The Impact of Women’s Smoking, Obesity and Mode of Delivery on Urinary Incontinence

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ACADEMIC DISSERTATION

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Helsinki 2018
To my beloved ones
ABSTRACT

Stress urinary incontinence and urgency urinary incontinence are the most burdensome and bothersome of all urinary storage symptoms in women – both from the population and from the individual perspective. They are associated with substantial physical and psychological morbidity and large societal costs. Established risk factors for urinary storage symptoms include age and parity, but there remains uncertainty about the impacts of other reproductive and lifestyle factors including smoking, obesity and mode of delivery. This thesis describes a series of studies to clarify and quantify the impact of these potentially modifiable risk factors for female urinary storage symptoms, especially stress and urgency urinary incontinence.

In the first two studies, we used data from the FINNO Study to measure the association of smoking status and smoking intensity, overweight and obesity with urinary storage symptoms. In the FINNO Study, questionnaires were mailed to 6 000 men and women (aged 18-79 years) in 2003-2004. Of the women, 2 002 responded (67.0%). In the multivariable analyses, current smoking was associated with both urinary urgency (OR 2.7, 95% CI 1.7-4.2) and frequency (OR 3.0, 95% CI 1.8-5.0), while nocturia, stress and urgency urinary incontinence were not associated with current or former smoking. Similarly, current heavy (versus light) smoking was associated with additional risk of urgency (OR 2.1, 95% CI 1.1-3.9) and frequency (OR 2.2, 95% CI 1.2-4.3). Obese women (body mass index 30 or more) had approximately two-fold increase in stress urinary incontinence (OR 1.9, 95% CI 1.2-3.0) and nocturia (OR 2.4, 95% CI 1.5-3.8), and a three-fold increase in urgency urinary incontinence (OR 3.0, 95% CI 1.2-7.4), compared to normal-weight (body mass index less than 25).

The third study was a comprehensive systematic review and meta-analysis of the long-term impact of the delivery mode (spontaneous vaginal, assisted vaginal and cesarean) on stress and urgency urinary incontinence. Pooled estimates from 15 eligible studies demonstrated an almost two-fold increase in the risk of developing moderate to severe long-term stress urinary incontinence after vaginal delivery compared to cesarean (OR 1.85, 95% CI, 1.56-2.19, I²=57%). We observed an absolute increase of approximately 8%, and a gradient that was larger in younger and smaller in older women. We found a small increased risk of moderate to severe urgency urinary incontinence (OR 1.30, 95% CI, 1.02-1.65, I²=37%), with an absolute increase of approximately 3% in vaginal delivery versus cesarean section.

As the long-term effects of different vaginal delivery modes, especially vacuum versus forceps remain uncertain, we conducted a fourth study using data from a large Norwegian prospective population-based cohort (The Nord Trøndelag Health Study, The HUNT Study). We obtained data linkage to the Medical Birth Registry of Norway. We assessed the risk of stress and urgency
urinary incontinence prevalence after different types of vaginal delivery (spontaneous vaginal delivery, vacuum and forceps) with adjustment for age, parity, body mass index, and years since last delivery. In the final analysis set including 13 694 women with vaginal deliveries only, we found an increased risk of stress urinary incontinence for forceps delivery in women aged <50 years (OR 1.42, 95% CI 1.09-1.86), but not for vacuum (OR 0.80, 95% CI 0.59-1.09), when compared to spontaneous vaginal delivery. The absolute increase was approximately 5% in bothersome stress urinary incontinence when comparing forceps delivery with spontaneous vaginal delivery. Among younger women, forceps also had an increased risk for stress urinary incontinence (OR 1.76, 95% CI 1.20-2.60) when compared to vacuum in the direct comparison. There was no measurable impact between different vaginal delivery modes for women aged 50 or more. This difference in results reflects the increasing incidence of urinary incontinence for reasons other than mode of delivery as women age.

In conclusion, this thesis used a variety of data sources and study designs. We extend previous research by providing symptom-specific associations between obesity and smoking and different urinary storage symptoms. Comparing different modes of delivery, we found a significant impact of vaginal delivery compared with cesarean delivery for younger women on stress urinary incontinence, and demonstrate for the first time the increased risks associated with forceps compared with vacuum. The association of delivery mode with urinary incontinence, however, is diminished in old age. As urinary storage symptoms are predicted to increase in prevalence as the world population ages, this work provides important directions for future public health efforts.

Tutkimuksen kaksi ensimmäistä osatyötä perustuvat väestöpohjaisen virtsaamishäiriöitä kartoittavan FINNOS-tutkimuksen aineistoon. Kirjekysely lähetettiin kuudelle tuhannelle satunnaisesti väestörekisteristä valitulle 18-79-vuotiaalle henkilölle. Kutsutuista naisista tutkimukseen osallistui 2 002 (67%). Selvitimme tupakoinnin ja lihavuuden yhteyttä ponnistus- ja pakkovirtsinkarkailuun, yövirtsaamiseen, virtsaamispakkoa ja tihentyneeseen virtsaamistarpeeseen. Osallistujista 23% kertoi tupakoivansa, 24% kertoi tupakoineensa aiemmin ja 53% ei ollut ollut koskaan tupakoinut. Monimuuttuja-analyysissa yövirtsaaminen, ponnistus- tai pakkovirtsinkarkailu ei ollut tupakoivilla yleisempää kuin tupakoimattomilla. Tupakoivat naiset raportoivat kuitenkin enemmän tihentyntää virtsaamistarvetta (OR 3.0, 95% CI 1.8-5.0) ja virtsaamispakkoa (OR 2.7, 95% CI 1.7-4.2) kuin tupakoimattomat. Myös tupakoinnin määrällä oli väliä: yli puoli askia päivässä tupakoivilla naisilla oli virtsaamispakkoa (OR 2.1, 95% CI 1.1-3.9) ja tihentyntää virtsaamistarvetta (OR 2.2, 95% CI 1.2-4.3) enemmän kuin alle puoli askia päivässä tupakoivilla. Lihavilla naisilla (painoindeksi 30 tai yli) ponnistusvirtsinkarkailu (OR 1.9, 95% CI 1.2-3.0) ja yövirtsaaminen (OR 2.4, 95% CI 1.5-3.8) olivat kaksi kertaa ja pakkovirtsinkarkailu kolme kertaa (OR 3.0, 95% CI 1.2-7.4) yleisempiä kuin normaalipainoisilla (painoindeksi <25) naisilla. Sen sijaan tihentynyt virtsaamistarve tai virtsaamispakko eivät olleet yhteydessä lihavuuteen.

Väitöskirjan kolmas osatyö oli laaja, synnytystavan pitkäaikaisvaikutuksia ponnistus- ja pakkovirksankarkailuun käsittävää, systemaattiseen katsaukseen. Meta-analyysin, johon sisällytettiin 15 tutkimusta (45 659 naista), mukaan alatiesynnytys lähes kaksinkertaistaa ponnistusvirtsinkarkailun riskin (OR 1.85, 95% CI 1.56-2.19, I2=57%) keisarileikkaukseen verrattuna. Absoluttinen riski suurenee noin 8 %. Riski on suurempi nuorilla naisilla ja pienenee ajan kuluessa synnytyksestä. Meta-analyysin (8 tutkimusta, 49 623 naista) mukaan myös pakkovirtsinkarkailun riski lisääntyy alatiesynnytyksen jälkeen verrattaessa keisarileikkaukseen (1.30, 95% CI 1.02-1.65, I2=37%), mutta absoluttinen riski lisääntyy vain 3 %.
Systemaattisessa katsauksessa havaitsimme, että aiempia tutkimuksia, jotka vertaavat imukuppi- ja pihtisynnytyksiä toisiinsa ei ole. Viimeisessä osatyössä selvitimme eri alatiesynnytysten vaikutusta ponnistus- ja pakkovirtsankarkailuun pitkällä aikavälillä. Aineistona käytimme norjalaista väestöpohjaista kohorttitutkimusta (The Nord Trøndelag Health Study, HUNT-tutkimus), jonka tiedot yhdistettiin Norjan syntymärekisteriin. Lopullisessa aineistossa oli yhteensä 13 694 naista. Monimuuttuju-analysissä totesimme, että alle 50-vuotiailla naisilla pihtisynnytys lisää ponnistusvirtsankarkailun riskiä verrattuna normaaliin alatiesynnytykseen (OR 1.42, 95% CI 1.09-1.86, absoluuttinen riski 5%), mutta imukuppisynnytyksen ja spontaanin alatiesynnytyksen välillä eroa ei ole. Pihtisynnytys lisää ponnistuskarkailun riskiä myös verrattuna imukuppisynnytykseen (OR 1.76, 95% CI 1.20-2.60). Yli 50-vuotiailla naisilla eroa eri alatiesynnytysten välillä ei enää ollut todettavissa.

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Tampere, October 2018

Riikka Tähtinen
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AIMS OF THE STUDY

The specific aims of this dissertation are:

1. To estimate the relation of smoking status and smoking intensity with urinary storage symptoms.

2. To estimate the relation of overweight or obesity with urinary storage symptoms.

3. To perform a systematic review and meta-analysis on the long-term impact of delivery mode on stress and urgency urinary incontinence.

4. To explore the long-term impact of different kinds of vaginal deliveries on stress and urgency urinary incontinence.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


The publications are referred to in the text by their roman numerals.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BFLUTS</td>
<td>The Bristol Female Lower Urinary Tract Symptoms questionnaire</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CS</td>
<td>Confounder scores</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DAN-PSS</td>
<td>Danish Prostatic Symptom Score</td>
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<td>EPINCONT</td>
<td>The Norwegian Epidemiology of Incontinence in the County of Nord-Trøndelag Study</td>
</tr>
<tr>
<td>EPIQ</td>
<td>The Epidemiology of Prolapse and Incontinence Questionnaire</td>
</tr>
<tr>
<td>FINNO</td>
<td>Finnish National Nocturia and Overactive Bladder</td>
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<tr>
<td>HRQL</td>
<td>Health-related quality of life</td>
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<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>IUGA</td>
<td>International Urogynecological Association</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>OAB-q</td>
<td>An Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>MHT</td>
<td>Menopausal hormone therapy</td>
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<tr>
<td>PFDI</td>
<td>Pelvic Floor Impact Questionnaire</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SUI</td>
<td>Stress urinary incontinence</td>
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<tr>
<td>SVD</td>
<td>Spontaneous vaginal delivery</td>
</tr>
<tr>
<td>UI</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UISS</td>
<td>Urinary Incontinence Severity Score</td>
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<tr>
<td>UUI</td>
<td>Urgency urinary incontinence</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
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INTRODUCTION

Stress urinary incontinence (SUI) and urgency urinary incontinence (UUI) are the most common and most bothersome urinary symptoms in women (Agarwal et al. 2014). They are associated with significant impact on the quality of life (QoL), and high societal costs (Subak et al. 2006, Wood & Anger 2014). Earlier epidemiological research in women has concentrated on urinary incontinence (UI) as one entity or analyzed all urinary symptoms as a single cluster. Since the various urinary storage symptoms and subtypes of incontinence likely have different etiologies (Hannestad et al. 2003, Parazzini et al. 2000), combining them may have obscured important associations and led to inconsistency in results between different studies.

Smoking is one of the biggest public health threats the world has ever faced, killing more than 7 million people a year (WHO 2015). The ratios of female-to-male smoking prevalence rates vary considerably across countries. In high-income countries, women smoke at nearly the same rate as men. However, in many low- and middle-income countries, women smoke much less than men. While women’s smoking prevalence rates are currently lower than men’s, they are estimated to rise in many low- and middle-income countries (Hitchman & Fong 2011). Despite increasing public awareness of smoking as a major source of morbidity and mortality, there is a lack of studies on relationship between smoking and urinary frequency or urgency.

Obesity is a worldwide epidemic with diverse health consequences. In Finland, two thirds of women are overweight and every fourth is obese (THL 2017). Several epidemiological studies have found an increased risk of SUI related to obesity in women (Hunskaar 2008), but earlier research has mainly focused on UI in women (Hunskaar 2008), and less is known about the relationship between being overweight and obese with specific urinary storage symptoms.

