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STUDIES ON RISK FACTORS FOR URINARY INCONTINENCE IN SWEDISH FEMALE TWINS

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ABSTRACT

Approximately half of all women in industrialized countries will experience urinary incontinence during their lifetime. Even though urinary incontinence is not a life threatening disease, it often has severe implications for daily function, social interactions, sexuality and psychological well-being. Moreover, urinary incontinence has a major impact on health economy and is increasingly recognized as a global health burden. Hence, identifying risk factors for urinary incontinence is of importance for individual women at risk, as well as for society's health care costs.

In the first study, the association between coffee and tea intake and urinary incontinence was evaluated. Women with a high coffee intake were at lower risk of overall incontinence, while no effect was observed between coffee intake and other urinary incontinence subtypes. A higher risk of nocturia and overactive bladder was found among women with a high tea intake. However, results from co-twin control analysis showed that these associations were likely confounded by familial factors.

In the second study, the effect of gestational diabetes mellitus on overactive bladder was investigated. Women with gestational diabetes mellitus had an almost two times higher odds of overactive bladder compared to women without gestational diabetes. The effect of gestational diabetes mellitus on overactive bladder was not mediated by body mass index or diabetes later in life.

In the third study, the association between depressive mood disorders (depressive symptoms and major depression) and neuroticism with urinary incontinence was investigated. In logistic regression analysis depressive mood disorders and neuroticism were positively associated with urinary incontinence. Results from quantitative genetic analysis showed that the association between depressive mood disorders, neuroticism and urinary incontinence was partly determined by genetic factors in common to the disorders.

In the fourth study, the effect of birth weight and being born small for gestational age on urinary incontinence later in life was evaluated. Results showed that birth weight and being born small for gestational age had no effect on urinary incontinence. However, women who had a low birth weight and then became overweight had a borderline statistically significant higher odds of overall and stress incontinence compared to overweight women who had a normal birth weight. This finding suggests that low birth weight in combination with elevated adult body mass index may contribute to the risk of urinary incontinence later in life.

LIST OF PUBLICATIONS

This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals:

I. **Tettamanti G**, Altman D, Pedersen NL, Bellocco R, Milsom I, Iliadou AN.
Effects of coffee and tea consumption on urinary incontinence in female twins.
BJOG. 2011 Jun;118(7):806-13.

II. **Tettamanti G**, Iliadou AN, Pedersen NL, Bellocco R, Altman D.
Association between a history of gestational diabetes mellitus and subsequent overactive bladder among premenopausal female twins.
BJOG. 2013 Sep;120(10):1289-95

III. **Tettamanti G,** Altman D, Iliadou AN, Bellocco R, Pedersen NL.
Depression, neuroticism and urinary incontinence in premenopausal women: a nationwide twin study.
Twin Res Hum Genet. 2013 Aug 28:1-8. [Epub ahead of print]

IV. **Tettamanti G**, Iliadou AN, Pedersen NL, Bellocco R, Altman D.
Does urinary incontinence have fetal origins? Results from a nationwide twin study.
Submitted manuscript

RELATED PUBLICATIONS

Tettamanti G, Altman D, Pedersen NL, Bellocco R, Milsom I, Iliadou AN.
Influence of smoking, coffee, and tea consumption on bladder pain syndrome in female twins.
Urology. 2011 Jun;77(6):1313-7.

CONTENTS

LIST OF ABBREVIATIONS

A	Additive genetic component
C	Shared environmental component
CI	Confidence interval
D	Dominant genetic component
DM	Diabetes mellitus
DZ	Dizygotic
E	Unique environmental component
GDM	Gestational diabetes mellitus
IUGR	Intrauterine growth restriction
LUTS	Lower urinary tract symptoms
MBR	Medical Birth Register
MZ	Monozygotic
OAB	Overactive bladder
OR	Odds ratio
SGA	Small for gestational age
STAGE	The Study of Twin Adults: Genes and Environment
STR	Swedish Twin Registry
UI	Urinary incontinence
UTI	Urinary tract infection

1 INTRODUCTION

The prevalence of urinary incontinence in women is relatively low early in life, has a peak around the time of menopause, and then rises steadily between the ages of 60 to 80 years.[1] Epidemiological studies suggest that urinary incontinence has an overall prevalence of 25-45% in adult women.[2]

Even though urinary incontinence is not a life threatening disease, it often has severe implications on daily function, social interactions, sexuality and psychological well-being. Moreover, urinary incontinence has a major impact on health economy and is increasingly recognized as a global health concern.[3] For example, it has been estimated that the cost for the society associated with urinary incontinence in the USA for year 2000 was close to 20 billion dollars.[4] Hence, identifying risk factors for urinary incontinence is of importance for women at risk, as well as for society's health care costs.

Recent data from twin studies suggest that familial factors such as common genes and shared environment may influence the occurrence of urinary incontinence.[5-8] It is therefore of importance to also investigate whether common genes and shared environmental factors are confounding the association with potential risk factors. For this purpose, twin data can be used to disentangle genetic from environmental effects and provide important clues to the etiology of female urinary incontinence.

This thesis builds on four studies (Study I-IV), all based on the Study of Twin Adults: Genes and Environment (STAGE),[9] a web-based survey performed in 2005 among all Swedish twins born between 1959 and 1985 that contained questions regarding common complex diseases and common exposures. The aim of these four studies was to evaluate the effect of potential risk factors for urinary incontinence and other lower urinary tract symptoms, such as nocturia and overactive bladder, using data from a cohort of premenopausal female twins.

2 BACKGROUND

2.1 CONTINENCE IN WOMEN

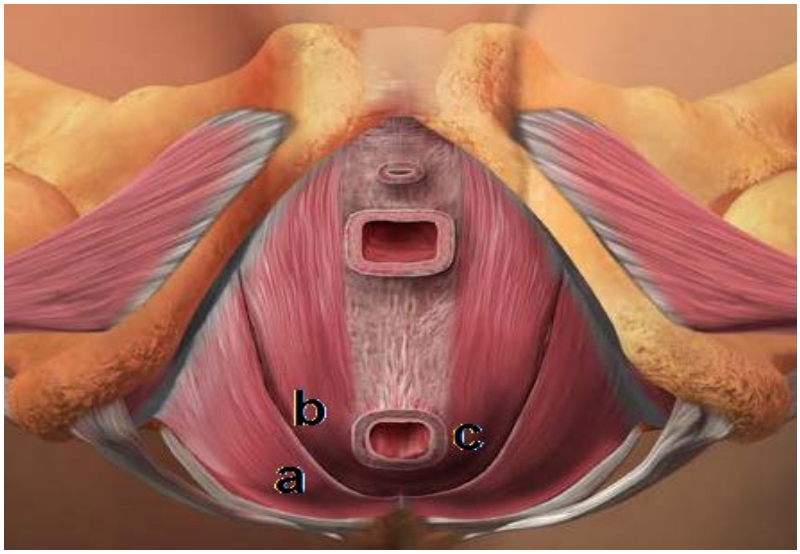
Continence in women is obtained through a complex coordination between the bladder, urethra, pelvic muscles, and surrounding connective tissues. The bladder is an elastic muscular organ located on the anterior surface of the uterus responsible for the storage and collection of urine excreted by the kidneys before disposal through urination. The middle layer of the bladder wall consists of smooth musculature, forming the detrusor muscle, whereas the inner and outer muscle layers consist of striated muscle fibers. Maximum bladder capacity is typically in the range of 500–600 mL, however, the bladder is capable of increasing the urinary volume without increasing bladder pressure. In infants, bladder fullness produces a contraction of the detrusor muscle that empties the bladder. In response to bladder training, we learn to control the sensation of urge when the bladder volume is approximately 200–300 mL and then decide whether the time and place for voiding is appropriate.

The female urethra is an approximately 3.5 cm long and 6 mm wide fibro muscular tube that connects the bladder reservoir to the body surface. The main role of the urethra is to maintain a sufficient pressure in order to prevent an involuntary loss of urine in situations in which the pressure may increase, such as sneezing, coughing or physical activity. The urethra is surrounded by both skeletal and smooth muscles that contribute to resting tone, but only skeletal muscle responds when the abdominal pressure increases.[10]

The muscles of the pelvic floor, particularly the levator ani muscles, have a critical role in supporting the pelvic visceral organs and play a major role in urinary, defecatory, and sexual function. The levator ani muscle has a three-dimensional structure in which its anterior portion (pubococcygeus and puborectalis) is oriented vertically as a sling around the mid-urethra, vagina, and anorectum (Figure 1). Instead the posterior portion of the levaror ani, the iliococcygeus, has a horizontal upwardly biconvex shape. While the posterior portion of the levator ani serves as a supportive diaphragm, the anterior portion serves to close the urogenital hiatus and pull the urethra, vagina, perineum, and anorectum toward the pubic bone. This upwards movement of the levator ani creates a backstop for the whole urinary tract that compresses the two walls of the urethra and prevents an involuntary loss of urine when the abdominal pressure rises.[10]

When voiding begins, the urethra relaxes in order to allow the urine to pass through and then the spinal reflex pathways are activated.[11] An increase in parasympathetic transmissions to the bladder causes a contraction of the detrusor muscle. These same pathways inhibit sympathetic and pudendal outflow to the urethra, maintaining also the urethra relaxed. Detrusor contraction increases the intravesical pressure sufficiently to empty the bladder.

Figure 1. The levator ani muscles of the female pelvic floor.



a) Ileocyccygeus
b) Pubococcygeus
c) Puborectalis

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Many aspects of the continence mechanism are not fully understood. These include the relation between anatomical support and function and the ability of the continence mechanism to adapt and repair after childbirth, pelvic surgery or neurological injury.

2.2 URINARY INCONTINENCE

Urinary incontinence indicates an involuntary loss of urine and is generally more common among women rather than in men. Women of all ages may be affected by urinary incontinence and its prevalence usually increases with age; moreover urinary incontinence is characterized by a wide range of severity and nature of symptoms. The prevalence of urinary incontinence depends also by the definition in use: while some studies used daily incontinence to define women affected by urinary incontinence, others used a weekly, monthly, or even a yearly occurrence to define incontinence.

2.2.1 Urinary incontinence subtypes

Urinary incontinence is usually classified as stress, urge, and mixed urinary incontinence. Stress incontinence involves the involuntary loss of urine that occurs during physical activity or suddenly increased abdominal pressure, for example coughing, sneezing, laughing, or physical exercise. The main identified disorders related to stress incontinence are impaired mid-urethral support and intrinsic sphincter deficiency.[12] This means that stress urinary incontinence may occur if the urethral sphincter does not work properly or if the pelvic floor muscles, that support the urethra and the bladder, are weakened. When this happens, the sphincter is not able to maintain urine inside the bladder when the abdominal pressure suddenly increases causing a leakage of urine.

Another urinary incontinence subtype is urge incontinence, which is a loss of urine that is accompanied by a sudden need to urinate. The pathophysiology of urge incontinence

is less clear than the pathophysiology of stress urinary incontinence. Urge incontinence usually is caused by the bladder that contracts too often because of some neurological problems or bladder irritation: it seems to be connected with poor transmission or processing of information between the bladder and the nervous system.[13]

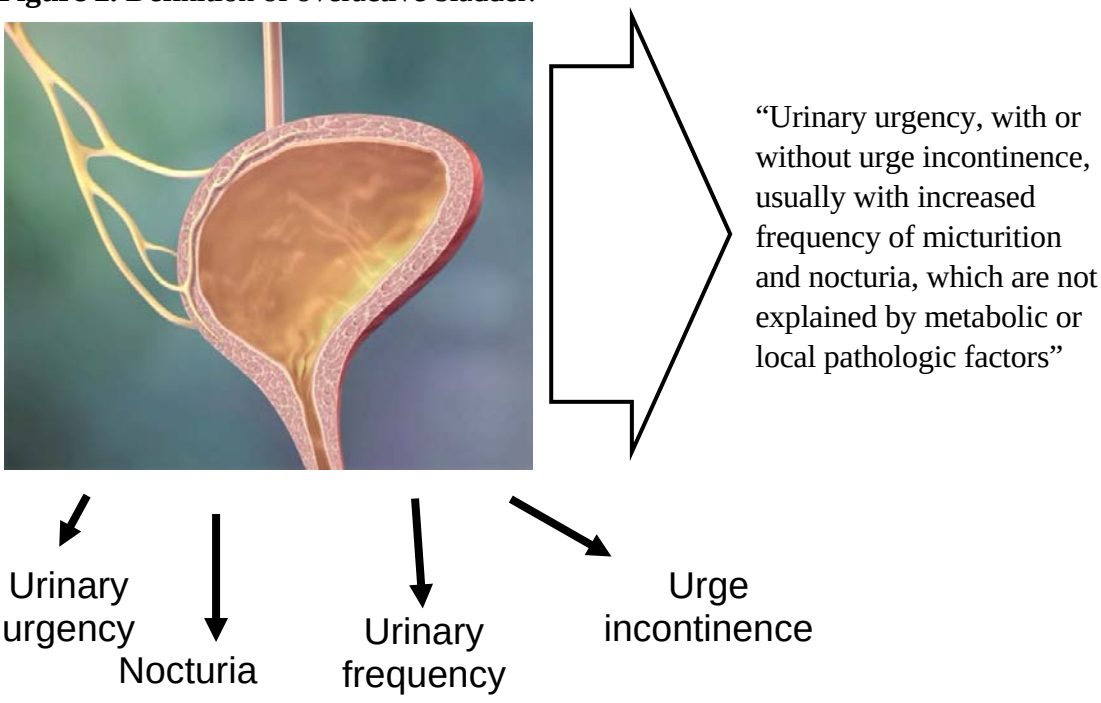
Women affected by both stress and urge urinary incontinence are defined as having mixed urinary incontinence, while women with either stress or urge urinary incontinence are defined as having overall urinary incontinence.

