine the completeness and the validity of a clinical urogynaecological database, and to assess certain patient characteristics before and after urogynaecological surgery in Danish women. The characteristics studied before and after surgery included the women´s own evaluation of the subjective symptoms, and use of symptom-relieving drugs and antibiotics for UTI.
The specific aims were to:
- describe the establishment of the Danish Urogynaecological Database, and to evaluate the completeness and the validity of surgery registration in the Danish Urogynaecological Database (Study I)
- study PROMs in women undergoing surgery for UI and POP in Denmark, and the changes in PROMs when comparing preoperative measurements to postoperative measurements (Study II)
- study the use of symptom-relieving drugs before and after surgery for UI in women, and the association between preoperative and postoperative use (Study III)
- study the use of antibiotics for UTI before and after surgery for UI, and the association between preoperative and postoperative use (Study IV)

2. METHODS AND MATERIALS

Setting and design
All four studies comprised surgeries for urogynaecological disorders in Danish women. Study I assessed completeness and validated details regarding surgeries for UI and POP based on national register data and clinical data registered by the gynaecological departments in the DugaBase. Study II was based on a national cohort of women undergoing surgery for UI and POP including clinical data registered by the gynaecological departments and on data from patient questionnaires. Study III+IV were cohort studies including Danish women undergoing UI surgery and their use of symptom-relieving drugs and antibiotics for UTI in relation to the surgery based on national register data and on prescription data.

Data sources
All Danish citizens are assigned a unique Civil Registration Number (CPN), which enables individual-based valid data linkage across a vast number of registers [48]. The following data sources have been used in this thesis.

The Danish Urogynaecological Database (study I and II)
The DugaBase comprises women residing in Denmark who at the age of 18 or more undergo one of the urogynaecological surgical procedures (Appendix 1) according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures. The DugaBase is funded by the five national regions running the Danish National Health services. The database is organised with a steering committee, consisting of specialists in obstetrics and gynaecology, administrative employees from the Region of Southern Denmark and the Center for Clinical Epidemiology (part of the National Danish Clinical Quality Improvement Programme), a project manager, and a secretary. The electronic recordings were initiated in April 2006. A web-based national input module is used by the public hospital departments and private hospitals/clinics. The DugaBase data consist of information from i) a preoperative patient questionnaire on baseline information and PROMs (the latter based on a validated patient questionnaire on symptoms and disease-specific quality of life) [49,50], ii) a questionnaire completed by the gynaecologist including a preoperative examination, iii) a questionnaire on the surgical procedure performed (e.g. procedure codes, the surgeons' experience, use of antibiotic prophylaxis, company specific products), iv) postoperative patient questionnaire including PROMs, possible complications and reoperations, and v) postoperative follow-up questionnaire for health care personal.
The data flow in the database is illustrated in Figure 1. All information is manually and consecutively entered at the respective clinical departments by health care professionals. The DugaBase operates under the Danish law of data protection, with license granted by the Danish Data Protection Agency and the Danish Health and Medicines Authority (Danish National Board of Health j.no. 7-201-03-11/1/KIKR); and to monitor the surgical quality, the DugaBase steering committee has defined clinical indicators with standard developed based on the available evidence (Appendix 2), and national results relating to these indicators are published in an annual report.

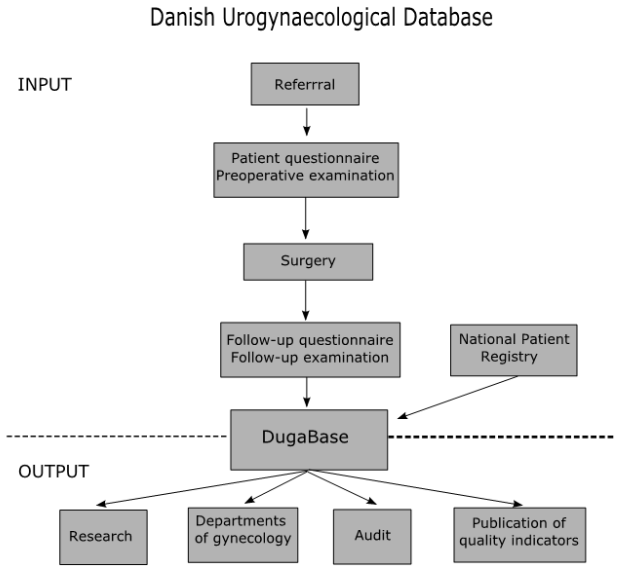

Figure 1
Data flow in the DugaBase

Medical records (Study I)
A randomly selected sample of women (100 undergoing surgery for UI, and 100 undergoing surgery for POP, all performed at public hospitals) registered in the DugaBase in the study period was retrieved, and the corresponding medical records were reviewed by a single physician (RG), using a detailed standardized form designed in close collaboration with the academic advisors (SB, UK, BN, LK). Medical records were carefully studied in order to find the relevant information, e.g. standard patient files, medicine records, anesthetist's records or discharge summaries. The

selected key variables represented administrative data, data according to the surgical procedure, objective measurements as well as parity and smoking.

The Danish National Patient Registry (Study I, III, IV)
The Danish National Patient Registry (NPR) was established in 1977, and comprises administrative data on discharges from public somatic hospitals in Denmark [51]. The completeness of recordings to the NPR has been estimated to be 99.4% [52]. The registry contains information about the unique CRN assigned for all Danish citizens, the dates of admission and discharge, the surgical procedures performed, and diagnoses for every discharge, classified according to the International Classification of Diseases (ICD); ICD-8 (1977-1993) and ICD-10 (1994 and onward) [53,54] as well as codes from the Danish classification system of surgical procedures [55].

The Odense University Pharmacoepidemiologic Database (Study III-IV)
The Odense University Pharmacoepidemiologic Database (OPED) is a regional pharmacy-based prescription register and captures reimbursed prescription. OPED contains person-identifiable data with complete coverage on all computerized prescription reimbursements from the County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended to the whole Region of Southern Denmark (population: 1.2 mio.). Each record includes the CRN, the date of purchase, the pharmacy, a full account of what has been purchased, including brand name, Anatomical Therapeutic Chemical (ATC) classification code, defined daily dose, dose unit, and quantity. The database does not contain information on drugs sold over the counter or drugs not reimbursed by the county authority (mainly oral contraceptives, sedatives, and hypnotics). Prescription reimbursements are offered as a part of the National Health Service to all legal inhabitants of Denmark; and given independently of patient income. All the drugs under study in this thesis are available only by prescription in Denmark.

Statistics Denmark (Study III-IV)
Statistics Denmark is a governmental institution collecting electronic records on different registers for statistical and scientific purposes. Detailed longitudinal information at individual level can be retrieved for the entire Danish population since 1980. The Register for Education Statistics and the Register of Family and Income Statistics have been used in study III-IV. The Register for Education Statistics includes individual-based information on education for all residents in Denmark since 1981 [56]. An annual update is performed on the basis of the Danish population of 1 January with information from educational institutions. Foreign national residents in Denmark voluntarily have to declare their educational status, when moving into the country [56]. The highest attained educational level was retrieved for each woman at the year of surgery. The Register of Family and Income Statistics collects annual individual-based information on income from Tax, Customs and Duties in Denmark (SKAT). From here, the personal annual income at the year of surgery was retrieved.

Study I
To assess the completeness of the DugaBase all recorded relevant procedures in the NPR were retrieved from 1 April 2006 to 31 December 2010 among women aged ≥ 18 years at the time of their surgery. The completeness of the DugaBase was assessed using the NPR as reference. The completeness was defined as the proportion of women with a relevant surgical procedure in both the DugaBase and the NPR, divided by the number of women recorded in the NPR [57,58].
Reported information in the DugaBase was validated against medical records. A random computerized sample of 100 women with UI procedures and 100 women with POP procedures performed in public hospitals from 1 January 2009 to 31 October 2010 was retrieved from the DugaBase. The validation was performed on selected key variables: date of surgery, surgical department, procedure codes, antibiotic prophylaxis, prior surgery for UI or POP, prior hysterectomy, height, weight, parity, and smoking. Data were collected by RG, and double data entry was performed.

Study II
Study II was based on data in the DugaBase from patient questionnaires completed pre- and postoperatively by women (≥ 18 years) undergoing surgery for UI and POP in Denmark from 6 April 2006 to 31 December 2011. To be included in the main analysis, the women had completed the questionnaires both pre- and postoperatively. In sub-analyses, all women with completed questionnaires were included (e.g. only pre- or postoperatively, or both).
Women with UI surgery were asked both pre- and postoperatively: “How often do you leak urine?” with the following response categories (=symptom score): 0 = Never, 1 = About once a week or less often, 2 = Two or three times per week, 3 = About once a day, 4 = Several times a day, 5 = All the time. Quality of life was assessed by “Overall, how much does leaking urine interfere with your everyday life?” on a visual analogue scale (VAS) from 0 to 10 (0 being the lowest and 10 the highest). The answers to the above questions are used as a surrogate outcome of patient satisfaction and success following surgery.
Women with POP surgery were asked both pre- and postoperatively: “Are you aware of a lump or bulge coming down in your vagina?” with the following response categories: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Most of the time, 4 = Always. Quality of life was assessed by “How much does this bother you?” on a VAS scale from 0 to 10.
Patient characteristics included age, body mass index, American Society of Anesthesiologists (ASA) classification, smoking, alcohol consumption, previous gynaecological surgery.
The symptom scores were categorised in three groups: (1) improved, (2) unchanged, and (3) worsened symptom score. An improvement of symptoms was defined as a reduction of one or more on the ordinal scale of symptom scores. When pre- and postoperative symptom scores were equal, this was recorded as unchanged, and when increased by one or more, as a worsening of symptoms.