A cesarean section can be a life-saving intervention when medically indicated, but this procedure can also lead to short-term and long-term adverse health effects for women and children. There is an alarming increase in cesarean section rates worldwide from about 6% in 1990 into 19% in 2014 (Betrán et al. 2016). An extensive body of evidence from the first year after delivery demonstrates that in this initial postpartum period, rates of SUI are higher in women delivering vaginally than those delivering by cesarean (Press et al. 2007, Thom & Rortveit 2010). The long-term effects of delivery mode, however, are more important to patients than transient postpartum incontinence.

Operative intervention is used to shorten the second stage of vaginal delivery in the indication of the fetus or of the mother. The vacuum extractor is an alternative to forceps (O’Mahony et al. 2010). Although operative delivery increases the risk of immediate pelvic floor trauma (Handa et al. 2012,
Introduction

O’Mahony et al. (2010), there are no prior studies directly comparing forceps and vacuum for risk of stress or urgency urinary incontinence.

This thesis describes two studies to clarify the impact of smoking and obesity on urinary storage symptoms and two studies to clarify the impact of different delivery modes on SUI and UUI.
REVIEW OF THE LITERATURE

GENERAL ASPECT OF URINARY SYMPTOMS

The International Continence Society (ICS) and the International Urogynecological Association (IUGA) define urinary incontinence (UI) as the complaint of involuntary loss of urine (Haylen et al. 2010). The most common UI subtypes are stress urinary incontinence (SUI), and urgency urinary incontinence (UUI). Mixed urinary incontinence (MUI) is a complaint of both SUI and UUI (Haylen et al. 2010). Other UI subtypes include nocturnal enuresis (occurs during sleep), postural incontinence (associated with change of body position), continuous incontinence (continuous involuntary loss of urine), insensible incontinence (UI where the individual has been unaware of how it occurred), and coital incontinence (loss of urine with coitus) (Haylen et al. 2010).

Lower urinary tract symptoms (LUTS) can be divided into storage, voiding, and post-micturition symptoms. Storage symptoms, include urinary urgency, frequency, nocturia, SUI, UUI (Table 1) (Haylen et al. 2010). A large majority of earlier studies have either not considered other urinary storage symptoms or subtypes of UI, or they have only reported on SUI (Milsom et al. 2017). The etiology of UI is multifactorial; UI is caused by pathophysiological impairments to the lower urinary tract and neurological system, as well as a range of external factors (Minassian et al. 2017). Established risk factors vary by type of UI (Hannestad et al. 2003, Parazzini et al. 2000) and combining them may bias results.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Definition</th>
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<tr>
<td>Frequency</td>
<td>Micturition occurs more frequently during waking hours than previously deemed normal.</td>
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<tr>
<td>Nocturia</td>
<td>Interruption of sleep one or more times because of the need to micturate.</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>Involuntary loss of urine on effort or physical exertion</td>
</tr>
<tr>
<td>Urgency</td>
<td>Sudden, compelling desire to pass urine which is difficult to defer</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>Involuntary loss of urine associated with urgency</td>
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Review of the literature

PREVALENCE
Prevalence estimates of UI vary widely in the literature, but most studies report a prevalence of any UI in the range of 25% to 45% (Milsom et al. 2017). In five population-based studies (Coyne et al. 2009, Hannestad et al. 2000, Hunskaar et al. 2004, Irwin et al. 2006, Melville et al. 2005) assessing UI prevalence in western countries, prevalence varied between 13% to 45%. The range of the estimates mainly result from the use of different definitions of UI, diverse study samples and other methodological differences (Vaughan et al. 2011, Tikkinen et al. 2012). Bothersome and symptoms important to patients are less common than the often suggested estimates of 25% to 45% (Vaughan et al. 2011, Tikkinen et al. 2012, Agarwal et al. 2014), and it is therefore crucial to also measure the severity/bother of UI. For instance, in the Norwegian Epidemiology of Incontinence in the County of Nord-Trøndelag (EPINCONT) study, incontinence was reported by 7%, when defined as moderate or severe UI (response options: slight, moderate and severe). Among women with slight incontinence, 10% answered that they were bothered by their symptoms. In comparison, 34% of those with moderate incontinence and 73% of those with severe incontinence were bothered (Hannestad et al. 2000). The severity of UI increases linearly with age (Hannestad et al. 2000, Melville et al. 2005). In a population-based US study (Melville et al. 2005), 8% of women between the ages of 30 and 39 years reported severe UI compared with 33% of the eldest women (aged 80-90 years).

Although the absolute prevalence rates vary widely in cross-sectional studies, the distribution of UI subtypes is quite consistent. SUI is the most common subtype in women with estimated 10-39% prevalence, followed by MUI with 8-25% prevalence (Botlero et al. 2008, Coyne et al 2012. Ge et al. 2015, Hunskaar et al. 2004, Lee et al. 2008, Milsom et al. 2017, Zhu et al 2009). UUI is less common, with 1-7% prevalence, and other causes of incontinence with approximately 0.5-1% prevalence (Botlero et al. 2008, Coyne et al 2012. Ge et al. 2015, Hunskaar et al. 2004, Lee et al. 2008, Milsom et al. 2017, Zhu et al 2009).

INCIDENCE AND REMISSION
Incidence refers to the occurrence of new cases of disease or condition (Gertsman 2013). In the longitudinal studies, UI is associated with incidence rates of 3-20% (Jahanlu et al. 2008, Komesu et al. 2009, Legendre et al. 2015, Nygaard & Lemke 1996, Samuelsson et al. 2000, Townsend et al. 2007, Waetjen et al. 2007, Viktrup & Lose 2008). In a meta-analysis including 16 studies (34 443 women), the age-specific incidence was less than 2/1 000 person-years before age 40, increased to 5/1 000 person-years at age 50, decreased to 3/1 000 person-years at 60-65, increasing again in the later decades of life (Stewart et al. 2014).

UI is a dynamic process and women with UI might cycle in and out of active and inactive symptom phases. Remission means absence of symptoms

**BOTHER AND IMPACT**

SUI and UUI are the most burdensome and bothersome of all urinary symptoms in women – SUI from the population and UUI from an individual perspective (Agarwal et al. 2014). They are both associated with increased risk of comorbidities and QoL impairment (Nygaard et al. 2003) as well as impaired social and physical relationships (Molinuevo & Batista-Miranda 2012). Although the ICS/IUGA definitions do not define symptoms in terms of severity/frequency or associated bother, it is useful to measure QoL in women with UI when evaluating the efficacy of a particular therapy or comparing symptom severity between patients or groups. There are a large number of urinary symptom questionnaires including measure of QoL (Table 2). These questionnaires have been validated in comparison to bladder diaries, pad tests, or urodynamics. They use varying terminology to assess SUI and UUI, and do not always capture all aspects of the standardized definitions. In Finland the standardized and validated Detrusor Instability Score (DIS) (Klovning et al. 1996, Kujansuu & Kauppila 1982) and the Urinary Incontinence Severity Score (UISS) with the Visual Analogue Scale (VAS) (Mäkinen et al. 1992, Stach-Lempinen et al. 2001) are widely used in clinical practise.
The degree of bother increases with the frequency of urinary storage symptoms (Agarwal et al. 2014, Melville et al. 2005, Patrick et al. 1999). However, the impact of urinary leakage on QoL differ between different subtypes. Women with UUI have lower levels of health-related quality of life (HRQL) compared with women with SUI (Coyne et al. 2003, Hannestad et al. 2002, Lasserre et al. 2009). This may be because the timing of leakage is less predictable with UUI, and therefore more distressing and limiting for patients (Minassian et al. 2015). Women with SUI can adapt their lifestyles by, for example, avoiding heavy lifting or exercising, thus preventing situations that lead to involuntary loss of urine. The reported difference in HRQL between SUI and UUI women may also be partly due to confounding: risk factors and comorbidities of UUI and SUI differ (see Risk Factors).
RISK FACTORS

AGE
UI affects women of all ages. The lowest prevalence is in the younger age groups, and the prevalence increasing with advancing age (Hannestad et al. 2000, Hunskaar et al. 2003). As life-expectancy increases globally, the subsequent rise in the proportion of older people is likely to result in an increase in the prevalence of UI.

UI prevalence patterns differ by UI subtype (Figure 1). SUI prevalence peaks during the 50’s and declines thereafter (Ge et al. 2015, Herschorn et al. 2008, Jahanlu & Hunskaar 2010, Lasserre et al. 2009, Minassian et al. 2008, Mishra et al. 2010, Ojengbede et al 2011, Waetjen et al. 2009). The prevalence of UUI is low, between 20 and 30 years of age, but it gradually increases with age (Ge et al. 2015, Herschorn et al. 2008, Ojengbede et al 2011). Many UI risk factors associate with age, and adjustment for relevant co-morbidities typically explains the association between age and UI (Grodstein et al. 2003, Tennstedt et al. 2008).

![Figure 1](image)
Figure 1. Prevalence of stress and urgency incontinence by age. Prevalence estimates of SUI and UUI are pooled estimates of several population-based studies (Hannestad et al. 2000, Hunskaar et al. 2003, Melville et al. 2005, and Minassian et al. 2008 in Milsom et al. 2017).
SUI, stress urinary incontinence; UUI, urgency urinary incontinence.

SMOKING
Smoking kills millions each year and costs society trillions of dollars. Despite increasing public awareness of smoking as a major source of morbidity and
mortality and health policy changes to reduce smoking uptake and encourage smoking cessation, 942 million men and 175 million women ages 15 or older globally are current smokers (Drope et al. 2018). The earlier decreasing trend in smoking prevalence in high-income countries has stalled in recent years, and smoking prevalence has continued to rise or remained at high levels in medium- or low-income countries (Drope et al. 2018). In high-income countries, women smoke at nearly the same rate as men. However, in many low- and middle-income countries, women smoke much less than men. While women’s smoking prevalence rates are currently lower than men’s, they are estimated to rise in many low- and- middle-income countries (Hitchman & Fong 2011).

Smoking increases illness burden for many conditions, but the relation between smoking and different urinary symptoms remains unclear (Holroyd-Leduc & Straus 2004). In previous studies, smoking has been associated with UI. In the SWAN study, current smoking was a risk factor for moderate to severe UI (odds ratio (OR) 1.38, 95% confidence interval (CI) 1.04-1.82) (Sampselle et al. 2002). In a Norwegian population-based study among women (Hannestad et al. 2003), current smoking was associated with SUI (OR 1.8, 95% CI 1.1-2.9), in those who smoked more than 20 cigarettes per day. In the prospective Leicester Medical Research Council Study (Dallosso et al. 2003), smoking was a significant risk factor for the onset of SUI. In a large study evaluating urodynamic findings, 2 476 of 11 678 (21.2%) women reported smoking cigarettes. In a study including 650 women, seeking surgical therapy for SUI, severity of SUI was associated current smoking (p=0.01) (Richter et al. 2005). Smoking was not shown to be significantly associated with SUI (OR 1.08, p=0.213) or urodynamic SUI (OR 0.86, p=0.001) (Madhu et al. 2015).

Earlier results in studies exploring the association between smoking and nocturia are inconsistent: in a Swedish study nocturia was more common among current smokers (1-15 cigarettes daily vs. no smoking OR 1.4, 95% CI 1.1-1.8, 16 or more cigarettes per day vs. no smoking OR 1.8 95% CI 1.1-2.8) (Asplund & Aberg 2004). However, Austrian (Schatzl et al. 2000) and Japanese (Yoshimura et al. 2004) studies reported opposite findings.

There is a lack of studies estimating the association of smoking and urgency. In a prospective study among British women, smoking was a risk factor for the onset of overactive bladder (defined as having either urgency, UUI or a combination of these) but not for SUI (Dallosso et al. 2003). Furthermore, in a Finnish study among elderly people, urgency was associated with current (age-adjusted OR of 2.8, 95% CI 1.4-5.3) and former (OR 1.6, 95% CI 1.0-2.7) smoking when both genders were combined (Nuotio et al. 2001). However, the association was not statistically significant with only women.
OBESITY AND OVERWEIGHT

Obesity is a worldwide epidemic. The Centers for Disease Control and Prevention (CDC) defines a body mass index (BMI) of 25.0-29.9 as overweight, and BMI 30kg/m² or more as obesity (Centers for Disease Control and Prevention 2016). Obesity increases the risks of hypertension, stroke, myocardial infarction, certain cancers, and, especially, type 2 diabetes. In Finland two-thirds of women are overweight and every fourth one is obese (THL 2017). The US has mirrored this same trend with more than two thirds of women being obese or overweight (Flegal et al. 2012) and with a significant year on year increase (Flegal et al. 2016).