The prevalence of urinary incontinence is relatively low early in life, has a peak around the time of menopause, and then rises steadily between the ages of 60 to 80 years.[1] Overall, approximately half of all women with incontinence are defined as having stress urinary incontinence. A smaller proportion of women are affected by urge and mixed urinary incontinence. A previous study performed among women of all ages have shown that stress incontinence reaches its peak for the 40-49 year old age group and then decreases, while mixed urinary incontinence increases regularly with age.[14]

2.2.2 Overactive bladder

Overactive bladder is a symptom based disorder, which has been defined as 'urinary urgency, with or without urgency incontinence, usually with frequency and nocturia' by the International Continence Society (ICS).[15] Overactive bladder causes a sudden need to urinate which is hard to control, and may result in the subsequent involuntary loss of urine. However, women might be affected by overactive bladder even if they do not experience an involuntary loss of urine since the complex symptom of overactive bladder is characterized by other symptoms such as frequency (i.e. women urinate more frequently) and nocturia, which is the complaint that women have to wake up several times at night to urinate.

Figure 2. Definition of overactive bladder.



Another prerequisite for the conditions of overactive bladder to be fulfilled is that symptoms are not explained by metabolic or local pathologic factors such as urinary tract infections, bladder tumors, or bladder stones which may give rise to symptoms that mimic overactive bladder.

Overactive bladder is a common condition. A study performed among community-dwelling adults living in five industrialized countries (Canada, Germany, Italy, Sweden, and the United Kingdom), reported that the overall prevalence of overactive bladder was approximately 12 percent.[16] Moreover, it has been estimated that 33 million people in the US are affected by overactive bladder.[17]

2.2.3 Effect of urinary incontinence on women and cost for the society

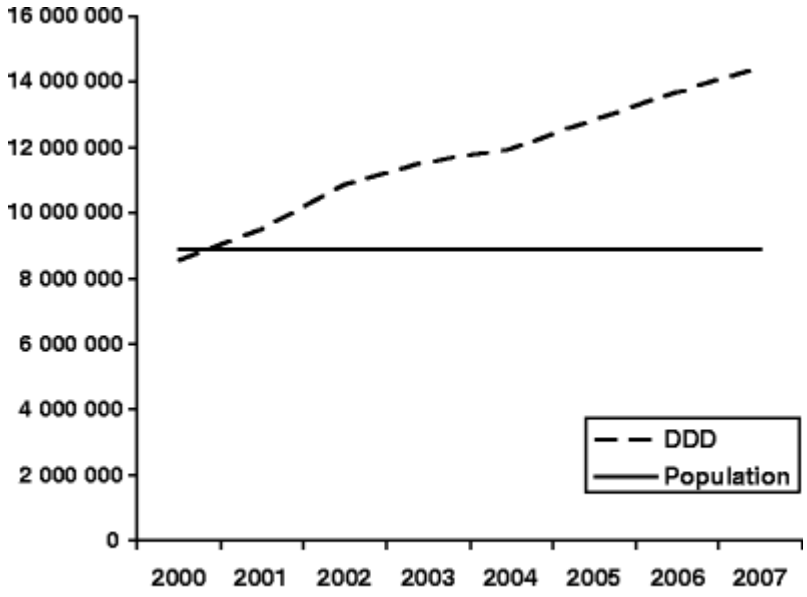
Lower urinary tract symptoms (LUTS) such as urinary incontinence and overactive bladder might have a tremendous impact on quality of life. Previous studies reported that the occurrence of urinary incontinence is negatively associated with quality of life.[18 19] It has been shown that the negative impact of overactive bladder on quality of life is greater than diabetes.[3] The presence of urinary incontinence or overactive bladder might generate feelings of sadness, anger, and embarrassment. Moreover, women with incontinence may lose self-confidence, avoid physical exercise and social gatherings. This could in turn affect sexual life, social interactions, emotional health, and quality of sleep.[20-22]

Even though urinary incontinence and overactive bladder are common conditions, many women with incontinence never report their symptoms to their general practitioners. Several studies have reported that the proportion of women affected by incontinence who have sought treatment in the past 12 months ranged between 12%-53%.[2] Women with urge or mixed incontinence are more likely to seek treatment: in fact an overactive bladder is more difficult to control since it will more likely interrupt sleep or other daily activity. Women with severe or daily incontinence are also more likely to seek treatment. However even among women with severe incontinence seeking treatment can be relatively low: a study performed among women with daily UI found that only half of them had ever reported their symptoms to their healthcare providers.[23] Women do not seek treatment for urinary incontinence mainly because of embarrassment. Other reasons for not seeking treatment are: the idea that incontinence is not a disease but only a normal part of ageing, low expectations of treatment, and thinking that they should cope on their own.[2]

Another important aspect of lower urinary tract symptoms, such as urinary incontinence and overactive bladder, is the cost for the society. It has been estimated that in the US the cost for the health care system associated with urinary incontinence and overactive bladder for year 2000 was respectively $ 19.5 billion and $ 12.6 billion.[4] Even if overactive bladder is more common than strict urinary incontinence, the lower costs associated with this condition are mainly determined by the fact that individuals affected by overactive bladder, but without incontinence, incurred in lower costs compared to individuals with incontinence. Already in 1999 Statens beredning för

utredning av hälso-och sjukvården (SBU) estimated that the nationwide annual costs for the direct care of stress urinary incontinence in Sweden exceeded 5 billion SEK. Moreover, from 2000 to 2007 in Sweden there was a 68.8% increase in dispensed anticholinergic drugs, a medication used to treat overactive bladder symptoms, while the Swedish population increased only by 3.4% (Figure 2) In 2007 the annual direct cost for anticholinergic drugs in Sweden was 22 million €.[24] Given the ageing of the population and the fact that urinary incontinence is very common among the elderly, it is expected that the costs associated with urinary incontinence and overactive bladder will further increase in the future.

Figure 3. Prescription of anticholinergic drugs per annum in relation to the total population



DDD= Defined Daily Dose.

2.3 ESTABLISHED RISK FACTORS FOR URINARY INCONTINENCE

2.3.1 Age

Almost every epidemiological study reports a positive association between urinary incontinence and age. The prevalence of urinary incontinence increases with age until middle age, remains stable until the age of 70, and then rapidly increases among the elderly.[2] Women may remain continent as long as they are able to compensate the effects of ageing, such as lower intrinsic lower pressure, by using other components of the continence mechanism. However with ageing, women might lose pelvic floor muscle strength and connective tissue resilience and become incontinent. Another explanation is that with ageing, women are more likely to be affected by medical problems or conditions associated with urinary incontinence, such as diabetes mellitus, cognitive impairment, connective tissue disorders and physical disability.[2]

2.3.2 Childbirth, pregnancy, and parity

Many studies have reported a positive association between parity and urinary incontinence later in life.[2] While some studies have reported that after the first delivery there is a little or no additional effect of subsequent deliveries,[26 27] others have shown that with increasing parity the risk of incontinence increases as well.[27 28] The association between parity and urinary incontinence relates primarily to stress and mixed urinary incontinence while several studies have found that in the long term there is no association between parity and urge urinary incontinence.[28-30] During pregnancy most women are affected by stress urinary incontinence to some extent, particularly during the third trimester. After childbirth, continence returns in most women while for others incontinence persists even after the delivery.[31 32] Moreover, women who were affected by incontinence during pregnancy are at higher risk of developing urinary incontinence later in life, even if they became continent after childbirth.[33 34]

One possible explanation for the association between parity and incontinence is obstetrical trauma which over time and ageing could lead to urinary incontinence. Childbirth may damage or weaken pelvic floor muscles, disrupt or traumatize bladder and urethral innervation, and injure supportive structures such as pubocervical fascia which may cause future incontinence. Studies have shown that vaginal delivery causes an increased pudendal nerve terminal latency and urethral mobility, perineal descent, widening of the levator hiatus, and levator avulsion.[35-37] Moreover, observational studies have reported that the prevalence of stress incontinence is higher among women who had vaginal delivery compared to women who had a cesarean section.[29 38 39]

However, the importance of obstetrical trauma has been put into question.[40] A study has shown that the highest prevalence of stress urinary incontinence is not postpartum, but rather in the prenatal stage (i.e. during the last trimester).[41] Another study reported that 12 months after the delivery, there is a substantial remission of stress urinary incontinence: in the postpartum period the prevalence of stress urinary incontinence is 19% and after one year it is reduced to 3%.[42] Moreover, even though observational studies seems to support the obstetrical trauma hypothesis, the protective effect of cesarean section, compared to vaginal delivery, can partly be explained by selection bias. Women who delivered by cesarean section might differ from women who had a vaginal delivery in respect to age, parity, and body mass index.[29]

Another explanation for the association between parity and urinary incontinence is that the physiological changes that occur in women during pregnancy may lead to incontinence later in life. Weight gain during pregnancy could explain the higher prevalence of stress incontinence during pregnancy and the subsequent remission after the delivery.[40] Moreover, hormonal and metabolic modifications that occur during pregnancy may lead to urinary incontinence later in life.[40]

2.3.3 Body mass index

Body mass index is another well-established risk factor for urinary incontinence. Studies have reported an association between body mass index and all types of incontinence (i.e. stress, urge and mixed urinary incontinence).[27 43 44] The association

increases in strength with increasing body mass index and obese women have the highest risk of incontinence: women in the highest quartile of body mass index are 2-4 times more likely to have incontinence compared to women in the lowest quartile. Evidence of the fact that body mass index is a risk factor for urinary incontinence comes also from longitudinal studies, where it has been shown that an increase in body weight, or in body mass index, is associated with a higher risk of incontinence.[45 46] Body mass index is a modifiable risk factor for urinary incontinence: studies have shown how weight reduction among incontinent women may be beneficial and could lead to incontinence remission.[47-49]

One possible explanation for this association is that overweight and obesity increases the intra-abdominal pressure and, with time, may weaken the pelvic floor muscles and the structures that support the urethra and the bladder. As mentioned previously, an increased abdominal pressure, a weakening of the pelvic floor muscles or a non-sufficient support of both the urethra and bladder might lead to an involuntary loss of urine. To support this hypothesis, studies have shown that waist to hip ratio is more strongly associated with stress incontinence than body mass index.[45 50] However, the fact that body mass index is associated with both stress and urge incontinence, suggests that there might be other mechanisms by which body mass index leads to urinary incontinence.

2.4 POTENTIAL RISK FACTORS FOR URINARY INCONTINENCE

Age, parity, and an elevated body mass index are well established risk factors for urinary incontinence. However, other factors may cause urinary incontinence in women.

2.4.1 Coffee and tea

Coffee and tea are two of the most consumed beverages in the Western world. Both these beverages contain caffeine, a stimulant drug, but the amount of caffeine contained in tea is usually one third of that in coffee.[51]

Previous studies regarding the association between coffee and tea consumption are conflicting: while some studies reported a positive association between caffeine intake or coffee and tea consumption,[52-54] others found no association.[44 55-57] One of the possible effect of caffeine on the lower urinary tract is that it may decrease the closure pressure of the urethra[58]: a lower closure pressure of the urethra could lead to an involuntary loss of urine particularly after an increase in the abdominal pressure, caused for example by sneezing or coughing. A previous study reported that women affected by overactive bladder responded to drinking caffeine citrate by an excitatory effect on the detrusor smooth muscle during the bladder filling phase.[52]

Population based studies failed to report a positive association between coffee consumption and urinary incontinence.[44 55 56] The study by Hannestad et al.,[44] found no effect of coffee intake on urinary incontinence, while a positive association between tea consumption and urinary incontinence was reported. Instead another study found no

effect of tea intake and a protective effect of coffee consumption, although not statistically significant.[56] Moreover, a randomized crossover study performed among women with urodynamically proven stress incontinence or idiopathic detrusor overactivity to determine the effect of caffeine restriction and fluid manipulation found that changing from caffeine containing to decaffeinated drinks produced no improvement in urinary symptoms.[57]

Despite the conflicting results, caffeine restriction is an internationally accepted treatment strategy for patients with urinary incontinence.

