

The Hordaland Women's Cohort

A longitudinal study on urinary incontinence in middle-aged women

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***My hero is not in the stories, I did cry on his shoulder and
he cried with me***

*I am dedicating this dissertation to my hero, Professor Eivind
Meland. He taught me how to not lose hope and showed me the true
meaning of empathy, by giving me the highest support in the most
difficult time of my life*

Scientific environment

The work of this thesis has been carried out by the General Practice Research Group, Department of Global Public Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen. The last 6 months, due to my residence in Oslo, I have benefitted from regular meetings with my supervisor in Bergen for finalizing this dissertation. In Oslo, I got the opportunity to use the scientific environment in the Department of General Practice, Institute of Health and Society.

The Norwegian Research Council and the University of Bergen have funded the project.

Professor Steinar Hunskaar has been my supervisor.

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University of Bergen, Norway

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Contents

Scientific environment	4
Contents	7
Acknowledgements.....	9
Abstract	12
Sammendrag (Abstract in Norwegian).....	15
List of publications	18
Abbreviations	19
1. Introduction	21
2. Definition of Urinary Incontinence	23
3. Epidemiology of Urinary Incontinence.....	26
3.1 Prevalence.....	26
3.2 Incidence and remission	30
3.3 Natural history of urinary incontinence	38
3.4 Risk factors.....	40
3.5 Impact and consequences.....	41
Aims of the study	45
4. Material and Methods.....	46
4.1 The Hordaland Women's Cohort.....	47
4.1.1 Sampling and Participants	47
4.1.2 Questionnaires	48
4.1.3 Definition of UI and its severity.....	50
4.1.4 Types of UI.....	51
4.1.5 Paper I	51
4.1.6 Paper II	52
4.1.7 Paper III	53
4.1.8 Ethical approval.....	54
5. Summary of Results	55
5.1 Paper I.....	56

5.2	Paper II.....	57
5.3	Paper III.....	59
6.	Discussion.....	61
6.1	Dicussion of methods.....	61
6.1.1	Design.....	61
6.1.2	Internal validity.....	61
6.1.3	External validity.....	64
6.1.4	Precision.....	65
6.2	Discussion of results.....	66
6.2.1	Prevalence.....	66
6.2.2	Incidence and remission of UI.....	68
6.3	Recommendation for further research.....	71
	Source of data.....	73
7.	Appendices.....	82
7.1	Paper I.....	83
7.2	Paper II.....	92
7.3	Paper III.....	100
7.4	Hordaland Women’s Cohort questionnaire (wave one).....	107
7.5	Hordaland Women’s Cohort questionnaire (wave six).....	110
7.6	Hordaland Women’s Cohort questionnaire in English.....	113

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Abstract

The Hordaland Women's Cohort

A longitudinal study on urinary incontinence in middle-aged women

David Jahanlu (PhD-dissertation)

Urinary incontinence (UI) is a prevalent problem among middle-aged women, and many epidemiological studies have investigated this problem. Most of these studies are cross-sectional and only few longitudinal studies have been conducted. Thus, the knowledge about incidence, remission and natural history of UI is scarce. The aim of that present dissertation was to answer major epidemiological questions about incidence, progress and remission of UI in middle-aged women.

The Hordaland Women's Cohort was established in 1997 and designed as a prospective longitudinal study for 15 years. The source population was from Hordaland Health Study (HUSK), which was a joint epidemiological research project and a part of national health project called Cohort of Norway (CONOR). HUSK invited all individuals in Hordaland County born between 1953-57, and among 14300 women in Hordaland, almost 9900 (70%) participated in HUSK. We took a one-fifth random sample of female HUSK participants and 2230 women consented to take part in the Women's Cohort. In 2007 the Cohort reached a ten-year follow up with six checkpoints and the present dissertation is based on the analyses of data for this period of the Cohort.

In the first sub-study (**Paper I**), the data from source (HUSK) population was used to compare the basic demographic data and urologic characteristics between the women who participated in the Cohort and rest of the women in HUSK. For demographic data, 2230 women in the Cohort were compared with 7746 women in HUSK, who were not selected for the Cohort. For urologic characteristics, we used a HUSK sub-questionnaire with 5320 participants. Of these, 1920 were in the Cohort and we

compared their urological characteristics with those of the rest of the women (n=3400). The results demographic data showed a very high similarity for demographic data. The only significant differences were observed for higher education (p=0.001) and higher annual family income (p=0.018) among the women in the Cohort.

Analyzing data for urinary conditions showed few statistical differences between women in the Cohort and the rest of the women; they had somewhat more UI (p=0.040), more stress UI (p=0.048) and less amount of leakage (p=0.015) in the Cohort participants. Prevalence rate of any UI was 28.9% in the Cohort and 24.8% in the rest of women in HUSK. This paper also described the research methodology in details with intention of using it as reference for any further data analysis from the Cohort.

The second sub-study (**Paper II**) explored the prevalence, incidence and remission of UI. In this paper the possibility of an early prevalence peak in middle-aged women was investigated. We first used all data from the Cohort, which was gathered during ten years in six waves, to analyze the prevalence curve of UI. Furthermore, for more detailed analyses of prevalence, incidence and remission, data from the women who answered all six questionnaires were used. We sorted data in terms of age with eight groups in the age span of 41-55 years. Definition of UI was based on the results from the Incontinence Severity Index (ISI) and women with an ISI of more than 0 were defined as having incontinence. Women with an ISI equal to 3 or more, who reported their UI to be bothersome, were defined as having significant UI. According to our data, the prevalence of any UI in women aged 41-42 year was about 37% and increased gradually up to 50% in the age of 51-52 years, after which it started to decrease gradually. The changing patterns for incidence and remission were the same until age 51-52, but then the incidence started to decrease while the remission was increasing, which could have caused the peak in the prevalence of UI. Stress UI was the major type and most cases of UI were of low severity. Over the observation period, while the proportion of mixed UI increased by age, the proportion of stress UI remained relatively stable and the proportion of urgency UI slightly varied between

aged groups. Regarding type shift, proportion of moderate UI remained relatively stable, while slight UI decreased and severe/very severe UI increased by age.

The main aim of the third sub-study (**Paper III**) was to investigate the natural history of UI with focus on finding the new-onset UI and its changes in types and severity. First we defined continent women in the baseline by using the same definition of UI as in **Paper II**. We followed them wave by wave during 10 years and 5 checkpoints. Almost half of them reported to have UI, at least once during 10 years. The types of new-onset UI by type were distributed as: 49.8% stress, 18.3% urgency and 20.3% mixed UI. By severity, 89.3% of women started with slight UI, none of them reported severe UI in the first report. In follow up of women for 2 waves after the new-onset UI, one-third of them had persistent UI, the type and severity was mainly stress UI with slight severity, with a low tendency for shifting the type or severity. We also suggest out that mixed UI is not necessarily the final stage of UI.

Sammendrag (Abstract in Norwegian)

Kvinnekohorten i Hordaland

David Jahanlu (ph.d.-avhandling)

Urininkontinens (UI) er et utbredt problem blant middelaldrende kvinner og mange epidemiologiske studier har undersøkt dette symptomet. De fleste av disse studiene er basert på tverrsnittsdata og det er bare gjort noen få longitudinelle studier på området. Som følge av dette har vi begrenset kunnskap om forekomsten, remisjon og forløpet av UI. Målet med avhandlingen var å finne svar på viktige epidemiologiske spørsmål som start, utvikling og remisjon av UI hos middelaldrende kvinner.

Kvinnekohorten i Hordaland ble opprettet i 1997 og hadde til hensikt å være en prospektiv longitudinell studie over 15 år. Kildepopulasjonen var fra Hordalandsundersøkelsen (HUSK), som var et felles epidemiologisk forskningsprosjekt og en del av det nasjonale helseprosjektet Cohort of Norway (CONOR). HUSK omfattet alle personer i Hordaland fylke født mellom 1953 og 1957, og blant 14300 kvinner i Hordaland deltok nesten 9900 (70%) i HUSK. Vi gjorde et tilfeldig utvalg av en femdel av kvinnene som deltok i HUSK, og 2230 kvinner gav sitt samtykke til å delta i Kohorten. I 2007 hadde man gjennomført oppfølging med seks kontrollpunkt og denne avhandlingen er basert på analysen av dataene for denne perioden av studien.

I den første delstudien (**Artikkel 1**) brukte vi data fra kildepopulasjonen (HUSK) for å sammenligne de demografiske data og urologiske forhold mellom kvinnene som deltok i Kohorten og resten av kvinnene i HUSK. 2230 kvinner i Kohorten ble sammenlignet med 7746 kvinner i HUSK. For urologiske forhold brukte vi et delspørreskjema fra HUSK svart av 5320 deltakere. 1920 av disse var i Kohorten og vi sammenlignet deres urologiske særtrekk med resten av kvinnene (n=3400). Demografiske data viste stor grad av likhet mellom gruppene av kvinner. De eneste

forskjellene vi fant av betydning var for høyere utdanning ($p=0,001$) og større årlig familieinntekt ($p=0,010$) blant kvinnene i Kohorten. Dataene for urologiske variabler viste få statistiske forskjeller mellom kvinnene i Kohorten og resten av kvinnene; men noe mer UI ($p=0,040$), mer stress UI ($p=0,048$) og mindre lekkasje ($p=0,015$) hos deltakerne i Kohorten. Prevalensen av UI var 28,9 % i Kohorten og 24,8 % hos resten av kvinnene i HUSK.

Analysen viste at deltakerne i Kohorten er like kildebefolkningen og således representativ for deltakerne i HUSK. Den viste også at for UI var resultatene forenlig med funn fra tidligere forskning i Norge. I artikkelen er forskningsmetoden også beskrevet i detalj og hensikten med dette er å kunne bruke artikkelen som en referanse for den videre bruken av data i Kvinnekohorten.

Den andre del (**Artikkel 2**) undersøkte prevalens, insidens og remisjon av UI. Vi ville også se om vi fant et mulig tidlig toppunkt for prevalensen hos middelaldrende kvinner. Vi brukte først hele materialet fra Kohorten samlet inn gjennom en 10- års periode i 6 bølger til å analysere forekomsten av UI. Deretter, for mer detaljerte analyser av prevalens og remisjon brukte vi bare data fra kvinner som hadde svart på alle de 6 spørreskjemaene. Vi sorterte dataene utifra alder (41-55) og fordelte vi kvinnene i 8 aldersgrupper.

Definisjon av UI var basert på resultatene fra Incontinence Severity Index (ISI), og kvinner som hadde mer enn 0 i skåre i følge ISI ble definert som inkontinente. Kvinner med 3 og mer på ISI og som beskrev sin UI som plagsom ble definert som å ha alvorlig UI. Ifølge våre data var forekomsten av en eller annen form for UI hos kvinner i alderen 41-42 år rundt 37% og den økte gradvis opp til 50% i alderen 51- 52 år. Etter denne alderen begynte prevalensen gradvis å synke. Insidens og remisjon fulgte samme mønster til kvinnene var 51- 52 år, men da begynte insidensen å synke mens remisjon økte. Dette er forklaringen på at man hadde et toppunkt i utbredelsen av UI. Hovedtypen var stress UI og de fleste hadde UI lav alvorlighetsgrad. I observasjonsperioden fant vi en forandring i fordelingen av både type og alvorlighetsgrad.

Hovedformålet med den tredje del (**Artikkel 3**) var å undersøke det naturlige forløpet for UI ved ulike typer av UI og ulike alvorlighetsgrader. Vi fokuserte på nyoppstått UI og dens utvikling de neste 4 årene. Ved å bruke den samme definisjonen av UI som i **Artikkel 2**, inkluderte vi kontinente kvinner i den første bølgen og fulgte dem gjennom de neste 5 bølgene. Nesten halvparten av kontinente kvinner i basislinjen rapporterte et frembrudd av UI i løpet av 10 år. Fordelingen av type var 49,8%, 18,3% og 20,3% for henholdsvis stress-, urgency- og blandet urininkontinens. Majoriteten av kvinnene (89,3%) fikk lett UI i begynnelsen og ingen rapporterte alvorlig UI allerede fra debut av UI. Studien viser at det blant middelaldrende kvinner med nylig frembrudd av UI er det stress- typen som er mest vanlig og at den er av lav alvorlighetsgrad. En tredel av kvinnene utviklet varig inkontinens med liten tendens til forandring av både type og alvorlighetsgrad gjennom årenes løp. Blandet UI er trolig ikke et siste stadium av UI i denne aldersgruppen.

