Author:
Alhababi, Nour A

Title:
Lower urinary tract symptoms

a prospective cohort study of risk factors and outcomes in parous middle-aged women

Author:
Alhababi, Nour A

Title:
Lower Urinary Tract Symptoms: A prospective cohort study of risk factors and outcomes in parous middle-aged women

Lower Urinary Tract Symptoms: A Prospective Cohort Study of Risk factors and Outcomes in Parous Middle-Aged Women

By

Nour Alhababi

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Population Health Sciences in the Faculty of Health Sciences

Bristol Medical School

University of Bristol, United Kingdom

December 2021

Word Count:

59,640

Abstract

Brief Rationale

Lower urinary tract symptoms (LUTS) are defined as storage, voiding and post micturition symptoms. LUTS are highly prevalent (45% to 76%) in women and are associated with lower quality of life. Unfortunately, LUTS are understudied especially in middle aged women as evidence mostly focuses on risk factors or outcomes related to urinary incontinence and neglects other subtypes of LUTS. Direction of association between some risk factor including constipation and physical activity and outcome of LUTS (such as depression and quality of sexual experience) are still not clear due to epidemiological research mostly focusing on cross-sectional association. This thesis will focus on disentangling the direction of association between determinants (physical activity and constipation) and outcomes (quality sexual experience and depression) associated with LUTS (by subtypes) in parous middle-aged women by examining the associations prospectively.

Overview of Methods

Avon Longitudinal study of Parents and Children (ALSPAC) is a population-based birth cohort in the southwest of England that have recruited pregnant women in early 90s (1991-1992). These women were followed up over 20 years using multiple questionnaires. Women self-reported LUTS at two timepoints using validated questionnaires British Female Lower Urinary Tract Symptoms questionnaire (2002-2004) and International Consultation on Incontinence Questionnaire on Female LUTS (2011-2012). LUTS were categorized according to International Continence Society definitions as stress urinary incontinence [UI], urgency UI, mixed UI, nocturia, increased daytime frequency, urgency, hesitancy, and intermittency.

In this thesis, two determinants of LUTS were examined prospectively. Women self-reported their physical activity (1999-2001) and were followed up since then for two time points (3 and 11.5 years) were their association with LUTS (2011-2012) was examined. Women who reported constipation symptoms (between 2001-2005) were followed up for approx. 10 years were their association with LUTS (2011-2012) was examined.

This thesis examined two outcomes associated with LUTS (quality sexual experience and depression).Association examined prospectively between women who self-reported LUTS (2002-2004) and reported measures of sexual experience (2012-2014) at two years of follow

up. Association between LUTS (2010) and depression (measured by Edinburgh Post Natal Scale) were examined at 10 years of follow up.

All associations were examined using logistic regression and multiple imputation.

Overview of Results

At 3 years of follow up, women (n=4126, mean age 40.5 years; SD 4.5) who performed higher categories of physical activity were prospectively associated with reduced risks of stress UI (adjusted OR=0.51; 95% CI 0.32, 0.80), mixed UI (adjusted OR=0.48; 95% CI 0.24, 0.99), and any type of LUTS (adjusted OR=0.64; 95% CI 0.46, 0.90) compared to women with lower categories of physical activities. At 11.5 years of follow up, women (n=2770, mean age 49.3 years; SD 4.4) who performed higher categories of physical activity were prospectively associated with reduced risks of stress UI (adjusted OR=0.56; 95% CI 0.39, 0.82), mixed UI (adjusted OR=0.34; 95% CI 0.19, 0.63), and any type of LUTS (adjusted OR=0.52; 95% CI 0.37, 0.73) compared to women with lower categories of physical activities.

At 10 years of follow up, women (n=3729, mean age 43.3 years, SD 0.5), who took medication for constipation had increased risks of urinary urgency (adjusted RR=1.35; 95% CI 1.04, 1.95) and hesitancy (adjusted RR=1.72; 95% CI 1.04, 3.01) compared with women who reported not using medication for constipation.

At two years of follow up, women (n=2672, mean age 49.3 years at baseline, SD 0.5) with any LUTS, stress UI, mixed UI and urgency had higher levels of worry and distress related to their sexual desire, orgasm experience and frequency of sex. Stress UI (adjusted OR=1.27; 95% CI 1.04, 1.52), urgency UI (adjusted OR=1.70; 95% CI 1.26, 2.30), and mixed UI (adjusted OR=1.86; 95% CI 1.35, 2.57), were all associated with a lower overall satisfaction of sex life.

Depression in women (n=3226, mean age 43.3years, SD 0.5) at 8 years of follow up was associated with urgency UI (adjusted RR=1.59; 95% CI 1.24, 2.00), mixed UI (aRR=1.70; 95% CI 1.08, 2.65), urgency (aRR=1.51; 95% CI 1.13, 2.01), any LUTS (aRR=1.25; 95% CI 1.10, 1.43).

Conclusion

Physical activity is prospectively associated with reduced risks of LUTS (especially stress UI) in parous middle-aged women. Constipation was prospectively associated with increased risks of LUTS including urgency and hesitancy in parous middle-aged women. LUTS are associated

with poorer measures of female sexual dysfunction and higher depression scores. Future studies should focus on causality with LUTS to understand underlying mechanisms and support clinical translation.

Acknowledgments

I would like to extend my sincerest appreciation and gratitude for may amazing supervisors Abigail Fraser, Carol Joinson and Maria Christine Magnus. I am very privileged to have the chance to meet those three powerful women who provided constant knowledge, support, and encouragement throughout my PhD journey.

I would also like to thank my friends Nancy, Charlie, Qian, and Lucy for the constant love they surrounded me with. We shared laughter, tears, experiences, and delicious food from all around the world. They really made the UK to feel like home.

Finally, and most importantly, I give my special thanks to my amazing family who taught me to approach my dream no matter how difficult it seems. Mum and dad thanks for teaching me to never give up. You are the best!

This thesis is dedicated to my amazing parents. I hope I made you proud.

Author declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programs and that it has not been submitted for any other academic award. Expect where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed: Nour Alhababi

Date: 17/12/2021

COVID statement

This statement is written to explain how COVID-19 have impacted my thesis. It includes extension dates because of COVID-19 impact. The statement does not suggest that the quality of my work or the final thesis outcome is different to what it should have been if COVID-19 did not occur.

Since COVID-19 was announced as pandemic (March 2020), I was forced to immediately leave everything and travel back to Kuwait. I did not even have time to evacuate my flat in the UK or take some of my important PhD resources. In Kuwait, I found myself locked in the house with my two kids (8 years old boys) as there was national lockdowns for many months. It was difficult to work in a quiet place with full concentration as my kids were constantly around with no schools. Kuwait weather reaches 50 degrees which is impossible to take the children out to the park to release their energy. This have affected how much focus I had and time to work faster and efficiently for my thesis work. However, I did manage to keep meeting my supervisors online and do the required work. The internet speed was poor, and it was difficult to work through remote desktop because it keeps disconnecting which slowed down running my analysis. The most challenging part was that I missed the office support with my colleagues and the exchange of thoughts about the process of the thesis that we would normally have in a normal office situation. I did not get the chance to present my published paper in workshops in a foreign country like I was planning to, as airports were closed and I could not fulfil that experience.

Unfortunately, my husband and I caught COVID, and we both got sick. I got better after 3 weeks but my husband condition was so bad that he got hospitalised. This made me take a step back for two months to focus on my husband health. Please note I did not ask for suspension I just worked slower.

Due to all the stressful situations, I went into severe depression and my supervisors asked me to take a step back, recover and ask for an extension. I asked for a 1-month extension from 2nd of October 2021 to submit my thesis. However, due to the editing and comments taking a long time I had to ask for a further 6 weeks extension to a final submission date 17/12/2021. Even now with three days before my submission date, my mother has been hospitalised because she caught COVID and had difficulty of breathing. It is stressful managing submitting my work on time or worry about my mother health. All I can say is that COVID was a time of uncertainty where you never know what to expect.

With all the challenges I underwent throughout the thesis, I was able to publish two papers. I also have one paper that is currently under review (in British Journal of Urology International) and a fourth paper that will be submitted soon to a journal. I am only glad I did not give up when it seemed impossible to move forward.

Abbreviations used in the thesis

LUTS	Lower urinary tract symptoms
UI	Urinary Incontinence
OAB	Overactive bladder
ICS	International Continence Society
EPDS	Edinburgh Post Natal Depression Scale
ALSPAC	Avon Longitudinal Study of Parents and Children
CNS	Central nervous system
DM	Diabetes mellitus
UTI	Urinary tract infection
HRT	Hormone replacement therapy
BMI	Body mass index
BFLUTS	British Female Lower Urinary Tract Symptoms
ICIQ-FLUTS	International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms
DAN-PSS	Danish Prostatic Symptom Score
DLW	Doubly labelled water method
METs	Metabolic equivalents scores
MET hours/week	Metabolic equivalents scores hours per week
FSFI	Female Sexual Function Index
FSDS	Female Sexual Distress Scale questionnaires
EPIQ	Epidemiology of prolapse and incontinence questionnaire
PFDI	Pelvic floor distress Inventory
ELSPAC-CZ	European Longitudinal Study of Pregnancy and Childhood
SIFCRAT	Sandwell Incontinence Following Childbirth Risk Assessment Tool
PND	Post-natal depression

NICE	National Institute for Health and Care Excellence
NHS	Nurse Health Study
OR	Odd ratios
RR	Risk ratios
aOR	Adjusted odd ratios
PRR	Prevalence rate ratios
CI	Confidence intervals
MI	Multiple imputation
RCT	Randomised Control Trials
UAB	University of Alabama at Birmingham
MR	Mendelian Randomisation

Thesis Preface

This PhD dissertation integrates publications as individual chapters. It has been formatted following guidance on the integration of publications as chapters within a dissertation as stipulated by the Academic Quality and Policy Office. All researched materials included in these publications derive from original research undertaken during my PhD study period.