Many studies on the relationship between body weight and urinary symptoms have focused on UI in women (Hunskaar 2008, Subak et al. 2009). Obese women have approximately double the risk of UI (Hunskaar 2008, Subak et al. 2009). A systematic review estimated that the risk of severe SUI is 1.5-times higher for overweight and more than 2.5-times higher for obese women, when compared to normal weight (Hunskaar 2008). In the U.S. Nurses’ Health Study, increased waist circumference, but not BMI predicted incident SUI among middle-aged women (Townsend et al. 2008). In intervention studies weight reduction in women, whether through conservative or surgical methods, can reduce the frequency of SUI episodes and more modestly UUI episodes (Wing et al. 2010, Burgio et al. 2007).

PARITY

Parity is a well documented risk factor for UI. The first delivery is associated with adjusted OR of around 1.3-1.6 for UI, and further deliveries almost linearly increase the risk up to an adjusted OR of 1.5-2.0 (Danforth et al. 2006, Grodstein et al. 2003, Rortveit et al. 2001, Waetjen et al. 2007). The effects of parity on UI are strongest in the third and fourth decades, and effects seem to disappear in older age (Buchsbaum et al. 2005, Connolly et al. 2007, Lukacz et al. 2006, Rortveit et al. 2001), as other risk factors begin to dominate.

The EPINCONT (Rortveit et al. 2001) and SWAN (Waetjen et al. 2007) studies have reported association only between parity and SUI or MUI. Also, in the Generalized Longitudinal Overactive Bladder Study (Hirsch et al. 2010), among 3,599 women 40 years of age and older, parity was not associated with UUI after individuals with SUI were excluded.

MODE OF DELIVERY

Operative intervention is used to shorten the second stage of delivery in the indication of the fetus or of the mother. When vaginal delivery can be safely accomplished the obstetrician uses forceps or vacuum to deliver the fetus; otherwise, cesarean delivery is the better option. The World Health Organization (WHO) has shown that the ideal rate for cesarean sections is
between 10% and 15% (WHO 2015). However, cesarean rates, especially elective cesareans, are increasing globally without any signs of slowing down (Betrán et al. 2016).

The focus of the studies assessing delivery mode and UI has been on post-partum incontinence within one year of delivery. A systematic review including 33 population-based studies, each with response rates over 50% (Thom & Rortveit 2010), concluded that the prevalence of UI in the first three months post-delivery was 30%, with infrequent SUI being the most common. There is a gradual decrease in prevalence during the first post-partum year. Another systematic review on post-partum UI (Press et al. 2007) including data from four large cross-sectional studies (MacLennan et al. 2000, Melville et al. 2005, Peyrat et al. 2002, Rortveit et al. 2003), suggested a significant protective effect of cesarean on SUI (OR 0.56) and MUI (OR 0.70).

There are two RCTs to address this topic. The Term Breech Trial (Hannah et al. 2004) randomized women with fetuses presenting in breech position to planned vaginal delivery or planned cesarean. At two years postpartum, there was no difference in SUI rates between the planned vaginal delivery or the planned cesarean group (incontinence in previous 3-6 months: 17.8% in cesarean section vs. 21.8% in planned vaginal delivery group, p=0.14). A very recently reported RCT (Hutton et al. 2018) included 2 804 mothers of twins, and the follow-up was complete in 2 305 women (82.2%). For women with no prior history of problematic SUI, a planned cesarean reduced the risk of a new SUI compared with a planned vaginal birth, at two years postpartum (6.8% vs. 11.6%, OR 0.56, 95% CI 0.41-0.76, p<0.001).

A longitudinal cohort study recruited women at 5-10 years after a first birth to annual follow-up over 5 years (Handa et al. 2014). At the baseline, the prevalence of SUI was 54% in vaginal versus 20% in cesarean delivery; for UUI, prevalence was 17% in vaginal and 7% in cesarean delivery.

There are no prior studies directly comparing different kinds of operative vaginal deliveries (forceps and vacuum) for risk of both SUI and UUI. In the previously mentioned longitudinal study (Handa et al. 2012), the prevalence of bothersome SUI was similar after vacuum delivery (14% n=49) and spontaneous vaginal delivery (SVD) (14% n=324), but higher after forceps delivery (22% n=76, OR 1.65-3.08). However, forceps delivery indicated history of forceps delivery with or without a history of vacuum delivery. In the Norwegian EPINCONT study (Rortveit et al. 2003), there was no difference in the risk of SUI when comparing instrumental vaginal deliveries and SVD. This study compared vacuum deliveries to a combination of spontaneous vaginal deliveries and forceps deliveries and compared forceps deliveries to a combination of spontaneous vaginal deliveries and vacuum deliveries. In a register-based Swedish cohort study (Nilsson et al. 2016) of primipara with 20 years follow up (response rate 65.2 %, n=5 236), there was no difference in the prevalence of UI (40.5 vs. 41.0 %, OR, 0.89, 95 % CI 0.75-1.06), UI >10 years (9.0 vs. 10.5 %, OR 0.78, 95 % CI 0.58-1.05), or bothersome UI (13.6 vs. 11.0 %, OR 1.20, 95 % CI 0.94-1.55) between vacuum and SVD.
SOCIOECONOMIC STATUS

Socioeconomic status is measured by variables such as education, occupation, income, wealth and place of residence (Winters-Miner et al 2015). It is strongly associated with many of the risk factors for UI including BMI (Newton et al. 2017), diabetes type 2 (Agardh et al. 2011), depression (Freeman et al. 2016, Sung et al 2009), smoking (Hiscock et al. 2012) and the timing of menopause (Luoto et al. 1994).

The evidence between socioeconomic status and UI prevalence or its bothersomeness is conflicting. In some studies, women with a lower educational level report a higher level of UI (Coyne et al 2009, Ge et al. 2015, Huang et al. 2006, Melville et al. 2005). Also, women reporting financial strain have increased odds of reporting a high level of bother (Sampselle et al. 2002). However, in some studies there is no association between socioeconomic status and UI (Tennstedt et al. 2008, Roe & Doll 1999, Saadoun et al 2006), or UUI (Kuh et al. 1999). In one study, women with a higher socioeconomic status had a higher risk for monthly SUI (Kuh et al. 1999), possibly because women with higher socioeconomic status are consistently shown to have an increased level for seeking care for UI (Milsom et al. 2017).

COMORBIDITIES

Diabetes

In many cross-sectional studies, diabetes types 1 or 2 are associated with UI (Coyne et al. 2009, Ebbesen et al. 2007, Ebbesen et al. 2009, Melville et al. 2005, Sarma et al. 2009, Waetjen et al. 2007). In the longitudinal studies, the evidence is, however, more conflicting. In the Nurses’ Health Study, the risks of prevalent UI (RR=1.28, 95% CI=1.18-1.39) was significantly greater in women with diabetes 2 compared to women without (Lifford et al 2005). Also, women with type 2 diabetes had significantly increased odds of UI developing (OR 1.2, 95% CI 1.0-1.3, p=0.01) compared to women without diabetes (Danforth et al. 2009). This increase was largely explained by significantly greater odds of UUI (OR 1.4, 95% CI 1.0-1.9, p=0.03), and there was no apparent association between diabetes and SUI (p=0.3) or MUI (p=0.6). In the SWAN study (Waetjen et al. 2007) despite significant associations with prevalent UI (OR 2.3, 95% CI 1.2-4.6), no association with either incident UI, or worsening of UI was found.

Neurological diseases

UI can affect 40-60% of people after a stroke, and 15 to 30% remain incontinent at one year (Barrett at al. 2001, Williams et al. 2012). The more severe the stroke is, the greater the likelihood of UI, and the effect is magnified with advancing age (Burney et al. 1996, Williams et al. 2012). In a meta-analysis, the prevalence of UI was 51% in patients with multiple sclerosis (14
studies included to meta-analysis), and 33% with Parkinson’s disease (seven studies included in the meta-analysis) (Ruffion et al. 2013).

UI has a strong association with memory disorders (Ouslander et al. 1987, Østbye et al. 2004), and severe incontinence correlates with an increase in dementia symptoms (Rose et al. 2013). Longitudinal studies have also identified an association between incident UI and memory disorders. The Australian Longitudinal Survey of Women’s Health followed 12 432 women aged 70-75 for nine years and demonstrated an association with diagnosed dementia (OR 2.34) (Byles et al. 2009). In another study (Thom et al. 1997) with follow up of nine years, for 3 004 women aged 65 years and over, diagnosed dementia was strongly associated with incident diagnosis of UI (RR 3.0 95% CI 2.4-3.7).

**Depression**

Several cross-sectional studies have shown a consistent association between UI and depression (Markland et al. 2008, Melville et al 2005, Moghaddas et al. 2005, Nuotio et al. 2003, Nygaard et al. 2013, Waetjen et al. 2007), but data is somewhat conflicting in longitudinal studies. In a follow-up of 3 004 women (Thom et al 1997) aged 65 years and older, diagnosed depression was associated with incident diagnosed UI over 9 years (OR 1.6, 95% CI 1.2-2.0). In the Health and Retirement Study (Hung et al. 2014), with 4 511 participants aged 54 to 65, the presence of UI was also associated with an increased risk of probable depression (adjusted hazard ratio, 1.43, 95% CI 1.27-1.62) in 14 years of follow-up. Increasing UI frequency was associated with greater risk. However, in the SWAN study (Waetjen et al. 2007) depression was not associated with incident UI. UI affects QoL and can lead to depression (Felde et al. 2012, Nygaard et al. 2003), but current evidence supports causality in the opposite direction (Markland et al. 2008, Melville et al 2005, Moghaddas et al. 2005, Nuotio et al. 2003, Nygaard et al. 2003, Nygaard et al. 2013, Waetjen et al. 2007).

**RACE/ETHNICITY**

Most of the population-based studies comparing the prevalence of UI by race/ethnicity originate in the US. Studies consistently suggest that Caucasian women report a higher prevalence and incidence of UI overall compared with Hispanic, Asian, and Afro-American women (Townsend et al. 2010, Waetjen et al. 2007).

Caucasian women have a two-fold increased prevalence of SUI compared to Afro-American women in adjusted analyses (Tennstedt et al. 2008, Townsend et al. 2010, Waetjen et al. 2007). When comparing the prevalence of UUI for Caucasian women and Afro-American women, there is little consistency. In the BACH survey (Tennstedt et al. 2008), prevalence differences between Caucasian and Afro-American women was 13% vs. 3% in
weekly UUI. However, in the Study of Women's Health Across the Nation (SWAN Study) (Waetjen et al. 2007), Black women had higher prevalences of monthly UUI (12% vs 8%). Socioeconomic, environmental and cultural differences may explain some of these observed prevalence differences (Milsom et al. 2017).

**MENOPAUSE AND MENOPAUSAL HORMONE THERAPY**

Menopause is a consequence of the deterioration of ovarian function. Menopause is defined retrospectively as the cessation of spontaneous menses for 12 months (Nelson 2008). Worldwide, most women enter menopause between the ages of 49 and 52 years. Menopausal hormone therapy (MHT) is used to alleviate menopausal symptoms, for example hot flushes, sleep disturbances, head and joint ache, palpitations and mood changes. Estrogen alone can be prescribed to hysterectomized women. If a woman has a uterus, estrogen must be combined with progestogen (Nelson 2008).

The lower urinary tract is hormone-sensitive, with estrogen receptors present in all squamous epithelia (Blakeman et al. 2000, Skala et al. 2010). Estrogen deficiency in postmenopausal women is known to cause atrophic urethral mucosal changes, and the commonly held assumption has previously been that estrogen plays an important role in the continence mechanism of the lower urinary tract (Cardozo et al. 2004, Rud 1980). However, this assumption has been challenged by epidemiological and biochemical data. The number of years since menopause does not seem to be associated with an increase in the risk of having any UI subtype (Trutnovsky et al. 2014). Also, a large Swedish community-based observational study discovered that higher serum estradiol levels were related with a higher prevalence of UI in middle-aged women (Teleman et al. 2009). No association between UI and serum levels of cortisol, testosterone, or androstendione was found (Teleman et al. 2009).