List of publications

This thesis is based on the following individual publications:

Paper I: Jahanlu D, Qureshi SA, Hunskaar S. The Hordaland Women's Cohort: A prospective cohort study of incontinence, other urinary tract symptoms and related health issues in middle-aged women. BMC Public Health 2008;8:296. DOI: 10.1186/1471-2458-8-296

Paper II: Jahanlu D, Hunskaar S. The Hordaland Women's Cohort: prevalence, incidence, and remission of urinary incontinence in middle-aged women. Int Urogynecol J Pelvic Floor Dysfunct 2010;21:1223-9. DOI: 10.1007/s00192-010-1172-7

Paper III: Jahanlu D, Hunskaar S. Type and severity of new-onset urinary incontinence in middle-aged women: The Hordaland women's cohort. Neurourol Urodyn 2010;30:87-92. DOI: 10.1002/nau.20966.

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Abbreviations

BACH	Boston Area Community Health Survey
BMI	Body Mass Index
CONOR	Cohort of Norway
EPINCONT	Epidemiology of Incontinence in the County of Nord- Trøndelag
FI	Fecal Incontinence
HUSK	Hordaland Health Study
ICD	International Classification of Diseases
ICIDH	International Classification of Impairment, Disability and Health
ICI	International Consultation on Incontinence
ICS	International Continence Society
ISI	Incontinence Severity Index
IUGA	International Urogynecological Association
LE	Level of Evidence
LUTS	Lower Urinary Tract Symptoms
NHS	Nurses' Health Study
NOK	Norwegian Kroner
QoL	Quality of Life
RTV	National Insurance Administration (of Norway)
SEK	Swedish Kroner
SWAN	Study of Women Across the Nation
UI	Urinary Incontinence
USD	United States Dollar
WHO	World Health Organization

1. Introduction

Urinary incontinence (UI) affects women of all ages, and is at least twice as prevalent, compared with men¹. This common problem, mostly regarded as a symptom, shows a wide range of severity and different types². Incontinence is not a life-threatening disease, but the symptoms may seriously influence the physical, psychological, and social wellbeing of the affected individuals.

In order to understand and manage UI, it is necessary to study the epidemiology and natural course of UI. This matter, especially in middle-aged women, is not very well described and rather little is known about onset and progress of UI in this period. Advancing the basic knowledge of epidemiology is also necessary for finding the risks and protective factors, which may lead to primary or secondary disease prevention. By finding epidemiological parameters (incidence, prevalence, remission), understanding the natural history of UI will be possible. Many studies are dedicated to find out the prevalence of UI, mostly cross-sectional epidemiological studies, that have shown an increase in prevalence of UI with aging and particularly by the time a woman enters the perimenopausal years³⁻⁵, and several authors have reported a prevalence peak in midlife⁶⁻⁹. However, prospective studies with detailed analyses of the incidence and remission of UI are scarce.

The present work is the first set of data analyses from the Hordaland Women's Cohort. This Cohort is a prospective longitudinal study with emphasis on prevalence, incidence, remission and natural history of UI during perimenopausal stages. To begin with, I refer to the previous and current consensus definitions of UI. I then go on to discuss the epidemiological terms and literatures regarding UI in middle-aged women.

The introductory part of this thesis is based on a review of the literature up to spring 2014. An extended literature search in PubMed and other relevant sources was performed, using a relevant series of key words. Major reviews and book chapters were also searched for relevant papers. The research group for UI, which I am part of, have for many years performed systematical literature searches every month. We use

a very broad search algorithm in order to retrieve all relevant papers: “urinary incontinence” [MeSH Terms] OR "incontinence pads"[MeSH Terms].

2. Definition of Urinary Incontinence

One of the challenges in all studies of diseases is to find out and agree upon a uniform definition of disease. The lack of a uniform definition of UI caused many discrepancies in assessing and particularly in comparing the findings from different epidemiological studies¹⁰.

UI may be diagnosed subjectively (self-reported) or objectively (clinically). The clinical aspects of UI should be approached differently compared to self-reported UI. Clinically, the diagnosis of UI should be based on sign and symptoms or specific diagnostic tests. A subjectively diagnosed UI is more suitable for epidemiological studies¹¹. One of the disadvantages of self-reported UI is however a possible misclassification of UI¹². This work is based on a subjective and self-reported definition of UI.

The pioneer of standardization of definitions of UI is the International Continence Society (ICS). ICS is an international multidisciplinary society and one major part of their aims is the study of lower urinary tract symptoms (LUTS). ICS is a co-organizer of several conferences called International Consultation on Incontinence (ICI). The extensive reports from the different consultation committees have been published and will be referred to, several times, in the present work. Most ICS reports are designed for clinical aspects of UI, but the latest case definition of subjective UI is as simple as: *Complaint of involuntary loss of urine*¹³. This definition was established in 2002 when ICS provided new definitions for lower urinary tract dysfunction, compatible with the WHO ICIDH-2 (International Classification of Impairment, Disability and Health) and the ICD10 (International Classification of Diseases)². Before that, “*the presence of a social or hygienic problem*”, was included in the definition of UI, but since those concepts are very variable by subjects and causes confusions, they were removed. However, in the new definition, ICS recommends that UI should be also described by specifying relevant factors such as type, frequency and severity of UI².

In the latest joint report on the terminology for female pelvis floor dysfunction, by ICS and International Urogynecological Association (IUGA) in 2010¹³, eight different types of UI based on symptoms were defined. Among these, three are related to this dissertation, and defined as follows:

Stress UI: Complaint of involuntary loss of urine on effort or physical exertion (e.g. sporting activities), or on sneezing or coughing.

Urgency UI: Complaint of involuntary loss of urine associated with urgency. (“Urgency” replaces “urge” as the “accepted” terminology for the abnormal rather than the normal phenomenon of an urge to urinate)

Mixed UI: Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing.

These definitions for major types of UI are not much changed compared with the report from 2002².

Regarding severity; as a relevant factor for describing subjective UI, there is no specific definition in the ICS reports. However, there are many studies that include data for severity of UI based on frequency and amount or volume of urinary leakage. One of the most popular methods is the Incontinence Severity Index (ISI) created by Sandvik et al^{8,14}. This index, which is used in the publications for this dissertation, is based on self-report on frequency and amount of leakage, which later can be calculated by multiplying the values and categorized to 3 or 4 grades. This index will be explained later in the “Material and Methods” section.

Despite of all modifications, the dispute about the definition of UI is still on. Some confusion arise from the ambiguity between researchers and clinicians and some other confusion arise from the translation of the definition in different languages¹⁵. For example, in the latest definition of UI, it is emphasized that instead of “Stress UI”, in some languages, “activity related UI” might be preferred to avoid confusion with psychological stress¹³. Variation in definition of UI can cause discrepancies among different epidemiological studies, even if the true prevalence and incidence

are the same. Høltedahl et al¹⁶ in a cross-sectional study, showed how the estimation of prevalence can distinctively change by different definitions in the same population. For example, while 42.7% of women in age group 50-54 reported UI as any involuntary leakage, only 16.0% of them could be confirmed with UI by the old definition of ICS (involuntary urine loss with social or hygienic problem).

3. Epidemiology of Urinary Incontinence

In the last three decades much progress has been made in the understanding of the prevalence rates and establishing risk factors of UI. However, since longitudinal studies are necessary to investigate the incidence, remission and natural history of UI, and this type of study is time-consuming and expensive, less research on these matters has been conducted¹⁰. In this part of introduction, the focus is mainly on the epidemiology of UI in women. After reviewing the prevalence, the incidence and remission of UI will be reviewed.

3.1 Prevalence

Prevalence of UI in women has been studied widely in different geographic and demographic settings. The results of these studies show very different and wide-range estimates of prevalence. In a review of articles¹⁷⁻¹⁹, reported in 3rd ICI, the prevalence of UI in women, in 36 different population-based studies in 17 countries, showed a range from 5.0%²⁰ to 69.0%²¹. Another systematic review²² showed a range between 4.8 and 58.4%. Hunška et al. in yet another study⁷ compared the prevalence of UI in women in 5 different European countries; the range of estimated UI was between 23.0% (Spain) to 44.0% (France). In a cross-national study²³ the estimation of prevalence for women 18 years and older was reported 18.0%. However, generally most of studies report a prevalence of UI in the range of 25% to 45%.

There are many different possible reasons for this variety in estimation of prevalence. Milsom et al.¹⁸ explain some of those reasons as follows; sampling frame, response rates, variation in definition of UI, types of UI, methodology of survey, cultural and language differences. To be able to compare epidemiological studies, all these reasons should be encountered. As an example, in 3 different large-scale studies, the prevalence of any urinary incontinence in women aged ≥ 40 was reported as 16.1%²³, 38.8%²⁴ and 67.6%²⁵. To understand the reason for differences in estimation of prevalence of UI, I briefly review these papers here.

The first study²³ was a population-based, cross-sectional telephone survey of adults, aged 18 and over, in five countries (Canada, Germany, Italy, Sweden, and the United Kingdom). The study was conducted in 2005. Among 58139 individuals (male and female), 19162 agreed to participate (33% response rate). The 2002 ICS definitions of UI were used and for women aged 18 and over, the prevalence rate for any UI reported as 13.1%, and after adjusting the age for women 40 years old and older (n=8611), the prevalence calculated as 16.1%.

The second study²⁴ was a prospective, population-based survey in Belgium, and was conducted in 2011. Women aged 40 plus, who visited a general practitioner, for any reason, were invited to participate in the survey (no response rate was given). A self-assessment questionnaire was used and one of the questions asked about the presence of incontinence. Data were collected on 7193 women, 38.8% reported any UI.

The third study²⁵ was a cross-sectional Internet survey, which was conducted in United States, United Kingdom and Sweden. The study was published in 2012. A total of 15861 women age 40 and plus participated in the survey (response rate for both men and women was 59.2%). Participants received equal of 2 US dollar as encouragement points. UI was defined as any urinary leakage during the last 4 weeks. Overall UI was reported in 67.6% of women.

There were thus major differences in mode of administration of questionnaires, recruiting samples, response rates and methodology, plus differences in cultural backgrounds and definitions of UI provide probably these factors a wide range of estimation of prevalence of any UI in the surveys. One of the limitations of such studies is the use of self-reported incontinence, which increases the inaccuracy relative to objectively diagnosed UI^{23,26}. The individual's interest in the subject of the research may also affect the results, clearly indicated when the distribution of UI is different in non-participants compared to sample. Therefore, demographic differences between sample and source population should be shown in all studies.

As an established finding, the prevalence of UI increases with increasing age^{6,10,19,27}. An interesting finding, noted by several investigators, is a slight decrease of

prevalence of UI in middle-aged women, which is then followed by an increase toward the elderly^{6,10,28-30}. A decrease in prevalence could happen due to treatment, remission or a decrease in incidence. A decrease in incidence could be the result of a biological effect or a reduction in the level of precipitating factors (e.g. sports or physical activity). As a biological effect, menopause, in some studies^{3-5,31}, was considered as a possible cause for increasing the occurrence of UI. In contrast, many cross-sectional studies show that the prevalence of UI does not increase or decrease with natural menopause³¹⁻³⁶. Some studies show evidence that stress UI is more related to menopause than urgency UI^{3,21}. However, since menopause is a long process, evolving during several years, it is difficult to establish its relationship to UI¹⁸.

There are several studies on epidemiology of UI in Norway; I am going to review some of them, as they are related to this dissertation.

In 1993, Sandvik et al⁸ conducted a study aiming to validate a simple Severity Index of UI in female with a subsequent epidemiological survey. They created the Index by multiplying the reported frequency (four levels) by the amount of leakage (two levels) and validated the Index against pad weighing test. Women with UI, who were referred to a gynecological clinic, were interviewed for calculation of Severity Index, and half of them performed pad-weighing test at home. Comparing the results between these two tests showed a significant correlation. In the epidemiological part, 1820 women aged 20 or more were studied and an overall prevalence of UI of 29.4% was reported. The overall prevalence was higher in the age groups 50-59 and 80+ years. Based on the Severity Index, 46.0% of women with UI were classified as having slight, 27.0% as moderate and 27.0% as severe UI. This study, for the first time, showed that there is a prevalence peak for UI in middle-aged women.