Publications arising from my work

During my PhD timeline, I published two papers on examining the association between risk factors (physical activity and constipation and LUTS) and LUTS which were aim one (Chapter 4) and two of my thesis (Chapter 5). Below are titles of my publications:

A prospective study of the association between physical activity and lower urinary tract symptoms in parous middle-aged women: results from the Avon Longitudinal Study of Parents and Children (1) (Journal of Urology)

Alhababi N, Magnus MC, Joinson C, Fraser A. A Prospective Study of the Association between Physical Activity and Lower Urinary Tract Symptoms in Parous Middle-Aged Women: Results from the Avon Longitudinal Study of Parents and Children. J Urol. 2019;202(4):779-86.

The association between constipation and lower urinary tract symptoms in parous middle-aged women: a prospective cohort study (2)(Journal of Women Health).

Alhababi N, Magnus MC, Drake MJ, Fraser A, Joinson C. The Association Between Constipation and Lower Urinary Tract Symptoms in Parous Middle-Aged Women: A Prospective Cohort Study. Journal of Women's Health. 2021.

I also completed a third paper examining the association of LUTS and quality of sexual experience (third aim thesis, Chapter 6). This paper is under review in British Journal of Urology International (BJUI) under the title of:

A Prospective Study of Lower Urinary Tract Symptoms and Quality of Sexual Experience in Parous Middle-Aged Women.

Authors of above paper include Nour Alhababi, Dr. Carol Joinson, Dr. Abigail Fraser, Dr.Maria Christine Magnus.

Finally, I have written a paper on my LUTS and depression analysis (aim four of my thesis, Chapter 7) but paused on that as I am prioritising the writing up and submission of my thesis.

Contribution of Authorship

I am first author of all of my publications, reflecting the fact that I lead this work, including conceptualising the study question, study design, assembling the datasets, conducting analyses, interpreting results and writing the manuscripts. I had important inputs from other co-authors including my supervisors Abigail Fraser, Carol Joinson and Maria Christine Magnus. They contributed to both published studies' design, to the interpretation of results and added important intellectual contributions to the manuscripts before approving the final version. All authors agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. For the constipation and LUTS paper, Dr Marcus Drake was also a co-author and provided his clinical view and intellectual contribution on the final draft of the paper.

We declare that the above articles were written by the author of this thesis, Nour Alhababi, with support from supervisors.

Signatures of supervisors

Prof Abigail Frasier **Prof Carol Joinson** **Dr Maria Christine Magnus**

Table of Contents

Table of Tables

Table of Figures

1 Chapter 1: A brief synopsis of my thesis

This chapter provides a very brief overview of my thesis. I start with a brief definition of lower urinary tract symptoms (LUTS), the set of symptoms that are the focus of my work. I then briefly present the overall and specific aims of the thesis. I then go on to describe the Avon Longitudinal Study of Parent and Children, the study that provided data for my work. I then provide some details on my own background and motivation for undertaking this work. I will then provide an outline of my thesis. Finally, I will provide a list of my publications.

1.1 Lower urinary tract symptoms

LUTS are defined by the International Continence Society (ICS) as storage, voiding and post micturition symptoms (3). Storage symptoms, as the term suggests, include increased daytime frequency of urination, nocturia and subtypes of urinary incontinence (UI). These include stress urinary incontinence, urgency urinary incontinence and mixed urinary incontinence (3). Voiding symptoms are defined as a departure from normal sensation or function experienced during the act of micturition (3) including hesitancy, intermittency, slow stream, straining to void, spraying of urinary stream. Post micturition symptoms are experienced immediately after micturition (3) including incomplete (bladder) emptying, postmicturition leakage, post micturition dribble, position-dependent micturition, dysuria, and urinary retention. All the above subtypes are defined in more detail in chapter 2 (section 2.1,
Table **1**).

1.2 Importance of the research area

Prevalence of LUTS in general population was reported highly (10%-30%) in both men and women (n=4979, ages ≥ 40 years) and there was no marked cultural variation (4). Prevalence of LUTS have been reported to increase with age in both genders (2). Middle aged women reported higher prevalence of LUTS (15.5%) than middle-aged men (10%) in a large sample of general population; therefore, this thesis will focus on middle aged women (2).

Estimates of the prevalence of LUTS in the general population of women are diverse, depending on the type of LUTS (details in Chapter 2, section 2.5). Studies reporting prevalence of any LUTS (i.e., storage, voiding and/or postmicturition) in women range from 45%-76% (5, 6). From the three subtypes of LUTS, storage LUTS have the highest prevalence estimates among women, ranging between 24% to 60% (7-9). Voiding symptoms range from 2% to 30%

and postmicturition symptoms ranged from 2 to 14% (7-9). Prevalence of UI ranges from 25%-45% (5, 8, 10) in women, while OAB prevalence ranges from 11%-30% (5, 9, 11). Although the reported prevalence of LUTS in women vary in the literature, they are common and may persist for years (5).

Established risk factors for LUTS in women include parity, delivery mode, older age, obesity, and a history of hysterectomy (12-14). LUTS have been linked to lower quality of life as LUTS can interfere with daily life and functioning, recreational activities, quality of life (13, 15). Although LUTS have a major impact on the quality of life, they are considered as underreported, underdiagnosed, undertreated, and understudied problems (16, 17). The overall aim of my thesis is to contribute to understanding the life course epidemiology of LUTS in women.

In order to make a meaningful contribution to the evidence base on LUTS in women, I first immersed myself in the literature. I identified relevant systematic reviews and studies, to identify knowledge gaps that I could fill and inform my analysis plans.

1.3 Aims of Thesis

The overall aim of my thesis was to improve our understanding of the life course epidemiology of LUTS in middle-aged women, by investigating LUTS risk factors and sequalae.

1. To estimate the prospective association between physical activity and risk of LUTS (by subtypes) in parous middle-aged women.

2. To study the prospective association between constipation (measured by medication intake) and the risk of developing LUTS (by subtypes) in parous middle-aged women.

3. To assess the cross-sectional and prospective associations of LUTS (by subtypes) on quality of sexual experience in parous middle-aged women.

4. To assess the prospective association between LUTS (by subtypes) and depression (measured by Edinburgh Post Natal Depression Scale and/or antidepressant intake) of parous middle-aged women.

1.4 The Avon Longitudinal Study of Parents and Children (ALSPAC) mothers' cohort

All my investigations were carried out using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Detailed information on ALSPAC is available on the cohort website (http://www.bristol.ac.uk/alspac), which includes a fully searchable data-dictionary (http://www.bristol.ac.uk/alspac/researchers/our-data/). ALSPAC is a prospective population-based birth cohort study which recruited pregnant women (n=14,541 pregnancies) resident in the former Avon Health Authority in England with an estimated date of delivery between 1st of April 1991 and 31st of December 1992. Both Mothers and their offspring have been followed up since the early 90s with detailed questionnaires administered approximately every 1-2 years to gather information on several characteristics including demographic, health related behaviours, psychological and health factors (see cohort profile) (18).In my thesis, I will be focusing on the mothers, and I will be using the self-reported questionnaires from ALSPAC to collect data on sample included in my analyses.

ALSPAC administered validated questionnaires to assess subtypes of LUTS (International Consultation on Incontinence Questionnaire on Female LUTS & The Bristol Female LUTS questionnaire). Detailed information about the measures of LUTS can be found in Methods of this theses (Chapter 3, section 3.1.2).

1.5 Reflexivity section

I come from a clinical background, working in a Maternity Hospital as a physiotherapist in women's health rehabilitation, including management of UI and female sexual dysfunction. Whilst working, I noticed that UI had a major impact on women's quality of life. Some of my patients were so embarrassed about their condition, that they isolated themselves and avoided their sexual partners. Patients who suffered from stress UI avoided physical activity. There was also a lack of knowledge and understanding about UI. For example, some of my patients thought that UI was just a normal part of life due to childbirth. Others avoided sexual intercourse because of coital incontinence which had a major impact on their relationships. Many of the women showed signs of depression and low self-esteem because of LUTS symptoms, especially UI. Therefore, I decided to improve my own knowledge by exploring the risk factors and consequences of LUTS in women. To provide better prevention and treatment, we need to have an understanding the association of risk factors and outcomes of LUTS, especially prospective associations. Understanding prospective associations helps clinicians

like myself to develop interventions to recognise and manage early risk factors that might increase the risk of onset of LUTS.

Overall, understanding the risk factors associated with the development of LUTS and the effects on women's quality of life is an important topic to explore because it has the potential to improve women's health.

1.6 Outline of Thesis

Chapter 1 includes a short thesis synopsis by briefly introducing LUTS, ALSPAC, importance of topic and aims of thesis.

Chapter 2 includes a more detailed overview of LUTS including definitions, diagnosis, treatments, pathogenesis, and epidemiology of LUTS. It also involves a literature review on risk factors and outcomes associated with LUTS to identify the gaps in literature. Detailed literature review is presented on the association of risk factors (physical activity and constipation) and outcomes (quality of sexual experience and depression) of LUTS studied in this thesis as these were the areas with gaps in the literature.

Chapter 3 describes the methods I used, providing an overview of the ALSPAC mothers' cohort, the LUTS measures and the statistical analysis I used in the thesis. Moreover, I present participant exclusion and inclusion criteria, measurement of risk factors (physical activity and constipation) and outcomes of LUTS (quality of sexual experience and depression). The chapter also includes measurement of confounders for each analysis of the thesis.

Chapters 4 and 5 presents and explain the results of the associations between examined risk factors for LUTS (physical activity and constipation) carried out in this thesis. Chapters 6 and 7 presents and explains outcomes (quality of sexual experience and depression) of LUTS carried out in the thesis.

Finally, Chapter 8 briefly summarises the main findings of the thesis. I then go on to provide a detailed discussion of the overall strengths, and limitations of my work. Individual discussions of each of the four results chapters. These include placing my results in the context of the existing evidence, discussing the potential mechanisms that may explain my results, addressing analysis specific strengths and limitations, describing the implications of these findings and the clinical message, future directions, and recommendations Finally, I will draw my overall thesis conclusions.