2.4.2 Gestational diabetes mellitus

Observational studies reported that urinary incontinence and overactive bladder are overrepresented among women with type 1 and type 2 diabetes mellitus.[59-63] The mechanisms by which diabetes could lead to urinary incontinence or overactive bladder in women are not clear, but different mechanisms have been suggested such as peripheral neuropathy, microvascular complications, decreased production of nerve growth factor in the bladder, and changes of nitric oxide regulation in the uroepithelium.[64 65] Many studies have investigated the association between diabetes mellitus and urinary incontinence; however very few studies have looked at the effect of gestational diabetes mellitus (GDM) on incontinence.[66 67]

Gestational diabetes mellitus is defined as carbohydrate intolerance resulting in hyperglycaemia, with first onset or detection during pregnancy.[68] GDM often debuts during the second trimester due to physiological changes in glucose metabolism and a gradual increase in insulin resistance, and is considered an established risk factor for diabetes type 2 later in life.[69] It has been estimated that gestational diabetes mellitus affects 2-6% of the pregnancies in Europe.[70] The prevalence of GDM depends on the population being studied and the diagnostic test utilized: there are no universally accepted diagnostic criteria for GDM and the prevalence of GDM in Northern Europe is mostly below 4% while in Southern Europe is above 6%.[70]

The main risk factors for GDM are advanced maternal age, family history of type 2 diabetes, being overweight or obese, and a previous diagnosis of GDM. In fact women may have gestational diabetes mellitus several times, even at each pregnancy.

Only two studies have evaluated the association between GDM and urinary incontinence. A cross sectional study performed among 228 women with GDM reported that stress urinary incontinence was common, with almost 50% of these women reporting weekly incontinence after the delivery.[15] However, in this study there was no control group (i.e. a group of women without GDM). A prospective study performed in Taiwan reported that women with GDM had a 2-3 times higher odds of stress, urge, and mixed incontinence compared to women with normal glucose level during pregnancy.[66 67]

2.4.3 Major depression and neuroticism

Other potential risk factors for urinary incontinence are major depression and neuroticism.

Major depression is a mental disorder characterized by episodes of low mood accompanied by low self-esteem and loss of interest in normally enjoyable activities. The prevalence of depression varies across different age groups but, on average, one out of five women will experience depression during their lifetime[71]: the most common time of onset is between the ages of 20 and 30 years.

Several studies, mainly cross-sectional, have found a positive association between major depression and urinary incontinence.[72-75] Different theories have been proposed to explain this association. The first theory claims that the increased activity of the hypothalamic-pituitary axis observed among depressed subjects may cause urinary incontinence. A second hypothesis proposes that the social isolation and the chronic embarrassment associated with urinary incontinence could lead to depression. A third theory suggests that urinary incontinence and depression are associated because they share a common biochemical or neurologic pathways: it has been suggested that a reduced serotonin function could predispose to both depression and bladder overactivity.[74] [75] Two prospective studies have evaluated the temporality of the association between depression and incontinence.[76] [77] While the first study used medical diagnosis of urinary incontinence and depression, the second study used self-reported information to evaluate whether women with depression at baseline had a higher risk of incontinence later in life and vice versa. Both studies found that women with depression at baseline are at higher risk of developing incontinence later in life. Instead no increased risk of depression among women with urinary incontinence at baseline was observed.

Contemporary psychology uses five personality traits to describe the human personality: openness, conscientiousness, extraversion, agreeableness, and neuroticism (also called emotional instability). Individuals who are emotionally unstable are more likely than the average to experience such feelings as anxiety, anger, envy, guilt, and depressed mood. Few studies have evaluated the association between neuroticism and incontinence in women: these studies have shown that women with UI tend to score higher on the neuroticism scale compared to women without incontinence. [78] [79]

2.4.4 Birth weight and being born small for gestational age

Previous studies have shown that birth characteristics such as being born small for gestational age (SGA) and low birth weight (LBW) are associated with adult disorders such as type 2 diabetes, hypertension and coronary heart disease.[80-84]

According to the developmental origins of adult disease and health, a stimulus or insult during a sensitive period of development has lasting effects on the structure or function of the body.[85] Poor intrauterine nutrition is an example of a stimulus that may influence the development of the fetus; in fact the fetus reacts to a lower maternal nutrition by reducing its body size and by developing insulin resistance. If reduced maternal nutrition is a stimulus that correctly predicts the external environment, then a reduced

body size and insulin resistance may provide better chance of survival to the baby after the delivery. However, when the baby expects to face a harsh environment but instead finds himself in an environment where food is abundant there is a mismatch. This mismatch between the "in utero" predicted and the actual environment may predispose these individuals to certain diseases later in life.[86 87]

In the literature there are no studies that have evaluated the effect of birth characteristics on the risk of developing urinary incontinence, however it is possible that women who were growth restricted are at higher risk of incontinence. Previous studies, performed in both animals and humans, have shown that maternal nutritional restriction and low birth weight affect the number and composition of skeletal muscle fibers[88-92] and also muscle strength in the offspring.[93-97] As a consequence, women with an impaired muscle development caused by intrauterine growth restriction could have weaker pelvic floor and detrusor muscles and therefore carry a higher risk of lower urinary tract dysfunction later in life, such as urinary incontinence.

2.4.5 Other potential risk factors

For many years oral estrogen replacement therapy has been widely used to treat urinary incontinence during or after menopause. However, results from a large placebo-controlled randomized trial of estrogen replacement therapy showed that women taking estrogen were more likely to experience worsening of their incontinence.[98 99] Moreover, the Women´s Health Initiative Hormone Replacement Trial found that women receiving estrogen were twice more likely to develop stress urinary incontinence after one year.[100]

Hysterectomy is another factor that may be associated with urinary incontinence via damage to the pelvic nerves and pelvic supportive structures. Several epidemiologic studies have reported a weak or moderate association between a history of hysterectomy and current urinary incontinence.[2] However, prospective studies regarding the effect of hysterectomy on incident incontinence showed conflicting results. Only one prospective study reported a positive association between a history of hysterectomy and urinary incontinence,[101] while two prospective studies found no association.[102 103]

Cross sectional studies have found that women with urinary incontinence are more likely to have a history of urinary tract infections (UTI).[2] However, UTIs are often diagnosed based on symptoms rather than culture confirmation. Therefore it is possible that some women may receive an erroneous diagnosis of urinary tract infection instead of urge incontinence. A prospective study of women aged 55-75 found that the baseline prevalence of urinary incontinence was two times higher among women who later develop a UTI.[104] Based on the current research, it is not possible to determine whether UTIs increase the risk of urinary incontinence or vice versa.

Results regarding the effect of smoking on urinary incontinence are conflicting.[2] An increased intra-abdominal pressure due to increased coughing among smokers could explain the association between smoking and urinary incontinence. The Nurses´ Health Study II found that smoking is a weak risk factor for incontinence,[105] while other four

prospective cohort studies found no association between smoking and incident urinary incontinence.[102 103 106 107]

3 AIMS

The overall aims of this thesis were to evaluate the association between urinary incontinence and potential risk factors using data from a cohort of premenopausal female twins and to investigate the contribution of genetic and shared environmental factors to these associations.

The specific aims were:

- To study the association between two of the most consumed beverages containing caffeine (coffee and tea) and urinary incontinence, and to evaluate the role of familial factors to these associations (Study I)

- To study the association between gestational diabetes mellitus and overactive bladder among parous women (Study II)

- To study the association between urinary incontinence, depressive mood disorders (depressive symptoms and major depression), and neuroticism and to quantify the genetic contribution to the correlation between these traits (Study III)

- To study the effect of birth characteristics, such as birth weight and being born small for gestational age, on urinary incontinence (Study IV)

4 STUDY POPULATION AND REGISTERS

4.1 THE SWEDISH TWIN REGISTRY

The Swedish Twin Registry (STR) is one of the world's largest twin resources and currently contains information on more than 194,000 twins. The registry was established in the 1950' to investigate the role of smoking and alcohol consumption on cancer and cardiovascular diseases, allowing researchers to take into account the effect of genetic factors. The registry is regularly updated with information obtained from the Swedish health registers. However, the health registers are not the only sources of information available: the twins have also been contacted to participate in survey studies, answering to questionnaires, sometimes repeatedly, covering a selection of common complex diseases and exposures. Among the twin pairs in the STR, zygosity has been determined for approximately 75 000 pairs using questions about intra-pair physical similarities in childhood. Tests of the validity of using self-reported information regarding similarity in zygosity assignment have found an accuracy estimate of approximately 98%.[108 109]

4.2 STUDY OF TWIN ADULTS: GENES AND ENVIRONMENT (STAGE)

In 2005, all Swedish twins born between 1959 and 1985 were invited to participate to the Study of Twin Adults: Genes and Environment (STAGE), a web-based survey containing approximately 1,300 questions regarding common complex diseases and exposures relevant during adulthood and midlife.[9] Participants had the possibility to perform a telephone interview, rather than the web-survey, if they preferred. The questionnaire contained 34 sections presented in a branching format, meaning that individuals had to reply to follow-up questions only if they responded positively to the introductory questions.

There were a total of 42,825 eligible twins and the total response rate was 59.6%. Almost fifty percent of the women contacted filled in the web-survey (49.9%) and an additional 16% completed a telephone interview. To assess test-retest reliability and to evaluate if there was a difference between the web questionnaire and the telephone interview, one hundred twins were recontacted after two months. Cohen's kappa values, a measure of concordance, were moderate, good, or excellent for most of the conditions: this finding indicates that it was possible to combine data from the two different sources.[9]

STAGE was the main source of information for the four studies of this thesis. Information regarding coffee and tea consumption (Study I), gestational diabetes mellitus (Study II), depressive symptoms, major depression, and neuroticism (Study III), birth weight (Study IV), urinary incontinence as well as information about possible confounding variables (body mass index, parity, educational level, and smoking status) was obtained from the survey. However, the Medical Birth Register has been used in Study II to collect additional information regarding gestational diabetes mellitus

diagnosis and in Study IV to obtain information about birth characteristics (birth weight, birth order, gestational age etc.) for the twins born between 1973 and 1985.

The Medical Birth Register (MBR) was established in 1973 and contains information about antenatal, obstetrical, and neonatal care for approximately 98% of the births that have occurred in Sweden.[110] For twins born between 1959 and 1972, birth characteristics have been obtained from original birth records stored in medical archives.

4.3 OUTCOME AND EXPOSURES DEFINITION

4.3.1 Urinary incontinence subtypes and overactive bladder

In this thesis, four urinary incontinence subtypes (overall, stress, urge, and mixed urinary incontinence) and other two lower urinary tract symptoms (nocturia and overactive bladder) have been analyzed. These definitions were based on recommendations from the International Continence Society[111] and referred to the 30-day period preceding the survey (Table 1).

Table 1. Definition of lower urinary tract symptoms based on recommendations from the International Continence Society

Lower urinary tract symptom	Definition	Questions in STAGE
Overall UI	Complaint of involuntary loss of urine	Do you have present involuntary loss of urine?
Stress UI	Complaint of involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing.	Do you have involuntary loss of urine in connection with coughing, sneezing, laughing, lifting heavy items?
Urge UI	Complaint of involuntary loss of urine associated with urgency	Do you have involuntary loss of urine in connection with a sudden and strong urge to void?
Mixed UI	Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing	A positive response to the question on stress and urge UI
Nocturia	Complaint of interruption of sleep one or more times because of the need to micturate	"Do you urinate at least twice per night?"
Overactive bladder	Urinary urgency, usually accompanied by frequency and nocturia, with or without urge urinary incontinence	"Do you experience sudden urgency to void with little or no warning?" or "Do you have involuntary loss of urine in connection with sudden and strong urgency to void?"

From a questionnaire it is possible only to evaluate the presence of urinary incontinence symptoms rather than performing a clinical diagnosis of urinary incontinence. Sandvik and coauthors validated these diagnostic questions against a final diagnosis made by a gynecologist after urodynamic evaluation: they found that the prevalence of women with stress incontinence was underestimated while mixed incontinence was overestimated. Instead the number of women affected by urge incontinence remained virtually the same.[111]

4.3.2 Exposures definition

Coffee and tea

In Study I the exposures of main interest were daily consumption of coffee and tea. Study participants were asked to report the number of cups of coffee and tea that they usually drink every day. This information has been categorized in three groups: zero cups, one or two cups, three or more cups per day.

Gestational diabetes mellitus

The aim of Study II was to investigate the association between overactive bladder and gestational diabetes mellitus. Information about the occurrence of gestational diabetes mellitus in the past was obtained from the STAGE survey. Additional information regarding gestational diabetes mellitus was obtained from the Medical Birth Register using ICD-9 codes 648A and 648W and ICD-10 codes O24.4–O24.5.

Depressive symptoms

The presence of depressive symptoms in the week preceding the survey was defined using the Center for Epidemiological Studies Depression Scale (CES-D).[112] The CES-D scale is a short self-report scale based on 20 items and designed to estimate the current level of depressive symptomatology in the general population. It has been shown that CES-D scores discriminate well between psychiatric inpatient and individuals from the general population. Seventy percent of the patients had a score above the arbitrary cut-off of 16 while in the general population only 21% of the individuals had a score greater than 16.[112]

In the STAGE survey a shorter version of the CES-D scale, based on 11 items, called the Iowa form, has been used (Table 2).[113] The 11-item Iowa form was used with a four point response format (0 = never or almost never, 1 = seldom, 2 = often, 3 = always or almost always). Using this inventory, respondents are defined as affected by current depressive symptoms if their total score is equal to or greater than 8. The scores for questions 5 and 8 have been reversed (3 = never or almost never, 2 = seldom, 1 = often, 0 = always or almost always) since these two items are worded in a positive direction.