In 1994, Holtedahl et al¹⁶ studied prevalence, incidence and remission of UI in women 50-74 years of age. Data were collected from 3 different North-Norwegian municipalities. A total of 698 women were invited by mail for two gynecological examinations with one-year interval. 507 women (response rate 72.6%) met for the

first consultation and 489 of women participated in the second consultation. Both participants and physicians filled out a questionnaire, containing questions about UI. Any UI was defined as self-reported urinary leakage of any kind and the prevalence was 47.3%. Two or more leakage episodes per month were defined as “regular” UI and the prevalence reported was 30.6%. The annual incidence of UI was reported to be 0.9%. Spontaneous remission was not reported and only 7 out of 59 women who reported UI, also reported remission as a result of medical treatment.

Another major study⁶ in Norway was the EPINCONT study, which was performed in a county in Norway during 1995-97 as part of the large HUNT study in Nord-Trøndelag. Everyone aged 20 years or more (n=47313) was invited and 74% of them participated in EPINCONT study and defined as source population of EPINCONT study. Among 80.0% (n=27,936) of women who answered the questions about UI, 25.0% had urinary leakage⁶. The prevalence of significant UI, which was defined as moderate to severe UI (by Severity Index) and presence of at least some bother was 7.0%. Half of the incontinence was of stress type, 11% had urgency and 36% mixed incontinence. The EPINCONT study has since been the source for a long series of publications (i.e. parity³⁷⁻³⁹, help seeking⁴⁰, diabetes⁴¹⁻⁴³ and lifestyle factors⁴⁴)

Klovning et al⁴⁵ compared the result of a web-based study on the prevalence of UI with results from the EPINCONT study. Women were invited to the survey by web-banners, and those who selected to participate by clicking the banner, were redirected to another link with a short introduction about the survey and then an online questionnaire. During two months 1812 women were recruited from different websites. After applying same inclusion criteria, 1619 of women, age range 20-69, were included in the analysis. Crude unadjusted prevalence of UI was 20.0% while the same results in the EPINCONT study (age-range 20+) was 25.0%⁶. Age-adjusted prevalence rates of UI (5-year age categories) showed a lower prevalence rate in age groups 20-24 and 25-29, but a higher prevalence in other compatible age groups. The software used for this data collection had not the ability for controlling multiple entries of one individual. As Internet researches are more attractive for younger people, conditions that are more prevalent in old ages, may not be suitable

for Internet surveys so far. The study also concluded that the web-based surveys might not be suitable for estimating the prevalence of UI due to interest bias. But such studies may be well suited for recruiting persons for studying women with UI⁴⁶

Ebbesen et al⁴⁷, in a study published in 2013, studied the changes in prevalence of UI in women in the Norwegian EPINCONT study. The study also used data from the second EPINCONT (2006-2008) and showed a 16.0% relative increase in prevalence of UI in the county of Nord-Trøndelag during 11 years. UI was defined as any involuntary loss of urine, and Severity Index was used for evaluation of severity. Some known UI risk factors, such as age, BMI, weight and parity, were suggested as some of the causes for increasing the prevalence of UI in this population. The study also reported the incidence and remission rate of UI, which will be discussed here later.

3.2 Incidence and remission

Incontinence is a dynamic condition¹⁸ with the possibility of remission (spontaneously or after treatment) and recurrence. The incidence rate is calculated by dividing the number of new cases by the number of continent women at baseline in a given time period. For calculation of remission rate the number of women who become symptom free is divided by the number of incontinent women at the start of study in the same given time period. Since the denominator for remission rate is usually much smaller than the denominator for incidence rate, the remission rate usually shows a larger percentage compared with incidence rate¹⁸.

Annual incidence of UI is estimated very widely (0.9%-18.8%)⁴⁸, which can be explained by several reasons such as different definitions or methodology of research. Studies that limited the definition of UI to “weekly UI”, has less variation in incidence (1.2%-4.0%) compared with studies with using “any” or “monthly UI” (0.9%-18.8%)⁴⁸. Besides the definition of UI, there are other important points that should be kept in mind in any systematic review of incidence of UI, such as duration of study, survey method and outcome measures⁴⁹. The length of a study has a

negative correlation with reported annual incidence rate⁴⁸, it means that studies with shorter duration (1-2 years) may overestimate the annual incidence rate.

In any cohort, for finding the incidence rate of UI, the population at baseline must be divided into continent and incontinent. However, some of the continent women at base line may be the subjects of remission, and based on the study design, they may or may not be counted as incident cases¹⁸. And even if the study is clear about this matter, some cases may be misplaced due to recall bias. It is also important to take types, severity and age groups into consideration when we compare the incidence rate between different studies.

The interval between data collections is also very important. Cohort studies with long intervals like 5-10 years⁵⁰ may report lower annual incidence than cohorts with reported 1 to 2 year follow-up²⁷. The accuracy of data increases in cohorts with several waves throughout the study period. To have a better picture of incidence of UI, I am going to review studies published since year 2000, chronologically. Table 1 also summarized the annual incidence and remission (if reported) of these studies.

Moller⁵¹ followed 2860 women, aged 40-60 years in a longitudinal study with a baseline and a one-year follow-up questionnaire. UI was defined as any involuntary loss of urine occurring weekly or more. Incidence was defined as the proportion of women in whom symptoms started or increased from sometimes to weekly or more. Conversely, the rate of remission was defined as the proportion of women with symptoms occurring weekly or more at baseline in whom symptoms decreased to less than weekly and eventually ceased at one year follow-up. Overall incidence and remission were reported as 10.0% and 27.8% respectively. The baseline data gathered in 1996 and compared with other studies, the higher percentages of results, might be due to differences in the study design and UI definitions.

Samuelsson⁴⁶ studied 382 women, aged 20-59 years with a questionnaire and a gynecologic examination at baseline (1993) and a follow-up questionnaire after 5 years (1998). UI was defined as any involuntary loss of urine. A 5-year incidence rate of 14.0% and a 5-year remission rate of 28.0% were reported. For the age group 30-

39 the annual incidence was 3.5% while it was 2.9% for the age group 40-49; the remission was 8.5% and 6.4% for age groups 30-39 and 40-49 respectively. If they had monitored the women with repeated annual questionnaire the true 1-year incidence would probably be higher than the mean annual incidence rate because women who were continent at baseline and at follow-up might have had periods of incontinence during the follow-up interval.

Sherburn⁵², with focus on association between UI and menopause, studied 438 women aged 45-55 years. At baseline, women were interviewed by telephone and then they were interviewed annually, face-to-face at their home. UI was defined if they answered yes to the question about any problem with control of your urine in the past 2 weeks. Over the 7-year follow-up, the incidence rate was 35.0%. They found no significant association between UI and the transition to postmenopause. Women who experienced a surgical menopause had higher incidence of urinary incontinence than women in the other menopausal transition groups. Beside the small sample size and narrow age-span, the study lacks questions for determining the types of incontinence.

McGrother⁵³ studied about 12,000 women aged more than 40 years in UK at two checkpoints with one-year interval. The article was published in 2004. UI was defined as any leakage occurring monthly or more. Severity was assessed by multiplying frequency (i.e. yearly=1, monthly=2, weekly=3, daily=4) and volume (any leakage=1, damp=2, wet=3, soaked=4); and the final scores (1-16) were categorized to minimal (1-2), moderate (3-4), severe (5-9) and profound (≥ 10). They also defined age groups with 10-year age-span. The annual incidence of any UI was 8.4% and 7.9% for age groups 40-49 and 50-59 respectively. The remission was 26.9% and 25.5% respectively.

Dallasso⁵⁴ assessed the association between the development of stress UI and diet in women aged 40 years and plus. The study was conducted in 1998 and published in 2004. With a follow-up after one year, 5816 women were included at baseline. Participants were considered to have stress UI if they reported leakage of urine with

laughing, coughing or exercise, with a frequency of at least several times a month during the previous 12 months. The results showed 9.3% and 7.2% incidence of stress UI in age groups 40-49 and 50-59 respectively. The incidence rate of stress UI was reported as highest in the perimenopausal group (40-49 years) and in the very elderly (80 years plus).

Ostbye⁵⁰ studied UI in a cohort study with 3 waves during 10 years. The study was started in 1991 with the second wave in 1996 and the last wave in 2001. A total of 5322 women, aged 65 and plus were included at baseline. For women aged 65-74 years at baseline, the incidence of UI was 14.3% and 18.3% in wave one and wave two respectively. The study confirmed that UI is a dynamic condition, with a relatively large number of both incidence and remission. The study did not distinguish between different subtypes of UI and there were no details on severity, duration, and impact of UI. As mentioned above, longitudinal studies on elderly people have a higher proportion of lost to follow up, due to high rates of mortality. In this study, also, to the extent that individuals who died or were lost between waves were more likely to develop UI than those who were followed up, the reported occurrence rates might be lower than the actual rate.

Hagglund⁵⁵ studied 248 women aged 22-50 years at two checkpoints with 4 years interval (1996 and 2000). At baseline, 118 women were incontinent and 130 were continent. The mean annual incidence and remission rates of UI were the same (4.0%). The majority of women (83.0%) reported unchanged UI after 4 years and 77.0% of these women had stress incontinence. In age group 41-50 years, the 4-year incidence and remission was 18.0% and 13.0% respectively. Beside the small sample size, one of the limitations of the study was the screening question for UI: *“For the present time do you have a problem with involuntary loss of urine?”* which could be confusing for participants due to using the words “present time” and “problem”, thus causing misclassification error, and underestimation of the incidence rate.

Wehrberger⁵⁶ in a follow up of women aged 20-84 years after 6.5 years included 441 women. The baseline data was gathered in 1999 and the second questionnaire was

sent in 2005. The mean annual cumulative incidence of UI was 3.9%, with the lowest rate (2.3%) in the youngest age group (29-39 years) and the highest (7.3%) in those aged 70 years or older. The mean annual full remission rate was 2.9% with no clear age dependency. More than half of women (55.6%) with a full remission had only a mild form of UI at baseline. After a multivariate analysis, they showed that urgency UI and age are correlated to risk of new-onset UI. The problem of following individuals over a prolonged time period is emphasized in this study, as almost 50% drop out rate was presented. This study should be interpreted with caution because of small number of cases, and since the study is not population-based, selection bias should be considered.

Waetjen⁵⁷ used data from the baseline (1995) and first five annual follow-up visits (up to 2001) from the American prospective cohort of the Study of Women's Health Across the Nation (SWAN). The mean age at baseline was 45.8 years. The prevalence of incontinence was 46.7% and the average incidence was 11.1% per year. Most women reported stress, but a higher proportion developed urgency UI (15.9% vs. 7.6% at baseline). This study was among the first to examine the prevalence and incidence of UI in a racially/ethnically diverse group. The study also showed that while parity was associated with increased odds of prevalent stress and mixed UI, it was not an important factor in the development of any type of incident incontinence over the 5 years of follow-up. This novel observation suggested that the impact of parity on incontinence presents in the reproductive years, while incontinence that develops in midlife is not related to child bearing.

Townsend⁵⁸ in a prospective analysis of 64650 women aged 36-55 years in Nurses' Health Study II (NHS II), established a 2 years follow-up (2001 and 2003). The overall 2-year incidence of UI was 13.7%, which corresponds to an average incidence of 6.9% per year. Incidence generally increased through age 50 and then declined slightly in older women. Among women with incident incontinence at least weekly, the incidence of stress incontinence increased through age 50 years (2-year incidence 1.7%) and the incidence of urgency UI was stable across age groups (2-year incidence 0.4%). Complete remission of symptoms occurred in 13.9% of women with

incontinence at baseline. Remission was more common in women with frequent than with occasional incontinence. Since the participants in this study are a selected group of largely Caucasian health professionals, the incidence estimates may not be generalizable.

Goode⁵⁹ determined the incidence of UI over 3 years in a community dwelling older adults. The study was published in 2008, but the study was conducted in 1999-2001. UI was defined as any degree of incontinence occurring at least once a month in the last 6 months. 490 women aged 65 years and plus were included at baseline. The study had 3 annual waves with the incidence rates of 15.0%, 13.0% and 8.0% in the first, second and third wave respectively. Cumulative incidence rate in 3 years was 29.0% (general annual incidence rate: 9.7%). One of the limitations of the study is the definition of UI, for this age group, which is not standard and may cause recall bias. The study is also small in sample size and the high rate of mortality in this age group may underestimate the incidence rate.

Komesu⁶⁰, studied 11591 women ≥ 50 years and have reported an annual incidence of any UI between 3.2% to 8.5% for fifth vs. ninth decade. The baseline data for this study was gathered in 1993 and the follow up data in two waves with four years interval (1998 and 2002). They determined any UI by asking the question, "During the last 12 months, have you lost any amount of urine beyond your control?". To determine the severity of UI they asked women a question about how many days in the last month they lost any urine. Mild UI was defined as ≤ 5 days/month, moderate UI as 6-15 days/month and severe UI as ≥ 15 days/month. 45.8% of women with severe UI reported improvement (change to moderate, mild or continent) over 4 years; women who got medical treatments were not excluded. Types of UI were not included in the study. Since the study included elderly subjects, mortality may have affected the incidence. Recall bias and non-standard questions may also count as limitations of this study.