The next section presents specific aims of my theses. I chose to study these aims based on my clinical experience and after conducting a thorough literature review to identify gaps in literature.

1.7 Publications arising from my work

Two chapters of my thesis have been published (Chapter 4 and Chapter 5). Details publication available in Thesis Preface.

Below are titles of my publications:

1- A prospective study of the association between physical activity and lower urinary tract symptoms in parous middle-aged women: results from the Avon Longitudinal Study of Parents and Children (1) (Published in the Journal of Urology).

2- The association between constipation and lower urinary tract symptoms in parous middle-aged women: a prospective cohort study (2) (Published in the Journal of Women Health).

2 Chapter 2: Lower Urinary Tract Symptoms

2.1 Definitions, types, and subtypes of LUTS

The International Continence Society (ICS) has provided leadership in terminology for lower urinary tract dysfunction over many years, by providing different definitions for men, women, children and adult neurogenic LUTS. However, In 2002, ICS published a report containing the traditional core terminology of LUTS (19). In this report, the ICS grouped LUTS into three groups of LUTS including storage, voiding and post micturition symptoms(20). Each group of LUTS have different subtypes which are defined in
Table **1**. In this thesis , I will be using the ICS definitions from the traditional core terminology of LUTS (20).

Group 1. Storage symptoms

Storage symptoms are experienced during the storage phase of the bladder and include the subtypes: increased daytime frequency and nocturia (3). Increased daytime frequency is the complaint by the patient who considers that they void too often by day (19). The definition of nocturia has been updated several times by ICS. In 2002, ICS defined nocturia as the complaint that the individual must wake one or more times a night to void (19). In 2010, the nocturia definition was updated to the complaint of interruption of sleep one or more times because of the need to micturate. Each void is preceded and followed by sleep (3). In 2019, ICS updated the definition of nocturia to include the number of times urine is passed during the main sleep period (21). Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep (21). This should be quantified using a bladder diary (21). A bladder diary is a chart used to document the frequency and characteristics of incontinence episodes in both research and clinical practice (26). Storage LUTS also include urgency defined as complaint of a sudden compelling desire to pass urine, which is difficult to defer. and urinary incontinence (UI) which is defined as the complaint of any involuntary leakage of urine (3).UI can be further categorised into several distinct types including stress UI, urgency UI, mixed UI, postural UI, continuous UI, insensible UI, and coital UI(21). Details of definitions are available in Table 1.

Group 2: Voiding symptoms

Voiding symptoms are defined as a departure from normal sensation or function experienced by the women during the act of micturition (3). This includes hesitancy, intermittency, slow stream, straining to void, spraying of urinary stream (3).

Group 3: Post micturition symptoms

These are experienced immediately after micturition(3). This includes feeling of incomplete (bladder) emptying, postmicturition leakage, post micturition dribble, position-dependent micturition, dysuria, and urinary retention(3).

In this thesis, I focus on the following specific subtypes of LUTS: stress UI, urgency UI, mixed UI, urgency, nocturia and increased daytime frequency which are all considered as storage LUTS (Table 1). My focus on these subtypes is partially driven by the fact that they are the most common subtypes (7-9) and partially based on the availability of data in ALSPAC (section 3.1.3, Chapter 3). Moreover, these subtypes have been reported from previous studies to have the greatest impact on women's quality of life (13, 15).

Table 1. ICS definitions of storage, voiding and postmicturition LUTS and their subtypes

Types of Storage Symptoms	Types of Voiding Symptoms	Types of Postmicturition Symptoms
Nocturia: the number of times urine is passed during the main sleep period. Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep. This should be quantified using a bladder diary.	**Hesitancy**: complaint of a delay in initiating micturition.	**Feeling of incomplete emptying:** Complaint that the bladder does not feel empty after micturition.
Urgency: complaint of a sudden compelling desire to pass urine, which is difficult to defer.	**Intermittent stream (Intermittency):** Complaint of urine flow, which stops and starts on one or more occasions, during micturition.	**Postmicturition leakage:** Complaint of a further involuntary passage of urine following the completion of micturition.
Increased Daytime Frequency (IDF): complaint that micturition occurs more frequently during waking hours than previously deemed normal.	**Straining to void:** Complaint of the need to make an intensive effort (by abdominal straining, Valsalva, or suprapubic pressure) to either initiate, maintain, or improve the urinary stream.	**Position-dependent micturition:** Complaint of having to take specific positions to be able to micturate spontaneously or to improve bladder emptying, for example, leaning forwards or backwards on the toilet seat or voiding in the semi-standing position.

Nocturnal enuresis: complaint of loss of urine occurring during sleep.	**Slow stream:** Complaint of a urinary stream perceived as slower compared to previous performance or in comparison with others.	**Dysuria:** Complaint of burning or other discomfort during micturition. Discomfort may be intrinsic to the lower urinary tract or external (vulvar dysuria).
Stress urinary incontinence (stress UI): Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.	**Spraying (splitting) of urinary stream:** Complaint that the urine passage is a spray or split rather than a single discrete stream.	**(Urinary) retention:** Complaint of the inability to pass urine despite persistent effort.
Urgency urinary incontinence (urgency UI): Complaint of involuntary loss of urine associated with urgency.		
Mixed urinary incontinence (mixed UI): Complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing, or coughing.		
Postural (urinary) incontinence: Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position.		
Continuous urinary incontinence (Continuous UI): Complaint of continuous involuntary loss of urine.		
Insensible (urinary) incontinence: Complaint of urinary incontinence where the woman has been unaware of how it occurred.		
Coital incontinence: Complaint of involuntary loss of urine with coitus. This symptom might be further divided into that occurring with penetration or intromission and that occurring at orgasm.		
Overactive bladder (OAB) syndrome: Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.		
Definitions are taken from Abrams et al., 2002 ICS LUTS terminology (20)		

2.2 Anatomy and physiology of the female pelvis and urinary tract

In this section, I will explain the anatomy and physiology of the female urinary tract. It is important to understand the anatomy and physiology of the female urinary tract as it will aid in interpreting research findings and justify choices of confounders. Moreover, it will help aid in understanding the possible mechanisms associated with risks of developing LUTS and the outcomes that are associated with LUTS.

The female pelvis consists of a complex structure of pelvic organs including the uterus, bladder and rectum which are all closely allocated (Figure 1) (22). The pelvic organs are supported by the pelvic floor muscles (Figure 2) which are important as they provide support for the abdominal viscera including the rectum and provide constricting mechanism to the urethral, vaginal, and anal orifices in women (23). When the pelvic floor muscles contract, they lift the internal organs of the pelvis and tighten the openings of the vagina, urethra, and anus. However, relaxing the pelvic floor muscles allows passage of urine and faeces (23). Weakness or dysfunction in those muscles may affect the ability to control of the passage or urine or faeces resulting in LUTS, constipation or faecal incontinence (24). Moreover, it may affect sexual experience as voluntary contractions of the pelvic floor contribute to sexual arousal and sensation (24).

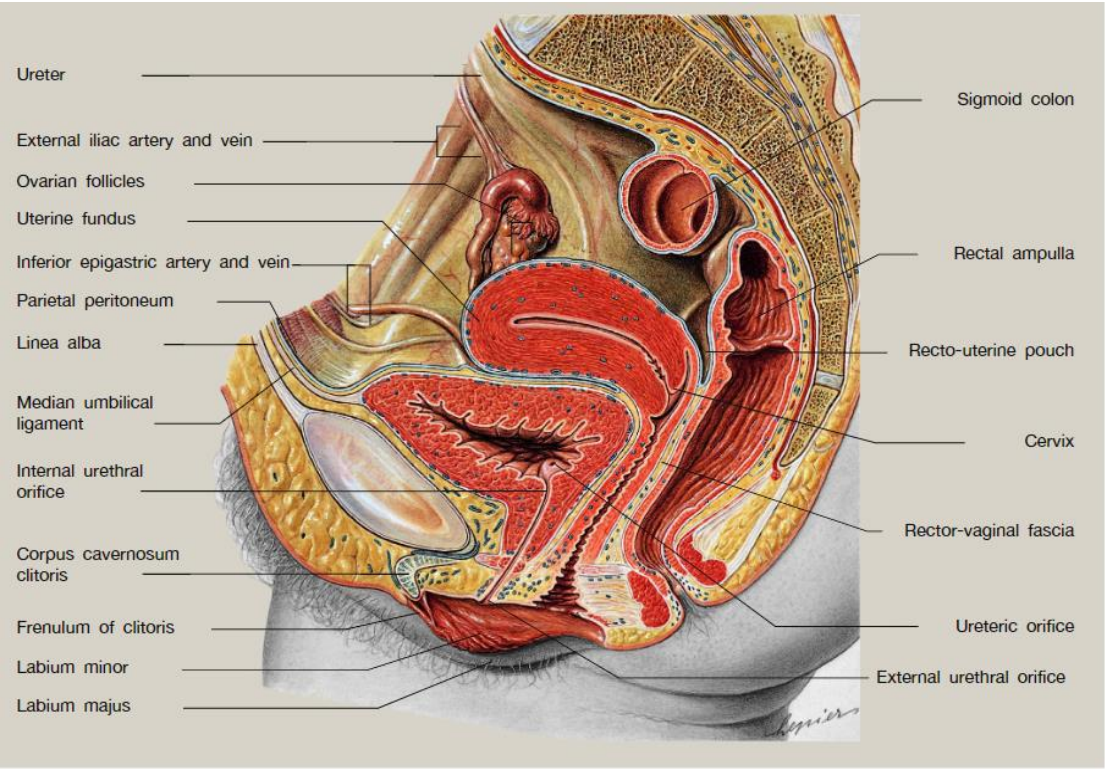


Figure 1 Sagittal view of female pelvic cavity showing relations of urinary bladder and relationship and the close proximity with rectum (22)