Table 2. Items used in STAGE to assess the presence of current depressive symptoms

During the past week:

1. I did not feel like eating; my appetite was poor
2. I felt depressed
3. I felt everything I did was an effort
4. My sleep was restless
5. I was happy
6. I felt lonely
7. People were unfriendly
8. I enjoyed life
9. I felt sad
10. I felt that people disliked me
11. I could not get "going"

Neuroticism

Neuroticism was defined using a short form of the Eysenck Personality Inventory (EPI-Q).[114] This short version of the questionnaire includes 9 yes/no questions (Table 3). The neuroticism score has been determined by adding the numbers of "yes" in the nine questions. To distinguish women who score high on the neuroticism scale from women with a normal score a cut-off value of 5 can be used (0-4 = low neuroticism, 5-9 high neuroticism).

Table 3. EPI-Q questions used in STAGE to assess the neuroticism score

1. Are you often uneasy, feeling that there is something you want without knowing it?
2. Are you sometimes happy and sometimes sad without any special reason?
3. Do you often reach decision too late?
4. Do you often feel tired and listless without any special reason?
5. Are you often lost in your thoughts?
6. Are you extremely sensitive in any respects?
7. Are you ever too restless to sit still?
8. Do you have any nervous problem?
9. Do you usually worry a long time after a distressing event?

In all statistical analyses the standardized log transformed scores for both depressive symptoms and neuroticism have been used instead of binary indicators in order to improve the statistical power particularly for the co-twin control analysis. In the co-twin control analysis only twin pairs that are discordant for both the outcome and the exposure contribute to the likelihood: using the standardized log transformed score rather than a binary variable the number of informative twin pairs was increased.

Major depression

In the STAGE survey, the definition of lifetime major depression was based on DSM-IV criteria (Table 4) and was measured using the computerized Composite International Diagnostic Interview-Short Form (CIDI-SF), which was adapted from its original design for 12-month prevalence to assess lifetime prevalence of major depression.[115 116]

Only questions related to criteria A, C, and E were present in the STAGE survey: study participants have been classified as affected by at least one episode of depression in the past if all these three criteria were present.

Table 4. Major Depressive Disorder DSM-IV Diagnostic Criteria

Criterion A

A minimum of five symptoms from the following list have been present during the same 2-week period and represent a change from previous functioning. One of the symptoms must be #1 or #2, as listed below:

1) Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated either by subjective account or observation made by others. Do not include symptoms that are clearly due to general medical condition or mood-incongruent delusions or hallucinations

3) Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day

4) Insomnia or hypersomnia nearly every day

5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6) Fatigue or loss of energy nearly every day

7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

Criterion B

The symptoms do not meet the criteria for a mixed episode

Criterion C

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Criterion D

The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)

Criterion E

The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

Birth weight and being born small for gestational age

In Study IV the aim was to evaluate the effect of birth characteristics, such as birth weight and being born small for gestational age, on urinary incontinence. Being born small for gestational age has been defined as a birth weight below the 10^{th} percentile for each gestational age.

To obtain information regarding birth weight we used data from the Medical Birth Register, for twins born 1973-1985, and data from original birth records store in medical archives for the twins born before 1973. Since it is possible that for certain twin pairs the birth record for a twin has been incorrectly associated with the personal identification number of his/her co-twin, we used two algorithms to determine whether this cross-over occurred or not. The algorithm for twins born 1959-1972 used birth weight, time of birth and name if this was given at birth. Instead the second algorithm, used for twins born 1973-1985, was based on the one developed by Johansson and Rasmussen and used information on birth weight, birth order and who was the heavier twin at birth.[117] Both algorithms used information from medical records and the STAGE survey.

4.4 STATISTICAL METHODS

4.4.1 Generalized estimating equations

Since women enrolled in STAGE are twins, it is possible that urinary incontinence is positively correlated within twin pairs. Therefore, when we evaluate the association between urinary incontinence and potential risk factors using twin data, the correlation within twin pairs must be taken into account. For this reason, a logistic regression model based on generalized estimating equations (GEE) has been used.[118] If we had analyzed our data with a simple logistic regression, rather than a GEE model, we would have introduced substantial bias in the estimates of regression coefficients variances, leading to an incorrect inference of the regression coefficients.[119] One of the advantages of using generalized estimating equations is that when the aim of the study is to evaluate the relationship between the population-averaged mean response and a set of covariates, the GEE method provides consistent inference under the assumption that the model for the mean is correctly specified. If the specification of the variance matrix is incorrect, there may be a loss in efficiency but consistency is retained.[120] The GENMOD procedure in SAS software (version 9.2 and 9.3; SAS Institute, Cary, NC, USA) has been utilized to analyze the data.

4.4.2 Co-twin control analysis

When twin data is analyzed and an association between a disease and a potential risk factor is established, it is possible to determine whether the association is confounded or not by familial factors, such as common genes or shared environmental factors, using a method called co-twin control analysis.[121] In the co-twin control analysis, only discordant twin pairs are analyzed: this means that only twin pairs where one twin is affected by a specific urinary incontinence subtypes while the other twin is not affected by that particular type of incontinence are included in the analysis.

This method resembles a matched case-control design, in which twins are matched for several factors: intrauterine exposures, maternal factors, 50% (for dizygotic twins) or 100% (for monozygotic twins) of their segregating genes, and childhood and adolescent environment. To analyze the discordant twin pairs, a conditional logistic regression model has been used: only twin pairs that are discordant for both the

outcome and the exposure of interest contribute to the likelihood of the conditional logistic regression model.

The conditional logistic regression model is stratified by zygosity. If there is no difference between results obtained from the co-twin control analysis, based on discordant twin pairs only, and the ones observed in the GEE model, where all twins were included in the analysis, then it is likely that familial factors do not confound the association of interest. However, if an attenuation of the association is observed in the co-twin control analysis then the association may be confounded by familial factors. Particularly, an attenuation of the association only among monozygotic (MZ) twins, and not among dizygotic (DZ) twins, suggests that the association could be confounded by genetic factors. An attenuation of the association in both MZ and DZ twins suggests that shared environmental factors may confound the association of interest.

4.4.3 Quantitative genetic analysis

One of the purposes of quantitative genetic analysis is to estimate the proportion of phenotypic variance (in case of univariate analysis) or covariance (in case of multivariate analysis) that is explained by genetic or environmental factors. This can be accomplished by comparing the similarity of monozygotic and dizygotic twin pairs.[122] A quantitative genetic analysis was performed in Study III in order to quantify the contribution of genetic factors to the correlation between depressive mood disorders (depressive symptoms and major depression), neuroticism, and urinary incontinence.

Univariate analysis

In univariate analysis, the variance of a phenotype (P) may be partitioned into different variance components: additive genetic effects (A), dominance genetic effects (D), shared environmental effects (C), and unique environmental components (E):

$$Var(P) = Var(A) + Var(D) + Var(C) + Var(E)$$

By standardizing the previous formula, i.e. dividing by Var(P), we obtain:

$$1 = a^2 + d^2 + c^2 + e^2,$$

where $a^2 = Var(A)/Var(P)$; $d^2 = Var(D)/Var(P)$; $c^2 = Var(C)/Var(P)$; $e^2 = Var(E)/Var(P)$.

This model relies on a series of basic assumptions:

- MZ twins share all additive and non-additive genetic variance
- DZ twins share half of the additive genetic and one-fourth of the dominance genetic effects
- MZ and DZ twins share all their shared environmental effects and none of the unique environmental effects
- all the variance components are uncorrelated
- no gene-environment interaction

Based on these assumptions we can specify the MZ and DZ correlation as:

$$Cor(MZ) = a^2 + d^2 + c^2$$
$$Cor(DZ) = 0.5a^2 + 0.25d^2 + c^2$$

The proportion of the phenotypic variance that is explained by genetic factors is called heritability (h^2). There are two different definitions of heritability: the narrow-sense heritability is the proportion of the phenotypic variance explained by additive genetic effects only, while the broad-sense heritability is the proportion of variation due to both additive and dominance genetic factors.[123]

One of the problems of using only twin pairs in a quantitative genetic analysis is that the model is underspecified. In fact, there are four unknown parameters (a^2, d^2, c^2, e^2) to predict three distinct statistics (Var(P),Cor(MZ),Cor(DZ)). For this reason we need to assume that one of the parameters is zero in order to estimate the three remaining. In a study of twins reared together, dominant and shared environmental effects are negatively confounded; for this reason it is not possible to estimate both these components in the same model.[122] In study III we therefore decided to ignore dominance genetic effect (D). The consequence of setting the dominant genetic component (D) to zero may inflate the additive genetic component (A).

Liability-threshold model

Quantitative genetic theory assumes that the phenotype of interest is a continuous and normally distributed variable. However, many phenotypes are not continuous but are rather binary or categorical. When the phenotype is binary, or categorical, the quantitative genetic model can be extended through the liability threshold model.[124] In the liability threshold model, every individual has a liability to develop a certain phenotype but only those with a liability score above a certain threshold actually develop this phenotype. These liability scores are unobservable but the liability threshold model assumes that their distribution is normally distributed.

Multivariate analysis

While in a univariate quantitative genetic analysis the aim is to partition the phenotypic variance, in a multivariate analysis the aim is to decompose the covariance between two phenotypes into a genetic and environmental component. In a trivariate setting, as in Study III, the covariance matrix is a 3x3 matrix where on the diagonal are present the variances of the two traits, while the off diagonal element represents the covariance between these two traits. This covariance matrix (C_p) can be decomposed as:

$$C_p = A + C + E$$

The matrices A, C and E respectively represent the additive genetic, shared environmental, and unique environmental covariance matrix. To estimate the elements of these matrices, the maximum likelihood method implemented in the structural equation modeling package Mx can be used.[125 126] At first a model where all these three sources of covariation were present is fitted and then subsequent models can be tested to examine the worsening of the model fit caused by the removal of the various sources

of variation. The goodness of fit of the reduced models can be evaluated using the likelihood ratio test and the Akaike´s Information Criteria (AIC). In Study III, where we performed a trivariate analysis using neuroticism, major depression (or depressive symptoms), and urinary incontinence, we have found that the best-fit model was the AE model. Therefore we can simplify the previous formula as:

$$C_p = A + E$$

The matrices A and E can explicitly be written as:

$$A = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \qquad E = \begin{pmatrix} e_{11} & e_{12} & e_{13} \\ e_{21} & e_{22} & e_{23} \\ e_{31} & e_{32} & e_{33} \end{pmatrix}$$

If A is diagonal, then this means that the three phenotypes are genetically independent. If A instead has a significant off diagonal element, then genetic influences might have an effect on the phenotypes: for example if the element a_{32} is significant, then there are genetic factors in common between the second and the third phenotype (depressive mood disorders and incontinence).

In order to estimate the matrices A and E, we have to impose that they are positive definite since they are covariance matrices. A symmetric n x n matrix M is said to be positive definite if z´Mz (where z´ is the transpose of z) is positive for any non-zero column vector z of n real numbers. If we do not impose this constraint, the estimated matrices might not be positive definite and therefore will provide incorrect values for the genetic and environmental correlation (for example above the unity). Any positive definite matrix (B) can be decomposed in the product of a triangular matrix (T, a matrix having zeros in all elements above the main diagonal) and its transpose (T´):

$$B = TT'$$

This decomposition is called Cholesky decomposition or Cholesky triangle. Therefore, to make sure that the matrices A and E are positive definite we can represent these matrices by using their Cholesky decomposition:

$$A = XX' \qquad E = ZZ'$$

Genetic and environmental correlations

Once we have obtained the genetic and unique environmental matrices (A and E), we can estimate the extent to which genetic influences in one trait overlap with those of the other trait. This information is provided by the genetic correlation (r_g) estimated with the following formula:

$$r_g = \frac{a_{32}}{\sqrt{a_{22} \times a_{33}}}$$

The genetic correlation indicates the extent to which genetic influences in one trait (the 3rd trait in this example) overlap with those of another trait (the 2nd trait).

Using a similar formula, we can also estimate the unique environmental correlation (r_e):

$$r_e = \frac{e_{32}}{\sqrt{e_{22} \times e_{33}}}$$

The observed phenotypic correlation (r_p) can be defined as a function of the genetic and environmental correlation as:

$$r_p = r_g h_x h_y + r_e e_x e_y$$

where h_x and h_y are the square roots of the estimated heritability for, respectively, the second and the third phenotype, and e_x and e_y are the square roots of the proportion of the variation of these two traits that is explained by non-shared environmental factors. The proportion of the phenotypic correlation explained by shared genetic factors can be estimated as:

$$r_g h_x h_y / r_p$$

This quantity is a measure of the extent to which shared genetic influence generates a correlation between two traits. If we found that this quantity is equal to 0.8, it means that 80% of the total phenotypic correlation is explained by shared genetic influences. However, the proportion of the correlation explained by shared genetic factors is distinct from the genetic correlation. Even if two traits have a very high genetic correlation, if neither trait is strongly heritable then shared genetic factors are unlikely to explain much of the observed correlation between the two traits.