Melville⁶¹ et al in a study published in 2009, used data from a population-based cohort to find the association between major depression and UI. Accumulated

incidence of UI among 5036 continent women (age range 27-76, mean age 59.3) at baseline (1996-97) after 6 years was 21.0%. UI was defined as any loss of urine beyond control in the past year and ≥ 1 day of incontinence in the past month. The definition of UI, wide age range, and recall bias may be considered as some of the limitations of this study.

Ebbesen⁴⁷ et al evaluated the incidence of UI in a large population of women (age 20+) participating in the EPINCONT study, by two data points with 11 years interval. This article was published in 2013. UI was defined if a woman answered affirmatively to the question: “Do you have involuntary loss of urine”. The accumulative incidence of any UI was 18.7% (1.7% annual incidence) and the remission 34.1% (3.1 annual remission). Women in age group 20-39 reported higher incidence and higher remission than other age groups (40-54 and 55+). The results show similarity with other large studies⁶².

Maserejian⁶³ in a recently published study (2014), analyzed data from Boston Area Community Health Survey (BACH). 3201 women aged 30-79 were included in the baseline and after 5 years 2534 women completed the follow up. UI was defined by answering the following question: “Many people complain that they leak urine (wet themselves) or have accidents. In the last 12 months, have you leaked even a small amount of urine?”⁶³. The incidence was reported as 14.1% for at least monthly and 8.9% for at least weekly urinary leakage. 44.2% of women with weekly UI at baseline reported complete remission and 14.1% reported partial remission to monthly UI after 5 years.

Legendre et al⁶⁴ recently (2014) published the result from the French GAZEL cohort on incidence and remission of UI at midlife. The study included 4127 women aged 45 and over in 1990 and followed them with a questionnaire every three years up to year 2008 (6 waves). UI was defined by answering, “Yes” to the question: Do you have trouble holding your urine? The results included 3828 women who responded ≥ 2 of questionnaires. A total of 941 (24.6%) women, with mean age 48.9 year reported UI at the baseline. The annual incidence and remission rate of UI were 3.3% and 6.2%

respectively. Aging and weight gain were reported as the only factors associated with persistence UI, while menopause onset reported as positively associated with UI remission. The study has a different definition for UI than ICS definition of UI in 2003. Type and severity of UI were not investigated.

These studies are summarized in Table 1. Each of the studies brings a piece to the puzzle of incidence and remission of UI in middle-aged women. However, more longitudinal studies of incidence and remission are needed to investigate the causal factors and predictors for incidence and remission of UI.

Table 1

Summary of studies on incidence and remission of UI, published since year 2000

	Author	Sample size	Baseline age	Number of wave(s)	Interval (year)	Incidence/year (%)	Remission/year (%)
1	Moller ⁵¹	2860	40-60	1	1	10.0	27.8
		UI: involuntary loss of urine weekly or more					
2	Samuelsson ⁴⁶	382	20-59	1	5	2.8	5.6
		UI: any involuntary loss of urine					
3	Sherburn ⁵²	438	45-55	1	7	5.0	-
		UI: any urinary leakage					
4	McGrother ⁵³	2860	40 +	2	1	8.8	25.2
		UI: involuntary loss of urine weekly or more					
5	Dallaso ⁵⁴	5816	40 +	1	1	8.3	-
		UI: only for stress UI					
6	Ostbye ⁵⁰	5322	65 +	2	5	14.3	-
		UI: Any UI					
7	Hagglund ⁵⁵	248	22-50	1	4	14	-
		UI: for the present time, any problem with urinary loss					
8	Wherberger ⁵⁶	441	20-84	1	6.5	3.9	2.9
		UI: involuntary loss of urine weekly or more					
9	Waetjen ⁵⁷	2703	40-60	5	1	11.1	-
		UI: any UI at least once per month					
10	Townsend ⁵⁸	64650	36-55	1	2	6.9	13.9
		UI: any urinary leakage at least once per month					
11	Goode ⁵⁹	490	65+	3	1	9.7	-
		UI: at least once a month urinary loss in last 6 months					
12	Komesu ⁶⁰	11591	50 +	2	4	4.0	6.2
		UI: any involuntary urinary loss in last 12 months					
13	Melville ⁶¹	5036	25-76	1	6	3.5	-
		UI: any UI in past year AND at least one day of UI in the past month					
14	Ebbesen ⁴⁷	2860	40-60	1	11	1.7	3.1
		UI: any involuntary loss of urine					
15	Maserejian ⁶³	3201	30-79	1	5	4.6	11.7
		UI: any urinary leakage in last 12 months					
16	Legendre ⁶⁴	3828	30-79	6	3	3.3	6.2
		UI: answering "Yes" to the question: do you have trouble holding your urine					

3.3 Natural history of urinary incontinence

By studying the natural history of UI, we can get a better understanding of the etiology, progression, and contribution of risk factors. Causal understanding of the disease is an important factor for disease prevention and control⁶⁵. Data are needed regarding the transition from continence to various levels of severity and types of incontinence^{4,5,10,66}.

Since urinary incontinence may be reported as a symptom in epidemiological studies (rather than a clinical condition), studying the natural history of UI may be approached differently. Social, cultural and even personal insights due to age may also affect an individual's report. Study of UI in a female population has some challenging aspects. The female life cycle, from childhood through the fertile years, pregnancy and childbirth, the menopausal years and beyond include many unique differences that need especial attentions for studying health status. Here, we focus only on middle-aged women. During middle age a woman may experience UI in different ways, it can be a short-term experience with spontaneous remission, or a serious problem for the rest of her life. To be able to explain the natural history of UI, defining new-onset UI and its development over time by types and severity is necessary.

Concomitant conditions may affect studies of UI. Many women with UI also have pelvic organ prolapse. One in five women will undergo surgery for incontinence or prolapse during her lifetime⁶⁷ and surgery for prolapse is three times more common than for stress incontinence in the US⁶⁸. These numbers underestimate the frequency of pelvic organ prolapse itself, since many women with this disorder are treated non-surgically or do not receive (or wish to receive) treatment at all, also prolapse is commonly a symptom-free disorder. Roughly one in five women with UI also have fecal incontinence (FI)⁶⁹. Although UI could reduce the quality of life, FI is even more devastating⁷⁰, and the particularly embarrassing nature of this disorder makes screening imperative in assessment of women with UI.

Many longitudinal studies provided information on risk factors for new-onset UI but studies on the progression or resolution of existing incontinence are scarce. This distinction is important since prognostic risk factors may differ from risk factors for incident disease. In addition, only a few groups have reported change by incontinence type and/or severity. Previous studies that followed the course of UI are mostly clinical or in related to one of the risk factors, for example it was showed that overweight middle-aged women have a higher risk of developing UI⁵⁷, or women with diabetes have significantly more weekly UI than women without diabetes⁷¹. Some of the studies are interventional e.g. Townsend⁷² examined the association of hormone therapy and incident UI in postmenopausal women, in Nurses' Health Study. The result showed that the odds ratio of incident UI was 1.39 in current users of menopausal hormone therapy.

Thom et al⁷³ investigated the factors that predict incidence progress, regression and resolution of UI in diverse women participants in a prospective cohort. At baseline 2109 women aged 40-69 were included and after 5 years 1413 of them completed the second part of survey. The frequency of UI was categorized as less than weekly, weekly and daily. At baseline 1027 women (72.7%) reported at least 1 episode of leakage in the last 12 months. After 5 years, 536 women (38.0%) reported a change in continence status. 12.0% of them reported a progress in UI, 9.1% reported resolution, 8.6% regression, and 8.4% reported a new-onset UI. The annual incidence of UI was reported as 6.0%. The study showed an increase in the incidence of urgency and mixed UI, while the incidence of stress UI was decreased in the middle age group. This finding was consistent with previous studies showing a decreased prevalence of stress UI with age in middle-aged and older women^{38,66,74,75} and in inverse association of age with new stress incontinence⁷⁴. Remission rate was about 2.4% per year, which was at the lower end of previous reports^{18,59,74,76}. The study provided additional valuable information on the dynamic change in UI.

Searching PubMed for UI and natural history gives us a limited number of articles, which are mostly clinical. This limitation is even more when we add "women" or "middle-aged women" to this search. Longitudinal studies on natural history of UI

have to span several years because of the slow progression of the condition. Costs of longitudinal designs and difficulties in following a substantial number of individuals over several years are the main reasons for the paucity of longitudinal data on this topic. However, the high prevalence of UI in women, particularly in perimenopausal period, underlines the importance of a thorough understanding of the natural history of this condition.

3.4 Risk factors

My own research has not included risk factors, but as a part of epidemiology, I have chosen to give a brief account of current knowledge in this regard.

Risk factors for UI in women have been investigated in many epidemiological studies. Most of these studies are cross-sectional and even if they reported a wide spectrum of risk factors, they cannot conclude about causality. Longitudinal studies, on the other hand, have a better possibility to assess causal risk factors for incident UI, but still they may not be able to measure confounding factors. However, some of the risk factors are well accepted, like age, obesity, parity and hysterectomy^{9,18,22,77,78}. In studying the risk factors of UI in women, most of the studies focus on older people or on women during pregnancy; and put rather less focus on the risk factors among middle-aged women⁷⁹. One of the studies⁷⁹ with focus on risk factors in middle-aged women was published in 2006. This cross sectional study used data from 83355 women (age 37-54) in Nurses' Health Study II, and the major UI risk factors in women were reported as: white race, high BMI, parity (compare to nulliparous women), current smoking, diabetes mellitus and hysterectomy⁷⁹.

The latest edition of the book "Incontinence" from the 5th International Consultation on Incontinence (ICI)⁸⁰ has a comprehensive review of risk factors of UI in women⁴⁸. ICI ranked the risk factors by level of evidence (LE), developed by Oxford Centre for Evidence-Based Medicine. Table 2 shows the different categories of UI risk factors based on LE from "Incontinence" book. LE1 indicates an established risk factor or highly evident, and LE3 indicates a suggested risk factor, which has not been

established as a proven etiology of UI. LE2 is the level in the middle, and is usually based on results from good quality cohort studies.

Table 2

Risk factors for UI, categorized based on level of evidence (LE)⁴⁸

LE1 (highly evident)	LE2 (moderately evident)	LE3 (suggested)
BMI	Instrumental delivery	Smoking
Age	Birth weight	Diet
Race	Physical function	Depression
Genetic	Diabetes	Constipation
Oral estrogen	Menopause	Urinary tract infection
Labor	Hysterectomy	Exercise
Vaginal delivery	Dementia	
	Cognitive function	

Several observational studies have showed that white, non-hispanic women are at a considerably higher risk for UI than black or Asian women^{57,81}. Pregnant women who go through the labor and have vaginal delivery have higher chance to get UI than women who have C-section^{37,82-84}, however, the strength of association for this factor is substantially reduced by age^{34,39}. Obesity is probably the most established general risk factor for UI in women beside age^{85,86}, and it especially predisposes women for stress UI. It is also reported from interventional studies that weight reduction, even moderately, can improve the symptoms of UI⁸⁷⁻⁸⁹.

3.5 Impact and consequences

UI is a very costly condition for both society and individuals. Any incontinence is associated with decreased health-related quality of life. Thus, effective prevention and treatment of UI may decrease routine care costs and improve quality of life. In this part, I review some articles on economic and other impacts of UI.

Wilson⁹⁰, in 1995, estimated the annual direct cost of urinary incontinence in the United States as \$16.3 billion, including \$12.4 billion (76%) for women and \$3.8 billion (24%) for men. Costs for community-dwelling women (\$8.6 billion, 69% of costs for women) were greater than for institutionalized women (\$3.8 billion, 31%).

Costs for women over 65 years of age were more than twice the costs for those under 65 years (\$7.6 and \$3.6 billion, respectively). The largest cost category was routine care (70% of costs for women), followed by nursing home admissions (14%), treatment (9%), complications (6%), and diagnosis and evaluations (1%).