Estrogen plays a role in the supportive mechanism of the pelvis by controlling the synthesis and breakdown of collagen (Chung & Bai 2006). Estrogen therapy has been shown to lead to a reduction in total collagen concentration and cross-linking, as well as increased periurethral vascularity, and it may be responsible for reduced urethral support (Steinauer et al. 2005). This finding is in concordance with studies showing a higher incidence or prevalence of UI in women on MHT. Current guidance recommends the use of topical estrogen (Cody et al. 2012, Weber et al. 2015). However, systemic menopausal replacement therapy is accompanied by increases in the risk of overall UI and is not recommended (Cody et al. 2012).

A recent Finnish register-study, including 44,389 women identified from the Finnish Population Register Centre, examined estradiol-based hormone therapy regimens and the risk of SUI. In this study, all the forms of hormone therapy were accompanied with consistent two to three-fold elevations in SUI risk. The rise in SUI risk was also related to the woman’s age at hormone therapy initiation, as a starting age above 55 years showed a significantly
higher SUI risk than a starting age under 55 years. This risk elevation appeared already within the first 3 years of hormone therapy use, and increased further with over 5 years of use (Rahkola-Soisalo et al. 2018). This is in concordance with large, randomized the Women’s Health Initiative (WHI) Hormone Replacement Trial (Manson et al. 2013). In the WHI trial, continent women receiving oestrogen, with or without progestogen, were approximately twice as likely to have developed SUI at 1 year (16% vs. 9%) (Hendrix et al. 2005), compared to women receiving placebo. The risks of MUI and UUI were also modestly increased.

**HYSTERECTOMY**

Hysterectomy has been associated with the development of UUI and SUI in several studies (Altman et al. 2007, Brown et al. 2000, Kudish et al. 2014, Parazzini et al. 2003). This may be caused by interrupting the local nerve supply to the urethra (Prior et al. 2000), and the procedure might cause changes in urethral pressure dynamics by distortion of the pelvic-organ anatomy (DeLancey et al. 1997).

In the WHI Observational Study, with women aged 50 to 79, hysterectomy was associated with UI at baseline (OR 1.25, 95% CI 1.19-1.32) and over the 3-year study period (OR 1.23, 95% CI 1.11-1.36). When women with UI at baseline were excluded, a higher incidence of UUI and SUI episodes was found after hysterectomy at year 3 (Kudish et al. 2014). However, other evidence is conflicting. A Finnish prospective longitudinal study (Aukee et al. 2018) evaluated the effect of hysterectomy for benign reasons among 286 women. A hysterectomy, with or without native tissue prolapse surgery, did not increase UI or urinary frequency, and the results were maintained up to the 5-year follow-up. In a French cohort study, vaginal hysterectomy for menorrhagia also did not increase the risk for SUI or UUI during the 4.6-year follow-up compared to conservative treatment (de Tayrac et al. 2007).

**DIET**

Dietary factors are recognized as contributing to the maintenance of good health, which is strongly related to low levels of UI. Dietary data are difficult to obtain reliably (Leatherdale & Laxer 2013), and women may change dietary habits in response to UI. Worsening of urinary urgency, frequency and incontinence is often reported after consuming caffeine, alcohol, fizzy (carbonated) drinks, sweetened diet drinks, or excessive fluids (Cartwright et al. 2007). However, overall it is unclear whether dietary factors are causal for incontinence, or whether any dietary interventions are helpful in the treatment of UI (Imamura et al 2015).
Physical activity is associated with a lower risk of obesity, which has been associated with increased risk of UI in earlier studies (Hunskaar 2008). On the other hand, high intensity physical exercise may be a risk factor for UI, because of increased intra-abdominal pressure generated during high-impact exercises that overloads the pelvic organs (Eliasson et al. 2002, Nygaard et al. 1996, Nygaard et al. 1997, Simeone et al. 2010). The most common subtype reported by athletes is SUI. In a systematic review of eight studies (1714 women included) (Teixeira et al. 2018) the pooled estimate for prevalence of UI among female athletes was 36%, and when assessing studies specifically measuring SUI (six studies included), the prevalence was as high as 44%. When pooling two studies (581 women) that compared female athletes to sedentary women, an increased risk of UI was found among athletes (RR 2.88, 95% CI 1.05-7.30; I2=83%). However, there is a lack of evidence from RCTs to support these findings (Imamura et al. 2015). Elite athletes are highly motivated to continue exercise, despite physical ailments, but for the broader population, UI during physical activity is a moderate barrier to exercise (Nygaard et al 2005).

On the contrary, increasing normal levels of physical activity seems to be beneficial, especially for obese women with UI (Qaseem et al. 2014). In the Nurses’ Health Study (Danforth et al. 2007), the population of US nurses aged 54-79, a higher level of physical activity across 14 years of follow-up had a 15-20% lower risk of developing UI, and specifically SUI (30%). In the same study (Townsend et al 2008), the risk of at least monthly UI decreased with increasing physical activity (RR 0.80, 95% CI 0.72-0.89) among younger women (aged 37-54). After adjustment for BMI, the overall association attenuated, but remained significant (RR 0.89, 95% CI 0.80-0.99), concurring with other findings that the benefit of physical activity is partly explained by its relation to adiposity. In the Nurses’ Health Study, for both SUI and UUI, women with the highest physical activity levels had lower rates of incontinence compared to less active women; RRs were 0.75 (95% CI 0.59-0.96) for SUI and 0.53 (95% CI 0.31-0.90) for UUI (Townsend et al 2008).
MATERIALS AND METHODS

THE FINNISH NATIONAL NOCTURIA AND OVERACTIVE BLADDER (FINNO) STUDY [I-II]

In Studies I-II, we used data from the Finnish National Nocturia and Overactive Bladder (FINNO) Study. The FINNO Study was carried out through postal questionnaires sent to a sample of 6,000 Finns aged 18-79 randomly identified from the Finnish Population Register Centre. Equal numbers of men and women were recruited from the general population. However, this dissertation focuses only on women. Stratification by age was used in subject selection, with oversampling of the younger age groups to achieve a similar number of subjects with nocturia or urinary urgency in all age groups regardless of the prevalence of these symptoms.

In Studies I and II women who were pregnant, in the immediate postpartum period (puerperium defined as six weeks after delivery), or experiencing a urinary tract infection were excluded. Information on pregnancy was based on both data from the Finnish Population Register Centre and the questionnaire. Delivery dates were drawn from the Finnish Population Register Centre, which also provided urbanity data.

Assessment of urinary incontinence

In Studies I and II, the main outcomes were urinary storage symptoms. Information on urinary storage symptoms were collected using the validated Danish Prostatic Symptom Score (DAN-PSS) questionnaire (Schou at al. 1993), with an additional nocturia question from the American Urological Association Symptom Index (AUA-SI) (Barry et al. 1992). Women reporting SUI, urgency and UUI to occur often or always were defined as having the disorder. Frequency was defined as the longest interval between each urination reported as <2 hours and nocturia as ≥2 voids/night (Table 3). Earlier findings support the use of these cut-off points as clinically meaningful (Agarwal et al. 2014, Tikkinen et al. 2010, Vaughan et al. 2011).
Table 3. Questions to assess urinary storage symptoms with response categorization in the Studies I and II.*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Defining question</th>
<th>Response categorization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Frequency</td>
<td>What is the longest interval between each urination, from when you wake up until you go to bed?</td>
<td>&gt; 3 hours or 2-3 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 hours or &lt;1 hour</td>
</tr>
<tr>
<td>Nocturia</td>
<td>How many times do you have to void per night (Schou et al. 1993)?</td>
<td>&lt;2 voids per night</td>
</tr>
<tr>
<td></td>
<td>How many times do you most typically get up to urinate from the time you go to bed at night until you get up in the morning (Barry et al. 1992)?</td>
<td>≥2 voids per night</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>Do you experience leakage of urine when you physically exert yourself (e.g. coughing, sneezing, lifting)?</td>
<td>Never or Rarely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often or Always</td>
</tr>
<tr>
<td>Urgency</td>
<td>Do you experience a sudden compulsion to pass urine?</td>
<td>Never or Rarely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often or Always</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>Is the compulsion to pass urine so strong that urine starts to flow before you reach the toilet?</td>
<td>Never or Rarely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often or Always</td>
</tr>
</tbody>
</table>

*The DAN-PSS has four response options for nocturia (none, 1-2 times, 3-4 times and 5 times or more [per night]) (Schou et al. 1993), whereas the AUA-SI has six (never, 1, 2, 3, 4, and 5 times or more [per night]) (Barry et al. 1992). Subjects who did not respond to the AUA-SI were not included in the analyses due to lack of precise information on the number of nocturnal voids. In case of conflict between the responses to the two questions, the DAN-PSS response nearer to the AUA-SI response was chosen. The DAN-PSS were applied for the past 2 weeks, while the AUA-SI pertained to the past month.

Assessment of potential risk and confounding factors

Questions modified from the National FINRISK Studies conducted by the Finnish National Public Health Institute were used to assess information on self-reported physician-diagnosed conditions, prescribed medications, other treatments, and use of alternative treatments. Medication use was based on self-reported medication lists and classified into 28 groups using the
Materials and methods

Anatomical Therapeutic Chemical classification (WHO Collaborating Centre for Drug Statistics Methodology 2004).

Lifestyle factors, including BMI, smoking, coffee and alcohol consumption and sociodemographic factors (marital status, education, employment) were assessed by a questionnaire, as well as information on menstrual history in past year, MHT, hysterectomy and surgery for SUI. Women were classified as premenopausal, postmenopausal, hysterectomized, or MHT users. Information on urbanity, parity (no information on delivery mode) and postpartum period (six weeks to one year after delivery; based on delivery dates) was derived from the Finnish Population Register Centre. Information on physician-diagnosed conditions, medications, specific symptoms, and lifestyle factors was available for 95%-100% of women. Only the question on alcohol consumption had a relatively low response (76% of women).

Statistical analysis

Subjects were stratified with age, and we used the population structure of Finland for age standardization (Population Register Centre 2004).

In Study I, subjects were classified as never, former or current smokers by questionnaire: “Have you ever smoked?” (yes/no) and “Do you still smoke?” (yes/no). Current smokers were also classified by smoking intensity: “How many cigarettes do you smoke per day?” (scale: 1-10 cigarettes/day, 11-20 cigarettes/day and >20 cigarettes/day). In Study II, individuals with BMI of 25 to 29.9 kg/m² were classified as overweight and those with BMI of 30 kg/m² or more were classified as obese.

Logistic regression models were used for the analyses, with the presence of individual urinary storage symptoms as the outcome. In Study I, analysis for prevalence difference, binomial regression with identity link was used with adjustment for age group and pertinent confounder score. In Study II, we performed secondary (sensitivity) model analyses using 1) forward selection approach and 2) alternative BMI categorization, which gave similar odds ratio estimates in all cases.

Confounder scores (CSs) were used to provide summary information about multiple potential confounders. It was used in the multivariate analysis to control for confounding by adjustment (Arbogast et al. 2008). CSs were calculated based on comorbidity and medication among subjects responding on all symptoms. An age-adjusted odds ratio with confidence intervals was then calculated for each comorbidity and medication. All factors associated with a symptom were used to construct the CS formulas (where OR rf is the odds ratio for a risk factor):

\[
CS = \sum (OR_{rf} - 1)n \quad \text{AND} \quad \text{only if } p < 0.05 \text{ for } OR_{rf}
\]
First, ORs were calculated for each symptom with adjustment for age (Age-adjusted). Secondly, multivariable analyses with adjustment for confounders were performed (Multivariable). Every factor was well reported, except alcohol consumption, which was not significantly associated with either symptom. All factors associated ($p<0.05$) with each symptom in the age-adjusted analyses were entered into the multivariable models as potential confounders. Finally, backward (stepwise) elimination techniques were used in logistic regression analysis to select variables for the final model of each symptom. At each step, the covariate that caused the smallest change in the exposure effect estimate (compared with the full model estimate) upon deletion was removed (Multivariable). The process was stopped when deletion of any of the remaining variables caused a relative change of >10% in the point estimate of the specific symptom (either frequency, nocturia, SUI, urgency or UUI (Appendix 2, Tables S1-S3).