5 RESULTS

5.1 CHARACTERISTICS OF WOMEN ENROLLED IN STAGE

More than fourteen thousand female twins were enrolled in STAGE (n = 14,094). The prevalence and frequency of women affected by different lower urinary tract symptoms is reported in Table 5.

Table 5. Prevalence of urinary incontinence (UI) and other urological conditions among women enrolled in STAGE

Lower urinary tract symptoms (LUTS)	Number of women affected by LUTS	Prevalence (%)
Overall UI	929	6.59
Stress UI	769	5.46
Urge UI	401	2.84
Mixed UI	312	2.21
Overactive bladder	1,185[a] 1,307[b]	8.41[a] 9.27[b]
Nocturia	3,138	22.3

a Definition used in Study I

b Definition used in Study II

Among women in STAGE, stress urinary incontinence is the most common urinary incontinence subtype, followed by urge incontinence and then by mixed urinary incontinence. Almost a quarter of the women (22.3%) reported that they usually wake up at least two times per night to urinate. While nocturia was the outcome of interest only in Study I, overactive bladder was analyzed in both Study I and Study II but the prevalence of overactive bladder was different in the two studies. The reason for this difference was that in Study I women were defined as affected by overactive bladder using only the question "Do you experience sudden urgency to void with little or no warning?", while in Study II also women affected by urge urinary incontinence were defined as having overactive bladder since urge incontinence is one of the main symptoms that characterizes individuals with overactive bladder.

The age distribution for all the female twins participating in STAGE and for women affected by lower urinary tract symptoms is shown in Figure 4. The age distribution of all the women enrolled in STAGE is quite constant except for 20 years old women: the number of women of this age is almost halved compared to the other ages since the invitation letter was sent out only to women who were already 20 years old before May 2005. For all urinary incontinence subtypes, the age distribution increases with age while for nocturia and overactive bladder the distribution is more constant.

Figure 4. Age distribution of women enrolled in STAGE

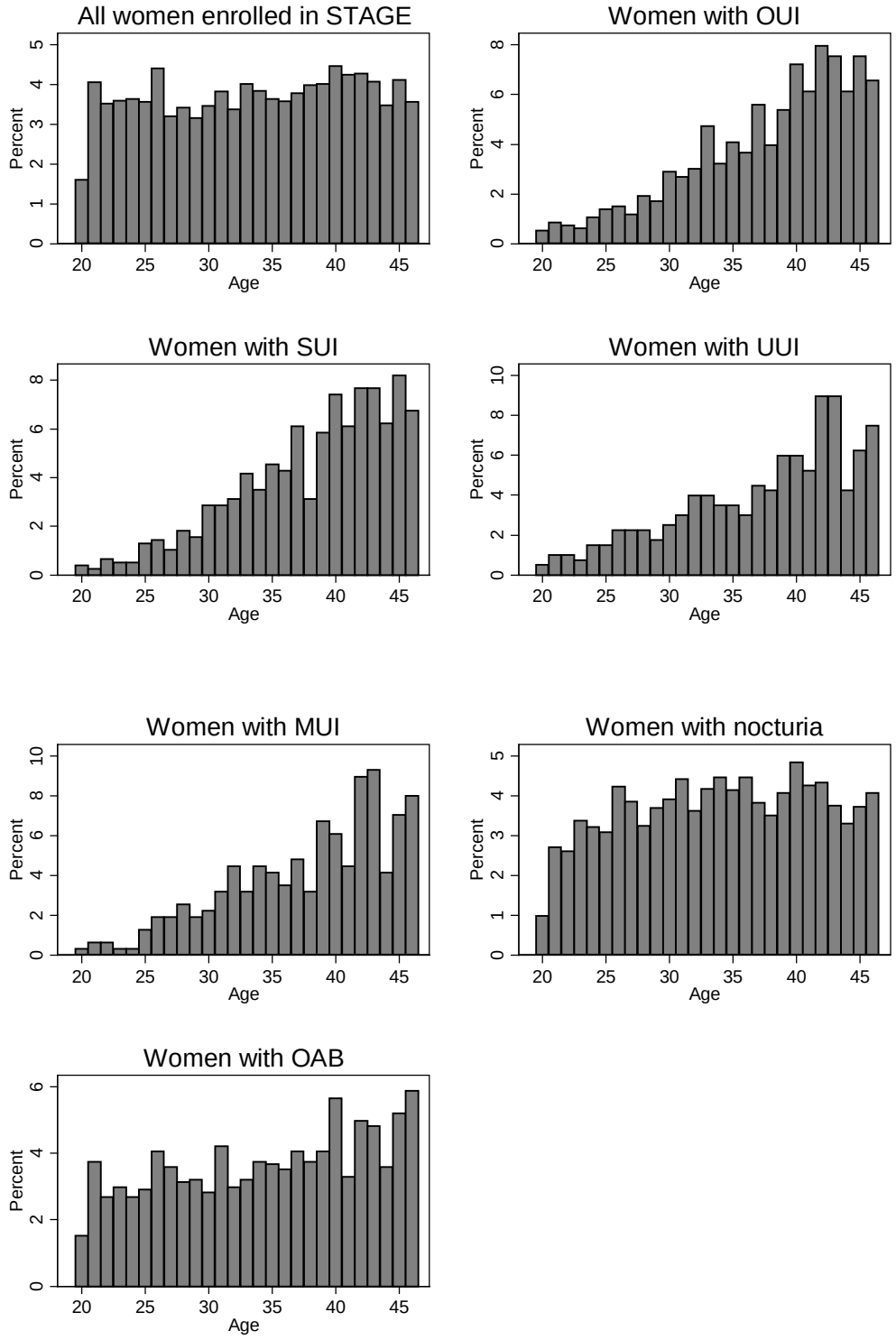


Table 6 reports the prevalence of lower urinary tract symptoms according to body mass index (categorized following World Health Organization guidelines [<18.5 = underweight, 18.5-24.9 = normal weight, 25-29.9 = overweight, >30 obese]). The prevalence of all lower urinary tract symptoms increases with body mass index: obese women have a particularly higher risk of LUTS. In this subgroup of women, the prevalence of incontinence is almost tripled compared to women with a normal weight, while the prevalence of overactive bladder is doubled.

Table 6. Prevalence of lower urinary tract symptoms according to body mass index

Body mass index	N	Overall UI[a]	Stress UI[a]	Urge UI[a]	Mixed UI[a]	Nocturia[a]	Overactive bladder[a]
Underweight	496	3.2	2.4	1.4	0.6	23.6	12.7
Normal weight	9,411	6.1	4.9	2.5	1.8	23.5	11.2
Overweight	2,213	8.5	7.3	3.7	3.1	30.0	14.8
Obese	733	17.4	15.1	8.8	7.4	35.9	22.2

a Values represent the prevalence of each LUTS

Also for nocturia the prevalence increases with body mass index, however the difference between obese and women with a normal body weight is less pronounced.

Another important risk factor for urinary incontinence is parity. For all urinary incontinence subtypes there is a substantial difference in the prevalence between nulliparous women and women who have given birth only once. Moreover, the prevalence of urinary incontinence increases with the number of deliveries. For nocturia and overactive bladder there is a pronounced difference between nulliparous women and women with only one child, but the prevalence does not increase with increasing parity (Table 7).

Table 7. Prevalence of lower urinary tract symptoms according to parity

Number of children	N	Overall UI[a]	Stress UI[a]	Urge UI[a]	Mixed UI[a]	Nocturia[a]	Overactive bladder[a]
0	5,719	2.5	1.5	1.3	0.7	21.2	11.1
1	1,901	8.8	7.8	3.7	3.3	35.9	15.7
2	3,678	10.6	8.9	4.2	3.5	25.9	12.2
More than 2	1,854	12.4	11.0	5.2	4.4	26.2	13.6

a Values represent the prevalence of each LUTS

5.2 STUDY I

The aim of Study I was to evaluate the association between coffee and tea consumption and urinary incontinence and to determine whether the effect of coffee and tea on incontinence was confounded by familial factors, such as common genes or environmental factors shared during childhood and young adulthood.

Among women who participated at the STAGE survey, seventy-two percent reported that they usually drank at least one cup of coffee per day while almost forty-seven percent drank at least one cup of tea (Table 8).

In crude analysis we found that tea consumption was not associated with overall and urge urinary incontinence. A negative association was observed in crude analysis between high tea intake and mixed urinary incontinence that however became not significant after adjusting the analysis for other covariates (age, body mass index, parity, educational level, and smoking). In adjusted analysis a negative association was

found between high tea intake and stress urinary incontinence (OR 0.72, 95% CI 0.53-0.99).

Table 8. Coffee and tea consumption for women enrolled in STAGE

Number of cups/day	Coffee	Tea
0 cups	3917 (27.7%)	7459 (52.9%)
1-2 cups	4392 (31.2%)	5425 (38.5%)
3 or more cups	5722 (40.6%)	1146 (8.1%)
Missing	63 (0.5%)	64 (0.5%)

Values are number of women (%).

A positive association was found between high tea consumption (three or more cups per day) and overactive bladder: the association remained statistically significant even after adjusting for possible confounding variables. Women who drank three or more cups of tea per day had a 34% higher odds of overactive bladder compared to non-tea drinkers (OR 1.34, 95% CI 1.07-1.67). Moreover, a small effect of tea intake on nocturia was found: in adjusted analysis, women who had a high tea consumption had a 18% higher odds of nocturia compared to non-tea drinkers (OR 1.18, 95% CI 1.01-1.38). With regard to coffee consumption, a high coffee intake was positively associated with all urinary incontinence subtypes (overall, stress, urge, and mixed urinary incontinence) but not with nocturia and overactive bladder. However, in age-adjusted analysis the positive effect of high coffee consumption on incontinence disappeared: the reason for this finding is shown in Table 9 and Table 10.

Table 9. Coffee consumption and age distribution of women in STAGE

	Coffee consumption		
Age	**0 cups**	**1-2 cups**	**3+ cups**
19-26	1 165 (48.6)	1 132 (33.0)	631 (18.4)
27-33	1 114 (32.4)	1 191 (34.7)	1 130 (32.9)
34-40	759 (19.8)	1 186 (30.9)	1 892 (49.3)
41-47	382 (11.4)	883 (26.5)	2 070 (62.1)

Values are number of women (%).

Table 10. Age distribution and occurrence of urinary incontinence of women in STAGE

	Overall urinary incontinence	
Age	**Yes**	**No**
19-26	3 112 (98.0)	63 (2.0)
27-33	3 040 (94.7)	169 (5.3)
34-40	3 300 (91.5)	308 (8.5)
41-47	2 762 (87.7)	389 (12.3)

Values are number of women (%).

Table 9 shows that older women had a higher coffee consumption compared to younger women: while approximately 18% of the women aged 19-26 had a high coffee consumption, among older women (age 41-47) the prevalence of women with a high coffee intake is tripled (62.1%). Moreover among older women, the occurrence of

urinary incontinence is much higher (Table 10). Therefore, in crude analysis we found a positive association between coffee and incontinence only because this association was completely determined by age. However, results from age-adjusted logistic regression models showed that there was no association between coffee and urinary incontinence. After adjusting the analysis for other potential confounders (body mass index, parity, smoking, and educational level) a negative association was found between high coffee intake and overall incontinence (OR 0.79, 95% CI 0.64-0.98).

The associations that were statistically significant in the logistic regression model (coffee and overall urinary incontinence, tea and stress urinary incontinence, tea and nocturia, tea and overactive bladder) were included in a co-twin control analysis (Table 11). Regarding the association between high coffee intake and overall urinary incontinence, a statistically significant association was still observed among DZ pairs (OR 0.41, 95% CI 0.18-0.94) but not among MZ pairs (OR 0.77, 95% CI 0.33-1.78): this finding suggests that the association between high coffee consumption and overall urinary incontinence may be confounded by shared genetic factors. Instead the effect of high tea intake on stress urinary incontinence, nocturia, and overactive bladder was no more significant in both MZ and DZ twins, suggesting that shared environmental factors may have confounded these associations

Table 11. Co-twin control analyses of coffee and tea consumption on discordant twin pairs

	MZ twins	**DZ twins**
Overall UI		
0 cups of coffee per day	1.0 (ref)	1.0 (ref)
3+ cups of coffee per day	0.77 (0.33-1.78)	0.41 (0.18-0.94)
Stress UI		
0 cups of tea per day	1.0 (ref)	1.0 (ref)
3+ cups of tea per day	0.57 (0.14-2.28)	0.69 (0.19-2.42)
Nocturia		
0 cups of tea per day	1.0 (ref)	1.0 (ref)
3+ cups of tea per day	1.24 (0.68-2.27)	0.82 (0.45-1.52)
Overactive bladder		
0 cups of tea per day	1.0 (ref)	1.0 (ref)
3+ cups of tea per day	0.80 (0.38-1.66)	0.65 (0.27-1.57)

Analyses adjusted for body mass index, parity, smoking, and educational level

5.3 STUDY II

The aim of Study II was to evaluate the effect of gestational diabetes mellitus on overactive bladder among parous women. For this reason the study was limited only to female twins who gave birth in 2005 or before (n = 7 855). Among women enrolled in STAGE who had given birth before 2005, 200 of them (2.5%) reported that they had a diagnosis of gestational diabetes mellitus in the past. Using the Medical Birth Register women who did not self-report GDM in the survey but have a diagnosis in the registers were identified using the following International Classification of Disease (ICD) codes: 648A and 648W (ICD-9), and O24.4–O24.5 (ICD-10). Twenty-five additional women

with a diagnosis of GDM were identified: therefore, a total of 225 women (2.9%) in STAGE had a history of gestational diabetes mellitus.