Doran⁹¹ estimated the economic cost of UI in community-dwelling Australian women aged 18 years and over for the year 1998. The total annual cost of this UI was estimated at \$710.44 million, or \$387 per incontinent woman, comprising \$338.47 million in treatment costs and \$371.97 million in personal costs. An estimated 60% of women with incontinence in 1998 were aged 40 years or over. Assuming the prevalence of incontinence remains constant and, allowing for inflation, they projected that the total annual cost in 20 years' time will be \$1267.85 million, 93% (\$1.18 billion) of which will constitute costs associated with women aged over 40 years. Subak⁹² reported \$ 900 individual annual cost of severe UI in women aged 45 years and more in 2006.

There are no recent data on the cost of UI in Norway or Scandinavia. Previously, in 1994, the National Insurance Administration (RTV) of Norway reported an approximately cost of NOK 200 million on incontinence pads (USD 7 per inhabitant)⁹³. In 1990 it was estimated that managing UI in Sweden cost almost 2 billion SEK, equal to two per cent of the total health expenses (USD 38 per inhabitant)²⁶.

Minassian⁹⁴ (2012) also explains the iceberg of health care utilization in women with UI. Despite of the high prevalence of UI, seeking for help is low; it may be due to lack of knowledge of available UI treatments, or considering UI as a natural part of ageing, or lack of the necessary medical interventions^{94,95}

Coyne⁹⁶ et al (2014) in a systematic review, divided the total economic burden of urgency UI in three different categories: direct, indirect and intangible costs. Direct costs are the costs of diagnosis, treatments and routine cares such as pads, diaper, laundry, dry cleaning and other comorbid conditions. Indirect costs are related to the economic burdens on individuals' work productivity due to sick leaves or diminished

job performance and mortality costs. Intangible costs are related to pain and suffering and also decrease in quality of life. This systematic review included 7 studies. The review showed annual direct costs in United States in 2007, for adults aged ≥ 25 estimated as 65.9 billion dollars, the projected costs for 2015 was estimated up to 82.6 billion dollars.

In a recent article, Milsom⁹⁷ et al (2014) did a systematic review on economic burden of urgency UI. Among 11 studies included in this review, 4 of them belong to Europe and Canada; the estimated annual cost of urgency UI was reported close to seven billion euros in Canada and 5 European countries (Germany, Italy, Spain, Sweden and United Kingdom) in year 2005⁹⁸. The study suggests a 25% increase in urgency UI costs in the next decade, because of the aging of the population and particularly due to increasing direct costs for nursing homes.

Beside the economic impact, several studies showed that UI can cause symptoms related to social, physical, and emotional functions, which can decline the quality of life (QoL) of affected person⁹⁹⁻¹⁰². However, assessment of QoL is a multidimensional concept and different studies focused on different outcomes with different methods for measuring QoL and so far, no standard questionnaire on QoL of women with UI is available¹⁰³.

The social impact of UI is highly individual and complex¹⁰⁴. Research has shown that the relationship between women's perceived impact of incontinence and objective measures of its severity are complex and not directly proportionate¹⁰⁵. Qualitative studies suggest that women's perceptions of impact of UI may change over time¹⁰⁶ and women who have experienced incontinence for a longer period of time are being less troubled by it¹⁰⁷. Others suggest that middle-aged women's perception of the impact of UI on their lives may be different to older women's perception because middle-aged women may have experienced symptoms for a shorter period of time and are more likely to be more socially active, making them more likely to rate their symptoms as severe⁸⁴. Some conditions like depression may impact UI or act as a risk factor¹⁰⁸. Comorbidity of severe depression and UI may affect the degree that the

patient perceives incontinence, and lead to lowering quality of life and functioning¹⁰⁹. It has also been reported that the incidence of depression is analogous to the degree of incontinence, as well as to the degree of social isolation and QoL⁶¹. Types and/or severity of UI also affect the impact of UI on QoL. A recent study shows that mixed UI, due to more severe symptoms, has a stronger effect on of QoL¹¹⁰. Bartoli¹⁰², in a systematic review, asks for increased awareness among clinicians for patients' QoL, especially those with urgency component of UI. Overall, several aspects should be kept in mind for evaluation of QoL in individuals with UI.

Aims of the study

The present dissertation is aimed at contribute to the knowledge about epidemiological questions about UI in middle-aged women. In this regard we used data from a prospective cohort that will be presented in detail later. Separate sub-studies (**Papers I-III**) were undertaken as follow:

Paper I: To evaluate the representativity of the Cohort compared with the source population (HUSK). The study estimated the prevalence of UI by type and severity in baseline and also presented the methodology of the Cohort.

Paper II: To investigate the prevalence, incidence rate and remission rate of UI in middle-aged women including type and severity. We especially wanted to search for a possible early prevalence peak in this age group, and determine how it was influenced by changes in incidence and remission rates.

Paper III: To investigate the natural history of UI in middle-aged women by type and severity of new-onset UI.

4. Material and Methods

The Hordaland Women's Cohort is based on one of the surveys in the Hordaland Health Studies, known as HUSK, which is also a part of a group of large-scale national health surveys, known as The Cohort of Norway (CONOR). The idea of CONOR was generated in the early 1990s. All universities, The National Institute of Public Health, The National Health Screening Service and the Cancer Registry discussed the possibility of CONOR as a national representative cohort. In 1994, the Ministry of Health selected the Steering Committee for the CONOR collaboration¹¹¹. In Hordaland County, the University of Bergen in collaboration with Hordaland's Municipal Health Service and the Norwegian Health Screening Service (now part of the National Institute of Public Health) conducted the Hordaland Health Studies.

The Hordaland Health Studies are composed of two baseline data sets. First study was conducted in 1992-93, known as The Homocysteine study. This study included two main age groups; all individuals in Hordaland County born between 1950-52 and also individuals born between 1925-27.

The second study, after establishment of the CONOR, was conducted in 1997-99 and is known as HUSK. In HUSK, beside the participants in the Homocysteine study, all individuals in Hordaland County born between 1953 and 1957 (n=29335, aged 40-44 at the time of data collection) were invited to the study. For this age group, a questionnaire and an invitation for a health check-up were sent to them and 63.0% (n=18581, male=8598, female=9983) answered the questionnaire and came to clinical examination. A randomly selected 65% of women at screening stations got an accessory questionnaire, with a comprehensive part on lower urinary tract symptoms (LUTS). They were asked to fill it at home and send it back by post. We used data from this accessory questionnaire for some analyses in the Hordaland Women's Cohort.

4.1 The Hordaland Women's Cohort

From this point, the Hordaland Women's Cohort will be referred as "the Cohort" in this dissertation.

4.1.1 Sampling and Participants

The female population aged 40-44, participating in HUSK, is the source population of the Cohort. In order to find the necessary sample size, within a margin of error not greater than $\pm 3\%$ ($c = 0.03$), and assuming 50% hypothesized possibility for UI ($p=0.5$), the sample size (ss) with 95% confidence level (Z value = 1.96) was calculated by:

$$ss = \frac{Z^2 * (p) * (1-p)}{c^2}$$

Sample size for finite population (pop) of women in HUSK was calculated by following formula:

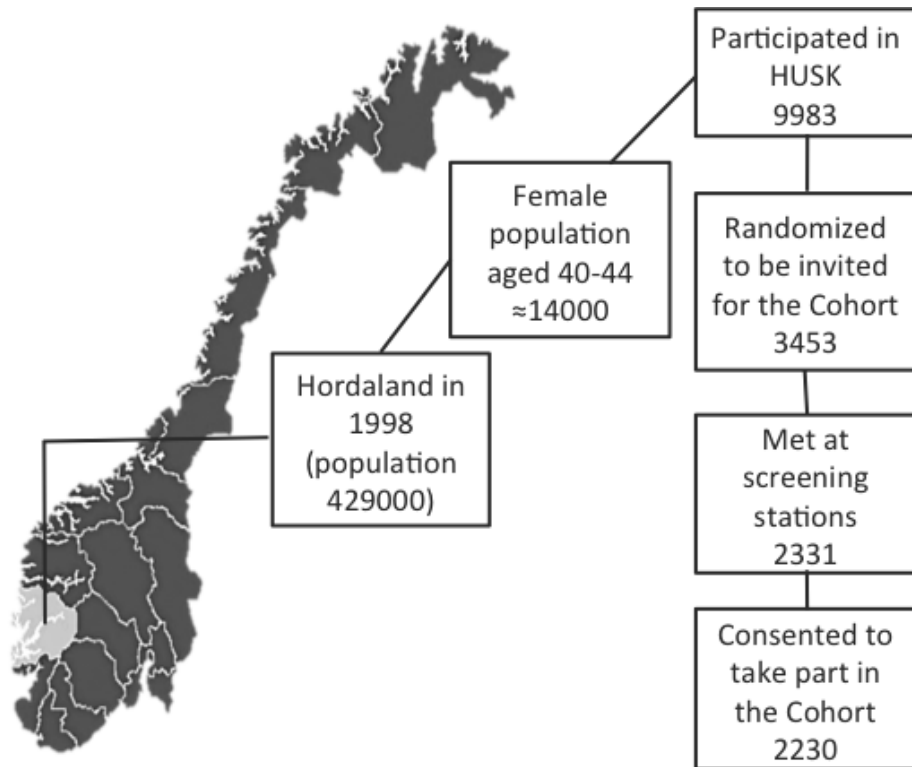
$$ss = \frac{ss}{1 + \frac{ss-1}{pop}}$$

By this calculation at least 900 women should remain in the Cohort after 10 years. Based on 5% annual attrition rate, at least 1501 women should answer the questionnaire in the first wave. Since the response rate for women in the HUSK was 70%, at least 2150 women should be asked to join the Cohort. Of all invited, 3453 female participants in HUSK, aged 40-44 were randomly selected, based on the last digit of their Norwegian Personal Number¹. Of these, 2331 (67.5%) met at the screening stations and 2230 (95.7%) women consented to take part in the Cohort. A brief summary of these numbers is shown in Fig 1.

¹ In Norway everybody had a personal number and it makes Norway very suitable for community-based surveys. The personal number has 11 digits, which is composed of the date of birth (DDMMYY), a three digit individual number (the third digit shows the gender), and two check digits.

Fig 1

The Cohort sample size (n=2230) related to source population (n=9983) and total population (n≈14000) of women aged 40-44 in Hordaland



4.1.2 Questionnaires

In **Paper I**, we used the HUSK accessory questionnaire, which contained a major part on LUTS, for baseline analysis of UI. The LUTS part of questionnaire had a total of 10 questions, the first 4 questions were general as follow:

1. During last 12 months, have you ever had problem with acute burning sensation, pain or unpleasant feeling during urination?
2. How often you urinate during a day?

-
3. Do you wake up during the night for urination? How often?
 4. Do you usually feel your bladder is empty after urination?

The fifth question, as the entrance question for UI:

5. Do you have involuntary urinary leakage?
(If yes, please answer the following questions)
6. How often do you have urinary leakage? (Less than once a month, ≥ 1 time(s) per month, ≥ 1 time(s) per week, Every day and/or night)
7. How much leakage of urine do you have each time? (Drop or little, Small splashes, Bigger amount)
8. Do you have urinary leakage with coughing, sneezing, laughing or lifting heavy objects? (Yes/No)
9. Do you have urinary leakage during strong desire for urination? (Yes/No)
10. How long have you had urinary leakage? (Less than 5 years, 5-10 years, more than 10 years)

Source of data in **Paper II and III** is the questionnaire, which was designed for several follow ups of the Cohort. This questionnaire has a simple design, easy to understand and easy to answer, and has 4 major parts:

- Health, lifestyle and physical activity
- Contraception and menopause
- Urinary conditions
- Consumption of any kind of medicine (prescribed or non-prescribed)

The details of the questionnaire are explained in **Paper I** and some examples of the questionnaires are available in the Appendices of this dissertation.

The questions in the 3rd part of the questionnaire (urinary conditions), in 6 different waves of the Cohort, have been used for the analyses of data in the present dissertation.

4.1.3 Definition of UI and its severity

In **Paper I**, any UI was defined by including everyone who answered “Yes” to the entry question OR answering confirmatively on frequency, type and volume of leakage, even if they answered “No” to the entry question.