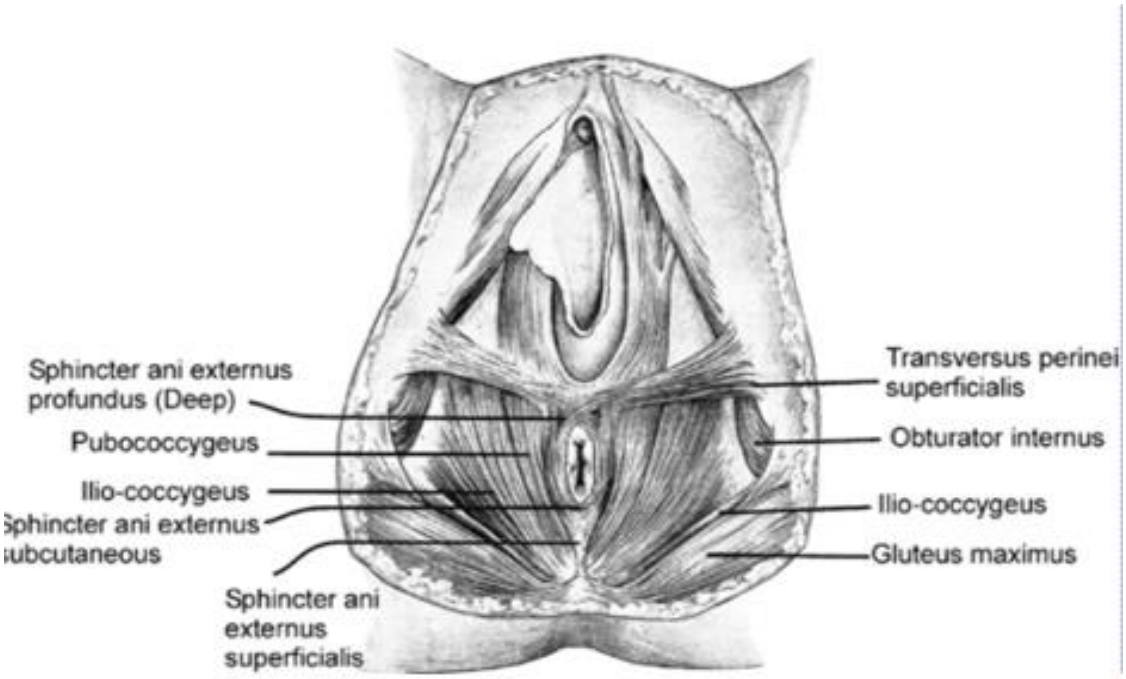


Figure 2 Sagittal view of female pelvic floor muscles (22)

The bladder is a balloon-like organ that has a function of storing and releasing urine. The bladder is found behind the pubic bone and is supported by the pelvic floor muscles (25). The detrusor muscle of the bladder wall consists of smooth muscle that can stretch up to prevent increase tension during bladder filling (21). The bladder is joined to the kidneys through two long tubes called ureters; their function is to expel urine from the kidney to the bladder (21). When the bladder fills with urine it relaxes, the muscle wall thins, and the bladder moves upwards towards the abdominal cavity allowing it to expand and accommodate urine (Figure 3) (21). The internal sphincter (a muscular valve) prevents urine from leaking out (21). The bladder has a triangular shaped base called the trigone and it helps prevent back flow of urine into the urethra or ureters (21). To urinate, the bladder contracts and empties by pushing the urine outside the urethra. A healthy adult voids up to 8 times a day with a micturition volume of 250ml-300ml (26).

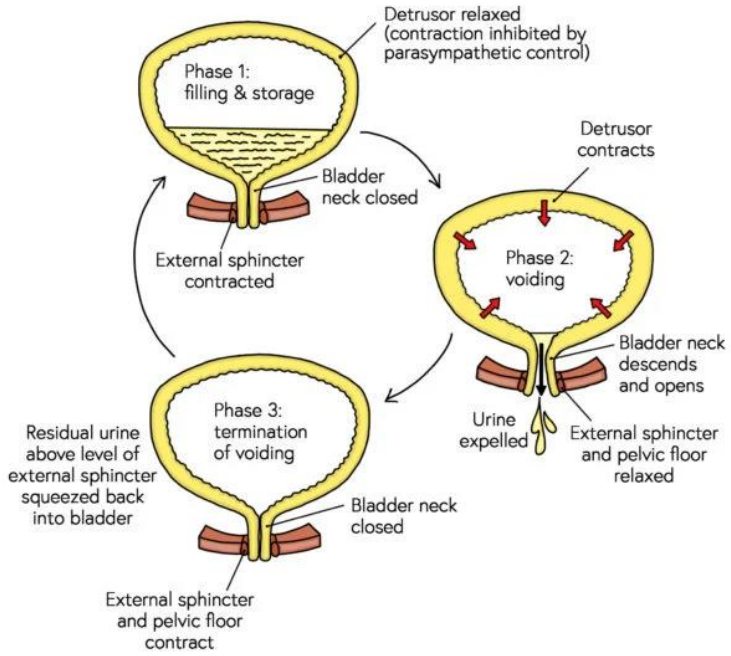


Figure 3 Process of bladder cycle of filling and emptying (copy right association of Association for Continence Advice. CC BY-NC)

2.3 Pathophysiology of LUTS

This section aims to explain the possible mechanisms that contribute to LUTS (by subtypes). Understanding conditions that causes LUTS helps in deciding the exclusion criteria used in the analyses of this thesis. For example, I am interested in women with functional incontinence rather than due to organic causes (i.e., due to illness / anatomical or neurological

problems) therefore women with physical conditions that may cause LUTS such as physical disabilities will be excluded from the analysis. Exclusion criteria for each analysis carried out in the thesis is discussed in the Method section (Chapter 3).

In healthy women, the urethra, bladder and sphincters work together to store urine at low pressure in the storage phase, and empty at appropriate times during the voiding phase (Figure 3). However, failure of storage or a failure of the sphincter mechanism may lead to LUTS. Stress UI occurs when there is a damage to the pelvic floor muscles supporting the urethra. The endopelvic fascia supports the urethra, the vagina and part of the uterine cervix. It divides the pelvic floor into the anterior and posterior compartments. This layer is itself suspended from the arcus tendinous fascia pelvis and the levator ani muscle (Figure 4). The urethra is compressed against this layer, to close its lumen, with the combined pressure with the sphincters exceeding that of the bladder. Damage to or weakness of the pelvic floor muscles or high abdominal pressure can overwhelm the combined sphincter mechanism. This causes urinary leakage especially when abdominal pressure is highest, such as during sneezing, coughing or exercise.

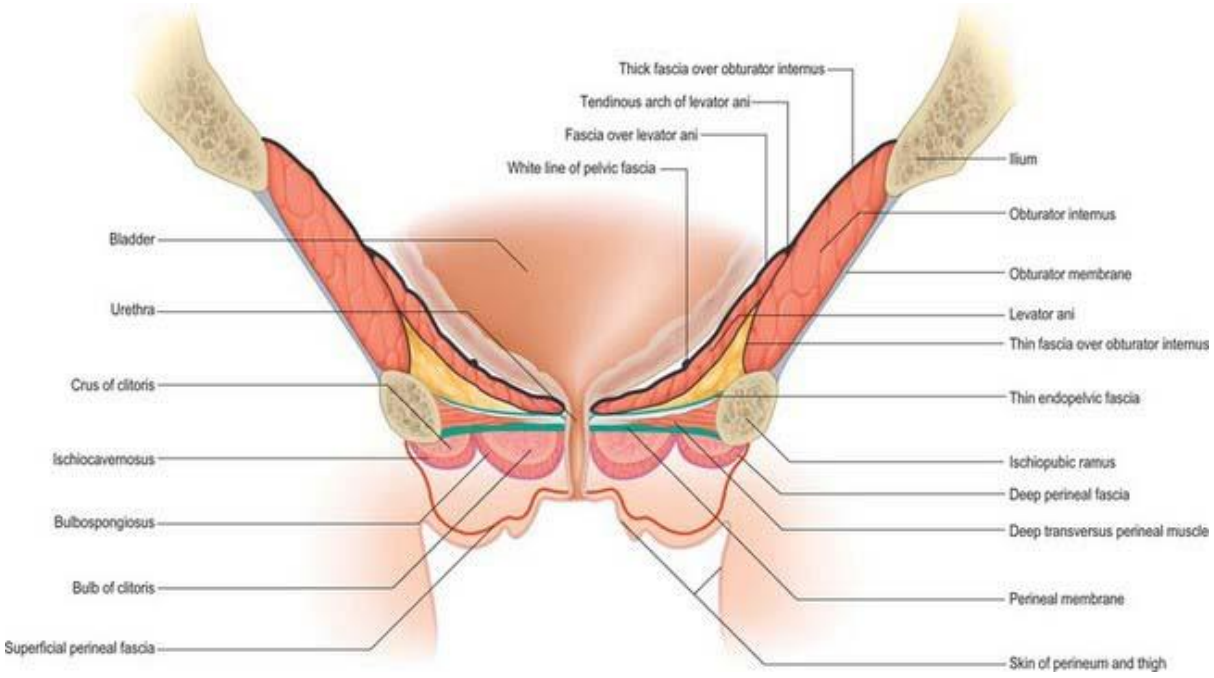


Figure 4 Muscle and facia of female perineum (Image taken from Basicmedical Key)

The central nervous symptom (CNS) plays a key role in the filling and emptying of bladder. Damage to CNS and or spine may result in LUTS especially UI (6). Urgency and urgency UI usually occur if there is detrusor overactivity (involuntary detrusor contractions during the filling phase that may be spontaneous or provoked). The neurogenic hypothesis suggests that

the detrusor overactivity pathophysiology is anatomically centred on the spine and parasympathetic motor supply to the bladder (27). Therefore, detrusor overactivity is common after spinal injuries, or diseases which affect the spinal cord such as multiple sclerosis (28). The urotheliogenic hypothesis suggests that the urothelium is a mediator for bladder function and inflammation or infection of urothelium could be a factor of the aetiology of urgency incontinence (27). However, some women with urgency UI have no physiological abnormality, thus they are considered as having idiopathic overactive bladder (29). Medical conditions including strokes, arthritis, and back problems, asthma also have been reported to be associated with LUTS especially UI (27).