Table 12 shows the crude association between gestational diabetes mellitus and overactive bladder. Approximately 2.6% of the women without overactive bladder had a history of gestational diabetes mellitus while among women who reported overactive bladder symptoms, the prevalence of GDM is almost two times higher (5.0%). Results from a crude logistic regression model showed that women with a history of gestational diabetes mellitus had a two times higher odds of overactive bladder compared to women without GDM (OR 2.13, 95% CI 1.49-3.05). After adjusting the logistic regression model for a set of potential confounders, the association remained almost identical to the one observed in the crude logistic regression model (OR 2.13, 95% CI 1.48-3.05).

Table 12. Gestational diabetes mellitus and overactive bladder among women enrolled in STAGE who gave birth before 2005

Gestational diabetes mellitus	Women without overactive bladder n = 6992	Women with overactive bladder n = 863	Crude OR (95% CI)
Yes	182 (2.6)	43 (5.0)	2.13 (1.49–3.05)
No	6125 (87.6)	734 (85.0)	1.0 (reference)
Missing	685 (9.8)	86 (10.0)	-

The logistic regression model has been further adjusted for a potential mediator, diabetes mellitus. Gestational diabetes mellitus is considered a risk factor for type 2 diabetes mellitus later in life and at the same time diabetes mellitus has been suggested as a potential risk factor for overactive bladder. Table 13 shows that women with diabetes mellitus had a higher prevalence of overactive bladder (17.5% vs. 11.1%). Moreover, more than 37% of the women with a history of gestational diabetes mellitus developed diabetes mellitus, while only 0.5% of the women without GDM had diabetes.

Table 13. Gestational diabetes mellitus, diabetes mellitus and overactive bladder

	Overactive bladder	
Diabetes mellitus	**Yes**	**No**
Yes	22 (17.5)	104 (82.5)
No	840 (11.1)	6752 (88.9)
Missing	1 (0.7)	136 (99.3)

	Diabetes mellitus	
Gestational diabetes mellitus	**Yes**	**No**
Yes	84 (37.3)	141 (62.7)
No	38 (0.5)	6821 (99.5)
Missing	4 (0.1)	636 (99.9)

After adjusting for diabetes mellitus, the association between gestational diabetes mellitus was attenuated but still statistically significant. Women with a history of GDM

had a 88% higher odds of overactive bladder (OR 1.88, 95% CI 1.26-2.80). While in the first two models diabetes mellitus was positively associated with overactive bladder, after adjusting for GDM the association between diabetes mellitus and overactive bladder was no more statistically significant indicating that the association observed in the previous models was confounded by GDM (Table 14).

Table 14. Odds ratios for overactive bladder in relation to gestational diabetes mellitus and diabetes mellitus in multivariable logistic regression analysis

	Adjusted OR[a]	**Adjusted OR[b]**	**Adjusted OR[c]**
No GDM or DM	1.0 (reference)	1.0 (reference)	1.0 (reference)
GDM	2.11 (1.47–3.03)	2.13 (1.48–3.05)	1.88 (1.26–2.80)
Diabetes mellitus	2.03 (1.23–3.34)	2.02 (1.23–3.33)	1.42 (0.83–2.43)

a Adjusted for age, body mass index, and parity.

b Adjusted for age, body mass index, parity, smoking, and educational level.

c Adjusted for age, body mass index, parity, smoking, and educational level. Gestational diabetes mellitus (GDM) and diabetes mellitus (DM) are included in the same model.

Two interaction terms between diabetes mellitus and GDM and body mass index and GDM were included in the logistic regression model to evaluate whether the effect of GDM differed among women with and without diabetes and among women with low and high body mass index. However, we found that both interaction terms were not statistically significant ($p = 0.09$ for diabetes mellitus and $p = 0.58$ for body mass index).

We also evaluated whether women with a recent diagnosis of GDM (time since diagnosis ≤ 5 years) had a higher odds of overactive bladder compared to women who had a diagnosis of GDM more than 5 years before the survey. Results are shown in Table 15.

Table 15. Effect of time since GDM diagnosis on overactive bladder

	Adjusted OR
No GDM	1.0 (reference)
GDM diagnosis ≤ 5 years	2.20 (0.83-5.83)
GDM diagnosis > 5 years	1.78 (1.10-2.87)

Analysis adjusted for age, body mass index, parity, smoking, educational level, and diabetes mellitus

Women who had gestational diabetes mellitus less than five years before the survey, had a two times higher odds of overactive bladder. This finding was not statistically significant (OR 2.20, 95% CI 0.83-5.83), probably because only 42 women had a diagnosis of GDM five years before the survey of which only seven had overactive bladder. Moreover, no difference between women who had recent diagnosis and women who had gestational diabetes mellitus more than five years ago was observed ($p = 0.69$). For 31 women with a diagnosis of gestational diabetes mellitus, no information regarding the time of diagnosis was available.

5.4 STUDY III

The aims of Study III were to evaluate the association between depressive mood disorders (major depression and depressive symptoms) and neuroticism with urinary incontinence and to determine the contribution of genetic factors to these associations.

Among the women enrolled in STAGE, 23.8% had current depressive symptoms (defined as a CES-D score equal to or greater than eight), 25.9% scored high on the neuroticism scale (i.e. had a score of five or greater), and 7.9% had major depression. UI subtypes were more common among women affected by depression (Table 16). Moreover, mean CES-D and neuroticism scores were higher among women with urinary incontinence.

Table 16. CES-D and neuroticism age-adjusted mean scores and prevalence of urinary incontinence among women with and without major depression

	All women N = 14 094	**Overall UI N = 929**	**Stress UI N = 769**	**Urge UI N = 401**	**Mixed UI N = 312**
CES-D					
Mean score[a] (SD)	5.71 (0.05)	7.55 (0.27)	7.33 (0.25)	8.45 (0.41)	8.16 (0.40)
Missing (%)	1 963 (13.9)	89 (9.5)	75 (9.7)	37 (9.2)	32 (10.2)
Neuroticism					
Mean score[a] (SD)	3.08 (0.02)	3.94 (0.12)	4.02 (0.12)	4.37 (0.16)	4.40 (0.16)
Missing (%)	3 115 (22.0)	212 (22.8)	173 (22.4)	86 (21.4)	66 (21.1)
Major depression[b]					
Yes	870	103 (11.8)	84 (9.7)	49 (5.6)	36 (4.1)
No	10 113	614 (6.1)	512 (5.1)	266 (2.6)	210 (2.1)
Missing	3 111	212 (6.8)	173 (5.5)	86 (2.8)	66 (2.1)

a Age-adjusted means
b Values are number of women with UI (% of women with UI).

In adjusted logistic regression analysis, depressive symptoms, depression, and neuroticism were positively associated with all urinary incontinence subtypes (Table 17). However, when all these three variables were included in the same logistic regression model, all associations were attenuated. The association between depression and overall and stress UI was almost halved (OR = 1.45, 95% CI 1.11-1.91 for overall urinary incontinence; OR = 1.38, 95% CI 1.03-1.86 for stress urinary incontinence), while the effect of major depression on urge, as well as mixed, incontinence was no longer statistically significant (OR = 1.20, 95% CI 0.83-1.73 for urge incontinence; OR = 1.05, 95% CI 0.68-1.61 for mixed incontinence).

Table 17. Associations between major depression, depressive symptoms, and neuroticism with urinary incontinence

	Adjusted OR[a]	Multi-adjusted OR[b]
Overall UI		
Depression	1.99 (1.55-2.55)	1.45 (1.11-1.91)
CES-D	1.38 (1.27-1.50)	1.22 (1.10-1.36)
Neuroticism	1.38 (1.27-1.51)	1.23 (1.10-1.38)
Stress UI		
Depression	1.89 (1.44-2.48)	1.38 (1.03-1.86)
CES-D	1.36 (1.25-1.49)	1.20 (1.07-1.34)
Neuroticism	1.39 (1.26-1.52)	1.24 (1.10-1.40)
Urge UI		
Depression	1.92 (1.35-2.73)	1.20 (0.83-1.73)
CES-D	1.58 (1.39-1.80)	1.31 (1.11-1.55)
Neuroticism	1.72 (1.49-1.98)	1.55 (1.29-1.86)
Mixed UI		
Depression	1.68 (1.10-2.56)	1.05 (0.68-1.61)
CES-D	1.56 (1.34-1.80)	1.29 (1.07-1.56)
Neuroticism	1.75 (1.50-2.05)	1.61 (1.30-1.99)

a Adjusted for age, parity, body mass index, and antidepressant medication

b Major depression, CES-D, and neuroticism were all included in the same model

The attenuation of the associations observed in the multi-adjusted logistic regression models was mainly determined by neuroticism. In fact, women who score high on the neuroticism scale were more likely to have both current depressive symptoms and major depression (Table 18).

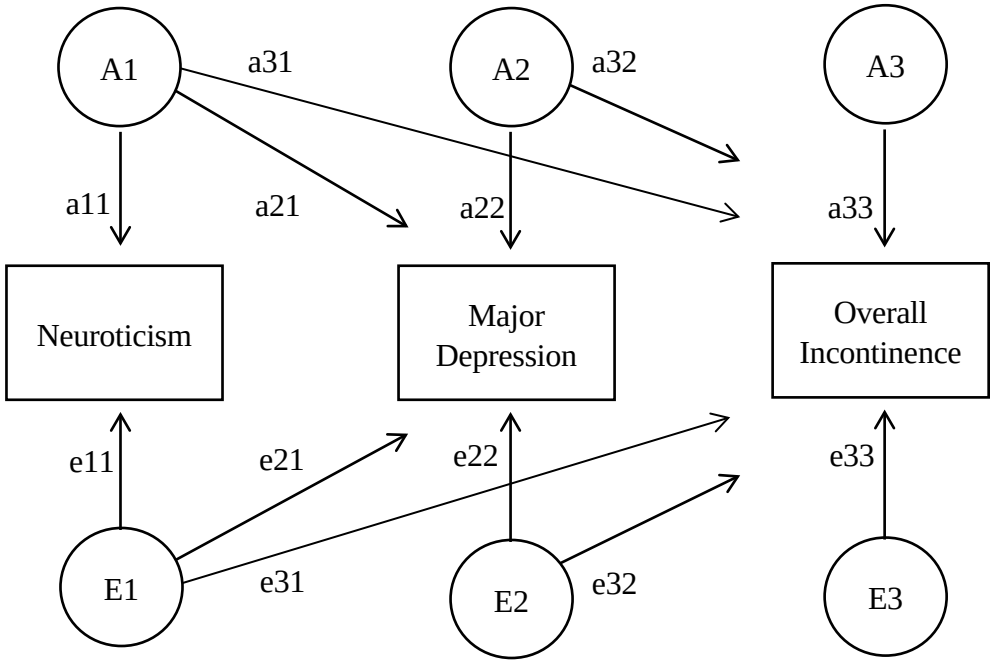
Table 18. Neuroticism, depressive symptoms, and major depression

	Depressive symptoms		Major depression	
	Yes	**No**	**Yes**	**No**
High neuroticism	1446 (55.0)	1185 (45.0)	463 (22.0)	1640 (78.0)
Low neuroticism	993 (13.0)	6642 (87.0)	379 (5.2)	6917 (94.8)

Since neuroticism confounded the effect of depressive symptoms and major depression on urinary incontinence, a trivariate Cholesky decomposition model was used to assess the proportion of the phenotypic correlation between depressive mood disorders (depressive symptoms and major depression) and urinary incontinence that was determined by common genetic factors. Moreover, in the trivariate Cholesky decomposition model with neuroticism, depressive mood disorders, and urinary incontinence it was possible to determine how much of the genetic factors that were shared between depressive mood disorders and incontinence were also in common with neuroticism.

In more detail, if we consider the trivariate model with neuroticism, major depression, and urinary incontinence, the best-fit model was the AE model (Figure 5).