In studies I-II and IV analyses were performed with the SPSS program in Studies I-II and IV (SPSS, Inc., Chicago, IL). Confidence Interval Analysis 2.0.0 software (Trevor Bryant, University of Southampton, UK) was used for calculating age-standardized prevalence rates.

**SYSTEMATIC REVIEW AND META-ANALYSIS [III]**

A search was performed on October 31, 2014, in Medline (1946 to present), Scopus (1995 to present), and CINAHL (1960 to present). We also searched abstracts published from the annual meetings of ICS and IUGA (1999-2014). The searches were conducted without language restrictions and adapted for each electronic database. The details of searches are available in Appendix 3. To Study III, we included any RCT, cross-sectional or cohort study that recorded the delivery mode as well as SUI or UUI outcome beyond 1 year after delivery among primi- and multiparous women and provided an analysis of the association between delivery and urinary outcomes. We included only cross-sectional or cohort studies with an analysis that adjusted/matched for at least one of the following risk factors: age, BMI, or parity. We excluded studies that did not report specifically on either SUI or UUI (e.g. ‘any urinary incontinence’). Reasoning that small studies are likely to be published only if they show anomalous results, we excluded studies with less than 100 participants.

Pairs of reviewers, independently and in duplicate, screened study reports. We recorded the study design, source of funding, sample size, response rate, number of participants, time from delivery, age distribution, questions used to ascertain SUI and UUI, source of these questions, severity assessment, prevalence, and adjusted odds ratios for SUI and UUI between delivery modes.

Delivery modes included cesarean section, SVD and instrumental vaginal delivery (vacuum or forceps). We contacted authors to confirm our data abstraction, and to provide additional data when required. We accepted the
definition of SUI and UUI used in each study, recognizing that there would be heterogeneity in definitions.

In risk of bias assessment, we evaluated each study according to six criteria: sampling and representativeness of the population, assessment of the exposure, assessment of the outcome, presence of the outcome at the start of the study, adjustment for confounding, and missing data. For each criterion, we judged studies to be either high or low risk of bias. Studies with high risk of bias for two or more criteria were classified as high risk of bias overall.

**Data synthesis and analysis**

For our primary analyses, we examined the association between mode of delivery and SUI or UUI. We examined age, parity, risk of bias (low vs high), composition of vaginal delivery group and the case definition of SUI or UUI variables as potential sources of heterogeneity.

To calculate the absolute risk increase of moderate or severe SUI or UUI with vaginal birth, we estimated the absolute risk of SUI or UUI after cesarean section using two large, population-based studies (Lukacz et al. 2006, Gyhagen et al. 2013): 12.2% for moderate or severe SUI, 10.1% for moderate or severe UUI after any cesarean section, and 5.0% for SUI after elective cesarean section. We then used the odds ratio to calculate the absolute risk increase with vaginal delivery (Rochwerg et al. 2014).

When primary papers had missing confidence interval information, (i.e. providing odds ratios and p values but not confidence intervals), we calculated the confidence intervals. We calculated pooled estimates of adjusted estimates using the DerSimonian-Laird random-effects inverse variance method, and the I² statistic (Higgins & Thompson 2002). Meta-analyses were performed using metan (Harris et al. 2008) and metareg in Stata (StataCorp, College Station, TX, USA), and the Harbord test to detect publication bias.

**VAGINAL DELIVERY MODES AND LONG-TERM RISK OF URINARY INCONTINENCE [IV]**

In Study IV we used data from the Nord-Trøndelag Health (HUNT) Study. Every citizen of Nord-Trøndelag County in Norway aged 20 years or older has been invited to participate in a series of questionnaires, interviews, clinical measurements and collection of biological samples (blood and urine). The questionnaires included questions on socioeconomic conditions, health related behaviors, symptoms, illnesses and diseases. The present analyses include data from HUNT2 (over the period 1995-97) and HUNT3 (2006-08). A total of 55 080 women participated either in HUNT2 or HUNT3 or both. Of these, 28 322 women were also included to the Medical Birth Registry of Norway and responded to the surveys.
We excluded women who had ever given birth before 1967, had any cesarean delivery, who had experienced both vacuum and forceps deliveries or were nulliparous, pregnant or in the postpartum year at the time of survey.

Assessment of urinary incontinence
HUNT 2 and HUNT3 surveys collected information about SUI and UUI using the validated questions “Do you leak urine when you cough, sneeze, laugh, or lift something heavy?” and “Do you have involuntary loss of urine in connection with sudden and strong urge to void?” with response options “yes” or “no”. Severity was assessed using the Sandvik Severity Index, with response options “slight”, “moderate”, or “severe” (Sandvik et al. 2000). The Severity Index is created by multiplying the results of questions (“How often do you experience urinary leakage?”, and “How much urine do you lose each time?”). Women reporting SUI and UUI with severity of “moderate” or “severe” were defined as having the condition. We linked these incontinence phenotypes to the Medical Birth Registry of Norway (MBRN) (Medical Birth Registry of Norway 2016), which has registered information on all deliveries in Norway since 1967. If a woman had participated both HUNT2 and HUNT3, we used survey information from HUNT3 to maximize the time from the last delivery to assessment of UI.

Assessment of potential risk and confounding factors
Pre-specified known risk factors were treated as confounders: age, BMI (<25, 25-30; ≥30 kg/m²), parity and years since last delivery. Parity and years since last delivery were obtained from the birth registry.

Statistical analysis
Based on Study III, we hypothesized that increases in both SUI and UUI associated with both forceps and vacuum deliveries would be greater in women younger than 50 vs. those 50 or older and tested the hypothesis with a test of interaction. Because we found significant interactions (p<0.01) consistent with all hypotheses (larger impact with both forceps and vacuum on both SUI and UUI in younger women), we present results separately for women aged less than 50 and 50 or more.

In the analyses, adjusted logistic regression was used separately for SUI and UUI, with presence of the SUI and UUI as the outcome. To calculate the absolute risk increase of SUI with forceps delivery, we estimated the absolute risk of patient important/ bothersome SUI after SVD using the large population-based study (Handa et al 2012): 12.0% for SUI after SVD among women aged <50, and then used the odds ratio to calculate the absolute risk increase with forceps delivery (Rochwerg et al. 2014).

We also performed longitudinal analyses including women who delivered during follow-up (except if surveyed during the first post-partum year or during pregnancy at baseline or follow-up). Although out of all HUNT2
participants, 72% of women also participated in HUNT3, these analyses were underpowered, with no statistically significant effects of delivery mode on SUI or UUI detectable. Summary data of these analyses are available in Appendix 5.

Analyses were performed with the SPSS program in Study IV (SPSS, Inc., Chicago, IL).

ETHICAL CONSIDERATIONS

Our studies comply with the Declaration of Helsinki. In accordance with Finnish regulations on questionnaire surveys, an exemption from ethical review was granted by the ethics committee of the Pirkanmaa Hospital District for the FINNO Study (Studies I-II). In Study III, we registered the protocol (PROSPERO: CRD42013006213). For Study IV, ethical approval was obtained from the Norwegian Regional Ethics Review Board. We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations in Studies I, II and IV (von Elm et al. 2007), and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance (Moher et al. 2009) in Study III.
RESULTS

THE POPULATION BASED FINNO STUDY [I-II]

Of the 3,000 women approached for the study, 2,002 (67.0%) participated; 11 were unavailable and 114 excluded because of pregnancy, puerperium, or urinary tract infection (Figure 2). Of the participants in Study I, 1,790 (94.8%) answered all urinary storage symptom and smoking status questions (Basic analysis population for age-adjusted smoking status analyses). Of the women, 24.1% (95% CI 22.1-26.2) were former and 23.2% (95% CI 21.2-25.1) current smokers. Of the included to participants to Study II, 1,744 (92.4%) of the women completed all questions related to all anthropometric measurements and urinary storage symptoms. Of the women, 14% were obese (BMI ≥30) and 32% were overweight (BMI 25-29.9). For more characteristics, including symptom prevalence estimates for Study I and II, see Table 4 and Figure 3 and 4.

![Flow chart for studies I and II.](image-url)
Table 4. Age distribution, smoking, prevalence of urinary storage symptoms among the 1,790 women included in Study I, and body mass index distribution among the 1,744 women included in Study II.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Crude N (%)</th>
<th>Age-standardized*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>451 (25.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>443 (24.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>393 (22.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>199 (11.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>209 (11.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>95 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status*b, c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>874 (48.8)</td>
<td>52.7</td>
<td>50.4-55.0</td>
</tr>
<tr>
<td>Former</td>
<td>457 (25.5)</td>
<td>24.1</td>
<td>22.1-26.2</td>
</tr>
<tr>
<td>Current</td>
<td>459 (25.6)</td>
<td>23.2</td>
<td>21.2-25.1</td>
</tr>
<tr>
<td>Smoking intensity*d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light smoking (1-10)</td>
<td>191 (42.8)</td>
<td>43.2</td>
<td>35.8-48.2</td>
</tr>
<tr>
<td>Heavy smoking (&gt;10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index*a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (non-overweight)</td>
<td>1025 (58.8)</td>
<td>54.6</td>
<td>51.0-58.3</td>
</tr>
<tr>
<td>25-30 (overweight)</td>
<td>501 (28.7)</td>
<td>31.8</td>
<td>28.8-34.9</td>
</tr>
<tr>
<td>≥30 (obesity)</td>
<td>218 (12.5)</td>
<td>13.5</td>
<td>11.6-15.5</td>
</tr>
<tr>
<td>Urinary storage symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>113 (6.3)</td>
<td>7.1</td>
<td>5.7-8.4</td>
</tr>
<tr>
<td>Nocturia</td>
<td>176 (9.8)</td>
<td>12.6</td>
<td>10.8-14.4</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>171 (9.6)</td>
<td>11.2</td>
<td>9.5-12.8</td>
</tr>
<tr>
<td>Urgency</td>
<td>153 (8.6)</td>
<td>9.7</td>
<td>8.2-11.3</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>41 (2.3)</td>
<td>3.1</td>
<td>2.1-4.1</td>
</tr>
</tbody>
</table>

CI, confidence interval

* Age-standardization was performed using the age structure of Finland (beginning of 2004).
* No differences were found in smoking status or smoking intensity between women responding at different mailing rounds.
* We also assessed snuff consumption. As only one woman (0.1%) reported current and 24 (1.4%) former snuff use, we did not include it in further analyses. Snuff use was not associated with any urinary storage symptom.
* Of the current smokers, 97.5% provided information also for smoking intensity. Two smoking intensity groups (11-20 cigarettes/day and >20 cigarettes/day) were combined as (>10 cigarettes per day; heavy smoking) due very low prevalence of smoking more than 20 cigarettes/day (4.8% of the current smokers).
* 54 female respondents (3.1%) were underweight. There was no difference in the prevalence of any urinary storage symptom among underweight women compared with normal-weight women. Hence, we used nonoverweight (normal-weight and underweight; BMI <25) persons as the reference group.
In the multivariable analyses (never smokers as reference) current smoking was associated with urinary urgency (OR 2.7, 95% CI 1.7-4.2) and frequency (OR 3.0, 95% CI 1.8-5.0) but not with SUI (OR 0.8, 95% CI 0.5-1.3), UUI (OR 1.5, 95% CI 0.6-3.8) or nocturia (OR 1.1, 95% CI 0.7-1.8) (Table 5). Consistent but weaker associations with urgency and frequency were found for former smoking (Table 5). Similarly, in the smoking intensity analyses (light smoking as reference), heavy smoking was associated with urgency (OR 2.1, 95% CI 1.1-3.9) and frequency (OR 2.2, 95% CI 1.2-4.3) but not with SUI, UUI or nocturia (Table 5).

**Smoking and urinary storage symptoms [1]**

Figure 3. Age-standardized prevalence of bladder symptoms among never, former, and current smokers. Error bars represent 95% confidence intervals.

Figure 4. Age-standardized prevalence of bladder symptoms among normal weight, overweight, and obese women. Error bars represent 95% confidence intervals.
Results

Absolute prevalence differences between never and current smokers were 6.0% (3.0%-9.1%) for urgency and 6.0% (3.3%-8.7%) for frequency (adjusted for age group and pertinent confounder score).

Table 5. Smoking status and smoking intensity analyses for urinary storage symptoms in Study I.