It is important to understand that there are many causes of urinary incontinence and LUTS in women that are not due to organic causes (structural, anatomical, or neurological) but arise from functional impairments in the bladder. For example, physical disabilities, alcohol or caffeine consumptions, and urinary tract infections (UTI) have all been reported to increase risk of LUTS (9-11, 29-32). Medications such as narcotics and diuretics were strongly associated with UI in women(30). Psychoactive medications and antidepressants were associated with subtypes of LUTS (urinary incontinence) in women (31).

2.4 Assessment of LUTS

According to NICE guidelines for clinical assessments, female LUTS are usually evaluated with a detailed history of symptoms followed by physical examination and urinary analysis such as bladder diaries and urodynamics diagnosis (26). Urodynamics diagnosis are a series of tests that evaluate how well the bladder, urinary sphincter, and urethra work focusing on how well the bladder fills and empties (32). These tests examine what the bladder and urethra are doing if urine leakage occurs by checking urine flow rates, pressure around and in the bladder and other factors.

In epidemiological research, LUTS are measured using different urinary symptoms questionnaires of varying validity.

Table 2 summarises the validated questionnaires for LUTS that are commonly used in epidemiological research. This is because in large population health studies, conducting clinical tests is not feasible. Validated self-reported questionnaires such as the British Female LUTS (BFLUTS), the International Consultation on Incontinence Questionnaire Female LUTS (ICIQ-FLUTS) and the Danish Prostatic Symptom Score (DAN-PSS) (33-35) are commonly used.

To understand the severity of LUTS, it is important to evaluate the degree to which LUTS may affect women's daily activities. However, some self-reported questionnaires such as BFLUTS only measure women severity of LUTS symptoms and neglect measuring the impact of quality of life. Therefore, it is important to combine information on frequency of leakage and/or quantity of loss, and the perceived impact of LUTS on daily activities. ICIQ-FLUTS and DAN-PSS (34, 35), are a good example of questionnaires that ask patients to report both the frequency of LUTS, and their impact.

Table 2 : Main validated questionnaires for LUTS assessment that are commonly used in epidemiological research

Validated questionnaires for LUTS assessment used in epidemiological research			
Questionnaire	**Year of Validation**	**LUTS subtypes included**	**Assess Quality of Life**
Dan-PSS	1993	Storage and Voiding symptoms	Yes
Urogenital Distress Inventory	1994	Frequency, urgency, stress UI and urgency UI.	Yes
BFLUTS	1996	Storage and Voiding symptoms	No
ICIQ-FLUTS	1996	Storage and Voiding symptoms	Yes
Kings' Health questionnaire	1997	Frequency, urgency, stress UI and urgency UI	Yes
Over active bladder questionnaire (OAB-q)	2002	OAB symptoms (urgency, urgency UI, nocturia, enuresis)	Yes
Epidemiology of prolapse and incontinence questionnaire (EPIQ)	2005	Stress UI and OAB symptoms	Yes
Pelvic floor distress Inventory (PFDI)	2005	Frequency, urgency, stress UI and urgency UI.	Yes

In ALSPAC (see Chapter 3), the cohort study that provided the data for my thesis, both the BFLUTS and the ICIQ-FLUTS questionnaires were administered in 2002-2004 and 2011-2012 respectively.

2.5 Prevalence of LUTS in women

Arriving at a single estimate of the prevalence of LUTS in women is challenging due to differences in study samples, methods of measurements of LUTS, definition of subtypes of LUTS used and survey methodology between studies. It is therefore more appropriate to provide a range of such estimates. To do so, I conducted a PubMed search, using the terms (lower urinary tract symptoms) AND (prevalence)) AND (urinary incontinence) AND (UI). Whilst this search falls short of the highest standards that are expected from a formal systematic review(36), I aimed to retrieve much of the relevant literature.

Table 3 provides a summary of estimates of the prevalence of LUTS in women from epidemiological studies. Prevalence of any LUTS (i.e., storage, voiding and/or postmicturition) in women ranged from 45%-76% (5, 6). From the three groups of LUTS, storage LUTS had the highest prevalence estimates among women, ranging between 24% to 60% (7-9). The prevalence of voiding symptoms ranged from 2% to 30%, while the prevalence of postmicturition symptoms ranged from 2 to 14% (7-9).

UI (a subtype of storage LUTS) prevalence estimates among women vary widely in different studies because of the use of different definitions, the heterogeneity of different study populations and population sampling procedures. In a review (Table 4) of 36 general population studies from 17 countries, the prevalence of UI among women ranged from 5 to 69%, with most studies reporting a prevalence of any UI (i.e., stress UI, urgency UI and or mixed UI) in a range of 25–45% (37). The review reported prevalence estimates of daily incontinence ranging between 5 and 15% among middle-aged and older women (37).

The Epidemiology of Lower Urinary Tract Symptoms study (EpiLUTS) studied the prevalence of OAB (n=10,470 women, ages 40+ years) using an online, cross-sectional, population-representative epidemiologic survey conducted in the US, UK, and Sweden (38). OAB was defined as experiencing urinary urgency or urinary urgency incontinence and were categorized as occurring at least “sometimes”. The study reported that OAB prevalence ranged between 27%-46% (38). Other studies (Table 3) reported prevalence of OAB ranging from 11% to 30% (5, 9, 11) .

In summary, current literature provide diverse estimates of prevalence for LUTS among general population of women. Storage LUTS are the most common type of LUTS (especially UI) among women.

Table 3: Summary of studies reporting prevalence of LUTS in women

Reference	Sample			Method (Outcome Measure)	Types of LUTS	*Prevalence (%)
	Country	No of Participants (n)	Age (Years)			
Hunskaar et al. 2004 (10)	France Germany Spain UK	Total n=29500 community dwelling women	18+	Postal Survey UI was defined as involuntary loss of urine. Any UI includes stress UI, urgency UI and mixed UI.	Any UI	44% in France
					Any UI	42 % in Germany
					Any UI	23% in Spain
					Any UI	42 % in UK
Irwin et al. 2006 (8)	Sweden Italy Canada Germany UK	Total n=19165 Random sample of Men and Women	18+	Web based Computer assisted telephone interview. Used ICS definition to estimate storage, voiding and postmicturition LUTS	Nocturia	55%
					Storage LUTS	60 %
					Voiding LUTS	20%
					Postmicturition LUTS	14%
					OAB	12 %
Coyne et al. 2009 (6)	US UK Sweden	Total n=30000	Mean age 57 (age range: 40-49)	Survey was conducted via the Internet. LUTS defined by two symptom frequency thresholds, i.e., at least ‘sometimes’	At least one LUTS at least ‘sometimes’	76%

				and at least 'often' for all LUTS except incontinence, where frequency thresholds were at least 'a few times per month' and at least 'a few times per week'.	At least one LUTS at least 'often' For a threshold of at least 'often', 'somewhat or more bother from split stream	53% ≥70%
Coyne et al. 2011(5)	Worldwide population	4.3 billion	≥20 years	An estimation model using gender- and age-stratified prevalence data from the EPIC study along with gender- and age-stratified worldwide and regional population estimates from the US Census Bureau International Data Base. LUTS defined using ICS definitions.	LUTS OAB UI	45% 11% 8%
Coyne et al. 2013(11)	US	Total n=10,000 (51% were women)	Ages 18-70 (mean age 42.2 years)	Cross-sectional, population-representative survey (Web based). The LUTS tool assessed how often participants experienced LUTS during the past 4	OAB ≥ "sometimes" OAB ≥ "often" Overall OAB	30% 20% 23%

				weeks on a 5-point Likert scale. OAB definition: presence of urinary urgency ≥ "sometimes" or ≥ "often," and/or the presence of urgency UI.		
Chapple et al., 2017(7)	China Taiwan South Korea	Total n=8284 (51% are women)	40+	Internet-based self-administered survey. LUTS was defined using ICS definitions.	Any LUTS Storage LUTS Voiding LUTS Postmicturition LUTS	60% 24% 2% 2%
Soler et al. 2018(9)	Brazil	Total n=5184 (53% were women)	40+	Study was conducted as a telephone survey with assessment of LUTS using a standardized protocol, which included the International Prostate Symptom Score (IPSS) and, for OAB, the OAB-V8 questionnaire	Any LUTS Storage LUTS OAB	82% 36% 24%
*Since women is the focus of my thesis, prevalence (%) reported in this table are for women only.						

2.6 LUTS risk factors in women

Table 4 summarises the systematic reviews that have looked at studies investigating associations of various potential risk factors with LUTS in women (12-14, 39-42). I identified these systematic reviews using a search in PubMed using the following keywords: (lower urinary tract symptoms OR urinary incontinence) AND (risk factors) AND systematic reviews.

Older age, higher BMI, multiparity and vaginal delivery are the most consistently reported risk factors. Presence of urinary incontinence in childhood, enuresis in childhood, high impact exercise, infections such as UTI and perineal infection have also been examined. Most studies have focused on risk factors of UI (stress UI, urgency UI and mixed UI) compared to other types of LUTS (such as urgency, nocturia, increased day time frequency, intermittency, and hesitancy).

A good example of potential reverse causality involves the association of physical activity and LUTS. Women who are physical active may have reduced risks of LUTS(43); while, women with LUTS (especially stress UI) might avoid physical activity to prevent urinary leakage during the activity(44). Prospective cohort studies examining associations of possible risk factors with LUTS are available but are limited by focusing mostly on UI, unmeasured confounding, short follow up period and or a small sample size(45, 46). I also noticed that the systematic reviews about risk factors for LUTS included mostly studies of elderly women (Table 4).

It is these gaps in the evidence base that I aim to fill in this thesis. In my review of systematic reviews, I identified physical activity and constipation as two potential risk factors for LUTS that have not been widely studied to date. In the next two sections, I present the more in-depth literature reviews I undertook to identify studies that examined associations between physical activity, constipation and LUTS.