Figure 5. Trivariate Cholesky decomposition model with neuroticism, major depression, and overall urinary incontinence



The additive genetic and unique environmental matrices were:

$$A = \begin{pmatrix} 0.47 & 0.25 & 0.07 \\ 0.25 & 0.44 & 0.15 \\ 0.07 & 0.15 & 0.62 \end{pmatrix} \qquad E = \begin{pmatrix} 0.53 & 0.19 & 0.08 \\ 0.19 & 0.56 & 0.08 \\ 0.08 & 0.08 & 0.38 \end{pmatrix}$$

In this particular case, the genetic correlation between major depression and overall urinary incontinence is given by:

$$r_g = \frac{0.15}{\sqrt{0.44 \times 0.62}} = 0.29$$

This means that 29% of the genetic influences of major depression was in common with overall incontinence.

Using the square roots of the estimated heritability of the two phenotypes, the proportion of the phenotypic correlation that is explained by common genes can be estimated as:

$$\frac{r_g h_x h_y}{r_p} = \frac{0.29 \times 0.66 \times 0.79}{0.23} = 0.64$$

This finding suggests that 64% of the phenotypic correlation between major depression and overall incontinence was explained by common genetic factors.

The fact that the best-fit model contained a path from major depression to overall incontinence indicates that some of the genetic factors that were in common between depression and overall incontinence were not shared with neuroticism. Moreover, by multiplying the genetic correlation between neuroticism and depression with the genetic correlation between neuroticism and overall incontinence, and by dividing this product by the genetic correlation between depression and overall incontinence, it is possible to determine how much of the genetic correlation between depression and overall incontinence was shared with neuroticism. Approximately 25% of the genetic factors that were shared between depression and overall incontinence were also in common with neuroticism.

Results from quantitative genetic analysis showed that there was a modest genetic correlation between depressive mood disorders and overall and stress incontinence. However, part of the variance that these traits shared due to genetic causes was also in common with neuroticism. In fact, approximately 25-35% of the genetic factors shared between depressive mood disorders and overall, or stress, urinary incontinence were in common with neuroticism. Also for urge and mixed incontinence a modest genetic correlation was observed: however, the genetic factors that were shared between depressive mood disorders and urge, or mixed, incontinence were completely in common with neuroticism since the best-fit models did not include the path from depressive mood disorders to urge or mixed incontinence.

Moreover, the majority of the phenotypic correlation, approximately 50-70%, between depressive mood disorders and incontinence was determined by shared genetic factors. These findings suggest that the association between depressive mood disorders and urinary incontinence are in part determined by genetic factors in common to the disorders.

5.5 STUDY IV

The aim of Study IV was to determine the effect of birth characteristics, such as birth weight and being born small for gestational age, on urinary incontinence.

The analysis was restricted only to female twins with known birth order (n = 11,175). Approximately nine percent of these twins (9.3%, n = 1039) were born small for gestational age while almost 43% of the twins had a low birth weight, i.e. a birth weight below 2,500 grams (n = 4,773). Among women born small for gestational age, the prevalence of urinary incontinence subtypes was very similar to the prevalence observed among women not SGA. Moreover, no differences in the prevalence of urinary incontinence across groups of women with different birth weight were observed.

Logistic regression analyses confirmed these findings. In both crude and adjusted analysis being born small for gestational age had no effect on all urinary incontinence subtypes: odds ratios ranged from 0.97 to 1.13. No association was observed also between birth weight and urinary incontinence.

An interaction term was added to the model to evaluate the interaction between low birth weight (or being born SGA) and body mass index later in life. No interaction was observed between SGA and body mass index, while the interaction between low birth weight and body mass index was borderline statistically significant for overall incontinence (p-value = 0.06) and statistically significant for stress urinary incontinence (p-value = 0.04).

Women who had a low birth weight and then became overweight later in life, or obese, had the highest prevalence of overall and stress urinary incontinence. Regarding urge and mixed urinary incontinence, the prevalence of these urinary incontinence subtypes among overweight women who had a low birth weight was almost identical to the prevalence among overweight women who had a normal birth weight.

Results from logistic regression models showed that women who became overweight or obese later in life had a higher odds of incontinence (overall and stress urinary incontinence) compared to women who were not overweight and had a birth weight above 2,500 grams (Table 19). The highest odds of urinary incontinence were observed among overweight women who had a low birth weight (OR = 1.84, 95% CI 1.39-2.45 for overall urinary incontinence; OR = 1.83, 95% CI 1.35-2.48 for stress urinary incontinence). The difference between overweight women with a low birth weight and overweight women who had birth weight above 2,500 grams was borderline statistically significant (p-value = 0.06 for overall urinary incontinence, p-value = 0.08 for stress urinary incontinence).

Table 19. Combined effect of low birth weight and body mass index later in life on urinary incontinence

	Crude OR	Adjusted OR[1]	Adjusted OR[2]
Overall UI			
Not LBW and not overweight	1.0 (reference)	1.0 (reference)	1.0 (reference)
LBW and not overweight	0.92 (0.77-1.11)	0.96 (0.77-1.20)	0.95 (0.75-1.21)
Not LBW and overweight	1.58 (1.28-1.94)	1.56 (1.25-1.95)	1.36 (1.08-1.73)
LBW and overweight	1.84 (1.46-2.31)	2.05 (1.58-2.67)	1.84 (1.39-2.45)
Stress UI			
Not LBW and not overweight	1.0 (reference)	1.0 (reference)	1.0 (reference)
LBW and not overweight	0.88 (0.72-1.08)	0.89 (0.69-1.14)	0.90 (0.69-1.17)
Not LBW and overweight	1.59 (1.26-1.99)	1.57 (1.23-2.00)	1.35 (1.05-1.75)
LBW and overweight	1.93 (1.51-2.47)	2.10 (1.58-2.79)	1.83 (1.35-2.48)

1 Adjusted for gestational age and maternal age

2 Adjusted for gestational age, maternal age, maternal parity, socioeconomic status, and birth cohort

LBW denotes low birth weight (<2,500 grams)

6 DISCUSSION

6.1 MAIN FINDINGS

Coffee and tea consumption and urinary incontinence

Study I showed that high tea consumption was associated with increased odds of overactive bladder and nocturia, as well as significantly lower odds of stress urinary incontinence. Moreover, women with a high coffee intake had lower odds of overall urinary incontinence. However, results from co-twin control analysis suggested that the associations were confounded by shared genetic and environmental factors.

Previous studies reported that coffee drinking was associated with an increased risk of urinary incontinence.[52-54] A study has shown that women with overactive bladder after drinking caffeine had a statistically significant increase in detrusor pressure during the bladder filling phase.[52] Given that caffeine beverages may exacerbate urinary incontinence, the 4th International Consultation on Incontinence recommended reduction of caffeine intake for women affected by incontinence symptoms.[127]

Our findings of no effect of coffee consumption on urinary incontinence are in agreement with results from Hannestad et al.,[44] in which no association was found between coffee drinking and incontinence in an age-adjusted cross-sectional analysis of Norwegian women aged 20–90 years. Moreover, a longitudinal study conducted in women aged 40 years or older found no effect of coffee and tea on overactive bladder and stress incontinence.[56]

A recent cross-sectional study performed among 4,309 nonpregnant US women, reported that women with a high caffeine intake (>200 mg/day) had a 47% higher odds of overall urinary incontinence compared to women with no caffeine intake.[128] However, no association was found between high caffeine intake and moderate/severe urinary incontinence. The different findings between the US study and ours can be explained by several differences. First of all, in our study we looked only at the effect of coffee and tea consumption on incontinence while in the US study other sources of caffeine were considered (i.e. soft drinks and chocolate). Moreover, in the US study a yearly definition of incontinence was utilized, while in our study women were defined as affected by incontinence if they had an involuntary loss of urine in the last month. Lastly, women enrolled in our study were mostly Caucasians while women of more divergent race/ethnicity participated in the US study.

A limitation of this study was the limited number of discordant twin pairs. In fact, it is possible that in the co-twin control analysis the associations were non-significant because of an insufficient number of discordant twin pairs rather than familial confounding. Another limitation of this study is that, since it was a cross-sectional study, information regarding disease and exposures were collected at the same time and it was not possible to determine whether the exposure preceded the disease or vice

versa. In fact, women with urinary incontinence may have decided to restrict their fluid intake, including coffee and tea, to improve their urinary symptoms.

Gestational diabetes mellitus and overactive bladder

In Study II we found that a history of gestational diabetes mellitus was positively associated with overactive bladder. Moreover, the association remained statistically significant even after adjusting for body mass index and diabetes mellitus, indicating that the effect of gestational diabetes mellitus on overactive bladder was not mediated by body mass index or diabetes later in life.

Few studies have evaluated the effect of gestational diabetes mellitus on urinary symptoms. A cross-sectional study of 228 women with a history of GDM reported that stress urinary incontinence was common among these women.[66] However, since there was no comparison group (i.e. a group of women without GDM) the authors were not able to evaluate the effect of gestational diabetes mellitus on stress incontinence. A recent prospective study performed among Taiwanese women reported that gestational diabetes mellitus was a risk factor for stress, urge, and mixed incontinence: women with GDM had an approximately two times higher odds of incontinence.[67] However, authors did not adjust for postpartum diabetes mellitus or postpartum body weight.

Even though it is not possible to determine the underlying mechanisms behind gestational diabetes mellitus and overactive bladder in our study, the positive association between OAB and GDM could be a result of subclinical cystopathy in the aftermath of pregnancy. This process may share pathoetiological mechanisms with diabetes mellitus, such as neurogenic, myogenic, and microvascular bladder sequela of chronic hyperglycaemia in individuals who may not have developed diabetes. Moreover, previous studies have reported that diabetes mellitus,[59-63] gestational diabetes mellitus,[67] and the metabolic syndrome[129] are positively associated with UI, suggesting that metabolic effects of pregnancy may explain some of the urinary symptoms observed after the delivery.

Due to the cross-sectional design of this study, it was not possible to determine whether women had overactive bladder symptoms before the diagnosis of gestational diabetes mellitus. However, it seems unlikely that overactive bladder syndrome preceded gestational diabetes given the young age at pregnancy of the study population. Another limitation of the present study was that there were insufficient numbers of discordant twin pairs to perform a co-twin control analysis: therefore it was not possible to determine whether the association was confounded by familial factors. Moreover, given the low number of women affected by gestational diabetes mellitus in STAGE, we were not able to evaluate how GDM severity affected overactive bladder.

In this study we found that women with a history of gestational diabetes mellitus had an almost two times higher odds of overactive bladder but only 3% of the women had GDM: therefore, very few women had overactive bladder because of GDM in our study. However, the prevalence of gestational diabetes mellitus is lower in Northern Europe (approximately 2-3%) compared to the South (~6%)[70]: since the prevalence of GDM is higher in Southern Europe, more women could be affected by overactive

bladder because of gestational diabetes mellitus in these countries. Moreover, the prevalence of gestational diabetes mellitus has increased by ~ 10/100% in several race/ethnicity groups in the last 20 years.[130] The trend toward older maternal age, the epidemic of diabetes and obesity, and the decrease in physical activity could increase the prevalence of gestational diabetes mellitus even further, causing more women to be affected by overactive bladder symptoms because of GDM.[130]

Neuroticism, depressive mood disorders and urinary incontinence

Several studies have evaluated the association between depressive mood disorders and incontinence.[72-75] Moreover, the importance of genetic factors for liability of urinary incontinence,[5-8] major depression,[131] and neuroticism[132 133] has been shown in previous studies. However, this is the first study that has assessed the contribution of familial factors to the co-morbidity of incontinence with depressive mood disorders and neuroticism.

Our study confirmed that neuroticism and depressive mood disorders are positively associated with incontinence. However, in the multi-adjusted model we found that the effect of major depression on urge and mixed incontinence was confounded by neuroticism. Moreover, in quantitative genetic analysis we found a modest genetic correlation between depressive mood disorders and incontinence. Another important finding of this study was that for overall and stress incontinence the genetic factors that were shared with depressive mood disorders were only partially shared with neuroticism, while for urge and mixed incontinence the genetic overlap with depressive mood disorders was completely in common with neuroticism. These findings suggest that genetic variants for neuroticism are driving the association between depressive mood disorders and incontinence.

Different theories have been proposed to explain the association between depressive mood disorders and incontinence. One possible explanations is that a decreased serotonin activity can lead to depression[134] and also have an effect on bladder function.[74] A different theory suggests that the increased activity of the hypothalamic-pituitary axis seen in depressed individuals may determine physiological changes in the bladder, causing incontinence.

One of the limitations of this study was that due to the low number of twin pairs that were discordant for both urinary incontinence and depressive mood disorders (or neuroticism), confidence intervals in the co-twin control analysis were wide: therefore it was difficult to determine if the associations were not significant because of familial confounding or simply because of low statistical power.