<table>
<thead>
<tr>
<th>Smoking status&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Smoking intensity&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking status</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Current smokers</strong></td>
</tr>
<tr>
<td>Former smokers</td>
<td>Current smokers</td>
</tr>
<tr>
<td>Frequency</td>
<td>1.7</td>
</tr>
<tr>
<td>Nocturia</td>
<td>1.0</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>1.4</td>
</tr>
<tr>
<td>Urgency</td>
<td>1.8</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>1.8</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval

<sup>a</sup> Adjusted for identified confounders (frequency: frequency confounder score, coffee consumption, menopausal status, employment and education; nocturia: age, nocturia confounder score, BMI, parity, postpartum period, menopausal status, employment and education; SUI: SUI confounder score, BMI, parity, menopausal status, employment and education; urgency: urgency confounder score, BMI, menopausal status and employment; UUI: age, UUI confounder score, coffee consumption and parity (Appendix 2, Table S1)).

<sup>b</sup> Adjusted for identified confounders (frequency: frequency confounder score and education; nocturia: nocturia confounder score and BMI; SUI: age, SUI confounder score and parity; urgency: urgency confounder score and education; UUI: age, UUI confounder score and BMI (Appendix 2, Table S2)).

Obesity or overweight and urinary storage symptoms [II]

In the age-adjusted analyses both SUI and UUI were associated with being overweight or obese (Table 6). After controlling for confounding factors, obesity was associated with SUI (OR 2.5, 95% CI 1.6-3.9), UUI (OR 3.0, 95% CI 1.2-3.9) and with nocturia (OR 2.37, 95% CI 1.48-3.82). However being overweight or obese was not associated with urinary urgency or frequency.

Table 6. Age-adjusted odds ratios for urinary storage symptoms by BMI status.<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>Non-overweight (BMI &lt;25 kg/m²)</th>
<th>Overweight (BMI 25-29.9 kg/m²)</th>
<th>Obesity (BMI ≥30 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>Nocturia</td>
<td>1.0</td>
<td>1.9</td>
<td>1.3-2.8</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>1.0</td>
<td>1.3</td>
<td>0.8-1.9</td>
</tr>
<tr>
<td>Urgency</td>
<td>1.0</td>
<td>0.9</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>1.0</td>
<td>1.6</td>
<td>0.7-3.8</td>
</tr>
</tbody>
</table>

BMI, body mass index; OR, odds ratio; CI, confidence interval

<sup>a</sup> Adjusted for identified confounders (frequency: age, frequency confounder score, smoking and employment; nocturia: nocturia confounder score and menopausal status; SUI: SUI confounder score, coffee consumption and parity (Appendix 2, Table S1)).
In Study III, our search yielded 3,487 potentially relevant reports of which 16 studies for SUI and 8 studies for UUI proved eligible (Table 7, Figure 5). In these studies, we identified 11 different comparisons between delivery modes assessing risk of SUI and 5 different comparisons assessing risk of UUI. The most common comparison was any vaginal delivery (including studies with SVD only, vaginal delivery only or at least one vaginal delivery) versus cesarean section (15 studies with 45,659 women for SUI, and 8 studies with 49,623 women for UUI) for both SUI and UUI, followed by instrumental delivery versus SVD for SUI (4 studies with 7,417 women) (Figures 5-6 and Figures 8-10).

Table 7 provides a description of the 16 studies. The Authors’ definitions of SUI and UUI are in Appendix 4 Table S4. We identified only two prospective studies (Hannah et al. 2004; Handa et al. 2014). One RCT of planned cesarean vs. planned vaginal delivery (Hannah et al. 2000, Hannah et al. 2002, Hannah et al. 2004) included only women with fetuses presenting in breech position, and we did not include it in our meta-analyses due to low generalizability. The other prospective study (Handa et al. 2014) reported longitudinal changes of pelvic floor disorders for parous women with and without a history of vaginal delivery. We used cross-sectional analyses of these baseline data (Handa et al. 2011, Handa et al. 2012) in our meta-analyses. The longitudinal data collection demonstrated that differences between vaginal and cesarean section diminished over time from delivery.
Results

Figure 5. Flow chart for Study III.
SUI, stress urinary incontinence; UUI, urgency urinary incontinence
Table 7. Characteristics of the 16 eligible studies in systematic review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of analysed participants (n)</th>
<th>Sampling frame</th>
<th>Type of survey</th>
<th>Specific inclusion criteria</th>
<th>Mean age (range)</th>
<th>Follow-up time postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Azab et al. 2007</td>
<td>1652</td>
<td>Living in upper Egypt</td>
<td>In person</td>
<td>Women 20 years and older</td>
<td>Not reported</td>
<td>Unclear</td>
</tr>
<tr>
<td>Fritel et al. 2004</td>
<td>307</td>
<td>2 hospitals in France</td>
<td>Mailed questionnaire</td>
<td>Primiparous women, with singleton, vertex, non-premature birth 1996</td>
<td>33 (21-51)</td>
<td>4 years</td>
</tr>
<tr>
<td>Fritel et al. 2005</td>
<td>2625</td>
<td>Employed by the French national power company</td>
<td>Mailed questionnaire</td>
<td></td>
<td>55 (50-62)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Goldberg et al. 2003</td>
<td>733</td>
<td>Participants of the National Organization of Mothers of Twins Clubs in the US</td>
<td>Given questionnaire</td>
<td>Mothers of multiples</td>
<td>37+ (22-75)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Goldberg et al. 2005</td>
<td>341</td>
<td>Annual gathering of the Twins Days Festival in the US</td>
<td>Given questionnaire</td>
<td>Identical twins</td>
<td>47 (15-85)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Gyhagen et al. 2013</td>
<td>5118</td>
<td>National birth registry in Sweden</td>
<td>Mailed questionnaire</td>
<td>Primiparae women with birth between 1985-88</td>
<td>53 (not reported)</td>
<td>At least 20 years</td>
</tr>
</tbody>
</table>
### Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Location/Setting</th>
<th>Data Collection Method</th>
<th>Target Population</th>
<th>Duration</th>
<th>Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handa et al. 2011/2012³</td>
<td>1011/449</td>
<td>1 hospital in the US</td>
<td>Given questionnaire</td>
<td>Women with first birth (singleton, non-premature) 5-10 years before enrollment</td>
<td>40³ (23-54)</td>
<td>5-10 years</td>
</tr>
<tr>
<td>Handa et al. 2014⁴</td>
<td>1481</td>
<td>1 hospital in the US</td>
<td>Given questionnaire</td>
<td>Women with singleton, non-premature delivery</td>
<td>38⁴ (not reported)</td>
<td>5-12 years</td>
</tr>
<tr>
<td>Kepenekci 2011</td>
<td>4002</td>
<td>6 different family medicine centers in Turkey</td>
<td>Questionnaire administered by trained staff</td>
<td>Women accompanying or supporting a patient⁵</td>
<td>41 (15-86)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Lukaczk et al. 2006</td>
<td>4103</td>
<td>Kaiser Permanente Southern California medical program in the US</td>
<td>Mailed questionnaire</td>
<td>Women from 4 different age groups (25-39, 40-54, 55-69, 70-84)</td>
<td>57 (25-84)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Manonai et al. 2006</td>
<td>1126</td>
<td>Population based study in one province in Thailand</td>
<td>Questionnaire administered by trained staff</td>
<td>39 (15-100)</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Rortveit et al. 2003</td>
<td>15307</td>
<td>Population based study in one county in Norway</td>
<td>Self administered questionnaire</td>
<td>38 (20-64)</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Singh et al. 2013</td>
<td>3000</td>
<td>1 hospital in India</td>
<td>Questionnaire administered by a doctor</td>
<td>Women attending obstetrics/gynecology clinic</td>
<td>40⁶ (unclear)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Song et al. 2003</td>
<td>5392</td>
<td>Population based study in one community in China</td>
<td>Mailed questionnaire</td>
<td>40 (18-87)</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Yang et al. 2004</td>
<td>548</td>
<td>1 hospital in China</td>
<td>Telephone interview</td>
<td>Primiparae women with birth between 2001-2002</td>
<td>29 (not reported)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Zhu et al. 2010</td>
<td>19024</td>
<td>Population based study in six provinces in China</td>
<td>Questionnaire administered by a doctor</td>
<td>45 (20-99)</td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>


a From the same study, two eligible articles (Handa et al. 2011, Handa et al. 2012) using the baseline data and one article (Handa et al. 2014) using the prospective data have been published.
b Median age
c Median age at study enrollment.
d Pregnant women, 6 months postpartum, and women with cognitive disorders or neurological diseases, a history of previous gastrointestinal, anorectal, or gynecological surgery or staying at nursing homes were excluded.
**Results**

**Risk of bias**

Eight studies met the criteria for high risk of bias (Figure 6). Thirteen (81%) studies had little missing data or used self-reported validated questionnaires or another method with demonstrated validity. Twelve studies (75%) adjusted/matched for all most important confounders (age, BMI, parity). No study collected information regarding SUI or UUI before delivery.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sampling/representativeness of population</th>
<th>Assessment of exposure (delivery mode)</th>
<th>SUI/UUI present at the start of the study</th>
<th>Matching: adjusting for confounding</th>
<th>Assessment of outcome</th>
<th>Missing data</th>
<th>Overall risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altman 2007</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>High</td>
</tr>
<tr>
<td>El-Azab 2007</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>High</td>
</tr>
<tr>
<td>Fritel 2004</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>Fritel 2005</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>Goldberg 2003</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>Goldberg 2005</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>Gynagen 2013</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>Kepenekci 2011</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<td>High</td>
</tr>
<tr>
<td>Lukacz 2006</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>High</td>
</tr>
<tr>
<td>Manonai 2006</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>Rortveit 2003</td>
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<td>-</td>
<td>-</td>
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<td>+</td>
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<td>Singh 2013</td>
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<td>-</td>
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<td>-</td>
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<td>Low</td>
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<td>Yang 2004</td>
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<td>-</td>
<td>-</td>
<td>+</td>
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<td>High</td>
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<td>Zhu 2010</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Figure 6. Risk of bias in individual studies in study III.*

**Long-term impact of delivery mode on stress and urgency urinary incontinence**

In the pooled estimates of 15 studies (7 at low and 8 at high risk of bias), the odds of reporting SUI were almost double after any vaginal delivery (spontaneous, or assisted) (adjusted OR 1.85, 95% CI 1.56-2.19, heterogeneity: \(p=0.003, I^2=57\%\), risk difference 8.2%) compared to any cesarean section (Figure 7). When comparing elective cesarean with the decision made before the onset of labour only, two (both high risk of bias) studies (Handa et al. 2011, Lukacz et al. 2006) reported a risk of SUI over three times higher with vaginal delivery (adjusted OR 3.53, 95% CI 2.55-4.90, heterogeneity: \(p=0.84, I^2=0\%\), risk difference 10.7%).
In the pooled estimates of 8 studies (3 at low and 5 at high risk of bias) demonstrated that the risk of UUI was modestly increased after vaginal delivery when compared to cesarean delivery (adjusted OR 1.29, 95% CI 1.02-1.65, heterogeneity: p=0.14, I²=37%, risk difference 2.6%) (Figure 8). No study reported the impact of elective cesarean only vs. vaginal delivery on UUI.

**Figure 7.** Forest plot, risk of stress urinary incontinence between vaginal delivery and cesarean section.

**Figure 8.** Forest plot, risk of urgency urinary incontinence between vaginal delivery and cesarean section.
The pooled analysis of 4 studies (2 at low and 2 at high risk of bias) demonstrated no significant difference in SUI between instrumental delivery, including vacuum and forceps, and SVD (adjusted OR 1.11, 95% CI 0.84-1.45, heterogeneity: p=0.11, I²=50%) (Figure 9). The results were similar when comparing vacuum to SVD (2 studies, both high risk of bias; adjusted OR 1.10, 95% CI 0.80-1.51, heterogeneity: p=0.60, I²=0%) (Handa et al. 2012, Kepenekci et al. 2011) or forceps to SVD (3 studies, 2 low and 1 high risk of bias; adjusted OR 1.16, 95% CI 0.71-1.89, heterogeneity: p=0.06, I²=65%) (Fritel et al. 2005, Goldberg et al. 2005, Handa et al. 2012). One high risk of bias study (Handa et al. 2011) reported a more than four-fold risk of SUI (adjusted OR 4.45, 95% CI 2.14-9.27) in instrumental delivery vs. elective cesarean.