Table 4: Summary of systematic reviews on risk factors of LUTS in women

Reference	Aim	Years covered, Database searched and Included study Types	Sample	LUTS subtypes	Risk Factors	Main Findings	Limitation of Study
Toroko et. al,2016 (13)	Identifying studies that examines risk factors and prediction strategies of UI in women.	Medical databases were reviewed online between July 1974 and 2016. Analysed 18 prospective longitudinal studies Predicting UI in women in later life. Patients follow up periods in the included studies ranged between 1-39 years.	Sample size ranged from 117-81445. Populations from UK, Denmark, Japan, Taiwan, Australia, France, Ethiopia, and USA Ages 50+ years	Stress UI Urgency UI Mixed UI Nocturia Enuresis	Age, BMI, constipation, hysterectomy, comorbidities, parity, menopause, >30 years at first delivery, small bladder, vaginal scarring, recurrent UTI, perineal trauma and infections, smoking, cognitive impairment, depressive mood, reduced activity of daily living, child enuresis, obstructive pulmonary diseases and diabetes mellitus (DM)	Most frequent reported risk factors include: depressed mood, comorbidities, require assistance with daily activities, menopause, DM, age at first delivery >30 yrs, childhood enuresis, chronic obstructive pulmonary disease, urethral involvement, having a small bladder and vaginoplasty.	Focuses only on few subtypes of LUTS

Offermans et. al, 2009 (39)	To examine risk factors associated with UI in nursing homes.	Cohort studies were reviewed using multiple databases including MEDLINE, EMBASE, CINAHL, PsycINFO and the Cochrane Library 12 cohort studies were included between period of January 1997 and April 2008.	Sample size ranged from 256 to 1,170,066 residents (median 2,722). The largest populations were investigated in the USA and The Netherlands. Mean age ranged from 80-85 years. Proportions of women included in the samples ranged from 61% to 86%.	Any UI Stress UI Urgency UI Mixed UI	Age, gender, race, education level, marital status, parity, residency time, hobbies, retirement/pension, administration of finances of the elderly, comorbidities, diabetes, cancer, prostate cancer, Parkinson's disease, Alzheimer's disease, stroke, arterial hypertension, kidney insufficiency, stroke, pulmonary disease, osteoporosis, rheumatic disease, mental disease, vaginal, anal-rectal, and prostate surgical records, consumption of alcohol, past and current tobacco consumption, urinary infections, hip fracture, and daily medicines	Most frequent risk factors for UI reported are: age, dementia, cognitive function, locomotion and bedfast and were associated with UI.	Focuses only on UI and no other LUTS.

Hunskaar et. al, 2008 (14)	Reviewing literature on obesity and BMI as potential risk factors for UI.	Literature searches involved publications of community-based prevalence studies with bivariate or multivariate analyses of the association between UI in women and overweight/obesity. The search period was until June 2008 Included studies involved cross-sectional studies longitudinal studies, and RCT.	Sample size of women included in the studies ranged from 10-1967 women (Ages 20+).	Stress UI Urgency UI Mixed UI	Overweight Obesity	BMI, waist-hip ratio and abdominal obesity were identified as independent risk factor for UI in women. Five studies report effect on UI after surgical weight reduction procedures one study after a weight reduction program. Three RCTs reported reduce UI symptoms after weight loss.	Focuses only on UI and no other LUTS.
Almousa et al., 2018 (40)	To examine prevalence of UI in nulliparous adolescent and middle-aged women. To identify risk factors associated with UI.	PubMed, EMBASE, CINAHL, and Cochrane Library were systematically searched of studies from their inception to January 2016 18 studies including 14 cross-sectional studies, 2 cohort studies, 1 comparative study and 1 case control.	Nulliparous women/Parous women. Studies samples ranged from 19 to 1936 participants. Ages14-50 years. Analysed studies were conducted in Italy, China, Brazil, Denmark, Iceland, and USA	Stress UI Urgency UI Mixed UI Any UI	Age, BMI, childhood enuresis, anxiety, depression, panic attacks, constipation, eating disorders, sexual activity, and combined oral contraception.	The most frequent reported risk factors associated with UI are listed below: age, BMI, childhood enuresis, and high impact exercising.	Focuses only on UI and no other LUTS.

Tähtinen et al., 2016 (12)	To examine the long-term effect of mode of delivery on urgency UI and stress UI	Data was searched using Medline, Scopus, CINAHL, and relevant major conference abstracts up to October 31, 2014. Studies included RCT, cross sectional and cohort studies examining the association between mode of delivery and stress UI or urgency UI ≥1 year after delivery.	15 studies included in meta-analysis of stress UI (n=45659 women). 8 studies included in meta-analysis of urgency UI (n=49623 women).	Stress UI Urgency UI	Mode of delivery (Vaginal delivery, Caesarean section, instrumental delivery)	Pooled estimates from 15 studies showed increased risk of stress UI after vaginal delivery vs C-section adjusted OR: 1.85; 95% CI, 1.56–2.19 I^2 = 57%; risk difference: 8.2%) 8 studies showed increased risk of urgency UI after vaginal delivery versus C- section (aOR: 1.30; 95% CI, 1.02–1.65; I^2 = 37%; risk difference: 2.6%).	Focuses only on stress UI and urgency UI.
Kaplan et al., 2013 (41)	To study the relationship between bowel and bladder function and its implications for managing coexisting constipation and OAB.	PubMed was searched for articles published between January 1990 through March 2011 A combination of terms were used in the search including bladder, bowel, crosstalk, lower urinary tract symptoms, OAB, incontinence, constipation, hypermotility, pathophysiology, prevalence,	Nulliparous women/Parous women. Studies samples ranged from 23 to 4684 participants. Ages ≥23 years.	OAB	Constipation Faecal incontinence Uterovaginal prolapse	Bowel distension affecting bladder activity and constipation can contribute in the development of OAB symptoms, including frequency and urgency.	Only focused on OAB and no other LUTS.

		management, and quality of life. 28 articles were identified (11 animal studies and 17 human studies) that addressed crosstalk or other functional relationships between the bladder and bowel.					
De Mattos et al, 2018(42)	To study the prevalence of UI in female athletes. To examine whether sports type might influence UI.	PubMed, the Cochrane Library, and LILACS were used as database search up to 23 January 2017. Keywords included pelvic floor disorders, urinary incontinence, athletes, and sports. 22 studies including 2 cross-sectional studies,15 case series,2 ecologic studies,2 retrospective studies and 1systematc review.	n=7507 women aged 12 to 69.	Stress UI Urgency UI Mixed UI	High and low impact activities	High-impact activities showed a 1.9-fold prevalence over medium-impact activities and 4,59-fold prevalence over impact activities.	

2.7 Physical Activity and LUTS

To conduct a literature review for studies on physical activity and LUTS, I searched PubMed and Google Scholar for articles published in English up to the year 2020. The search was conducted including the following search terms: (lower urinary tract symptoms) AND (urinary incontinence)) AND (storage LUTS) AND (physical activity) OR (exercise).

Although there were systematic reviews (Table 4) on physical activity and risk of LUTS, the reviews did not include any prospective studies (40, 42). That is why I decided to update the review with prospective studies (Table 5) examining physical activity and LUTS to understand the gaps in literature.

A systematic review (details in Table 4) assessed the prevalence of UI in female athletes (22 studies, 7,507 women aged 12 to 69 years) and examined whether exercise type might influence UI (42). The review reported that UI prevalence ranged from 5.56 % in athletes undertaking low-impact activity (such as swimming) to 80% in athletes undertaking high-impact activity (such as trampolining)(42). The review examined 17 different moderate and high impact sporting activities, and found that gymnastics, volleyball, basketball, tennis, and football were associated with the highest risk of UI. The review also reported that high impact activities were associated with a 1.9-fold increase in prevalence of UI over medium-impact activities (42). The studies included in the review mostly have modest sample sizes and limited adjustment for confounders. Moreover, the studies are limited by selection bias. The review only focused on studies examining associations between UI and physical activity and did not examine other types of LUTS. The review did not include any prospective study to disentangle the direction of association between physical activity and LUTS. However, it included cross-sectional studies and retrospective studies that have limited ability to establish the temporal relationship between exposure and outcome (physical activity and LUTS, respectively, in the current context). Also, they may be affected by recall bias because participants reported the exposure retrospectively. Finally, the review only included athletes therefore, the result cannot be generalised to non-athletic women.

Table 5 summarises the existing prospective studies investigating the associations between physical activity and LUTS. One prospective study examined the relationship of various lifestyle factors, including physical activity, with OAB and stress UI in 6,424 women with a median age of 21 years (range 18 to 44) at baseline (45). The investigators reported a lower risk of stress UI, and wet and dry OAB at 1 year of follow up in women who were more

physically active compared to women who were less physically active(45). Another prospective study based on the US Nurse Health Study (NHS) examined physical activity in relation to UI risk in 31,355 women with a mean age of 66 years (range 54 to 79) at baseline (43). The study revealed that higher levels of physical activity as measured in average MET scores per week were associated with a reduced risk of UI symptoms at 2 years of follow up. In the NHS II study, women with a baseline mean age of 46 years (range 37 to 54) with higher levels of physical activity had a reduced risk of UI symptoms at 14 years of follow up (47). Both prospective studies reported that physical activity is associated with reduced risk of LUTS which conflicts with findings from the previous systematic review of studies among athletes conducting more high-intensity physical activity (36,40). It therefore remains unclear what role lower to medium impact physical activity might have in development of LUTS.

It is important to conduct more research that fill the gaps and limitations discussed above.
ALSPAC data could provide more robust assessment to the association between physical activity and LUTS. This is because ALSPAC data is collected prospectively thus may address the limitation discussed above by minimising recall bias that may be introduced from retrospective designs. Since prospective studies examining the association between physical activity and LUTS are limited, it is important to perform more prospective designs examining the prior association as replication of studies strengthen evidence of associations. Most of the studies were cross-sectional (Table 4) which are limited with reverse causality due to the nature of design. Therefore, prospective designs may help in disentangling the temporal relationship between physical activity and LUTS thus minimising reverse causality that occurs from cross-sectional design studies.
ALSPAC involves a large sample of general women (non-athletic) which could address the limitation of the recent systematic review above that examined only athletic women and give a better understanding on the association between physical activity and LUTS in general population of women.