Study III+IV
In study III+IV, data from the NPR, OPED, and the Statistics Denmark were retrieved. From the NPR all women (≥18 years), undergoing first time surgery for UI from the county of Funen, Denmark, from 1 January 1996 to 31 December 2006, and extended to the Region of Southern Denmark from 1 January 2007 to 31 December 2010, were included. For study III, the use of the symptom-relieving drugs and oestrogen were retrieved from OPED based on ATC codes. For study III, the included symptom-relieving drugs and corresponding ATC codes are shown in Table 1. For study IV, the included antibiotics were pivmecillinam (ATC

J01CA08), sulfamethizol (ATC J01EB02), trimethoprim (ATC J01EA01), and nitrofurantoin (ATC J01XE01). The indications are not registered in the OPED, therefore Pivampicillin and amoxicillin were excluded, because these antibiotics are also used to treat upper respiratory tract infection. Broader spectrum antibiotics such as cephalosporins and quinolones were not included, as they are not commonly used for UTIs in Denmark. Oestrogenes (ATC G03C) were retrieved for both studies, and both local and systemic oestrogens were included.

Exposed women were defined by having redeemed at least one prescription of the relevant drugs within 365 days preceding the date of surgery. Unexposed women were defined by not having redeemed at least one prescription of the drugs within the same time frame. The primary outcomes for both groups were the postoperative use of the symptom-relieving drugs (study III) and antibiotics for UTI (study IV) within 1) 0-60 days after surgery (short term postoperatively), and 2) 61-365 days after surgery (long term postoperatively). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively. The considered confounders were age, procedure type, preoperative oestrogen use, comorbidity, educational level, personal annual income, and calendar year of surgery. The different types of UI surgery were divided into four groups according to the surgical procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types of UI surgeries. The preoperative oestrogen use of the included women were divided into those who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and those who had no preoperative oestrogen use. Regarding comorbidity the Charlson comorbidity Index (CCI) was used [59,60]; a well-known, validated and widely used quantitative measure of comorbid illness [61]. CCI was computed for each women based on her complete hospital discharge from the NPR since 1977. According to CCI, different weights (1, 2, 3, and 6) are assigned to 19 different disease categories. A categorised version of the CCI with scores grouped 0 (low), 1-2 (medium), and 3+ (high) was used [62]. For each woman, educational level and annual personal income was estimated based on data from the year of her surgery. Highest attained educational level was categorised into three groups: "Basic" (basic school/high school education: 7-12 years of primary, secondary and grammar-school), "Secondary" (vocational education, 10-12 years of education), and "Higher" (a university degree or an examination in another higher institution requiring an average total of 13 years or more) [63]. Annual income was categorised into three groups as well: low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile).

Ethics and approvals

The studies in this thesis were approved by the Danish Data Protection Agency (no. 2009-41-3564). None of the studies needed approval by the regional Ethics Committee because they are register-based studies (http://www.dnvk.dk/CVK/Home/English.aspx).

Study I was further approved by the Danish Health and Medicines Authority (no. 3-3013-2/6) for the review of medical records.

Agent	Trade name(s)	ATC	Comments
Antimuscarinics for treatment of urgency UI/overactive bladder:			
Emepronium	Cetiprin Novum	G04BD01	Withdrawn from market 5 July 2004
Flavoxate	Urispadol	G04BD02	Release 26 October 1971
Oxybutinin	Kentera	G04BD04	Release 20 June 2005
Tolterodine	Detrositol Detrositol Retard	G04BD07	Immediate-release marketed from 18 May 1998 to 1 April 2002. Extended-release marketed from 10 December 2001
Solifenacin	Vesicare	G04BD08	Release 16 August 2004
Trospium chloride	Spasmo-lyt, Spasmoplex (and generics)	G04BD09	Release 12 November 2001
Darifenacin	Emselex	G04BD10	Release 10 October 2005
Fesoterodine	Toviaz	G04BD11	Release 2 June 2008
Treatment for stress UI:			
Duloxetine	Yentreve	N06AX21	Release 11 August 2004

Table 1
Symptom-relieving drugs for treatment of UI available in Denmark 1995-2011.

Statistical analyses

Data analyses in all four studies were performed using Stata version 12.1 (StataCorp, College Station, TX, USA).

Study I: The database completeness was defined as the proportion of patients subject to urogynaecological surgical procedures in both the DugaBase and the NPR, divided by the number of patients recorded in the NPR , based on details regarding the CRN, date of surgery (+/- 30 days), and type of surgery. The NPR was used as reference. Whenever relevant, statistical measures are presented with 95% confidence interval (CI).

Study II: Patient characteristics were analysed within the three groups (improved/ unchanged/worsened). The chi-square test was used to compare categorical variables and one-way analysis of variance (ANOVA) to compare continuous variables. The VAS scores were reported as medians with 25th–75th percentiles. Comparisons of median VAS scores pre- and postoperatively were analysed by the Kruskal-Wallis test.

In sub-analyses we compared baseline characteristics prior to surgery between included women and women who had only completed either the preoperative or the postoperative patient questionnaire. We thus compared the preoperative questionnaire on symptom score and VAS score between the included women and women who had only completed the preoperative questionnaire. Likewise, we compared the postoperative questionnaire on symptom score and VAS score between the included women and women who had only completed the postoperative questionnaire. A p value of less than 0.05 was considered significant.

Study III+IV: The drug use was described in a flowchart within the first 365 days after surgery for both exposed and unexposed women for both studies. Multivariate logistic regression models were used to compute the odds ratio (OR), with 95%CI. The following covariates were used in the adjusted analyses: age (18-39, 40-59, ≥60 years reference), procedure type (toMUS (reference), rpMUS, Bulking, others), education (basic (reference), secondary, higher), annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+), calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen (No (reference), Yes) within 365 days preceding surgery. Furthermore, in study IV stratified analyses were performed according to use of oestrogens before surgery to examine the association between preoperative use of antibiotics for UTI and postoperative use in oestrogen users.

3. MAIN RESULTS

Study I:

Establishment of the DugaBase

By 31 December 2010, a total of 16,509 urogynaecological surgical procedures were recorded in the DugaBase from both public hospitals and private hospitals/clinics. There were 4,313 UI surgical procedures in 4,092 women: 3,887 women had one UI surgical procedure, 189 women had two UI surgical procedures, and 16 women had three UI surgical procedures. There were 11,574 POP surgical procedures in 10,964 women: 10,392 women had one POP surgical procedure, 535 women had two POP surgical procedures, 36 women had three POP surgical procedures, and one woman had four surgical procedures.

In 158 instances, UI and POP surgical procedures were performed concomitantly, leaving 711 surgical procedures classified as neither UI nor POP procedures (e.g. unspecified vaginal or perineal repairs, and other vaginal procedures not classified as UI or POP surgery by definition).

Database completeness of the DugaBase

The completeness of recorded UI and POP surgical procedures in the DugaBase is increasing by calendar year (Table 2), with public hospitals having a higher completeness than private hospitals/clinics throughout all years. We identified a small number of patients in the DugaBase who were not in the NPR in 2010: 93 with POP procedures and 37 with UI procedures out of 4,574 and 1,740, respectively.

Validation of selected DugaBase variables

Medical records for all 200 included women were retrieved, information was collected, and I keyed the data into a database with a double entry of 60% showing no errors. The calculated agreements of selected variables are shown in Table 3. The agreements were 90% or higher - when adjusted for explainable disagreement in recorded procedure codes, due to differences in coding practice of cystoscopy (n=6) and leaving out gynaecological procedure codes (n=4) not relevant for the DugaBase. The lowest agreement was on the use of antibiotic prophylaxis (142/158=90%), and the highest agreement on date and department. Among the 14 recorded procedure codes with disagreement, 11 were POP procedures and 13 were surgical procedures with multiple procedure codes. There was no difference in agreement for the presented variables when stratifying by UI and POP.

	Completeness UI			Completeness POP		
Year	% (n)	95%CI	Public/Private	% (n)	95%CI	Public/private
2006	13.8 (156/1,128)	11.9-16.0	14.0/0	12.3 (378/3,082)	11.1-13.5	12.8/0
2007	39.1 (625/1,598)	36.7-41.6	39.9/0	36.9 (1,630/4,417)	35.4-38.3	38.2/0
2008	46.3 (674/1,456)	43.7-48.9	48.8/11.2	53.4 (2,096/3,922)	51.9-55.0	60.1/5.6
2009	62.1 (1,188/1,913)	59.9-64.3	64.4/29.0	65.3 (3,233/4,950)	64.0-66.9	68.4/26.1
2010	89.2 (1,532/1,718)	87.6-90.6	93.2/21.9	86.7 (3,960/4,565)	85.7-87.7	90.9/22.5

Table 2

The database completeness of urinary incontinence (UI) procedures and pelvic organ prolapse (POP) procedures in the Danish Urogynaecological Database (DugaBase) using the Danish National Patient Registry as a reference

	Verified in medical records / Total* in the DugaBase	Agreement % (95% CI)	Kappa** K
Date of surgery	200 / 200	100 (-)	1
Surgical department	200 / 200	100 (-)	1
Procedure codes	186 / 200	93 (86-96)	0.48
Antibiotic prophylaxis	142 / 158	90 (84-94)	0.75
Prior surgery for UI	142 / 146	97 (93-99)	0.70
Prior surgery for POP	138 / 144	96 (91-98)	0.87
Prior hysterectomy	143 / 147	97 (93-99)	0.90
Height (+/- 2 cm)	138 / 151	91 (86-95)	0.91
Weight (+/- 2 kg)	136 / 151	90 (84-94)	0.94
Parity (no. of children)	142 / 145	98 (94-100)	0.97
Smoking (yes/no)	129 / 132	98 (94-100)	0.93

UI=urinary incontinence, POP=pelvic organ prolapse, N=number

*Varies because not all information was available

**Kappa: poor agreement if k ≤ 0.40, fair to good agreement if 0.4< k <0.75 and excellent agreement if k ≥ 0.75

Table 3

Agreement between selected variables from a random sample of 200 women in the Danish Urogynaecological Database (DugaBase) from 1 January 2009 to 31 October 2010 and the same information from their medical records was expressed as a percentage of the exact agreement and by Kappa coefficients.