Since this is the first study that has evaluated the genetic contribution to the association between depressive mood disorders, neuroticism, and incontinence, it was not possible to compare our findings with previous studies. However, the heritability estimates for urinary incontinence, depression, and neuroticism that we reported in our study were similar to the estimates reported in previous studies.[5 131 132]

Birth characteristics and urinary incontinence

In Study IV we found that birth weight and being born small for gestational age had no effect on urinary incontinence. However, when we included in the model an interaction term between low birth weight and body mass index later in life we found that women who had a low birth weight and then became overweight had a borderline statistically significant higher odds of incontinence compared to overweight women who had a normal birth weight. These findings suggested that while birth weight and being born SGA had no effect on incontinence, a low birth weight in combination with an elevated body mass index later in life may contribute to the risk of urinary incontinence.

This is the first study that has evaluated the effect of birth characteristics, such as birth weight and being born SGA, on urinary incontinence. However, results from previous studies partially support our finding. Animal studies have shown that maternal nutritional restriction in early to mid-gestation impaired muscle development by affecting the number and composition of fibers in the offspring.[89-92] Moreover, a human study reported that those born with a low birth weight have a different muscle fiber composition.[88] Growth restriction may affect not only muscle composition but also muscle strength in humans.[93-96] A study performed among college-aged women reported that women who had a low ponderal index have decreased muscle strength.[97]

Being overweight or obese is a well-established risk factor for stress urinary incontinence, due to the increased intra-abdominal pressure associated with increasing body mass index. Thus, the combined effect of a low birth weight (and lower tissue resilience) and chronically elevated intra-abdominal pressure may adversely affect the intricate urethral sphincter complex and increase the risk for stress urinary incontinence.

6.2 METHODOLOGICAL CONSIDERATIONS

Study design

All the four studies of this thesis are based on data from the STAGE survey. Self-reported information regarding urinary incontinence subtypes was collected from the survey as well as information regarding most of the exposures and confounding variables that were used in the studies.

Urinary incontinence symptoms were defined as an involuntary loss of urine that occurred in the month preceding the survey. However, there were no questions to determine when the urinary incontinence symptoms started: therefore it was not possible to determine whether the exposures preceded urinary incontinence or not. This problem affected Study I-III while in Study IV the exposures of interest (birth weight and being born small for gestational age) clearly occurred before the onset of urinary incontinence symptoms.

In Study II, even though the diagnosis of gestational diabetes mellitus has occurred years before the survey, we could not entirely rule out the possibility that overactive

bladder symptoms started before the diagnosis of gestational diabetes mellitus. While it is implausible that overactive bladder may cause GDM, the inclusion of women who had overactive bladder symptoms before the diagnosis of gestational diabetes mellitus may have overestimated the effect of GDM on overactive bladder. The same problem was apparent in Study III since the definition of major depression in use was a lifetime assessment and there were no information regarding when this episode of depression has occurred, as well as the time of onset of incontinence. Therefore findings from these studies can be interpreted only in terms of association: the association observed could be determined by both the exposures causing incontinence or vice versa.

The problem of not being able to determine if the exposure preceded incontinence or not affected also Study I, but the consequences on the association were different. While in Study II and III we may have overestimated the effect of the exposures on incontinence, in Study I we may have underestimated the effect of coffee and tea intake on urinary incontinence. The lack of association between coffee and tea consumption and incontinence can be determined by women that have decided to reduce their coffee and tea intake as a response to urinary incontinence. However, studies have shown that the proportion of women affected by incontinence that seek medical treatment is generally low[2] and it is more likely that women reduce their overall fluid intake in response to incontinence rather than focusing on coffee and tea in specific.

Information bias

Information bias occurs when the exposure or the outcome of interest are measured or classified incorrectly.[135] Misclassification can be of two types: differential or nondifferential. Differential misclassification refers to the situations in which the measurement of the exposure is dependent from the disease status or where the classification of the disease is related to the exposure: for example if the ascertainment of the exposure is more accurate among individuals who had the disease compared to healthy individuals. A particular case of differential misclassification is recall bias: this type of bias may affect a study if individuals with the disease had a better recall of their previous exposures compared to healthy individuals. When the misclassification of the exposure does not depend on the disease status, or vice versa, it is called nondifferential misclassification: in presence of nondifferential misclassification the exposure is misclassified equally among healthy subjects and individuals with the disease.

Differential and nondifferential misclassifications have different effects on the association observed in a study. The presence of differential misclassification can either overestimates or underestimates the association, while the presence of nondifferential misclassification dilutes the association between exposure and disease when the exposure is binary. In case of exposures with three or more categories, the association for the intermediate category can be bias away from the null.[136]

In epidemiological studies there always might be a risk for differential misclassification. However, due to the fact that the STAGE survey did not present the participants with specific a priori hypothesis and the questions on exposure and outcome did not follow each other during the survey, the misclassification may not be differential but rather nondifferential.

Nondifferential misclassification was present to some extent in all four studies. In Study I women may have underreported or over reported their daily consumption of coffee and tea. In Study II women may not have reported the fact that they had a diagnosis of gestational diabetes mellitus. To minimize the exposure misclassification in Study II, the Medical Birth Register was utilized to identify women with a history of gestational diabetes mellitus who did not report GDM in the survey. Regarding Study III, women with depression may have decided to not respond to the questions contained in the section about depression, depressive symptoms, and neuroticism. Therefore, the prevalence of depression could have been underestimated but the level of misclassification should be the same among women with and without urinary incontinence. A possible source of misclassification in Study IV was that for like-sexed twin pairs their birth weight could have been mixed. To minimize this source of misclassification, the analysis was restricted only to twin pairs with known birth order: two algorithms were used to determine the birth order of all twin pairs enrolled in STAGE. However, both these two algorithms used self-reported birth weight that could be mistakenly reported by the study participants.

Selection bias

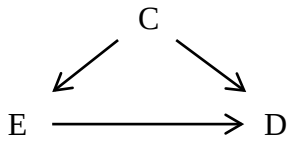
Selection bias is a distortion that may result from the procedures that have been used to select the study subjects or from the factors that influence the decision to participate in a study.[135] A common consequence of selection bias is that the association between exposure and outcome observed among individuals enrolled in a study differs from the association among the individuals that were eligible. Since the general aim of the STAGE survey was to obtain information regarding several common complex diseases, and not urinary incontinence only, it is unlikely that women with incontinence were less willing, or more willing, to participate in the study. Moreover, the invitation letter was sent to all Swedish twins born between 1959 and 1985 with no exclusions.

A previous study has shown that STAGE participants and non-participants did not differ by age, birth weight or whether they had been diagnosed with a neurological condition.[137] However, compared with STAGE participants, a higher proportion of non-participants were male, had at least one parent born outside of Sweden, had been convicted of any type of crime, were less educated, and had been diagnosed with a psychiatric disorder. Therefore it is possible that we may have underestimated the prevalence of depressive symptoms and major depression in Study III.

Confounding/mediation analysis

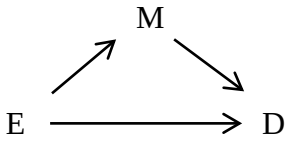
Confounding may be considered as a mixing of effects that distorts the association between exposure and outcome. A variable can be considered a confounder if it has the following three properties:

1) It is a risk factor for the disease of interest or a surrogate for an actual cause of the disease
2) It must be associated with the exposure
3) It must not be affected by the exposure or the disease

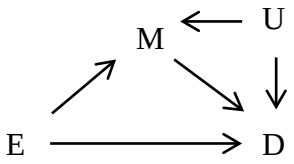


The presence of a confounding variable can create an association between the exposure and the outcome even if neither is a cause of the other. Moreover, a confounder can also change the direction of an effect or lead to an overestimation or underestimation of the effect of the exposure. For these reasons it is necessary to adjust the analysis for a potential confounder in order to obtain an unbiased estimate of the effect of the exposure on the disease. In the four studies the analyses have been adjusted by all the factors that were potential risk factors for urinary incontinence, were associated with the exposure of interest, and were not a consequence of the exposure.

A mediator variable is a consequence of the exposure that has an effect on the outcome of interest. To estimate the total causal effect of an exposure on a certain outcome it is not necessary to adjust for a mediator variable, but to estimate the direct effect, i.e. the effect that is not mediated by the mediator, the analysis must be adjusted for the mediator.



However, adjusting for a mediator variable can introduce substantial bias if there is an unmeasured confounder between the mediator and the outcome.[138 139]



In presence of an unmeasured confounding variable (U) between the mediator M and the outcome D, the total effect of the exposure on the outcome is not biased. However, adjusting for the mediator M will create a non-causal association between the exposure and the outcome. Therefore, the estimation of direct effects requires the absence of unmeasured confounding for both the effect of the exposure and the mediator on the outcome.

In Study II and IV the analyses were adjusted for potential mediator variables: body mass index (Study II and IV) and diabetes mellitus (Study II). Moreover, in Study III we adjusted the analysis for use of antidepressant medications in the last month that could be both considered as a confounder or as a mediator variable. In fact women who had a diagnosis of major depression are more likely to take antidepressant medications

and women who are taking antidepressant medications are less likely to become depressed. Since in Study III we defined women with depression using a lifetime assessment, it is more likely that antidepressant medication mediates the effect of major depression on incontinence while confounds the effect of current depressive symptoms and neuroticism on urinary incontinence.

Generalizability

The study population in the four studies consisted of premenopausal Swedish female twins; therefore findings from these studies cannot for sure be generalized to other populations.

First of all twins might differ from singletons regarding the occurrence of urinary incontinence and levels of exposures. While it is unlikely that twins have a different coffee and tea consumption compared to singletons, the prevalence of gestational diabetes mellitus observed among the women enrolled in STAGE (2.9%) is slightly higher compared to the prevalence reported in previous studies, where the prevalence ranged between 1.2-2.3%.[140-143] However, the higher prevalence of GDM could be explained by individuals who mistakenly reported a diagnosis of gestational diabetes mellitus rather than GDM being more common among twins. Moreover, in Sweden there is no consensus regarding the screening and diagnostic of GDM. A previous study demonstrated that in a specific region of Sweden (Skåne) where all pregnant women are offered an oral glucose tolerance test, the prevalence of GDM is doubled compared to an adjacent geographical region using random glucose level measurements.[143] Therefore, the higher prevalence of GDM observed in STAGE could be explained by the fact that the proportion of women to whom was offered an oral glucose tolerance test to diagnose gestational diabetes mellitus was higher among the study participants than in the general population.

In STAGE approximately eight percent of the women had major depression (7.9%), However, since it has been shown that STAGE non-participants had a higher prevalence of psychiatric disorders compared to the study participants,[137] it is possible that we may have underestimated the prevalence of major depression.

Twins usually have a lower birth weight and a shorter gestational age compared to singletons. However, a recent study has shown that there are no differences in mortality and morbidity between twins and singletons.[144] Moreover, the prevalence of incontinence observed in STAGE is comparable to the one reported by a study conducted in Canada, Germany, Italy, Sweden, and the United Kingdom.[145]

Since the Swedish population is mainly Caucasian, results from this thesis cannot be generalized to other ethnicities. In fact Black and Asian women have a substantially lower prevalence of incontinence compared to White women.[2] Moreover, the prevalence of gestational diabetes mellitus in Sweden is much lower than in other countries/ethnicities.[146]

Another problem in terms of generalizability is that women in these studies were premenopausal. In fact, the prevalence of urinary incontinence in premenopausal

women is lower than among postmenopausal women. Moreover, the effect of obstetrical factors such as gestational diabetes mellitus might be diluted among postmenopausal women because of ageing or hormonal changes.[40]

7 CONCLUSIONS

- Coffee and tea consumption had little or no effect on lower urinary tract symptoms such as urinary incontinence, nocturia, and overactive bladder. A negative association was found between high coffee intake and overall incontinence, while a positive association was found between high tea consumption and nocturia and overactive bladder. However, after analyzing only discordant twin pairs, all these associations were found to be confounded by familial factors.

- Women with a history of gestational diabetes mellitus had an approximately two times higher odds of overactive bladder compared to women without gestational diabetes mellitus. The effect of gestational diabetes mellitus on overactive bladder was not mediated by body mass index later in life or diabetes mellitus. Given the increasing prevalence of gestational diabetes mellitus in the past years, it is expected that in the future more women will be affected by overactive bladder because of gestational diabetes mellitus.

- Depressive mood disorders (current depressive symptoms and major depression) and neuroticism were positively associated with urinary incontinence. However, the associations between depression and urge and mixed incontinence were confounded by neuroticism. A modest genetic correlation was found between depressive mood disorders and overall, as well as stress, incontinence: however, part of the variance that these traits shared due to genetic causes was also in common with neuroticism. Moreover, all the variance that was shared between depressive mood disorders and urge, or mixed, incontinence was completely in common with neuroticism. These findings suggest that genetic variants for neuroticism are largely driving the association between depressive mood disorders and incontinence.

- Birth weight and being born small for gestational age had no effect on urinary incontinence. However, a statistically significant interaction was found between low birth weight and body mass index for overall and stress incontinence. Women who are overweight or obese and had a low birth weight had a borderline statistically significant higher odds of incontinence compared to overweight women who had a normal birth weight. Even though birth weight and being born small for gestational age had no effect on urinary incontinence, a low birth weight in combination with adult body mass index may contribute to the risk of urinary incontinence later in life.

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