In both **Paper II** and **III**, we used the Incontinence Severity Index (ISI) for definition of UI. ISI was created by Sandvik et al^{8,14}, and is based on information about the frequency and amount of leakage. The frequency of UI can be scaled in reply to “how often you have urinary leakage?” as follows:

None=0, less than once a month=1, more than once a month=2, more than once a week=3 and every day and/or night=4

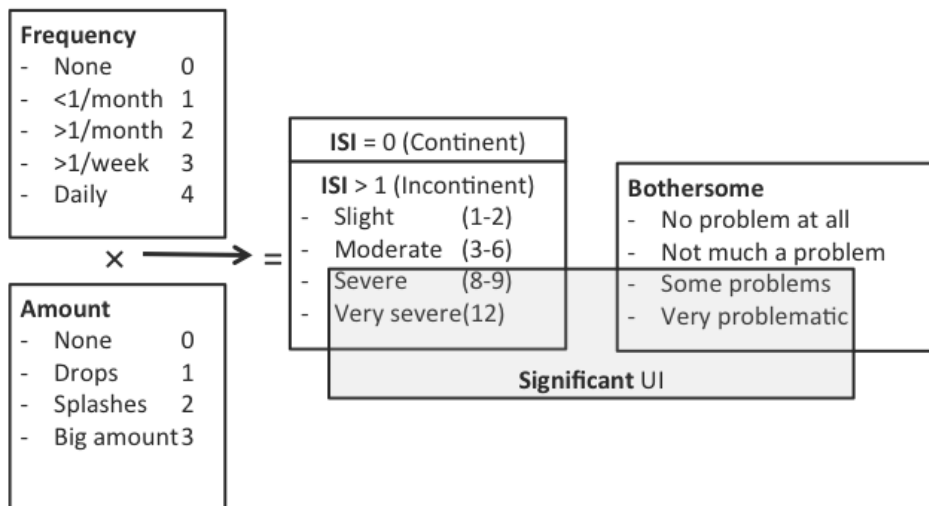
The amount of leakage can be scaled in reply to “how much leakage of urine you have each time?” as follow

None=0, drops=1, splashes=2, big amount=3

By multiplying the grades of frequency and amount, ISI was calculated and interpreted as None (0), Slight (1-2), Moderate (3-6), Severe (8-9) or Very severe (12).

In **Paper II** and **III**, the definition of UI was done by use of ISI. Continent women were defined as ISI equal to zero, even if they answered affirmative to the entrance question. All the women with slight to very severe UI, based on ISI, were defined as urinary incontinent. Due to small number of cases with “very severe” UI, we combined this group and “severe” group into one group for the analyses.

We also defined the women with UI as having a significant or non-significant UI. For this we used the question: How bothersome is your urinary leakage? The answers were dichotomized to “Non-bothersome” in case of choosing one of the first two choices (no problem at all, not much a problem) and “Bothersome” for the last two choices (some problems, very problematic). Based on severity and bothersomeness we defined *significant UI* as women with bothersome moderate to severe UI (Fig 2).

Figure2**Calculation of Incontinence Severity Index and definitions of UI and Significant UI****4.1.4 Types of UI**

In all three **Papers** types of UI were determined by the same questions in HUSK and the Cohort questionnaires. Women with stress UI were defined by answering “Yes” to involuntary loss of urine with coughing, sneezing, laughing or lifting heavy items. Urgency UI was defined by answering “Yes” to involuntary loss of urine connected to a sudden and strong desire to void. Mixed UI was defined by answering, “Yes” to both questions. And in case of having UI and answering “No” to both questions, they were categorized as non-classified.

4.1.5 Paper I

Paper I was published as the study protocol, to be used as the reference for further publications of the Cohort. This paper also evaluated the representativeness of the participants, compared with the source population in HUSK. Demographic variables (e.g. marital status, income, BMI, lifestyle, etc.) and urological characteristics were compared between the participants (n=2230) and the rest of women in HUSK who were not in the Cohort.

4.1.6 Paper II

Data for this paper were based on data from six different waves of the Cohort and 8 age groups (Table 3). Participants in the first wave were 41-45 years and in the sixth wave they became 51-55 years; it makes the total age span as 41-55 years. We defined 8 age groups with age span of two years in the first 7 groups and age 55 solely in the last one allowing each woman to contribute to the data sets more than once, depending on their age, but only once in each age group. We defined two data sets; the first data set includes all data in all 6 waves.

Table 3

Age of the women while participating in groups by their age in different waves

	Age groups														
	41-42		43-44		45-46		47-48		49-50		51-52		53-54		55
1 st wave	41	42	43	44	45										
2 nd wave			43	44	45	46	47								
3 rd wave					45	46	47	48	49						
4 th wave							47	48	49	50	51				
5 th wave									49	50	51	52	53		
6 th wave											51	52	53	54	55

For more sophisticated analyses, we analyzed the second data set, which included only women who answered all six questionnaires (complete data set). Women who did not answer one or more of the questionnaires were excluded. This “complete” data set was used to find the incidence and remission of UI.

All women with ISI equal to zero were defined as continent and also as the risk group for being incontinent. Remission was defined as a change from “any UI” to continent. Type and severity of UI with 95% confidence interval were calculated in these analyses.

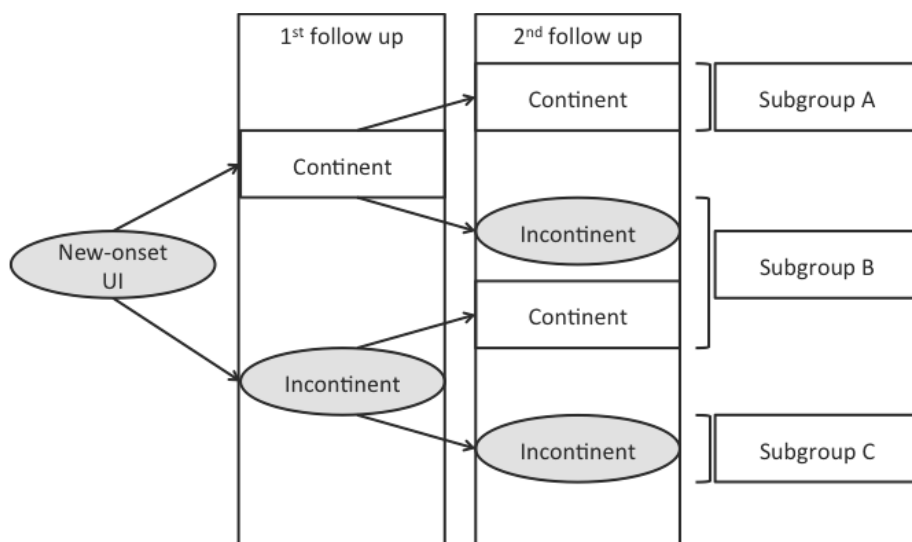
For each data set, we calculated the prevalence of UI for all and each of age groups. We also calculated the prevalence for types and severity of UI and compared it between age groups. All the prevalence values were also compared between the two data sets.

4.1.7 Paper III

In this paper we analyzed the natural history of UI in two steps; first the continent women at baseline were followed during 10 years in next 5 waves of the Cohort. For the second step of analysis, the women with new-onset UI, by type and severity, were defined and followed for the next 2 waves (if available). The exclusion criteria were lack of data in follow up waves or women who visited a doctor for UI. By this we obtained a continuous data set with four registrations during six years (from continent to new onset UI and 2 follow-ups). Based on the existence of UI in follow-up waves, the women were defined in 3 different subgroups (A, B and C). Subgroup A had no UI in two following reports, subgroup B had only one UI report in following reports and subgroup C had UI in both following reports (Fig 3).

Figure 3

Definition of Subgroups in analyses of results in Paper III



In this paper, the first report of new-onset UI was compared between these subgroups, and exclusively for subgroup C, the first and last report of UI were compared for changes in types and severity. The algorithm of changes by type of UI in two follow-ups was made to visualize the interchanges between type and severity of UI.

4.1.8 Ethical approval

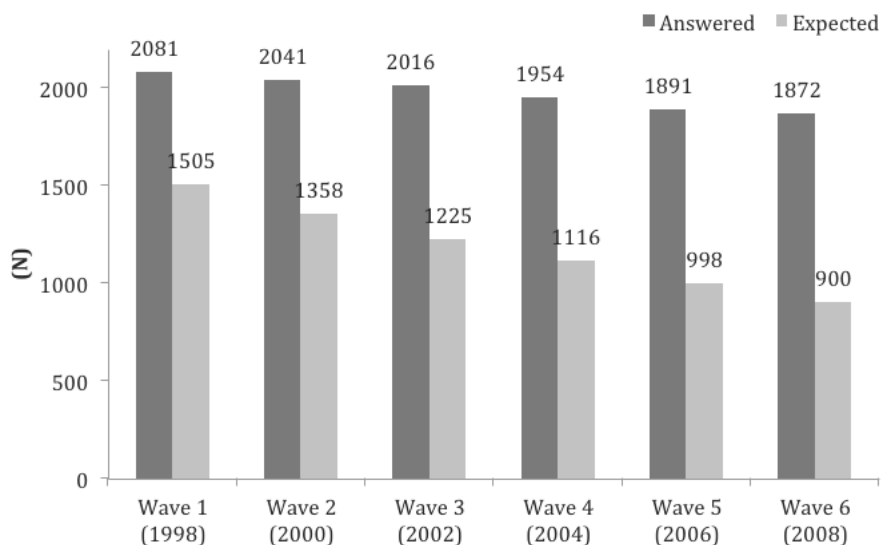
The Cohort was approved by the Norwegian Data Inspectorate (Norwegian data protection authority) and Regional Committee for Medical Research Ethics. This approval allowed us to access the full 11-digit personal identification number for necessary merging and extending data with other sources (e.g. different national registries). All personnel and staff involved in the survey are bound by an oath of confidentiality.

5. Summary of Results

The response rates, in all waves of the cohort, were much higher than the anticipated calculated response rates. Fig 4 shows the response rate during different waves and compares it with the anticipated response rate (calculated by the power calculation).

Figure 4

Comparing the number of participants in different waves (year) with the anticipated numbers by power calculation



During 10 years, 17 (0.8%) women died, 12 (0.5%) women emigrated from Norway and 37 (1.6%) women asked for withdrawal from the survey. We also had some missing data; in the first wave 2229 questionnaires were sent instead of 2230, other missing data are mainly due to changed or unknown postal addresses. For each wave two reminders were sent to non-respondents, except for the 6th wave, which had three reminders. Figure 5 shows more details on lost in follow-ups in the first six waves of the Cohort.

Figure 5**Details on participations in different waves of the cohort**

1 st wave (2229 sent)	2 nd wave (2215 sent)	3 rd wave (2212 sent)	4 th wave (2202 sent)	5 th wave (2174 sent)	6 th wave (2161 sent)
Answered 2081 (93.4%)	Answered 2041 (92.1 %)	Answered 2016 (91.1%)	Answered 1954 (88.7%)	Answered 1891 (87.0%)	Answered 1872 (87.0%)
No answer 148 (6.6 %)	No answer 156 (7.0 %)	No answer 170 (7.7%)	No answer 170 (9.9%)	No answer 263 (11.9%)	No answer 289 (11.9%)
Missing 14	1 Dead	5 Dead	4 Dead	5 Dead	2 dead
	2 withdraw	5 withdraw	8 withdraw	8 withdraw	14 withdraw
			Missing 16		

5.1 Paper I

In the first part of analysis we divided 9983 HUSK female participants into two groups as “in the Cohort” and “not in the Cohort” (Figure 6). Comparing the 2230 women (mean age 41.9 year), who consented to take part in the Cohort, with the rest of the women in the HUSK (n=7746, mean age 42.1 year), we found no significant difference at inclusion regarding age, marital status, parity, body mass index (BMI), self-rated health, lifestyle and medical condition. However, the women in the Cohort had higher education and larger annual family income compared with the rest of women in HUSK. The differences were statistically significant (p=0.001 for education and p=0.018 for annual family income). Details of this comparison are showed in Table 2 in **Paper I**.

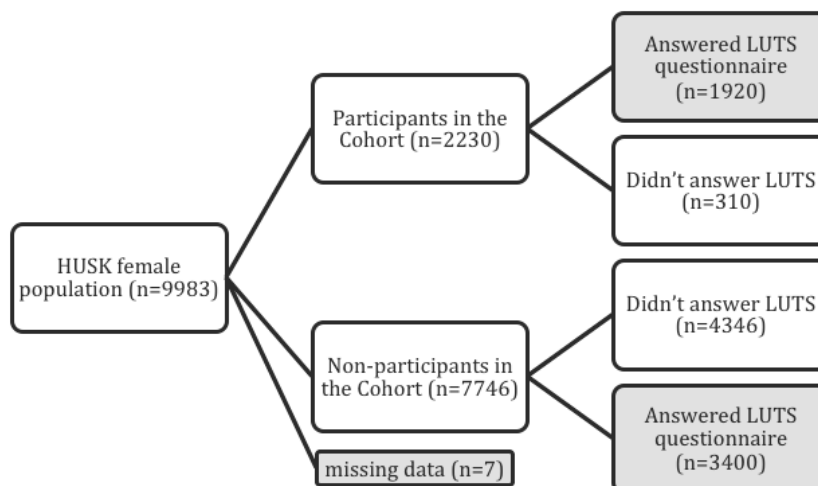
A total of 5320 female participants in HUSK answered the accessory questionnaire for LUTS. Among them 1920 women were participants of the Cohort. Figure 6 also shows the number of participants and non-participants for the LUTS questionnaire.