Study II:

Between April 2006 and December 2011, a total of 20,629 surgical procedures for UI and POP were registered in the DugaBase. Of these 5,612 and 15,204 were UI and POP procedures, respectively. Concomitant surgery of UI and POP was performed in 187 women.

For UI surgery a total of 3,600 (64%) had completed the patient questionnaire for symptom score preoperatively, and of these 1,778 (49%) had completed the same questionnaire during follow-up. Similarly, a total of 3,562 (63%) had completed the patient questionnaire for VAS preoperatively and 1,697 (48%) of these had completed this questionnaire postoperatively. For POP surgery, the equivalent numbers were 10,144 (67%) with preoperative completed questionnaire for symptom score and 4,652 (46%) of these completed the questionnaire during the follow-up, and 10,066 (66%) filled-in the VAS score preoperatively of which 4,288 (43%) completed the questionnaire for VAS during follow-up.

Surgery for UI

The distribution of changes in the symptom score is shown in Table 4. The majority of women had improved score after surgery (83%). Unchanged score was seen in 13%, and worsened score only in 4%. The results on the symptom score are shown in Figure 2 in two-year periods, and illustrate the difference in the score at the individual level both by circles and exact numbers. The majority of women were in the group with preoperative symptoms of UI “Several times a day” (=4), and within this group the majority had improved symptom score. For all three calendar periods, the results were overall the same with the majority of women having a symptom score of 4 preoperatively and reduced to a lower score postoperatively.

The changes in VAS score are illustrated in box plots, Figure 3, according to three calendar periods. For UI surgery, the VAS score median was 9 (25th-75th percentiles: 7-10) preoperatively and 1 (0-4) postoperatively ($p<0.001$) overall in the study period. Through all the calendar periods, there was a considerable reduction in the VAS score postoperatively.

Surgery for POP

The distribution of changes in symptom scores is shown in Table 4. As in UI, the majority of women had improved symptom score (80%), 17% had unchanged scores, and 3% had worsened symptom scores. The results on symptom scores are shown in Figure 4 in two-year periods. The majority of women were in the group with preoperative symptoms of POP "Always" (=4), and the majority within this group had improved symptom scores to "Never" (=0) postoperatively. For all three calendar periods, the results were overall the same with the majority of women having a symptom score of 4 preoperatively, and reduced to a score of 0 postoperatively.

The changes in VAS score are illustrated in box plots, Figure 5, according to three calendar periods. For POP surgery, the overall VAS score median was 8 (25th-75th percentiles: 5-10) preoperatively and 0 (0-1) postoperatively (p<0.001). Through all the calendar periods, there was a considerable reduction in the VAS score postoperatively.

Symptom score after surgery							
	Total	Improved		Unchanged		Worsened	
	N	n	(%)	n	(%)	n	(%)
UI surgery	1,778	1,484	(83)	224	(13)	70	(4)
POP surgery	4,652	3,725	(80)	806	(17)	121	(3)

Table 4

The changes in symptom score after urinary incontinence (UI) and pelvic organ prolapse (POP) surgery in Denmark 2006-2011.

Sub-analyses

For UI, there were no differences found in the baseline characteristics prior to surgery between included women and women who had not completed both the pre- and postoperative questionnaires. The preoperative VAS score did not differ between included women and women who had only completed the preoperative questionnaire. The only difference was encountered for the postoperative symptom free score (40.8% of patients with both questionnaires completed and 47.4% of patients with only postoperative questionnaire completed (p=0.002). For POP, minor differences were seen in the baseline patient characteristics prior to surgery: mean age (61.5 years vs. 62.2, p=0.001), alcohol units per week (3.2 vs. 2.9, p<0.001), ASA (ASA 1-2: 89.5% vs. 92.4%; ASA 3-6: 10.5% vs. 7.6%, p<0.001), and prior POP surgery (21.5% vs. 19.6%, p=0.014). Minor differences were seen for the preoperative symptom free score (11.0% of included women vs. 7.4% of women with only the preoperative questionnaire completed, p<0.001), preoperative VAS score 10 (26.2% vs. 29.3%, p<0.001), and postoperative symptom free score (80.1% vs. 76.5%, p=0.026).

Study III:

A total of 2,151 women were included in the study. All women had a primary surgical procedure for UI performed in the Funen/Region of Southern Denmark registered in the NPR between 1 January 1996 and 31 December 2010; of which 2,073 had a solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse.

Of the 2,151 included women, 358 (16.6%) were exposed to symptom-relieving drugs within 365 days before surgery. The number of redeemed prescriptions of symptom-relieving drugs and oestrogen, according to the OPED within the time frame of 365 days before and after a UI surgical procedure performed between 1 January 1996 and 31 December 2010, is shown in Table 5.

Approximately, one third of the women redeemed only one prescription of symptom-relieving drugs before surgery, and one quarter of the women redeemed five or more prescriptions. For further details on the distribution of the number of prescription per women, please refer to Figure 6. The most commonly prescribed symptom relieving drugs before surgery were solifenacin and tolterodine accounting for more than 70% of women.

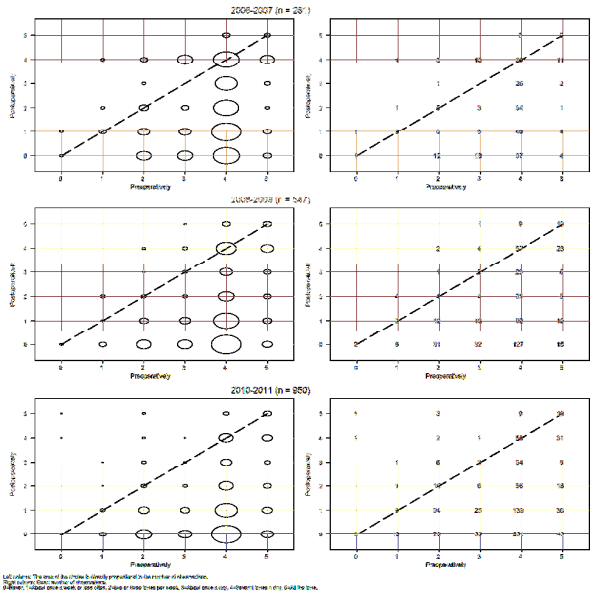

Figure 2

Symptom score "How often do you leak urine?" for UI surgery pre- and postoperatively (n=1,778) in two-year periods. The area of the circles is directly proportional to the number of the observations represented in the circle.

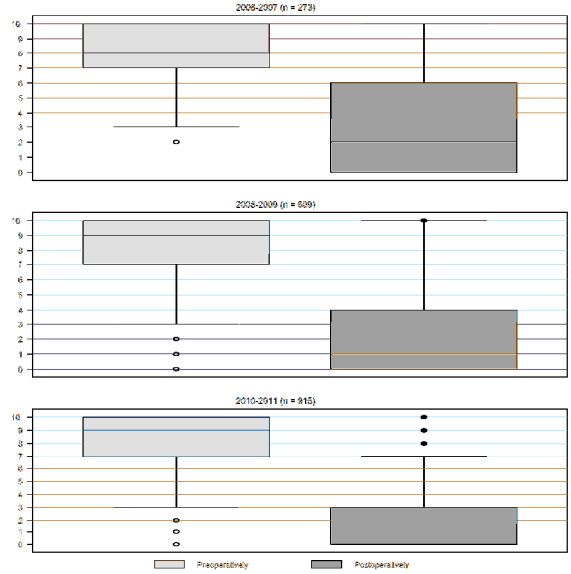

Figure 3

VAS score for UI surgery pre- and postoperatively (n=1,697) in box plots in two-year periods. The bottom and top of the boxes are the 25th and 75th percentiles, and the line near the middle of the boxes is the median.

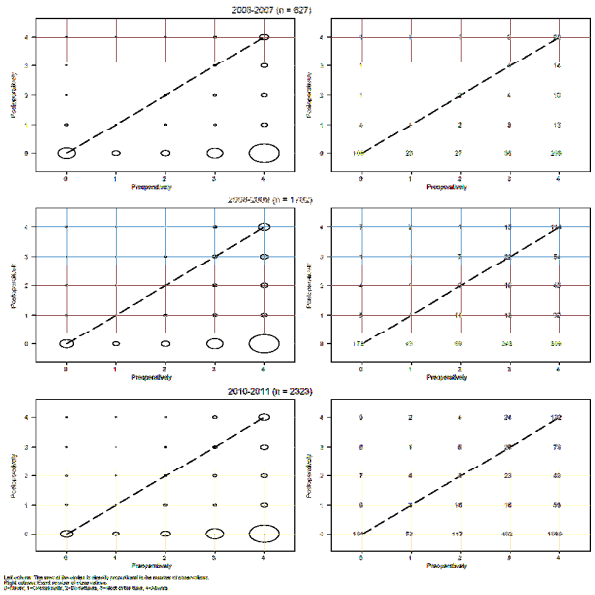

Figure 4
Symptom score "Are you aware of a lump or bulge coming down in your vagina?" for POP surgery pre- and postoperatively (n=4,652) in two-year periods. The area of the circles is directly proportional to the number of the observations represented in the circle.