Since some studies reported that physical activity may increase LUTS, and other studies reported that low to moderate physical activity may provide protective mechanism against LUTS. It is important to understand how different intensities of physical activity my influence LUTS. ALSPAC provided data on different intensities of physical activity that can be used to examine the association with LUTS.

To address limitations of the existing evidence, the first aim of my thesis was to examine the prospective association between physical activity and the risk of LUTS in a general population sample of parous middle-aged women.

Table 5: A summary of prospective studies on physical activity as a risk factor of LUTS

Authors Year of Study	**Sample size (n), Population Age at baseline**	**Study Aim**	**Outcome measure and frequency of symptoms**	**Exposure**	**Duration of follow up**	**Confounder**	**Results (main numerical result)**	**Limitations**
Danforth et al., 2007(43)	Nurse Health Study (NHS) n=31,355 White nurses from US. (Mean age 66 years, Age ranging 54-79 years)	Examining prospective association between physical activity and risk of developing UI.	Self -reported UI (stress UI, urgency UI and mixed UI) using a mailed questionnaire.	Self -reported physical activity using a mailed questionnaire Activities were then translated into metabolic equivalent task hours per week (MET hour/week).	2 years	Age, BMI, parity, race/ethnicity, cigarette smoking status and postmenopausal hormones.	Higher levels of physical activity were associated with a reduced risk of UI. (top versus bottom quintile of metabolic equivalent task hours per week, OR 0.81, 95% CI 0.71– 0.93; P for trend across quintiles <.01).	UI was not measured or defined by a validated questionnaire. Important confounders were not adjusted for.

Townsend et al.,2008(47)	Nurse Health Study II (NHS II) n=30,135 ages of 37-45 years Middle aged white nurses	To assess association between moderate physical activity and UI in middle aged women.	UI was self-reported using mailed questionnaire about sample medical history. Investigated LUTS included stress UI, urgency UI, mixed UI, functional UI, and occasional UI.	Self- reported physical activity using mailed questionnaire. Reported activities were translated into (MET hour/week).	14 years	Age, BMI, parity, race/ethnicity, cigarette smoking status, oral contraceptive use, and menopausal status.	Higher levels of physical activity were related to decreases risks of stress and urge incontinence. For stress UI Risk ratios (RRs) were 0.75 (95% CI 0.59-0.96 for top versus bottom quartiles); while, for urgency UI 0.53 (95% CI 0.31-0.90 for top versus bottom quartiles). Among the most active women, there was evidence of decreased risk ratios of urgency UI 47% (95% CI 10%-69%) The risk of UI decreased with increasing quantiles of moderate physical activity.	Data self - reported. UI were not measured by a validated questionnaire. UI was not defined using standard definitions. Important confounders were not adjusted for.
Dallosso et al., 2003(45)	To assess the relation between diet and other lifestyle factors including	Sample size involved 6424 women, Median age: 21, range:	LUTS (stress UI and OAB) were self-reported using postal questionnaire.	Physical activity (over past year) self-reported using questionnaire.	1 year	Age, BMI, and smoking	Lower risk of stress UI aOR: 95%CI 0.87 :0.68–1.12) and wet and dry OAB (aOR:95%CI 0.88:0.69–1.11)	Limited adjustment of confounders Old ICS definitions for OAB.

	physical activity, with overactive bladder (OAB) and stress UI in women.	18-44 years at baseline.	LUTS were defined using ICS definitions.				among women who were more physically active.	

2.7.1 Background Information on measurements of physical activity

Physical activity has been reported to have benefits on physical and mental well-being(48). Sedentary lifestyles have reported to have a negative impact on general well beings(49). However, employing a valid, reliable measurement of physical activity in research is challenging. Table 6 shows methods used in previous research to measure physical activity and states their strength and limitations; these methods are taken from practical guide to measuring physical activity (78). Doubly labelled water method (DLW) is the gold standard method for assessing total energy expenditure; however, it is and expensive method, time consuming and cannot capture qualitative data, therefore, not often used for research studies (78). Other methods of measurement physical activity include using devices such as pedometers, accelerometers, armbands and heart rate monitors. However, these methods are not suitable to use on a large population as they are expensive and may require technical expertise (78).

Self-reported questionnaires are the most common method used to assess physical activity (78). These questionnaires rely on participants' recall ability and their content vary with regards of measures of mode, duration, or frequency of physical activity. Methods of reporting data varies from paper and pencil assessment to computerized questionnaire, or interview. Validation studies comparing self-report questionnaires to DLW are still inconsistent; however, their advantages include cost-effectiveness, ease of administration, and accuracy in measuring intense activity and the ability to determine discrete categories of activity level (e.g., low, moderate, or high). Potential disadvantages include recall bias, social desirability, and complexity of the questionnaire.

Table 6 Summary of methods for measuring physical activity

*Method of measuring physical activity	Definition	Advantages	Disadvantages
Doubly labelled water method	A tool for assessing total energy expenditure.	1-Does not interfere in participant's daily activity. 2-Provides criterion validity for estimates of total energy expenditure and reported energy intake. 3-Easy to administer in all populations. 4-Provides a measure of body composition.	1-Expensive 2-High subject burden 3-Time-intensive 4-Cannot capture qualitative data
Self-Report Questionnaires	Method of measuring physical activity depending on participants' recall ability.	1-Cost-effectiveness 2-Easy to administer 3-Accuracy in measuring intense activity. 4-Ability to determine discrete categories of activity level. 5-Provide details about the physical activity. 6-Show improvement across groups or individuals.	1-Less robust in measuring light or moderate activity and in assessing energy expenditure. 2-Limited by dependency on written language (i.e., questions. 3-Social desirability 4-Recall bias
Self-report diaries	Require participants to record physical activity in real time.	1-Provides the most detailed data on physical activity. 2-Less susceptible to recall errors.	1-Questionnaires not completed in real time could be subject to memory bias.

		3-Less susceptible to social desirability bias and measurement bias	2-Participant reactivity, the phenomenon of behaviour changes due to awareness of being observed.
Accelerometers	Measure acceleration (counts) in real time and detect movement in up to three orthogonal planes (anteroposterior, mediolateral, and vertical). These counts are then translated into a metric of interest that can be biological (e.g., energy expenditure) or physical activity patterns (e.g., stationary).	1Devices can be worn in numerous places on the body, including waist, hip, and thigh.	1-Expensive 2-Require technical expertise. 3- Lack a standard protocol for managing or reducing data. 4-Can induce a reactivity bias. 5- Do not provide any contextual information. 6- Some accelerometers are unable to differentiate body position (i.e., sitting, lying, or standing) or walking intensity. 6- Relationship between accelerometer activity counts and energy expenditure depends on the count cut-point applied to the data; choosing different cut-points can differentially influence measurements of physical activity intensity.
Direct Observation	An independent observer monitors and records physical activity.	It is also a popular method for young children because they have difficulty recalling their physical activity.42 This flexible	Disadvantages include high cost of time and energy,30 potential reactivity,35, 36, 37 difficulty obtaining ethical

		method is valuable in gathering contextual information (e.g., preferred location, time, and clothing) and details of the physical activity (e.g., type of activity and personalized variations to activities).	approval,37, and the lack of objective measures of energy expenditure.37
Devices: Pedometers	Measure number of steps taken with a horizontal, spring-suspended lever arm that is deflected when a subject's hip accelerates vertically with a force beyond a chosen threshold.	Simplicity, low cost, and ability to pick up short durations of physical activity (often missed by self-report measures) make these devices popular.	Inability to record physical activity involving horizontal motion occurring during periods of inactivity, leisure activity, or solely upper body movements. do not record intensity, frequency, or duration of physical activity,53, 61 have significantly less data storage capacity than accelerometers,53 and can also induce reactivity in subjects.

ALSPAC uses self-reported questionnaires to measure physical activity this will be discussed in detail in the next section as this is the method.

2.8 Constipation and LUTS

I searched PubMed for articles reporting on the association between constipation and LUTS published in English up to the year of 2020. The search included the following search terms: ((lower urinary tract symptoms) AND (urinary incontinence)) AND (storage LUTS) AND (constipation)

The bowel tracts and urinary tract are interrelated structures (Figure 1) that have anatomical proximity. Therefore, any dysfunction in the bowel may affect the bladder (41, 50). A systematic review (Table 4) of human and animal studies examined the relationship between bowel and bladder function and its implications for managing coexisting constipation and overactive bladder symptoms (OAB) (41). It concluded that bowel distension affects bladder activity and that constipation can contribute in the development of OAB symptoms, especially frequency and urgency (41). However, this systematic review only focused association between constipation and other subtypes of LUTS such as UI. Therefore, I decided to search other studies exploring the association between constipation and LUTS (by subtypes). These studies were summarised in Table 7. Several cross-sectional and retrospective studies reported that constipation is associated with increased the risk of LUTS in women (41, 50). However, due to the nature of cross-sectional and retrospective designs of these studies, the temporal relationship between constipation and LUTS is still unclear. For example, it has been reported that constipation could increase risk of onset of LUTS in women (34, 41); whilst, it was also reported that urinary symptoms are more common in constipated women making LUTS a plausible risk factor for constipation (51). Other limitations of conducted studies include limited adjustment for potentially important confounders such as physical activity and hysterectomy (5, 52-55), modest sample sizes, and recall bias when participants report constipation retrospectively.

To my knowledge, only a single prospective study examined the association between constipation and UI in women (n=234 women recruited whilst pregnant). This study found that chronic constipation (women scoring ≥9 using the Sandwell Incontinence Following Childbirth Risk Assessment Tool (SIFCRAT) risk scale) was associated with an increased risk of stress UI 6 months after childbirth (46). However, this study included a sample of pregnant women

and thus results cannot be generalized to a wider population of women. Moreover, the study is limited by a short follow up period, small sample size and a focus on UI symptoms only.