Prevalence rate of any UI was 24.8% and 28.9% in the Cohort women and the rest of women in HUSK (n=3400) respectively, and this difference was statistically significant ($p=0.04$). Distribution of type of UI also showed a significant statistical difference ($p=0.05$) between those two groups. Participants in the Cohort had a higher percentage of stress UI (55.4% vs. 51.8%) and urgency UI (11.0% vs. 8.1%) while the mixed UI (26.4% vs. 31.8%) showed a smaller percentage in the Cohort.

Comparing other urological characteristics (dysuria, nocturia, duration of UI) between the Cohort group and the rest of women in HUSK showed no significant statistical differences. Some of the variables had a borderline non-significant p-value, like frequency of UI. Details on urological characteristics are showed in Table 3 in **Paper I**.

Fig 6

Comparing the number of included participants in different parts of data analyses in Paper I



5.2 Paper II

In this paper the results were presented from analyses of two different data sets. First, we added data from all six waves (age range 41-55). We recorded 5246 (40.2%) with “Any UI” and 960 (7.3%) with “Significant UI”. The second data set included 1430

women who answered the questionnaires in all 6 waves. In this data set we added data from 8580 questionnaires. The prevalence was 46.6% for “Any UI” and 8.0% for “Significant UI”. Both data sets showed a peak in the prevalence of UI in the age group 51-52.

In analyses of the second data set for different age groups, the prevalence of any UI in the first age group (41-42) was 38.9%, which increased gradually with age up to a peak prevalence of 50.3% in age group 51-52 and then reduced in age groups 53-54 and 55. Prevalence of significant UI showed almost the same pattern as any UI, but the absolute values of prevalence, for significant UI, in age group 41-42 (4.5%) was doubled compare with age group 51-52 (10.0%).

The type and severity of UI were also analyzed in the second data set. Table 4 compares distribution of types of UI between any UI and significant UI, for all ages.

Table 4

Comparing types of UI for distribution of Any and Significant UI in Paper II

	Stress %	Urgency %	Mixed %	Unclassified %
Any UI	42.6	12.3	36.0	9.1
Significant UI	25.5	8.4	61.7	4.4

Those distributions were also calculated for different age groups. In the matter of severity, most of women reported the UI as slightly severe, this proportion decreased by age. Distribution of moderate UI didn’t change much during the aging, but severe UI relatively doubled, from 5.0% in the first age group to 10.0% in the eldest age group.

In analysis of complete data set, while the remission of any UI showed an increasing pattern after age 51, the incidence showed a decreasing pattern, exactly where we had the peak of prevalence. The same pattern was also found for the significant UI. The total annual incidence, based on proportion of all women who reported UI during 10 years (cumulative incidence), was 4.9%.

5.3 Paper III

The results in this paper are based on data from 1274 continent women at the baseline. Fig 7 shows the number of women who had new-onset UI, wave by wave. During 10 years, a total of 514 women reported a new-onset UI, 449 women stayed continent, and 311 women were excluded due to missing data. The new-onset UI in 89.3% of cases was reported as slight UI, with the majority (49.8%) of stress type. Only 10.0% of new-onset UI was reported as moderate or worse.

Fig 7

New-onset UI for each wave

Wave 1 (41-45)	Wave 2 (43-48)	Wave 3 (45-49)			Continent 449
				Continent 541	New-onset 52
			Continent 625	New-onset 48	
	Continent 932	Continent 772	New-onset 86		
Continent 1274	New-onset 207	New-onset 121			
			Wave 4 (47-51)	Wave 5 (49-53)	Wave 6 (51-55)
Missing (n)	135	39	61	36	40

We could follow 337 women with new-onset UI in three pre-defined subgroups over next 2 waves (Figure 3). The distributions were 29.8% (n=100), 33.3% (n=112) and 36.9% (n=125) for subgroups A, B and C respectively. Type distribution of new-onset UI showed no significant difference between subgroups A and B or between subgroups B and C. But it was a significant difference between subgroups A and C, with a higher proportion of non-classified UI in Subgroup A versus a higher proportion of mixed UI in Subgroup C.

More than 50% of women in subgroup A had a stress UI. Distribution of urgency, mixed and non-classified UI were 12.0%, 15% and 20% respectively. 95% of women reported “slight” UI and the rest reported only “moderate” UI.

Comparing the type and severity of new-onset UI with the second report of UI in Subgroup B is summarized in Table 5 (non-classified UI is not shown). The distributions of new-onset UI were 58.1%, 13.4% and 16.1% for stress, urgency and mixed UI respectively. In the next report, the proportion of stress UI was reduced to 46.5%, while urgency and mixed UI increased to 18.8% and 17.7% respectively. None of the changes were statistically significant. Severity of UI was reported as the same in 76% of women in both reports, 13.4% of women had an increase in the severity of UI and 7.1% reported a decrease. None reported severe UI in both reports.

Table 5

Comparing types and severity of UI in Subgroup B, Paper III

Subgroup B TYPES of UI		Second UI report		
		Stress (%)	Urgency (%)	Mixed (%)
New-onset UI	Stress (%)	66.1	6.2	13.9
	Urgency (%)	19.8	60.4	19.8
	Mixed (%)	22.3	22.3	50.4
Subgroup B SEVERITY of UI		Second UI report		
		Slight (%)	Moderate (%)	Severe (%)
New-onset UI	Slight (%)	76.0	13.4	-
	Moderate (%)	7.1	3.6	-
	Severe (%)	-	-	-

In subgroup C, women who reported at least one non-classified UI were excluded to simplify the complexity of algorithm of changes in types and severity of UI. As new-onset UI, 56.7% of women reported stress UI, 15.4% urgency and 27.9% mixed UI. Type distribution in the last report (after 4 years) showed a reduction of stress UI to 49.0%, while urgency UI increased to 21.2% and mixed UI had increased to 29.8%.

6. Discussion

6.1 Discussion of methods

6.1.1 Design

The Hordaland Women's Cohort is a prospective longitudinal study, which was planned before 1997 for 15 years with every other year data collection up to 2012. In 2008 after completing the sixth wave of the Cohort, adequate data were available for studying the set hypotheses. Since the Cohort was performed in a community-based population, all stages of severity and symptom expressions would be represented. This could uncover a part of the "iceberg" that is hidden outside the health care system and provide more insight in the natural history of UI. The longitudinal design is well suited for investigating incidence and remission, and also to follow the natural history of UI, which are all main issues in this dissertation. Multiple checkpoints with short intervals, plus including a very selective age group allowed us to focus on epidemiological details, especially the natural history of UI. The Cohort has high standards in these matters.

The use of questionnaires allows the collection of data on many symptoms and conditions as well as medical background, and thus will give an opportunity to investigate the association between UI and several potential risk factors in the future¹⁸. Using the same questionnaire in different waves and following the same women increase the quality of the Cohort.

6.1.2 Internal validity

Internal validity depends on lack of systematic errors and some of such possible errors will be discussed here.

Selection of subjects

Selection bias results from improper methods of selection of subjects and it may form factors that influence study participation¹¹². A major advantage of using HUSK as

our source population is the fact that the whole population of the Hordaland County, born between 1953-1957, was invited, and that the survey achieved a fairly high participation rate (70.0% for women). The one-fifth random sampling of the Cohort lead to a relatively large sample of about 15.0% of the total female population of the Hordaland born between 1953-1957. Thus, the study is population based with low risk of selection bias.

In this study, there may however be some minor selection biases. In **Paper I**, for socio-demographic data, we compared the participants in the Cohort (n=2230) with all the rest of women in HUSK (n=7746). For the urologic data we could compare 86.0% (n=1920) of participants in the Cohort with only 44.0% (n=3400) of the women in HUSK. In the second part of analyses in **Paper II**, we have analyzed data from 1430 women, who contributed in all six waves. The enthusiasm for participating in all 6 waves is appreciated, but there is a possibility that those women were especially interested in urinary problems, or generally, more concerned about their health status. In **Paper III**, we used the first wave as baseline data and we followed 1274 women who were continent in the first wave. In the second part of analyses for **Paper III**, for the 4-year follow-up data, we could follow only 337 women. We also excluded women who had visited a doctor for UI, and it may cause a selection bias, as it has been shown that severity of UI is associated with help seeking^{40,113}. Also since we aimed to follow up for next two waves, we couldn't include women with new-onset UI from wave 5 and 6.

Choosing a narrow age span, 41-45 years at the baseline, may be considered as one of the limitations of the study, whereas this was done on purpose to make the Cohort more exclusive for middle-aged women in the peri- and postmenopausal stages. We consider the narrow age span as one of the strengths of the study.

The response rate

Using power calculation, based on 70% response rate at inclusion and 5% annual attrition rates, we were supposed to recruit 2150 women at the baseline to have at least 900 women remain in the study after 10 years. Nevertheless in reality, the

participation rate was surprisingly high in the Cohort; we had much higher response rates than anticipated (Fig 4). After 10 years almost 1800 women still responded to the questionnaire. High response rate (87.0-93.0%) and very few dropouts thus added more strength to this study.

As a matter of fact, participation rates for epidemiologic studies have been declining during the past 30 years, with even steeper declines in recent years¹¹⁴. The reason(s) behind the high participation rate in the Cohort is not clear. A recent study¹¹⁴, on declining participation rate in epidemiological studies, explains two central reasons for decreasing participation rate in a survey. First, refusing participation due to:

- Increased number of requests for participate in studies
- Increased skepticism
- Lack of interest in participating in studies that do not have personal advantage

The other reason is a difficulty for finding potential participants. However, the high participation rate in the Cohort could be due to small influence of any of these negative factors.

The questionnaire

Epidemiological studies on incontinence rely on questionnaires and self-reported UI. The use of questionnaires is an effective tool for the collection of data from a large number of subjects but we are only able to register UI as a symptom and do not identify women with UI as a condition. The quality of the information gained this way is dependent on whether the questions measure what they intend to measure (validity) and that the measurements are reproducible (reliability). Moreover, several studies suggest that self-reported symptoms are valid when assessing incontinence at a single time point¹¹⁵ and when examining changes in incontinence severity over time¹¹⁶. Validation studies of self-reports of type of incontinence compared with clinical diagnoses indicate that self reported stress and urgency symptoms tend to have good specificity but low sensitivity. In our study, the questionnaires contain many validated questions and the UI data set is in accordance with the recommendations from the 3rd ICI⁷⁸. However, at this point, an information bias should be kept in mind. Information bias, which occurs from errors in obtaining the

required information, is a problem among subjects already selected for a study¹¹². For example, women with UI may be more, or less, tending to answer the questions about incontinence than continent women. The direction of such a bias is difficult to predict. It should be noted that the definition of UI in **Paper I** was different from UI definition in **Paper II** and **III**. The HUSK questionnaire, which was used in **Paper I**, had an entrance question, which reduced the threshold for identifying UI and was intended to have a high sensitivity including symptoms of a wide range of severity. All women who answered “yes” to this question were defined as having UI, but we found out that some women who didn’t answer this question or even who answered “no”, still had answered confirmatively regarding frequency, volume and type of leakage. These women were also defined as UI cases in this study. Since the entrance question is in present tense, it may be confusing for the participant.

In **Paper II** and **III** we didn’t use the entrance question to define UI, and the definition of UI was based on $ISI \geq 1$, which increased the threshold for identifying UI, but the results on prevalence of UI were not very different from the previous similar studies. Our aim was to detect all women who define themselves as leaking urine with amount and frequency more than “none”. A conceptual problem, at this point, could be the “self-diagnosis” of these parameters, which may vary considerably from woman to woman. This problem also exists for types of UI.

6.1.3 External validity

External validity or generalizability considers the extent to which the results of a study hold true for a population beyond those who participated in the research. One of the main advantages of population-based cohort studies is boosting external validity, thus, it is relevant to discuss the extent to which it can be achieved in real life. HUSK, as our source population, is representative of women aged 40-44 years in Hordaland, because 70.0% of total population was participated in this study. However, representativeness of the Cohort depends on eligibility criteria for inclusion, initial response of the sample, and the stability of the Cohort on follow-up. In addition, this quality cannot be achieved if there is lack of confidence in the

internal validity of the findings of the study. In **Paper I**, we showed that the Cohort is similar to source population in many aspects; thus, the external validity or generalizability can be considered as good. To generalize the result from the Cohort to the Norwegian population, we may need to compare demographic data from HUSK with nationally representative data like CONOR.