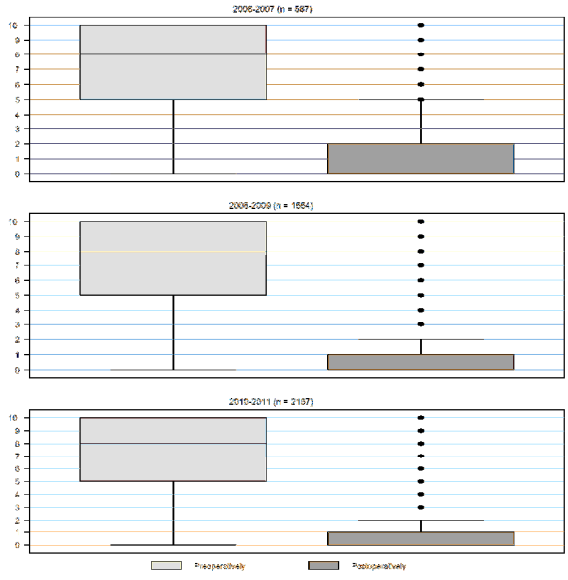

Figure 5
VAS score for POP surgery pre- and postoperatively (n=4,288) in box plots in two-year periods. The bottom and top of the boxes are the 25th and 75th percentiles, and the line near the middle of the boxes is the median.

Of the 2,151 included women, 1,793 (83.4%) were not exposed to symptom-relieving drugs within 365 days before surgery.
The use of symptom-relieving drugs within 365 days after surgery is detailed in both cohorts, Figure 7.

Women having redeemed prescriptions for symptom-relieving drugs before surgery (exposed)
Out of the 358 women with prior drug use of antimuscarinic drugs or duloxetine, 110 (30.7%) women redeemed prescriptions for these drugs within 0-60 days after surgery, and 98 (26.8%) also within 61-365 days postoperatively. A total of 248 (69.3%) women did not redeem a prescription for these drugs within 0-60 days after surgery, and the majority of these women (53.6%) also continued being non-users.

Women with no usage of symptom-relieving drugs before surgery (unexposed)
Of the 1,793 unexposed women, only 25 (1.4%) redeemed a first time prescription for symptom-relieving drugs within 0-60 days after surgery, and the majority of these women continued the use (20 women). A total of 1,768 (98.6%) remained non-users within 0-60 days, and the unexposed women typically continued as non-users (91.6%).

Comparing the exposed with the unexposed cohort
Baseline characteristics of exposed and unexposed are not presented in the overview of this thesis, please refer to 9.3 Paper III instead. The most frequently used procedure was toMUS in both cohorts. Among the exposed women the second most frequently used procedure was bulking, whereas it was rpMUS among unexposed women. Compared to unexposed women, the exposed women tended to be older, more frequent oestrogen-users, have higher comorbidity, a lower educational level, and a lower annual income.
Among women with prior drug use, the unadjusted OR of being short or long term user of symptom-relieving drugs after surgery was 31.1 (95% CI 19.9-49.4) and 8.4 (95% CI 6.4-11.0), respectively. The adjusted OR of being short or long term user of symptom-relieving drugs after surgery was 33.0 (95% CI 20.0-54.7) and 7.2 (95% CI 5.4-9.6), respectively. The details from logistic regression models are presented in Table 6 showing the impact of each risk factor included. Preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor of postoperative use (both short and long term); i.e. compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative user.

Study IV
As in study III, the study population included 2,151 women having a primary surgical procedure for UI between 1 January 1996 and 31 December 2010; 2,073 had a solitary UI surgery and 78 had concomitant surgery for pelvic organ prolapse.
Of the 2,151 included women, 496 (23.1%) were exposed to antibiotics for UTI within 365 days before surgery. The number of redeemed prescriptions of antibiotics for UTI and oestrogen according to the OPED within the time frame of 365 days before and after a UI surgical procedure performed between 1 January 1996 and 31 December 2010 are shown in Table 5. Before surgery, 76% redeemed a maximum of two prescriptions of antibiotics for UTI, 16% redeemed three or four prescriptions, and 8% redeemed five or more prescriptions. For further details on the distribution of the number of prescription per women, please refer to Figure 8. The most commonly prescribed antibiotics preoperatively were sulfamethizol and pivmecillinam accounting for the vast majority.
Of the 2,151 included women, 1,655 (76.9%) were not exposed to antibiotics for UTI within 365 days before surgery.
The use of antibiotics for UTI within 365 days after surgery is detailed in both cohorts, Figure 9.

Drug type	365 days before surgery	0-60 days after surgery	61-365 days after surgery	Total
Symptom-relieving	1,360	255	1,387	3,002
Antibiotics for UTI*	1,085	473	1,094	2,652
Oestrogen	3,531	488	2,728	6,747
Total	5,976	1,216	5,209	12,401

*UTI=urinary tract infection

Table 5

The number of redeemed prescriptions before and after surgery for urinary incontinence performed between 1 January 1996 and 31 December 2010.

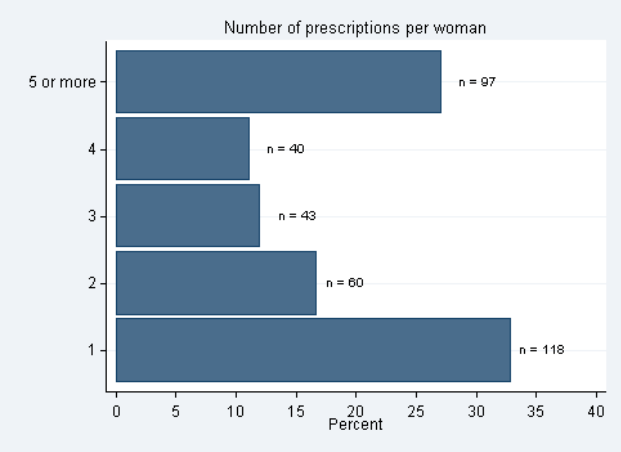

Figure 6

The distribution of the number of preoperatively redeemed prescriptions on symptom-relieving drugs based on 358 surgeries for urinary incontinence in Denmark, 1996-2010.

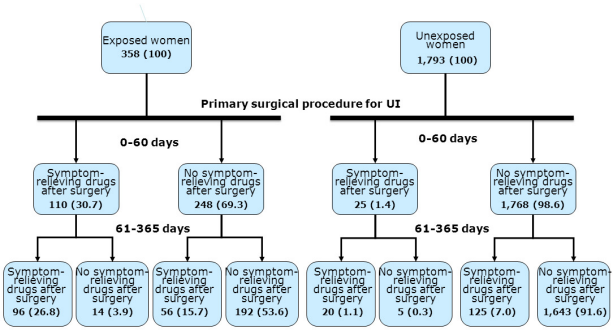

Figure 7

Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.

Women having redeemed prescriptions for antibiotics for UTI before surgery (exposed)

Of the 496 women with use of antibiotics for UTI prior to UI surgery, 129 (36.0%) did redeem prescriptions for these drugs within 0-60 days after surgery, and 85 of the 496 women (17.1%) even within 61-365 days after surgery, Figure 9. A total of 215 (43.3%) of the exposed women continued to redeem prescriptions within 61-365 days postoperatively, Figure 9.

	Post op non-use	Post op short term use		Post op non-use	Post op long term use	
	Number	Number	OR (95 % CI)	Number	Number	OR (95% CI)
Preoperative use						
No	1,768	25	reference	1,648	145	reference
Yes	248	110	33.0 (20.0-54.7)	145	152	7.2 (5.4-9.6)
Age group						
18-39	209	3	0.3 (0.1-1.4)	204	8	0.3 (0.1-0.7)
40-59	1,063	44	0.6 (0.3-0.9)	999	108	0.6 (0.4-0.8)
60-	744	88	reference	651	181	reference
Procedure						
rpMUS	659	16	0.6 (0.3-1.2)	612	63	0.6 (0.4-0.9)
toMUS	894	78	reference	842	130	reference
Bulking	322	38	1.2 (0.7-2.0)	262	98	0.5 (0.3-0.7)
Others	141	3	0.5 (0.1-2.6)	138	6	0.3 (0.1-1.0)
Preoperative use of oestrogen*						
No	1,159	49	reference	1,090	118	reference
Yes	857	86	0.8 (0.5-1.4)	764	179	1.0 (0.7-1.4)
Comorbidity (CCI)						
0	1,442	70	reference	1,352	160	reference
1-2	467	53	1.5 (0.9-2.4)	419	101	1.5 (1.1-2.0)
3+	107	12	0.9 (0.4-1.9)	83	36	1.9 (1.2-3.2)
Educational level**						
Basic	846	71	reference	761	156	reference
Secondary	727	43	0.9 (0.6-1.5)	674	96	0.9 (0.6-1.2)
Higher	407	17	1.1 (0.6-2.3)	385	39	0.8 (0.5-1.3)
Annual income						
Low	489	48	reference	442	95	reference
Middle	1,010	67	0.7 (0.4-1.2)	929	148	0.9 (0.6-1.2)
High	517	20	0.9 (0.4-1.8)	483	54	1.1 (0.7-1.9)
Year of surgery						
1996-2006	448	11	0.7 (0.3-1.7)	427	32	0.5 (0.3-0.9)
2007-2008	739	52	reference	675	116	reference
2009-2010	829	72	0.9 (0.6-1.4)	752	149	1.0 (0.7-1.4)

* Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
**Unknown highest attained educational level: 40 women

Table 6

Risk factors of postoperative use of antimuscarinic drugs/duloxetine. Results from multivariate logistic regression models on: i) short term (0-60 days after surgery), and ii) long term use (61-356 days after surgery).
Abbreviations: Post op = postoperative, OR = odds ratio, CI = confidence interval, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Women with no usage of antibiotics for UTI before surgery (unexposed)

Of the 1,655 women who did not redeem prescription on antibiotics for UTI before surgery, 182 (11.0%) redeemed a first time prescription for antibiotics for UTI within 0-60 days after surgery and 64 (3.9%) women continued within 61-365 days postoperatively. A total of 1,473 (89.0%) women remained non-users within 0-60 days after surgery, and the vast majority of these women (1,302/1,655=78.7%) continued as non-users also within 61-365 days after surgery, Figure 9.