![Figure 9](image.png)

Figure 9. Forest plot, risk of stress urinary incontinence between instrumental delivery and spontaneous vaginal delivery.

**Variability across studies**

In the in univariable meta-regressions addressing the association between vaginal versus cesarean delivery and SUI, we found that the mean sample age at ascertainment of outcome (p=0.005) modified the effect of delivery mode on SUI (older age, smaller effect). Based on the results of the meta-regression, we were able to calculate the estimated OR for the association between delivery mode and SUI, at various levels of mean sample age (Figure 10). Ascertained at age 30, the OR associated with vaginal delivery was 2.51 (95% CI 1.96-3.21); ascertained at age 60, the OR was 1.29 (95% CI 0.97-1.72). In addressing the risk of UUI between vaginal delivery and cesarean, the small number of studies limited the power of the meta-regressions.

We did not identify statistically significant sources of heterogeneity in effect size for these meta-analyses. There was no evidence of publication bias, either on visual inspection of funnel plots (Appendix Figure S1), or when applying the Harbord test.
Of the 55,080 women participating either in HUNT2 or HUNT3, 28,322 women were also included in the Medical Birth Registry of Norway. We excluded women who had ever given birth before 1967, had any cesarean delivery, had both vacuum and forceps deliveries or were nulliparous, pregnant or in the postpartum year at the time of survey. The final analyzable sample was 13,694 women (Figure 11). Moderate to severe SUI and UUI were reported by 1,745 (12.7%) and 1,157 (8.4%) women. Characteristics are summarized in Table 8. In comparison of responders (n=13,694) and non-responders (n=2,834), we found that women who did not answer the UI questions were slightly younger and had lower BMI, but without differences in parity, delivery mode and time since last delivery.

**VAGINAL DELIVERY MODES AND LONG-TERM RISK OF URINARY INCONTINENCE [IV]**

Of the 55,080 women participating either in HUNT2 or HUNT3, 28,322 women were also included in the Medical Birth Registry of Norway. We excluded women who had ever given birth before 1967, had any cesarean delivery, had both vacuum and forceps deliveries or were nulliparous, pregnant or in the postpartum year at the time of survey. The final analyzable sample was 13,694 women (Figure 11). Moderate to severe SUI and UUI were reported by 1,745 (12.7%) and 1,157 (8.4%) women. Characteristics are summarized in Table 8. In comparison of responders (n=13,694) and non-responders (n=2,834), we found that women who did not answer the UI questions were slightly younger and had lower BMI, but without differences in parity, delivery mode and time since last delivery.
Results

Figure 11. Flow chart for Study IV.
Table 8. Age distribution, demographic characteristics, and prevalence of moderate to severe stress and urgency urinary incontinence among the 13 694 included women. *

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SVD (n=12 276)</th>
<th>Vacuum (n=713)</th>
<th>Forceps (n=705)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD / N (%) / N (%)</td>
<td>N (%) / Mean</td>
<td>N (%) / Mean</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>47.2±10.52</td>
<td>43.5±9.90</td>
<td>46.7±10.01</td>
</tr>
<tr>
<td>≥50 years</td>
<td>6896 (56.2)</td>
<td>520 (72.9)</td>
<td>437 (62.0)</td>
</tr>
<tr>
<td>Years since last delivery</td>
<td>5380 (43.8)</td>
<td>193 (27.1)</td>
<td>268 (38.0)</td>
</tr>
<tr>
<td>Parity</td>
<td>18.30±10.58</td>
<td>13.32±9.42</td>
<td>16.47±15.89</td>
</tr>
<tr>
<td>Parity</td>
<td>2.38±0.87</td>
<td>2.23±0.89</td>
<td>2.34±0.87</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;25</td>
<td>5348 (43.6)</td>
<td>298 (41.8)</td>
</tr>
<tr>
<td></td>
<td>25-29.9</td>
<td>4649 (37.9)</td>
<td>262 (36.7)</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>2279 (18.5)</td>
<td>153 (21.5)</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>1553 (12.7)</td>
<td>84 (11.8)</td>
<td>108 (15.3)</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>1026 (8.4)</td>
<td>60 (8.4)</td>
<td>71 (10.1)</td>
</tr>
</tbody>
</table>

SVD, spontaneous vaginal delivery; SD, standard deviation.

*Spontaneous vaginal delivery indicates a history of spontaneous vaginal deliveries only. Vacuum indicates a history of at least one vacuum delivery but no forceps deliveries. Forceps indicates a history of at least one forceps delivery but no vacuum deliveries.

For women aged <50, forceps delivery had a higher risk of SUI (OR 1.42, 95% CI 1.09-1.86) for forceps delivery, but not for vacuum (OR=0.80, 95% CI 0.59-1.09) when compared to SVD (Figure 12). The absolute increase was approximately 5.0% in bothersome SUI when comparing forceps delivery with SVD in women aged <50. When comparing forceps to vacuum delivery, forceps again had a higher risk of SUI in women aged <50 (OR 1.76, 95% CI 1.20-2.60) (Figure 12). When comparing forceps delivery to SVD, forceps delivery had a near significant increased risk of UUI in women aged <50 (OR 1.39, 95% CI 0.98-1.97), but not in women aged 50 or more (Figure 13). In other analyses of UUI, there were no statistically significant differences between different modes of vaginal delivery (Figure 13).
Results

**Figure 12.** Age-stratified, less than 50 years vs. 50 years or more, impact of mode of vaginal delivery on SUI in the multivariate analyses.

**Figure 13.** Age-stratified, less than 50 years vs. 50 years or more, impact of mode of vaginal delivery on UUI in the multivariate analyses.
DISCUSSION

SMOKING AND URINARY STORAGE SYMPTOMS

In our study, smoking was associated with urgency and frequency. There is a lack of studies on this topic. In a Finnish study among elderly people, urgency was associated with current and former smoking when information on both genders was combined (Nuotio et al. 2001). However, the association was not statistically significant in women, probably due to a smaller sample size (n=531; OR 2.5, 95% CI 0.8-8.2). The observed risk for urgency and frequency in smokers could be related to anti-estrogenic hormonal effects (Ouslander 2004, Tanko & Christiansen 2004), nicotine-induced detrusor muscle contraction (Narkiewicz et al 1998), or ischemia-related neurogeneration (Azadzoi et al 2007).

We found no association of nocturia with smoking. Other studies corroborate with our results (Bing et al. 2008, Shiri et al. 2008).

No association was observed between current smoking and SUI in our study or in earlier investigation (Madhu et al. 2015, Parazzini et al. 2000). However, it has been proposed that SUI might be caused by chronic smoker’s cough damaging the urethral sphincter (Bump et al. 1992), and in some studies current smoking has been associated with SUI (Hannestad et al. 2003, Richter et al. 2005).

Smoking was not related to UUI in our analyses. There were trends towards increased UUI among smokers (OR 1.5 for current smoking and 1.7 for heavy smoking), but the findings were not statistically significant. The point estimates could be regarded as borderline clinically meaningful, but because of limited statistical power, we could not exclude the possibility of this association being due to chance. In the baseline analysis of a weight loss trial (Phelan et al. 2009), ever smoking was associated with UUI (OR 1.7, 95% CI 1.2-2.2). In the EPINCONT Study, also including intensity analyses, former or current smoking was not associated with UUI (Hannestad et al. 2003). These results agree with our findings.

In spite of that smoking may cause some urinary symptoms, full adjustment for potential confounders including differences in lifestyle and comorbidities between smokers and nonsmokers is difficult, and these issues require careful scrutiny.

OVERWEIGHT OR OBESITY AND URINARY STORAGE SYMPTOMS

The association of overweight and obesity with SUI has been shown in numerous previous studies (Hunskaar 2008, Wing et al 2010), concurring
with our results of obese women having almost double the odds of SUI compared to non-overweight women. Excess weight may bear down on pelvic tissues, causing chronic strain, stretching and weakening of the muscles, nerves, and other structures of the pelvic floor (Bump et al. 1992, Richter et al. 2008). The scientific basis for these mechanisms is, however, weak. Intervention studies have suggested that weight reduction in women, whether through conservative or surgical methods, can reduce the frequency of SUI and UUI episodes (Burgio et al. 2007, Wing et al. 2010). Weight reduction of 5-10% of initial body weight can improve UI severity and effect QoL in obese women (Auwad et al. 2008, Subak et al. 2005), and weight loss should be first line therapy of UI in the obese woman (Subak et al. 2005).

It has been also suggested that metabolic syndrome associated with obesity predisposes to UUI and overactive bladder (Bunn et al. 2015, Tai et al. 2010, Uzun & Zorba 2012). In our study obese women had triple the odds of UUI. Previous studies have sought to determine the association of BMI with UUI, MUI, or overactive bladder among women (Hunskaar 2008, McGrother et al. 2006, Townsend et al. 2007, Whitcomb et al. 2009). Depending on the specificity of the question used to elicit symptom information, the interpretation of an association between BMI and urgency and/or overactive bladder may be muddled. We measured the association of BMI with the symptoms of urgency and UUI separately, which makes this study a unique addition to the existing literature on this topic. While urgency was associated with obesity in the age-adjusted analyses, the relationship did not persist after adjustment for confounding. Additionally, BMI was associated with UUI, but not with urgency after multivariate logistic regression. These results highlight the importance for assessment of specific symptoms and potential confounding factors.

**DELIVERY MODE AND URINARY INCONTINENCE**

Cesarean rates vary widely between countries. In the most low-income countries, rates are less than 10%, but in middle- and high-income countries, there has been a substantial increase since the 1970s. Between 1990 and 2014, the global average cesarean rate almost tripled from 6.7% to 19.1%. Latin America and the Caribbean region had the highest cesarean rates (40.5%), followed by Northern America (32.3%), Oceania (31.1%), Europe (25%), Asia (19.2%) and Africa (7.3%) (Betrán et al. 2016, WHO 2018). In Finland, the cesarean section rate has risen only 2% during the last three decades, and between 2007 and 2017, delivery rates have been somewhat constant at 17% for cesarean section. The increasing use of cesarean section has substantial negative health consequences for both mother and child including peripartum infection, bleeding and thromboembolism, with more respiratory problems in newborn babies, and with more autoimmune and obesity related problems in
offspring (Visser 2015, Blustein & Liu 2015). Any positive consequences from the increased use of cesarean have not been quantified.

Cesarean delivery, particularly prelabor cesarean, is believed to offer substantial protection against such pelvic floor trauma. While previous systematic reviews have demonstrated an increased risk of early postpartum incontinence after vaginal delivery compared to cesarean section (Press et al. 2007, Thom & Rortveit 2010), no-one has previously conducted a rigorous review of long-term effects. One earlier systematic review focused entirely on the short-term postpartum period and included only studies with follow-up less than a year (Thom & Rortveit 2010), whereas the other one (Press et al. 2007) included two appropriately adjusted cross-sectional studies of incontinence beyond the first postpartum year (Fritel et al. 2004, Rortveit et al. 2003). In contrast, our own search found 16 studies that could be included in meta-analyses. These much larger pooled analyses have provided more precise estimates of the impact of vaginal delivery compared to cesarean section on SUI (Waltregny 2016).

In our systematic search, we found only one RCT (Hannah et al. 2000, Hannah et al. 2004, Hannah et al. 2002), counting only breech presentations. At two years postpartum, there was no difference in SUI rates between the planned vaginal delivery or the planned cesarean group. However, there was a significant cross-over between the groups: for women randomized to the planned cesarean section group, 941 (90.4%) delivered by cesarean section, but for those randomized to the planned vaginal delivery group, only 591 (56.7%) were delivered vaginally. One new RCT (Hutton et al. 2018) has been published after our systematic review. In this RCT (only twin pregnancies) women in the planned cesarean group had lower problematic SUI rates compared with women in the planned vaginal birth group (8.11% vs 12.25%, OR 0.63, 95% CI 0.47-0.83), consistent with our systematic review results. There was also a significant cross-over between the groups: of the 1150 women randomized to the planned cesarean section group, 1035 (89.6%) had a cesarean section for the birth of both infants, 7 (0.6%) had a combined vaginal birth/cesarean birth and 113 (9.8%) delivered both twins vaginally. For those randomized to the planned vaginal delivery group, only 700 (60.8%) delivered both twins vaginally or had a combined vaginal birth/cesarean section. A strength of this study was the exclusion of women reporting incontinence before delivery, something that has rarely been possible in earlier studies.