External validity is also dependent on other aspects. The descriptive results from **Paper II** and **III** - prevalence, incidence, remission, and severity of symptoms - may differ from other “unselected” populations if there are differences in age distribution, ethnic diversity, inclusion of specific risk factors or other factors that influence the epidemiological parameters. One should for example not expect to find the same distribution of types and severity among incontinent women in clinical studies, as other studies have showed that only a minority of the incontinent women seeks help and the help-seekers have more severe symptoms^{40,113}. In addition, due to different characteristics in different populations, the generalizability of our descriptive results may be fairly limited to Norwegian or Scandinavian women.

Initial nonresponse of individuals chosen for inclusion in a population-based cohort study obviously limits the external validity. One of the important influences of nonresponse bias is the extent of which nonparticipation is associated with the outcome of interest^{117,118}. In **Paper II** and **III**, in each wave of the Cohort, the matter of personal interest may change in women for different reasons like age, or severity of UI. Furthermore, the level of representativeness may also vary as a function of interactions between variables. For example, mixed UI, as a combination of existence of both stress and urgency symptoms may change the threshold of participation in a study. This matter will be discussed later in discussion of results in **Paper III**.

6.1.4 Precision

Precision in epidemiologic measurements corresponds to the reduction of random error. “Random” is used to denote unsystematic error as opposed to systematic error or bias. Random error can occur during data collection, coding, transfer, or analysis. Sampling error is a random error in sampling procedures, which causes a difference

between survey result and population value. Unlike bias, sampling error can be predicted, calculated, and accounted for. There are several measures of sampling error, like confidence intervals and p-values. Precision evaluation is linked to power calculation and a larger sample size means more power and increased precision. However, it should be noted that precision will be reduced when we analyze subgroups with small sample size, which can reduce the statistical power and increase the chance of Type II errors. Type II error is the error in testing a hypothesis of failing to reject a hypothesis when it is false and also describes possible errors made in a statistical decision process. For example in **Paper II** and **III**, studying women in eight different age groups, can reduce the precision due to reduction of power. This problem is even larger when analyzing smaller subgroups, for example the women with significant UI.

6.2 Discussion of results

6.2.1 Prevalence

The prevalence of UI has been studied in many countries and in many settings. Differences in definitions and methodology make comparisons and reviews challenging as described in the introductory chapter.

In **Paper I**, we used an entrance question “Do you have involuntary loss of urine?” to define any UI and the results showed that 26.3% of women in age range of 40-44 years answered “yes”. This prevalence rate was somewhat higher than the EPINCONT study for the same age range (22.3%).

After splitting these women into two groups as participants in the Cohort and the rest of them that did not participate in the Cohort, it was revealed that women who participated in the Cohort had a significantly higher UI percentage (28.9%) than the rest of women in the HUSK (24.8%). Since the selection of women was truly random, there is no apparent reason for this difference. The very high response rate for the Cohort cannot explain this difference by bias alone.

In **Paper II**, we used the severity index (ISI) to determine the UI. The overall prevalence rate for any UI was 40.2%, which was in the suggested range of reasonable prevalence by ICI in 2004 (6). However, despite of the fact that we somewhat limited the definition of any UI by using ISI, the estimates of UI prevalence in **Paper I** was lower than **Paper II**. Two main reasons could explain this difference, first, the difference in definition of UI and second the methodology. It should be noted that we had different age ranges in **Paper I** (40-44 years) and in **Paper II** (41-55 years). In **Paper II** same women contributed to the results more than once in different waves depending on their age (but not more than once in each age group). Another possible reason for the prevalence differences could be the nature of questionnaires. In **Paper II**, the questionnaire was mainly focused on urinary symptoms, while in the accessory questionnaire from HUSK, used in **Paper I**, the UI problems was a minor part.

By using the year of birth we categorized women by age. This categorization may draw a sharp line between different age groups but it may also include some women in a wrong age subgroup and cause some information bias. First, we calculated the prevalence of UI by using all questionnaires, and then we did the same calculation by using data from women who participated in all six waves. Comparing results from these two calculations showed that changing patterns of UI prevalence are the same in both, but the prevalence rate was slightly higher in the latter. Prevalence of UI steadily increased up to age 51-52 years and then started to decrease. Over a period of 10 years, we found a relative increase of about 30% in prevalence for any UI and more than a doubling of significant UI. Compared with previous longitudinal studies, we have studied a rather narrow age span and we found the peak of prevalence in this age group more precise than previous studies. Some studies have found a peak in the prevalence of UI at age 50-55 years^{6,30} and other studies at age 50-59 years^{8,9}. However they found different prevalence levels (27-60%). This difference may partly be due to the definition of UI and/or the age-range of subgroups¹⁹. Our similar findings of a reduction trend of prevalence of UI after the peak, make us believe that it is a real epidemiological effect.

We defined “significant UI” by including both ISI and bothersomeness. This rather restrictive definition of significant UI was used before in the EPINCONT study, which reported 7.0% significant UI, similar to our result (8.0%). This definition for significant UI may include most women that should be denoted potential patients. Different from any UI, the changing patterns of prevalence of significant UI didn’t show exactly the same curves. As mentioned above, the nonparticipant bias, due to the matter of interest, may play the main role for higher percentage of significant UI, when we used all questionnaires. It means that some women may participate in some waves of the Cohort because they had more UI bothersomeness and vice versa.

6.2.2 Incidence and remission of UI

Results from **Paper II** revealed significant information about incidence and remission of UI. We used data from women who participated in all 6 waves and since we had the prevalence of UI from the same women in 10 years, we could study an accurate relation between changing pattern of prevalence with changing patterns in incidence and remission. Unfortunately, we didn’t have permission to connect our data from the Cohort to data from HUSK/LUTS questionnaire at the time of analysis and we used the first wave of the Cohort as the baseline to find incidence and remission rates. Incidence rate was relatively stable until the prevalence reached to its peak. Previous studies have also reported an incidence rate close to ours^{52,55,58}. Not showed before, we were able to identify that the decrease in prevalence after the peak was due to a mutual effects of decreased incidence and increased remission rates. Also our overall remission rate fits well with previous literature^{27,46,51,58}. However, the biological processes underlying the prevalence peak are still unclear.

We also analyzed the type and severity of UI in different age groups. Our data was in favor of earlier concepts about the dynamic nature of UI with possibility for not only both remission and exacerbation, but also in shifting the types and severity distributions.

In **Paper III**, the main focus was on natural history of UI. We used the same definitions for UI as in **Paper II**. One of the challenges in analysis of the results was

the high variability of changes in types and severity of UI from wave to wave. At the time of analysis we still didn't have permission to connect our data to HUSK/LUTS questionnaire. Thus, we used the first wave as baseline. The term "new-onset UI" was mostly used in clinical studies before. The concept of "new-onset" is not different from "incident", but we used this term with attempt to follow up the cases.

Our study showed that the new-onset UI in middle-aged women is mainly of stress type and of slight severity. We also found that the distribution of new-onset urgency and mixed UI are almost the same. Nevertheless, women with new-onset UI almost never experienced severe UI directly from start. Distributions of women in all three pre-modified subgroups were almost the same.

In subgroup A, women experienced a transient UI. Our study showed that women in this subgroup had a larger proportion of non-classified UI and a smaller proportion of moderate UI compare to other subgroups. Women in Subgroup B had experienced an on-and-off UI and they had also mostly slight stress UI. But compared to Subgroup A, moderate new-onset UI was reported slightly more. In Subgroup B, severity of UI showed a small increase in severity in the second time. In subgroup C, UI was persistent. However, the type and severity of UI did not change in most cases, especially not in women with stress new-onset UI. Compared with other subgroups, it seems that women with mixed new-onset UI, had more tendency to get persistent UI.

Compared with previous studies on natural history of UI, our study had some strong features such as: the number of waves, narrow age-spans and the short interval durations. Previous studies had one or two follow-ups, a wide age-span, and long intervals between checkpoints^{46,53,56-58,73,119-121}. However, in those studies, despite of differences in definitions of UI and age distribution, they showed the dynamic nature of UI. The results for incidence and remission of UI, from Townsend et al⁵⁸ and Lifford et al¹²¹, are in the same range as our results in **Paper II**. The result for type shifts in our study is compatible with two other studies; one⁴⁶, which reported one-third of women with stress or mixed UI at baseline had the same type after five years,

and another¹²¹, which reported a similar results after 2 years. Thom et al⁷³ also reported a 31.0% incidence of new-onset UI during approximately 5 years.

Studies have shown that mixed UI is far more common than expected if pure stress and pure urgency UI are assumed to be independent, but the reasons for this finding is not known. A recent empirical study¹²² discussed three possible explanatory models for this finding. First, the “Risk Factor model” suggests a common set of risk factors (including obesity, parity, prolapse) exists for both stress and urgency UI. Second, the “Liability model”, which assume that if a woman has already one type of UI (stress or urgency), she has higher risk to get the other type and develop mixed UI; or if the likelihood of remission of symptoms is lower for mixed UI than for either stress or urgency UI. Third, the “Severity model” is supported if UI symptoms are more persistent with mixed UI than with pure stress or urgency UI, specifically, the severity model would dictate that on any given day, women with mixed UI are more likely to exhibit UI symptoms. The authors explored the extent to which evidence supported each model. They found little support to indicate that the excess prevalence of mixed UI was explained by common risk factors. In contrast, they found evidence to indicate that onset of one UI subtype increased risk of onset of the other subtype. Although they found the Severity model attractive, they had little epidemiological evidence to support it.

Our study did not include risk factor data and hence we could not evaluate the Risk Factor model. But regarding the Liability model, our data showed no support, because we found a high transition from mixed UI to stress or urgency UI, which indicated that mixed UI is also very dynamic with high remission rate to its two components. This finding was against previous studies that claimed the likelihood of remission of symptoms is lower for mixed UI than for either stress or urgency UI^{27,46,57,58,74}. Our data is more in favour of the Severity model, because we included women with new-onset UI through follow-ups and not by invitation, thus we removed the factor of “personal tendency for participation in a survey”. We found that the proportion of mixed UI is less than 13.0% at each checkpoint, while previous cross-sectional studies have found a proportion between 30-45% for the same age-

group^{9,123}, even in a Norwegian study that used the same questionnaire⁶. The high prevalence of mixed UI in cross-sectional studies may possibly be explained by response bias. Previous studies showed that women with mixed UI have more severe symptoms compared to pure stress or urgency UI^{9,123,124}. Therefore, based on the Severity model, we suggest that women with mixed UI, due to more severe symptoms, exhibit their problem more than women with single stress or urgency UI. We also suggest adding a new dimension to this model, namely response bias.

6.3 Recommendation for further research

Epidemiologic survey of UI, as a symptom, is different from clinical study of UI. This feature is different from many other studies that use self-reports of diagnosed disease states. It is recommended that more sustained research on measurement of UI should be performed including, its types and severity to move the research ahead. More longitudinal study designs are needed to estimate incidence of UI and describe the course of the condition and its different forms and to investigate its risk factors and possible protective factors. Per 2014, two more completed waves of the Cohort are available for analyses. Data presented in this dissertation may therefore be expanded in future.

There is still room for improvement of knowledge related to incidence, remission and natural history of UI in middle-aged women. It is recommended that age-specific epidemiological data should be encouraged, and tailored to the different phases of menopause and other risk factors in perimenopausal women. Development of UI must be studied in a way that links population-based methods to clinical assessment of UI. In middle-aged women, such a design is necessary because the effect of natural physiological and hormonal changes may become clear only during longitudinal studies with multiple checkpoints and short intervals.

In order to combine data, studies should be done only with recommended and validated questionnaires. Control for confounders, stratification, and multivariate techniques should be increasingly used because of the need for more advanced

epidemiological analyses of risk factors and comorbidity. There should be more emphasis on the associations between UI and specific diseases. Genetic components should be investigated. Primary prevention is the main goal on the management of human disease. An important strategy would thus be to identify the individuals at risk, and then take measures to reduce the risk among those individuals or in certain risk groups. Based on current knowledge there are no well-documented efforts that can be done in order to avoid the occurrence of UI in large populations. Primary prevention studies should be encouraged, but the epidemiological basis for choosing appropriate intervention is weak.

Source of data

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