Comparing the exposed with the unexposed cohort

Baseline characteristics of exposed and unexposed are not presented in the overview of this thesis. The most commonly used procedures were mid-urethral slings with toMUS being the preferred procedure in both cohorts. The exposed women were more likely to have bulking agent injection compared to unexposed women. Compared to unexposed women, the exposed women tended to be older, more frequent oestrogen-users, higher comorbidity, whereas there was no difference in educational level and annual income between the exposed and unexposed.

Among women with prior use of antibiotics for UTI, the unadjusted OR of being short and long term user of antibiotics for UTI

after surgery was 2.8 (95% CI 2.2-3.7) and 4.6 (95% CI 3.7-5.8), respectively. The adjusted OR of being short or long term user of antibiotics for UTI was 2.6 (95% CI 2.0-3.5) and 4.5 (95% CI 3.5-5.7), respectively. The details from logistic regression models are presented in Table 7 showing the impact of each risk factor included. Preoperative use of antibiotics for UTI was a strong risk factor of postoperative use (both short and long term); high comorbidity and procedure type (rpMUS, others) were also risk factors of postoperative short term use of antibiotics for UTI.

4. METHODOLOGICAL DISCUSSION

Establishment of cohorts

This thesis is based on data from women undergoing surgical procedures for UI and/or POP, and we believe that we have used well-established and valid cohorts for our studies.

A population-based approach is logic and feasible in Denmark because of a unique availability of county/region and nationwide registries based on mandatory reporting of all operations and procedures in both public and private hospitals and clinics. In addition, we had access to data from a national clinical database (DugaBase) and on out-patient drug prescriptions since 1 January 1990 from the county/regionwide prescription database, OPED. The data from the OPED are of high quality as a result of direct computerized transfer of information when a prescribed drug is dispensed at a pharmacy, and the age and distribution of this population is very similar to that of a Danish population as a whole [64]. We used these unique Danish possibilities to identify cohorts of women who had undergone surgery for UI or POP. The studies in this thesis are dependent on accurate registration of procedure codes for UI and POP in the NPR, and in general the validity of procedure codes in the NPR is high [65,66]. Furthermore, in study I we compared the procedure codes for UI and POP with registrations in the DugaBase and found very high agreement. Therefore, we have good reason to believe in a valid establishment of cohorts based on procedure codes from the NPR on UI and POP, and cohorts based on the DugaBase.

The pharmacological cohort studies were based on a complete prescription database (county/regionwide) because of the computerized accounting systems sending key data directly to the prescription database. Using the CRN, we were able to obtain the prescription history of each woman with a surgical procedure for UI or POP, and could classify the time of drug prescription according to the surgical procedure.

Thus, we believe that 1) study I is based on valid cohorts from the NPR and the DugaBase, 2) study II was based on a valid part of the DugaBase including approximately 1/3 of the population because of restrictions of completion of both pre- and postoperative questionnaires. Sub-analyses comparing women who had completed either pre- or postoperative questionnaires with women who had completed both only showed minor differences, 3) study III+IV were based on valid cohorts of women with all relevant surgeries in a well-defined region in Denmark (county/regionwide) including information on drug prescriptions.

Random error

The possibility that positive results obtained in a study may be due to chance can never be excluded. It has become customary to attach special significance to P values below 0.05 (1 in 20), because it is generally agreed that a chance of less than 1 in 20 of being wrong is acceptable. Regarding the risk of chance findings of the studies in this thesis i) the conducted studies were all based on a priori hypotheses, ii) the assessment of the role of chance was done by "estimation" (instead of hypothesis testing and P values), i.e. computation and measurement of the magnitude of the association and a 95% CI providing the information that the true value was most likely close to the point estimate, less likely to be near the outer limits of the interval, and could (5 times out of 100) fall outside these limits altogether. When making sub-group analyses, problems with multiple comparisons may arise. Again, our studies were based on a priori hypotheses and the associations under study were not examined according to the hypotheses to be accepted or rejected on the basis of P values, but, on the contrary, on estimates with 95% CIs [67].

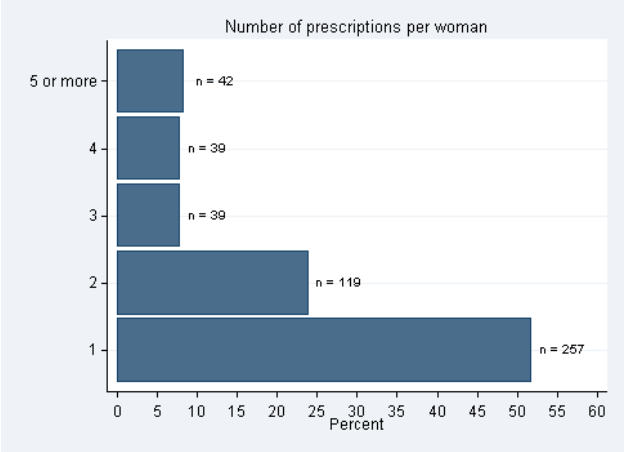

Figure 8
The distribution of the number of preoperatively redeemed prescriptions on antibiotics for urinary tract infection based on 496 surgeries for urinary incontinence in Denmark, 1996-2010.

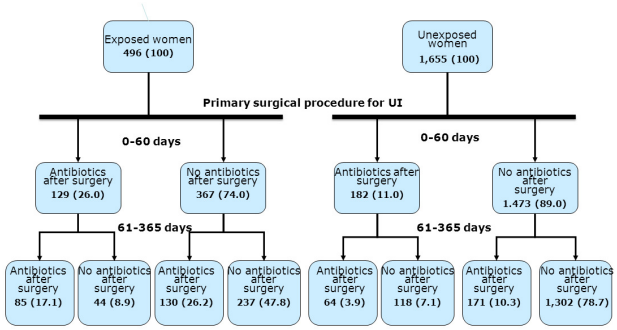

Figure 9
Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of antibiotics for urinary tract infection before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antibiotics within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antibiotics within 365 days preceding the date of surgery.

	Post op non-use	Post op short term use		Post op non-use	Post op long term use	
	Number	Number	OR (95% CI)	Number	Number	OR (95% CI)
Preoperative use						
No	1,473	182	Reference	1,420	235	reference
Yes	367	129	2.6 (2.0-3.5)	281	215	4.5 (3.5-5.7)
Age group						
18-39	185	27	0.9 (0.5-1.5)	163	49	1.5 (0.9-2.3)
40-59	981	126	0.6 (0.5-0.9)	931	176	0.7 (0.5-0.9)
60-	674	158	Reference	607	225	reference
Procedure						
rpMUS	568	107	1.7 (1.1-2.7)	529	146	1.3 (0.9-1.9)
toMUS	849	123	Reference	782	190	reference
Bulking	315	45	1.4 (0.9-2.0)	278	82	1.1 (0.8-1.5)
Others	108	36	3.1 (1.6-5.9)	112	32	1.5 (0.8-2.8)
Preoperative use of oestrogen*						
No	1,059	149	Reference	992	216	reference
Yes	781	162	1.2 (0.9-1.6)	709	234	1.2 (0.9-1.5)
Comorbidity (CCI)						
0	1,328	184	Reference	1,241	271	reference
1-2	425	95	1.5 (1.1-2.0)	384	136	1.4 (1.1-1.8)
3+	87	32	3.1 (1.6-5.9)	76	43	1.5 (1.0-2.4)
Educational level**						
Basic	775	142	Reference	702	215	reference
Secondary	665	105	1.1 (0.8-1.5)	623	147	1.0 (0.7-1.1)
Higher	362	62	1.3 (0.9-2.0)	342	82	0.9 (0.6-1.3)
Annual income						
Low	434	103	Reference	404	133	reference
Middle	930	147	0.9 (0.6-1.2)	847	230	1.0 (0.8-1.3)
High	476	61	0.9 (0.6-1.4)	450	87	0.9 (0.6-1.3)
Year of surgery						
1996-2006	363	96	1.4 (0.9-2.2)	352	107	0.9 (0.7-1.1)
2007-2008	692	99	Reference	628	163	reference
2009-2010	785	116	1.0 (0.8-1.4)	721	180	1.0 (0.8-1.4)

* Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
**Unknown highest attained educational level: 40 women

Table 7
Risk factors of postoperative use of antibiotics. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii), long term (61-356 days after surgery).
Abbreviations: Post op = postoperative, OR = odds ratio, CI = confidence interval, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Selection bias
This thesis is based on studies on all women undergoing surgery for UI or POP in the defined study periods and therefore we believe that we have a (nearly) complete population during the study periods. Our population-based (county/regionwide), register-based, cohort studies reduce the risk of selection bias produced by differential patient recruitment as in hospital-based studies and incomplete follow-up.

Misclassification of exposure
While collecting data from medical records in Study I, the registrar was blinded for data in the DugaBase. This prevented a potential influence on data collected from the medical records because of knowledge of already registered data in the DugaBase. The issue about misclassification of exposure is mainly relevant for study III and IV. In our register-based studies, very detailed measurements of exposure are usually impossible to assess and some misclassification of exposure may occur. In the cohort design misclassification of our exposure is likely to be unrelated to the outcome, and with two exposure categories the risk estimates will be biased towards the null hypothesis. This means that a non-differential misclassification will tend to produce risk estimates closer to the no-effect than the actual effect. We have several reasons to believe that there is no major misclassification.

One of the strengths in pharmacoepidemiological studies is the combination of valid surgical procedure codes from the NPR and redeemed prescriptions. Information on redeemed prescriptions was not based on recall, as drug exposure based on self-reported use may lead to severe recall bias or under-ascertainment [68]. However, we used redeemed drugs as a proxy measurement of drug intake. A prescribed drug, even if it is redeemed, is not necessarily taken, or – if taken - not necessarily by the person itself. A patient noncompliance, regarding drug use, would tend to underestimate our risk estimates. There are other arguments for the occurrence of misclassification to be small: i) there is no over-the-counter sale of the drugs included, ii) the drugs are expensive with a patient payment, which increases the likelihood of compliance, and - probably most importantly - iii) women with UI or POP have impaired quality of life and therefore have a high motivation for daily medication to obtain symptom-relief. Prescription databases have therefore been found to be of great value for drugs prescribed for serious diseases that need continuous treatment [69]. The indications for the prescribed drugs are not registered; therefore pivampicillin and amoxicillin have been excluded from the analyses in study IV in order to minimize misclassification, as these antibiotics are also used to treat upper respiratory tract infection, and including these could therefore introduce an overestimation of our results.