One longitudinal study (Handa et al. 2014) has addressed the same question of interest. In this study, symptoms related to SUI and UUI were more common and of greater severity after vaginal than cesarean birth. Consistent with results in our meta-regression of age on effect size, SUI symptom differences between these two groups decreased with increasing time from childbirth. The potential impact of delivery mode on UUI has received little consideration compared to the impact of delivery mode on SUI (Nygaard 2010). The only available prior review found no statistically
significant difference between vaginal delivery and cesarean section (Press et al. 2007).

There remains wide practice variation in both the overall rates of operative vaginal delivery and choice of method (O’Mahony et al. 2010). Forceps are less likely than vacuum to fail to achieve a vaginal birth (O’Mahony et al. 2010). However, with forceps, facial injury is more likely (O’Mahony et al. 2010), and forceps delivery is associated with an increased prevalence of pelvic organ prolapse, whereas vacuum delivery is not (Handa et al. 2012, O’Mahony et al. 2010). In low- and middle-income countries, less than 1% of institutional deliveries are operative deliveries, with vacuum preferred over forceps (Bailey et al. 2017). In the US between 2005 and 2013, approximately 5% of deliveries were vacuum and 1% forceps deliveries (Merriam et al. 2017). In Norway in 2016, approximately 9% of deliveries were vacuum and 1.6% forceps (Delivery mode data Norway 2016). In Finland, 9% for of all deliveries are vacuum deliveries, and forceps are used in less than 0.1% (THL 2018).

There are no RCTs comparing the risk of SUI or UUI between SVD, vacuum and forceps deliveries, or observational studies comparing the risk of SUI or UUI between vacuum and forceps deliveries. In the Norwegian EPINCONT study (Rortveit et al. 2003) also using HUNT2 data, results were given for any incontinence, whereas our study defines cases based on moderate or severe cases and distinguishes SUI and UUI. The former study also compared vacuum deliveries to all other vaginal deliveries, that is, a combination of spontaneous vaginal deliveries and forceps deliveries, and compared forceps deliveries to a combination of spontaneous vaginal deliveries and vacuum deliveries. This means that both control and comparison groups included one form of instrumental delivery; this was especially relevant as 46% of the instrumental deliveries were vacuum and 54% forceps.

In Study III meta-analysis, no difference was found in the long-term prevalence of SUI between vacuum delivery and SVD, concurring with study IV results. No difference was found either in the risk of SUI between forceps and SVD, and this pooled analysis is inconsistent with our study (IV). However, in Study IV, we included substantially more participants than there were in these three earlier studies combined (Fritel et al. 2005, Goldberg et al. 2005, Handa et al. 2012). Furthermore, there are methodological concerns regarding earlier work, including reliance on maternal recall of obstetric exposures (Fritel et al. 2005, Goldberg et al. 2005), which is known to be unreliable for classification of forceps and vacuum (Quigley et al. 2007). In a cohort study (Handa et al. 2011, Handa et al. 2012) the prevalences of bothersome SUI were similar to our study after vacuum, forceps and SVD, but there was no significant difference between forceps delivery and SVD due to small sample size (OR 1.65, 95% CI 0.88-3.08).

Prevalence of both SUI and UUI increase with age; prevalence of SUI increases especially from younger age until the 50s (Ge et al. 2015, Herschorn et al. 2008, Jahanlu & Hunskaar 2010, Ojengbede et al. 2011, Waetjen et al. 2009). Many UI risk factors are also associated with age (Grodstein et al. 2005).
The likely explanation for the association with delivery mode decreasing over time is that, as women get older, although there is still probably an underlying association with mode of delivery, it is more difficult to detect because of competing causes of incontinence. Other studies concur with decrease in the magnitude of association of parity and UI (Buchsbaum et al. 2005, Grodstein et al. 2003, Rortveit et al. 2001, Tennstedt et al. 2008).

**STRENGTHS AND LIMITATIONS**

**The population based FINNO Study**

The FINNO Study’s strengths include a study population well representative of the source population, symptom assessment with validated instruments, a high response proportion and an excellent completeness of questionnaires, likewise systematic control for confounding with a large number of relevant factors. Furthermore, our data were unaffected by the selection bias typical of clinic-based studies due to treatment seeking (overrepresentation of severe symptoms and subjects with abundant health care service use).

The FINNO study has some limitations. No information on pack years of smoking was available to us. If the impact of smoking on urinary storage symptoms is cumulative, this may have caused misclassification bias attenuating any true effect. However, the effect of smoking on these symptoms may also be transient (e.g. caused by nicotine-induced bladder contractility), which is plausible given that we found the effect of smoking status and intensity. BMI was based on self-report of height and weight, and may underestimate the measured BMI, potentially biasing the results towards unity. Additional anthropometric and adiposity measures, such as waist circumference, may be important in assessing the relationship of body fat distribution to LUTS, but no other measures were available for this analysis.

Despite extensive adjustment for potential confounders, we were unable to adjust for delivery mode. This may not be a major limitation: in Studies III and IV, we showed that vaginal birth has an impact on SUI in the first two decades after childbirth, but not thereafter. The greater the passage of time after the delivery of children, the lower the impact of childbirth on the development of SUI. Regarding other urinary storage symptoms than SUI, there is a paucity of studies on the impact of delivery mode. Although the response proportion was high, nearly a third did not participate, and the number of women with UUI was insufficient for precise analyses. Finally, these results from the Finnish population of women may not be generalizable to all other groups.

**Systematic review and meta-analysis**

The strengths of Study III include the comprehensive search without language restrictions, the duplicate assessment of eligibility and data abstraction, and
Discussion

the appraisal of risk of bias. We explored possible sources of heterogeneity, demonstrating that apparent effects of SVD versus cesarean section on SUI decreased with increasing age of assessment of SUI. We have also separately quantified the larger benefit associated with elective pre-labour cesarean, compared to any cesarean section (either before or during labour). Finally, we not only estimated relative effects but also provided absolute estimates.

The limitations of our review are largely the weaknesses of the eligible studies. Although there were numerous comparisons between delivery modes assessing risk of SUI and UUI, it was frequently impossible to quantitatively compare data. In particular, most primary studies combined all cesarean sections, irrespective of timing. We were able to conduct analyses specifically for pre-labour cesarean compared to vaginal delivery, but we were not able to compare pre-labour cesarean with cesarean after cervical dilatation, nor were we able to compare elective cesarean with planned vaginal delivery (i.e. including both vaginal deliveries and cesarean after cervical dilatation). Furthermore, the effect estimates in the analysis comparing instrumental delivery and cesarean section, and elective cesarean and vaginal delivery were imprecise due to the lack of statistical power. In addition, 11 studies had unknown follow-up time (Goldberg et al. 2005, Lukacz et al. 2006, El-Azab et al. 2007, Fritel et al. 2005, Goldberg et al. 2003, Kepenekci et al. 2011, Manonai et al. 2006, Singh et al. 2013, Song et al. 2003, Yang et al. 2004, Zhu et al. 2010). However, median of mean/median ages of the women included in these studies was above 40 years, implying that these studies also examined long-term the impact of delivery mode on SUI and UUI.

Vaginal delivery modes and long-term risk of urinary incontinence

The strengths of Study IV include a study population representative of the Norwegian general population in income, age distribution, morbidity and mortality (Holmen et al. 2003), assessment of UI symptoms with validated instruments, adjustment for major established risk factors of SUI and UUI and linking of incontinence data to the Medical Birth Registry of Norway. Furthermore, our material was unaffected by the selection bias typical of clinic-based studies as a result of treatment seeking. Finally, we not only estimated relative effects but also provided absolute estimates that are typically more useful for clinical decision making.

Study IV has some limitations. Although this is the largest available study of the impact of different types of operative delivery on UI subtypes, we did not have enough statistical power for longitudinal analyses. Women in this study were also predominantly of European heritage, and results should be interpreted with caution for other ethnic groups. We did not know how many of the women were incontinent before delivery. There may be confounding between the nature of the delivery and the choice of delivery method: clinicians may have chosen forceps for more obstructed labours, with greater cephalopelvic disproportion, or may be used if vacuum was already attempted but failed to achieve delivery. Given the long time period over which eligible
women for these analyses might have delivered (1967-2008), it can be questioned whether these results are generalizable to current obstetric practice. Certainly in Norway during these decades, there were measurable shifts in practice, with more cesareans, more vacuum deliveries, and a rise and then fall in forceps deliveries (Delivery mode data Norway 2016). It is unclear if the changes in frequency of use of the procedures are associated with different impacts on incontinence, however, we adjusted both for maternal age and years since last delivery in multivariate analyses, which should have helped to control for differences due to changes in proportions of each kind of delivery over time. In common with almost all surveys of UI, the response rate for UI items was less than for questions about less stigmatizing conditions. Approximately 17% of potentially eligible women did not answer the incontinence questions. We found that non-responders were slightly younger and thinner than responders, but found no differences in other characteristics. How this non-response might have impacted on estimates of association between mode of delivery and UI remains uncertain.

**IMPLICATION OF FINDINGS**

Our Studies I and II add to the body of evidence regarding the negative outcomes associated with smoking and increased body weight and may offer care providers an additional rationale for counseling women with urgency and frequency to quit smoking or lose weight.

Increasing the use of cesarean section may potentially have substantial benefits for pelvic floor health, including decreased need for SUI and pelvic organ prolapse surgery (Leijonhufvud et al. 2011, Volløyhaug et al.2015). However, post-partum pelvic floor dysfunction is only one of many important maternal outcomes that differ between cesarean and vaginal delivery, and so this information will not form the sole basis for a decision for delivery mode. Planned cesarean section confers an increased risk of neonatal intensive care admission for the baby, and a substantially longer hospital stay for the mother (NICE Guidelines 2012). A prior cesarean also carries risks in future pregnancies, including an increased risk of uterine rupture, and abnormal placentation (NICE Guidelines 2012). In general, the medicalization of pregnancy associated with planned cesarean may also be undesirable from both individual and societal perspectives (Johanson et al. 2002).

For decision-making between forceps and vacuum, we need accurate, unbiased estimates about their immediate and long-term consequences. Study IV provided an additional rationale for vacuum over forceps, at least when considering long-term incontinence.
Conclusions

CONCLUSIONS

I. Smoking status and intensity are independently associated with urinary urgency and frequency even after controlling for important confounders, whereas nocturia, stress urinary incontinence and urgency urinary incontinence are not.

II. Obese women have twice the risk of nocturia and stress urinary incontinence and tripled the risk of urgency urinary incontinence compared to normal weight individuals. However, being overweight or obese was not associated with urinary urgency after careful adjustment for confounders.

III. In vaginal delivery versus cesarean section, there is an almost two-fold increase in the risk of developing long-term stress urinary incontinence, with an absolute increase of approximately 8%, and a gradient that is larger in younger and smaller in older women, and a small increased risk of urgency urinary incontinence, with an absolute increase of approximately 3%.

IV. Forceps delivery, but not vacuum, is associated with significant increased long-term risk of stress urinary incontinence when compared to spontaneous vaginal delivery, with an absolute increase of 5%. The impact is age dependent: the risk of stress urinary incontinence for forceps delivery is increased among women aged <50, but there is no longer a measurable impact for women aged 50 or more.
REFERENCES


References


Chung DJ, Bai SW. Roles of sex steroid receptors and cell cycle regulation in pathogenesis of pelvic organ prolapse. Curr Opin Obstet Gynecol 2006;18:551-4.


Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study, BJU Int 2009;104:352-60.


References


References


Leatherdale ST, Laxer RE. Reliability and validity of the weight status and dietary intake measures in the COMPASS questionnaire: are the self-reported measures of body mass index (BMI) and Canada's food guide servings robust? Int J Behav Nutr Phys Act. 2013;10:42.


PROSPERO International prospective register of systematic reviews. National Institute for Health Research (NHS). Available at https://www.crd.york.ac.uk/prospero/.


Visser GHA. Women are designed to deliver vaginally and not by caesarean section: an obstetrician’s view. Neonatology 2015; 107: 8-13.


Wood LN, Anger JT. Urinary incontinence in women. BMJ. 2014;349:g4531.