Misclassification of outcome
In study III+IV the outcome data were obtained independently of the questions investigated, and independently of exposure measurement, thereby effectively reducing the risk of differential misclassification of the outcome. The outcome measurement (drug use after surgery) was based on computerized, valid information from a prescription database.

Confounding
A confounding variable is an extraneous variable correlating with both the dependent and the independent variable and may thereby lead to wrong conclusions. To avoid a false positive (Type 1) error, researchers must control for confounders.
For study I and II it is not relevant to address confounding.
In study III+IV we believe that we have been taking into consideration the most important confounders in the multivariate logistic regression analyses: age, procedure type, preoperative oestrogen use, comorbidity, educational level, personal annual income, and calendar year of surgery. We were not able to control for all potential factors such as body mass index, parity, severity and duration of symptoms of UI, and conservative treatment for UI. As it is not possible to control for all confounders there might be some factors, which have not been taken into account in these studies, leaving the possibility for residual confounding.

Generalisability
Generalisability of study results is only relevant if there are no major problems with bias, chance findings, and uncontrolled (residual) confounding. This can be illustrated by the possible pathways from "Association and cause" as done by Fletcher & Fletcher, Figure 10 [67]. In the above sections these different aspects have been addressed (selection bias, chance findings, and misclassification of exposure and outcome).
Study I: the results from this study mainly apply to the DugaBase. Through the validation study, the procedure codes in the DugaBase were compared to medical journals and the completeness of the DugaBase compared to the LPR, giving general results according to valid use of procedure codes and selected key vari-

ables from the DugaBase.
Study II: the main analyses included approximately 1/3 of the population in the DugaBase because of restriction to women, who had completed both the pre- and postoperative questionnaires. Sub-analyses comparing women who completed either the pre- or the postoperative questionnaires with women who completed both showed only minor differences. Based on this we believe this study is representative of the women in the Danish population undergoing surgery for UI or POP in the period 2006-2011.
Study III+IV: These studies are population-based studies and the source data are of high quality [64–66,70]. We have adjusted for several confounders, we have close to complete information in the follow-up period, and both drugs and surgical procedures have no other indications than UI. We found very strong associations in both short term and long term drug use for both studies, which makes it less likely that the results could be explained by the chance and confounding alone. Based on this, we believe our study to be generalized to women undergoing surgical treatment for UI in Denmark.

5. CONCLUSIONS

These studies provide new evidence on the following subjects according to the aims of the thesis:

Study I
This study showed a high completeness of the DugaBase using NPR as reference, and a high validity of reported key data in the DugaBase compared to information in medical records. This study offers a unique possibility for continuing quality assessment of UI and POP surgery in Denmark and for future research based on data from the DugaBase.

Study II
Based on data on PROMs, surgery for UI and POP is effective in alleviating symptoms of UI or POP in women undergoing surgery in Denmark. Pre- and postoperative questionnaires are useful tools in assessing improvement in patient reported symptomatic outcome measures after surgery.

Study III
A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of surgery. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs postoperatively. Compared to preoperative drug use no other factors in the regression model contributed considerably to the risk of being short or long term postoperative user of symptom-relieving drugs.

Study IV
One in four women undergoing surgery for UI was treated for UTI before surgery, and half of these women continued the tendency of UTI postoperatively. In women not using antibiotics for UTI prior to surgery only a minor proportion initiated use of antibiotics for UTI after surgery. The strongest risk factor of postoperative use of antibiotics for UTI was the use of these antibiotics before surgery.

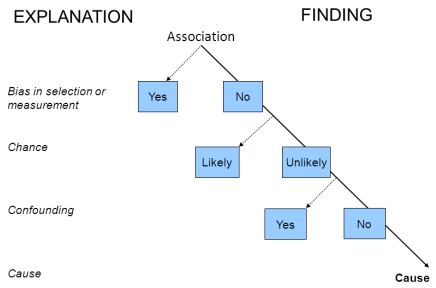

Figure 10
Association and cause from Fletcher & Fletcher "Clinical Epidemiology: The Essentials" (Ref. Fletcher 1996)

6. PERSPECTIVES

This thesis has contributed with findings giving rise to increased knowledge of the DugaBase, PROMs after urogynaecological surgery, and certain pharmaco-epidemiological characteristics in Danish women before and after surgery for UI.

Databases and registries – the value of cohort studies
Most developed countries share common goals to improve the health of their populations and to improve the quality in health care. One of the approaches to do this is by using clinical databases. To be useful, health care data should be organised in a systematic and efficient way, and structured to allow linkage across different data sources. The data need to be accessible, and at the same time be confidential, protecting privacy rights. If these conditions are met, health care data such as clinical databases constitute a significant resource.
Even though surgery for UI and POP are well documented routine surgical procedures, there are still several issues to be discussed: i) the right choice of sling procedure for the treatment of stress UI (retropubic vs. transobturator), ii) to whom the bulking procedure should be offered? iii) the best surgical options for POP, especially in recurrent cases, and iv) missing registration of complications and recurrence of surgical procedures in the NPR. Such topics call for further quality monitoring and here the clinical databases have an important role. These databases provide the opportunity to perform research on a population-based level, research that is relatively cheap because data are already available, and at the same time provide data on important clinical details.
There are also some disadvantages of clinical databases. Thus, database structure and variables have to be carefully considered, and the databases need to be constantly improved to keep up with clinical practice and evidence based medicine. The quality of output, both regarding quality monitoring and research, is determined by the quality of input.
This thesis has demonstrated that the DugaBase in the period of 2006-2010 constitutes a potentially valuable tool for future research settings on a number of issues. It is of special interest that the DugaBase could be a valuable source for research on complications and repeated surgeries. In addition, the DugaBase data can be merged with primary data from cohort or survey studies, and even collaboration between urogynaecological databases from other countries. Although this thesis supports that the DugaBase already has a number of strengths, the DugaBase

should be continuously developed and updated in order to secure long term data quality.

Patient reported outcome measures

PROMs are a means of collecting information on the effectiveness of care delivered to patients as perceived by the patients themselves. The collection of such data will add to the set of information available on the care delivered to patients, and such information may complement and be used in conjunction with existing information on the quality of services. In the treatment of many diseases objective measures are usually used to assess the efficacy of a given treatment without necessarily involving the subjective measures from the patient; e.g. anatomical outcome measures or laboratory measurements. It is well known that surgeons are poor at evaluating the results of their own performance and therefore the use of PROMs is crucial. Supplementing objective with subjective measurements (such as PROMs) will lead us to a better understanding of the quality of the health care provided.

This thesis has demonstrated the feasibility of using PROMs for research. Our study has drawn attention to the importance of continuing focus on further optimizing registrations of PROMs both pre- and postoperatively. E.g. perhaps an electronic online version of the pre- and postoperative patient questionnaires could increase the motivation for completing the forms.

Pharmacoepidemiological studies

The results of the pharmacoepidemiological studies add important knowledge to the counselling of women undergoing surgery for UI and POP. Based on our results, the counselling can include information on expectancies of reduction in the need for symptom-relieving drugs and antibiotics for UTI in preoperative users. There is, however, an increased risk of continuing use compared to preoperative non-users. These studies also emphasized the importance of future studies on what characterised the sub-group of women, who are at increased risk of continuing use of symptom-relieving drugs and an increased risk of UTI. Future studies thus need to characterise women who have a continuing need of symptom-relieving drugs postoperatively, as well as what characterises the women with the complication of de novo urge after surgery for UI leading to the use of symptom-relieving drugs. According to UTI, future studies need to characterise women who have recurrent UTI after surgery not only shortly after surgery, but also in a more long term perspective: a genetic predisposition for UTI? An anatomic predisposition for UTI? Or are women postoperatively more likely to have a prescription if they suffered from UTI preoperatively, based on increased awareness of symptoms of UVI in the women and/or a greater attention of the general practitioner? Furthermore, it should be studied if prolonged use of oral antibiotics in combination with prophylactic perioperative intra venous antibiotics reduces the risk of UTI postoperatively.

We measured whether the women had redeemed prescriptions of symptom-relieving drugs or antibiotics for UTI. However, we have no measurement of compliance or other relevant clinical data on such symptoms, urine dip stix, urine culture, the type of UI, or other possible potential confounders such as body mass index. Such data would be valuable in future studies and could be assessed by supplements from medical journals, patient questionnaires, or from the DugaBase.

7. SUMMARY

This PhD thesis was performed during my employment at the Center for Clinical Epidemiology, Odense University Hospital and University of Southern Denmark, 2010-2013. It comprises an overview and four papers, two published in international peer-reviewed scientific journals, one under review, and one in draft.

Introduction: Urinary incontinence (UI) and pelvic organ prolapse (POP) are prevalent disorders among women worldwide, affecting their psychological and social wellbeing, with reductions in quality of life. Treatment options are conservative (e.g. pelvic floor exercises, weight loss, and bladder training), pharmacological, and surgical. Surgery has especially for UI undergone an improvement during the last decades with development of minimally-invasive sub-urethral sling procedures, and the number of surgeries has increased in Denmark and other countries.

Aims:

In a population of Danish women undergoing surgery for UI or POP, we aimed:

- To describe the establishment of the Danish Urogynaecological Database (DugaBase), and to evaluate the completeness and the validity of surgery registration in the DugaBase
- To study patient reported outcome measures in Danish women undergoing urogynaecological surgery
- To study the use of symptom-relieving drugs before and after surgery for UI
- To study the use of antibiotics for urinary tract infection (UTI) before and after surgery for UI

Methods

Study I The completeness of DugaBase was assessed by comparing procedure codes in the DugaBase to codes registered in the National Patient Registry, 2006-2010. The study also included review of medical journals from 200 women (computed randomly from DugaBase), representing 22 departments in Denmark. Information on selected variables was compared to registered data in the DugaBase. Data sources: the National Patient Registry, the DugaBase, and medical records.

Study II was based on a national cohort of women undergoing surgery for UI and POP registered to the DugaBase, 2006-2011. Clinical data and data from patient questionnaires were retrieved. Data sources: the DugaBase.

Study III+IV were cohort studies based on national register data and prescription data. A total of 2,151 women with a first time surgical procedure for UI within 1996-2010 were included. The data were supplemented with registry information on redeemed prescriptions on symptom-relieving drugs/antibiotics for UTI/oestrogen, comorbidity, and educational level and income. Data sources: the Danish National Patient Registry, Odense University Pharmacoepidemiologic Database, and the Register for Education Statistics, and the Register of Family Income.

Results

Study I: A total of 16,509 procedures were registered in the DugaBase by 31 December 2010. The database completeness has increased from 38.2% to 93.2% during the years. According to the validation, all 200 medical records were retrieved. The overall percentage agreement between medical records and the DugaBase was at least 90% for selected key variables: procedure code, date, hospital department, use of antibiotics, prior surgery, height, weight, parity, and smoking.

Study II: In the study period, 20,629 urogynaecological procedures were performed in Denmark and reported to the DugaBase. For approximately 1/3 of these women, the patient questionnaires on severity of symptoms and quality of life were completed

both pre- and postoperatively, and thus included. After both UI and POP surgery, more than 80% had improved symptoms and showed a significant improvement in quality of life.
Study III: A total of 2,151 women with a primary UI procedure were included. Of these, 358 (16.6%) were exposed to symptom-relieving drugs preoperatively, and 1,793 (83.4%) were not. Preoperative usage of symptom-relieving drugs was the strongest risk factor of postoperative use, both within 0-60 days OR (adjusted) = 33.0 (95% confidence interval (CI) 20.0-54.7)) and 61-365 days OR (adjusted) = 7.2 (95% CI 5.4-9.6)). Adjusted for age, procedure type, calendar year, comorbidity, preoperative use of oestrogen, educational level, and personal annual income. Only a minority of preoperative non-users started using symptom-relieving drugs postoperatively.
Study IV: The same study population as in study III. Of the 2,151 women, 496 (23.1%) were antibiotic users prior to surgery, and 1,655 (76.9%) were non-users. Preoperative usages of antibiotics for UTI was a strong risk factor of postoperative use of the same antibiotics, both within 0-60 days OR (adjusted) = 2.6 (95% CI 2.9-3.5), and within 61-356 days OR (adjusted) = 4.5 (95% CI 3.5-5.7)). Adjusted for age, procedure type, calendar year, comorbidity, preoperative use of oestrogen, educational level, and personal annual income. Comorbidity and procedure types were found to be significant risk factors as well, although less important than preoperative antibiotic use.
Conclusions
Due to a high completeness and data of high validity the DugaBase offers a unique possibility for continuing quality assessment of urogynaecological surgery in Denmark, as well as for future research. Surgeries for UI and POP performed in Danish women were effective in alleviating symptoms of UI and POP and improvement in quality of life based on patient reported outcome measures. Our pharmacoepidemiological studies showed that preoperative use of symptom-relieving drugs and antibiotics for UTI were strong risk factors of postoperative usage of the same drugs.

8. REFERENCES

1. Olsen A, Smith V, Bergstrom J, *et al.* Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* 1997;89:501–506.
2. Wu JM, Kawasaki A, Hundley AF, *et al.* Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. *Am J Obstet Gynecol* 2011;205:230.e1–5.
3. Haylen BT, Ridder D De, Freeman RM, *et al.* An International Urogynecological Association (IUGA)/ International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction. *Int Urogynecol J* 2010;21:5–26.
4. Weber A, Abrams P, Brubaker L, *et al.* The Standardization of Terminology for Researchers in Female Pelvic Floor Dysfunction. *Int Urogynecol J* 2001;12:178–186.
5. Melville JL, Delaney K, Newton K, *et al.* Incontinence severity and major depression in incontinent women. *Obstet Gynecol* 2005;106:585–592.
6. Hunskaar S, Burgio K, Diokno A, *et al.* Epidemiology and natural history of urinary incontinence in women. *Urology* 2003;62:16–23.
7. Minassian VA, Drutz HP. Urinary incontinence as a worldwide problem. *Int J Gynaecol Obstet* 2003;82:327–338.
8. Møller LA, Lose G, Jørgensen T. The prevalence and bothersomeness of lower urinary tract symptoms in women 40-60 years of age. *Acta Obstet Gynecol Scand* 2000;79:298–305.
9. Hørding U, Pedersen K, Sidenius K, *et al.* Urinary incontinence in 45-year-old women. *Scand J Urol Nephrol* 1986;20:183–186.
10. Irwin DE, Milsom I, Chancellor MB, *et al.* Dynamic progression of overactive bladder and urinary incontinence symptoms: a systematic review. *Eur Urol* 2010;58:532–543.
11. Ebbesen MH, Hunskaar S, Rortveit G, *et al.* Prevalence, incidence and remission of urinary incontinence in women: longitudinal data from the Norwegian HUNT study (EPINCONT). *BMC Urol* 2013;13:27. [Epub]
12. Athanasiou S, Anstaklis A, Betsi GI, *et al.* Clinical and urodynamic parameters associated with history of urinary tract infections in women. *Acta Obstet Gynecol Scand* 2007;86:1130–1135.
13. Raz R, Gennesin Y, Wasser J, *et al.* Recurrent urinary tract infections in postmenopausal women. *Clin Infect Dis* 2000;30:152–156.
14. Danforth KN, Townsend MK, Lifford K, *et al.* Risk factors for urinary incontinence among middle-aged women. *Am J Obstet Gynecol* 2006;194:339–345.
15. Hannestad YS, Rortveit G, Daltveit AK, *et al.* Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. *BJOG* 2003;110:247–254.
16. Dumoulin C. Postnatal pelvic floor muscle training for preventing and treating urinary incontinence: where do we stand? *Curr Opin Obstet Gynecol* 2006;18:538–543.
17. Fenner DE, Trowbridge ER, Patel D a, *et al.* Establishing the prevalence of incontinence study: racial differences in women's patterns of urinary incontinence. *J Urol* 2008;179:1455–1460.
18. Ulmsten U, Petros P. INTRAVAGINAL SLINGPLASTY (IVS): AN AMBULATORY SURGICAL PROCEDURE FOR TREATMENT OF FEMALE URINARY INCONTINENCE. *Scand J Urol Nephrol* 1995;29:75–82.
19. Rapp D, Kobashi K. The evolution of midurethral slings. *Nat Clin Pract Urol* 2008;5:194–201.
20. Kirchin V, Page T, Pe K, *et al.* Urethral injection therapy for urinary incontinence in women (Review). *Cochrane Database Syst Rev* 2012, Issue 2
21. Mohr S, Siegenthaler M, Mueller MD, *et al.* Bulking agents: an analysis of 500 cases and review of the literature. *Int Urogynecol J* 2013;24:241–247.
22. Kuo Y-C, Kuo H-C. Botulinum toxin injection for lower urinary tract dysfunction. *Int J Urol* 2013;20:40–55.
23. Ammendrup A, Bendixen A, Sander P, *et al.* Urinary incontinence surgery in Denmark 2001-2003. *Ugeskr Laeger* 2009;171:339–404. [Danish]
24. Cammu H, Saeys F, Haentjens P. Dramatic increase (1997-2007) in the number of procedures for stress urinary incontinence in Belgium. *Int Urogynecol J* 2010;21:1511–1515.
25. Bump RC, Mattiasson a, Bø K, *et al.* The standardization of terminology of female pelvic organ prolapse and

pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10–17.
26. Beck R, McCormick S, Nordstrom L. A 25-year eperience with 519 anterior colporrhaphy procedures. *Obstet Gynecol* 1991;78:1011–1018.
27. Nygaard IE, Heit M. Stress urinary incontinence. *Obstet Gynecol* 2004;104:607–620.
28. Luber KM, Boero S, Choe JY. The demographics of pelvic floor disorders: Current observations and future projections. *Am J Obstet Gynecol* 2001;184:1496–1503.
29. Smith F, Holman C, Moorin R, *et al.* Lifetime risk of undergoing surgery for pelvic organ prolapse. *Obstet Gynecol* 2010;116:1096–1100.
30. Shah AD, Kohli N, Rajan SS, *et al.* The age distribution, rates, and types of surgery for pelvic organ prolapse in the USA. *Int Urogynecol J 2008;*19:421–428.
31. Elliott CS, Rhoads KF, Comiter C V, *et al.* Improving the accuracy of prolapse and incontinence procedure epidemiology by utilizing both inpatient and outpatient data. *Int Urogynecol J* 2013 [Epub]
32. Mouritsen L, Larsen JP. Symptoms, bother and POPQ in women referred with pelvic organ prolapse. *Int Urogynecol J* 2003;14:122–127.
33. Bugge C, Ej A, Gopinath D, *et al.* Pessaries (mechanical devices) for pelvic organ prolapse in women. *Cochrane Databases Syst Rev* 2013, Issue 2.
34. Maher C, Feiner B, Baessler K, *et al.* Surgical management of pelvic organ prolapse in women. *Cochrane Databases Syst Rev* 2013, Issue 4.
35. Altman D, López A, Gustafsson C, *et al.* Anatomical outcome and quality of life following posterior vaginal wall prolapse repair using collagen xenograft. *Int Urogynecol J* 2005;16:298–303.
36. Altman D, Väyrynen T, Engh ME, *et al.* Short-term outcome after transvaginal mesh repair of pelvic organ prolapse. *Int Urogynecol J 2*008;19:787–793.
37. Elmer C, Alman D, Engh M, *et al.* Trocar-guided transvaginal mesh repair of pelvic organ prolapse. *Obstet Gynecol* 2009;113:117-126.
38. Diez-Itza I, Aizpitarte I, Becerro a. Risk factors for the recurrence of pelvic organ prolapse after vaginal surgery: a review at 5 years after surgery. *Int Urogynecol J* 2007;18:1317–1324.
39. Barber MD, Kleeman S, Karram MM, *et al.* Risk factors associated with failure 1 year after retropubic or transobturator midurethral slings. *Am J Obstet Gynecol* 2008;199:666.e1–7.
40. Rodríguez LV, Blander DS, Dorey F, *et al.* Discrepancy in patient and physician perception of patient's quality of life related to urinary symptoms. *Urol* 2003;62:49–53.
41. Marshall S, Haywood K, Fitzpatrick R. Impact of patient-reported outcome measures on routine practice: a structured review. *J Eval Clin Pract* 2006;12:559–568.
42. Kingsley G, Scott IC, Scott DL. Quality of life and the outcome of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2011;25:585–606.
43. Wijnhoven BP, Lally CJ, Kelly JJ, *et al.* Use of antireflux medication after antireflux surgery. *J Gastrointest Surg* 2008;12:510–517.
44. Madan A, Minocha A. Despite high satisfaction, majority of gastro-oesophageal reflux disease patients continue to use proton pump inhibitors after antireflux surgery. *Aliment Pharmacol Ther* 2006;23:601–605.
45. Bodhare TN, Valsangkar S, Bele SD. An epidemiological study of urinary incontinence and its impact on quality of life among women aged 35 years and above in a rural area. *Indian J Urol* 2010;26:353–358.
46. Novara G, Galfano A, Boscolo-Berto R, *et al.* Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and d. *Eur Urol* 2008;53:288–308.
47. Nygaard I, Brubaker L, Chai TC, *et al.* Risk factors for urinary tract infection following incontinence surgery. *Int Urogynecol J* 2011;22:1255–1265.
48. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–25.
49. Abrams P, Avery K, Gardener N, *et al.* The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. *J Urol* 2006;175:1063–1066.
50. Price N, Jackson SR, Avery K, *et al.* Development and psychometric evaluation of the ICIQ Vaginal Symptoms Questionnaire: the ICIQ-VS. *BJOG* 2006;113:700–712.
51. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–33.
52. Andersen T, Madsen M, Jørgensen J, *et al.* The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:262–268.
53. WHO. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-8)*. Geneva, Switzerland: 1967.
54. WHO. *Internatinal Classification of Diseases - 10th revision (ICD-10)*. 2013. http://www.who.int/classifications/ics/en/
55. NOMESCO. Classification of Surgical Procedures. In: version 1.15. 2011. no.93:2010 Copenhagen.
56. Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health* 2011;39:91–94.
57. Pedersen A, Johnsen S, Overgaard S, *et al.* Registration in the danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. *Acta Orthop Scand* 2004;75:434–441.
58. Fleiss J, Levin B, Peik M. *Statistical methods for rates and proportions*. New York: : Wiley 2003.
59. Charlson M, Pompei P, Ales K, *et al.* A new method of classifying prognostic comorbidity in longitudianl studies: development and validtion. *J Chronic Dis* 1987;40:373–383.
60. Thygesen SK, Christiansen CF, Christensen S, *et al.* The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.
61. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. *Int J Epidemiol* 2000;29:891–898.
62. Thomsen R, Riis A, Christensen S, *et al.* Diabetes and 30-Day Mortality From A Danish population-based cohort study. *Diabetes Care* 2006;29:805–810.
63. Dalton SO, Steding-Jessen M, Engholm G, *et al.* Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 2008;44:1989–1995.

64. Gaist D, Sørensen H, Hallas J. The Danish Prescription Registers. *Dan Med Bull* 1997;44:445–448.
65. Ottesen M. Validity of the registration and reporting of vaginal prolapse surgery. *Ugeskr Laeger* 2009;171:404–408. [Danish]
66. Andersen T, Madsen M, Loft A. Validity of surgical information from the Danish National Patient Registry with special attention to the analysis of regional variations in hysterectomy rates. *Ugeskr Laeger* 1987;149:2420–2422. [Danish]
67. Fletcher R, Fletcher S. *Clinical Epidemiology: The Essentials*. 4th ed. Lippincott Williams & Wilkins 2005.
68. West SL, Savitz D, Koch G, *et al.* Recall accuracy for prescription medications: self-reported compared with database information. *AM J Epidemiol* 1995;142:1103-1112.
69. Olsen J, Czeizel A, Sørensen HT, *et al.* How do we best detect toxic effects of drugs taken during pregnancy? A EuroMap paper. *Drug saf* 2002;25:21–32.
70. Mosbech J, Jørgensen J, Madsen M, *et al.* The national patient registry. Evaluation of data quality. *Ugeskr Laeger* 1995;157:3741–3745. [Danish]

9. APPENDICES

Appendix 1: Procedural codes reporting to the DugaBase

Procedural codes for urinary incontinence surgery
KDG00 Retropubic suspension of urethra
KDG01Percutaneous endoscopic retropubic suspension of urethra
KDG10 Abdominovaginal suspension of bladder neck
KDG30 Suprapubic sling urethrocystopexy
KDG31 Percutaneous endoscopic suprapubic sling
KDG40 Suprapubic urethrocystopexy
KDG50 Transabdominal plastic repair of pelvic floor for urinary incontinence
KDG96 Other operation on urethra or bladder neck for incontinence
KDG97 Other percutaneous endoscopic operation on urethra or bladder neck for incontinence
KDV20 Submucous urethral injection
KDV22 Transluminal endoscopic submucous urethral injection
LEG00 Vaginal urethrocystorrhaphy
LEG10 Vaginal urethrocystopexy with use of sling
LEG10A Vaginal urethrocystopexy with use of sling through foramen obtuarum
LEG20 Plastic repair of female pelvic floor with levator division
LEG96 Other vaginal operation for incontinence

Procedural codes for pelvic organ prolapse surgery
LEE10 Repair of vagina using graft or flap
LEF00 Anterior colporrhaphy
LEF00A Anterior colporrhaphy with mesh
LEF00B Manchester operation
LEF03 Posterior colporrhaphy
LEF03A Posterior colporrhaphy with mesh
LEF10 Colpoperineoplasty
LEF13 Colpoperineoplasty and vaginal hysterectomy
LEF23 Complete colpocleisis
LEF40 Vaginal repair of enterocele
LEF40A Vaginal operation for enterocele with mesh
LEF41 Laparoscopic repair of enterocele
LEF40A Vaginal operation for enterocele with mesh
LEF43 Abdominal operation for enterocele
LEF43A Abdominal operation for enterocele with mesh
LEF50 Colpopexy after previous hysterectomy
LEF50A Abdominal apical colpocleisis after previous hysterectomy with mesh
LEF51 Laparoscopic colpopexy after previous hysterectomy
LEF51A Laparoscopic colpopexy after previous hysterectomy with mesh
LEF53 Vaginal colpopexy after previous hysterectomy
LEF53A Vaginal colpopexy after previous hysterectomy with mesh
LEF53B Vaginal sacrospinous colpopexy
LEF60 Vaginal lateral colpopexy
LEF63 Abdominal lateral colpopexy
LEF64 Laparoscopic lateral colpopexsy
LEF96 Other operation for prolapse of uterus or vaginal vault
LEF97 Other laparoscopic operation for prolapse of uterus or vaginal vault
LCD10 Vaginal hysterectomy in combination with ICD-10 DN81
LDC10 Partial excision of cervix uteri in combination with ICD-10 DN81

Appendix 2: Clinical indicators

The clinical indicators used for annually reporting from the DugaBase (version 2010)

Indicator domain	Indicator	Type	Standard	Calculation (numerator / denominator)
Waiting time 30 days	Time from receipt of referral at the hospital to the first specialist-contact	Process	Minimum 90%	Number of patients with ≤ 30 days between referral and first visit at hospital / Total number of patients with a surgery date
UI: Subjective patient assessment of success	Subjective patient assessment of success after surgery for UI	Result	Minimum 70%	Number of patients with the answer "Never" or "About once a week or less often" to "How often do you leak urine?" / Number of patients with surgery for UI and an answer to the question
UI: Obstruction after surgical treatment	Degree of obstruction after surgery for UI, assessed by the amount of residual urine. Should be < 50 ml	Result	Minimum 90%	Number of patients with < 50 ml residual urine at follow-up visit / Number of patients with surgery for UI and a measure of the residual urine at follow-up visit
POP: Objective score on POP after surgery	Objective measure of success of surgery for POP, assessed by grade of prolapse. The goal is ≤ grade 1	Result	Minimum 90%	Number of patients with postoperative assessment of POP** ≤ 1 / Number of patients with surgery for POP and a recording of prolapse degree
POP: Subjective patient assessment of success	Patient satisfaction after surgery for POP	Result	Minimum 80%	Number of patients at follow-up who have recorded "Never" to "Are you aware of a lump or bulge coming down in your vagina?" / Number of patients with surgery for POP and an answer to the question
UI: Further need for treatment	Need of further treatment after surgery for UI	Result	Maximum 10%	Number of patient with the recording of a large or small need for further treatment at follow-up visit / Number of patients with surgery for UI and a recording on the need for further treatment
POP: Further need for treatment	Need of further treatment after surgery for POP	Result	Maximum 10%	Number of patient with recording of a large or small need of further treatment at follow-up visit / Number of patients with surgery for POP and a recording on the need for further treatment