After assessing and discussing the gaps of literature that examines the association between constipation and LUTS. I will be addressing these gaps by using rich data available from ALSPAC to provide more robust assessments and results. For example, studies mostly focused on UI (stress UI, urgency UI and , mixed UI) and not other subtypes of LUTS when examining the association between constipation and LUTS. However, I will use ALSPAC data to examine the association between constipation and other subtypes of LUTS including nocturia, increased daytime frequency, urgency, hesitancy, and intermittency.

I am aware that it is recommended by the National Institute for Health and Care Excellence (NICE) guidelines to screen for constipation in women with LUTS as symptoms my co-occur (53). However, examining whether currently having constipation might increase risk of LUTS in later life is still not clear. This is because previous studies were mostly cross-sectionally designed, they focus only on how constipation is associated with LUTS at the same timepoint. However, ALSPAC has an advantage of providing prospective data on constipation and LUTS which will help understand and examine the long-term association between constipation and LUTS. This could have important implications for understanding the nature of the relationship between constipation and LUTS and for the prevention of LUTS.

Most of the studies have adjusted for limited confounders that may influence the association between constipation and LUTS. However, ALSPAC has extensive data on several confounders that has not been examined extensively in previous studies including hysterectomy. Therefore, my analysis will have the advantage of examining several important confounders which will strengthen the evidence base.

Other advantages of using ALSPAC includes having validated questionnaires to assess LUTS and providing large sample size of women. ALSPAC has an advantage of providing long follow up periods (approx. 8 years) between assessments of constipation and LUTS which addressed the limitation of short follow up periods that previous studies provided.

Therefore, the second aim of my thesis was to contribute to the evidence base by examining the prospective association between constipation and risk of various LUTS (including storage and voiding symptoms) in parous middle-aged women.

Table 7 below summarises studies on constipation as a risk factor of LUTS

Authors	Study Design	Study Aim	Sample	Outcome measure	Exposure	Follow up period	Confounders	Results	Limitations
Soligo et al., 2006 (56)	Retrospective design	To analyse the prevalence and characteristics of constipation in women presenting to a tertiary referral urogynecologic centre for urinary or prolapse-related symptoms	Consecutive urogynecologic women (n=786) Ages=19-90 yrs (average=60 yrs)	Assisted 100 mm visual analogue scale (VAS) was used to assess: physical sensation, physical prolapse, stress UI, urge UI, nocturia & completeness of urinary voiding.	A physician-assisted specific bowel questionnaire was administered to each woman, detailing any history of constipation &anal incontinence.	NA	Age, menopausal status, vaginal delivery &and birth weight.	No differences in prevalence of constipation were observed for urinary symptoms or urodynamic diagnosis. Women with stress UI & no prolapse vs controls (no stress UI, no prolapse) showed a higher rate of constipation in the former group (P=0.036)	Recall bias Small sample size Reverse causality
Ewings P et al 2005., (46)	Cohort study with a nested randomized controlled trial (pilot trial).	Assessing risk factors for developing urinary incontinence following childbirth	Women (n=234) were recruited from those giving birth in Taunton and Somerset Hospital over a 19-week period from November 2001 to March 2002. Women were randomized to an intervention (n=117) or control group (n=117) using serially numbered opaque envelopes containing codes	Women recruited to the study were sent the Bristol Female Lower Urinary Tract Symptoms questionnaire at 6 months after delivery. Question used to define incontinence for the main analysis: 'Does urine leak when you are physically active,	Women had to score nine or higher on the 'Sandwell incontinence following childbirth risk assessment tool' (SIFCRAT) risk scale (Dandy 1999) and/ or to have already experienced incontinence. The SIFCRAT contains items on birth weight, parity,	6 months	Age group, BMI, family history, previous incontinence (yes/no), epidural/spinal (this delivery), constipation, parity (one, two or more), episiotomy in at least one delivery.	Chronic constipation (OR 1.86 (95%CI :1.03, 3.34) and episiotomy in at least one delivery OR 1.96, (95% CI:1.25, 3.07) were independent risk factors for UI, while an epidural or spinal {OR 0.62(95%CI: 0.42, 0.92)} was protective for UI.	Reverse causality Small sample size

			produced from computer generated pseudo-random numbers. Intervention group underwent pelvic floor exercises. Ages of women were stratified into: <20, 20-40, 25-29, 30-34 & 35+.	exert yourself, cough, or sneeze? Responses: 'never', 'occasionally' 'sometimes', 'most of the time' and 'all of the time'. For the analyses reported here, these responses are dichotomised into never and all other responses.	prolonged pushing in labour, forceps delivery, episiotomy, third-degree tear, epidural/spinal analgesia, multiple pregnancy, chronic constipation, obesity, and age (if first baby).				
Varma et al., 2008(54)	Cross sectional study	To estimate the prevalence of obstructive defecation by frequency and impact on quality of life in middle aged and older aged women. To identify independent risk factors associated with obstructive defecation in these women.	The study cohort included 2,109 community-dwelling women who were enrolled in the Reproductive Risks for Incontinence Study at Kaiser (RRISK). This cohort of women had a mean (± standard deviation) age of 55.9 ± 8.6 years. Forty-eight percent were white, 18% African-American, 17% Latina and 16% Asian.	Self-report questionnaires were on obstructive defecation. Questions: "During the last 12 months, how often have you experienced difficulty passing stool (bowel movements), having to sit on the commode (toilet) for more than 15 min, hard stools (bowel movements), or a sense of incomplete bowel movements (constipation)?"	Pelvic floor symptoms were assessed by self-report of urinary incontinence ("During the last 12 months, have you leaked urine, even a small amount?") or pelvic organ prolapse [ever having "dropped or prolapsed female/pelvic organs (bladder, uterus, vagina, rectum)"	N/A	Age, BMI, income, self-reported health status, irritable bowel syndrome (IBS), current smoker, menopause status, ≥ weekly UI, pelvic organ prolapses, pelvic organ prolapses surgery and urinary tract infection (UTI)	Factors independently associated with a higher prevalence of obstructive defecation in the past year were irritable bowel syndrome (1.8-fold increase), vaginal or laparoscopic hysterectomy (twofold increase), unemployment (2.3-fold increase), taking more than three medications (1.8-fold increase), pelvic surgery (1.4-fold increase), symptomatic pelvic organ prolapse (2.3-fold increase) and	Reverse causality Non-validated questionnaire was used to assess constipation or UI. Sample is healthy community dwelling women thus results cannot be generalized.

				Frequency was reported as daily, weekly, monthly, less than monthly or never in the past year				urinary incontinence surgery (2.5-fold increase).	
Ng Sc et al. 2002,(57)	Retrospective study	To evaluate the prevalence of anorectal dysfunction among women with urinary storage or voiding symptoms. To investigate the risk factors associated with anorectal symptoms.	Women (n=320, mean age ±SD: 45.14±11.15) recruited from urogynaecology outpatient clinic for urodynamic evaluation. Women were recruited after undergoing an interview where they were asked directly if they have UI or Anorectal dysfunction.	Structured self-reported questionnaire. Stress incontinence was defined as involuntary urine leakage during exertion or with increased intra-abdominal pressure, and was confirmed by a urodynamic examination. Our definitions of frequency, urgency, nocturia and urge incontinence were those approved by the ICS. An overactive bladder was defined by the symptoms of frequency, urgency, or nocturia, with or without urge incontinence. Women who had both stress incontinence and	Structured self-reported questionnaire. Anal incontinence was defined as any involuntary leakage of solid or liquid faeces or gas, such as: flatus incontinence; flatus and/or liquid stool incontinence; flatus and/or liquid and/or solid stool incontinence. Faecal incontinence was identified by asking, 'Upon sensing the urge of defecation, have you ever experienced involuntary leakage of liquid or solid stool, which caused a	N/A	Age, menopausal status, vaginal delivery history, prior pelvic surgery, uterovaginal prolapse, BMI	A high prevalence of constipation among women suffering from urinary dysfunction. (OR=1.69; 95% CI=0.77, 3.69 for stress incontinence; odds ratio=0.81; 95% CI:0.39,1.69 for OAB; for mixed UI; OR=1.35; 95% CI=0.54,3.38) Main risk factors associated with anal incontinence and constipation was the presence of uterovaginal prolapse (odds ratio=5.02; 95% CI=2.19,11.5 for anal incontinence; odds ratio=1.78; 95% CI=1.03,3.09 for constipation)	Recall bias Selection bias Small sample size Reverse causality

				urge incontinence were defined as having mixed incontinence. As they are presented in the following results, stress urinary incontinence, overactive bladder, and mixed incontinence are mutually exclusive of each other	sanitary or social problem?' Flatus incontinence was verified by the question, 'Have you ever experienced an involuntary loss of control of bowel gas passage?' Constipation was defined as less than three bowel movements per week.				
Maeda T et al., 2017(52)	Cross-sectional study	To evaluate whether Overactive Bladder Symptoms Score (OABSS) of female patients with latent FC is higher than that of patients without latent FC at the urological department of the general hospital or not. To investigate the associated factors for latent FC and mild to	Female patients were recruited from urological department (n=145, age ≧40 years). Only women who had been on stable oral medication for at least 3 months were included in this study.	Urinary symptoms were evaluated by OABSS. The OABSS was developed to assess the presence and severity of OAB symptoms as a self-administered four-item questionnaire (score: 0 to 15). OAB was defined as OABSS ≥ 3 and Q3 ≥ 2 and it was classified into "wet OAB," which was OAB with urinary	Constipation was evaluated by the Rome III criteria. The Rome III criteria include six items related to defecation: straining, lumpy hard stools, sensation of incomplete evacuation, use of digital manoeuvres, sensation of anorectal obstruction or blockage with 25 percent of bowel	N/A	Age diabetes, hyperlipidaemia drug therapy (calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antipsychotic drugs, and diuretics)	Moderate to severe OAB symptoms were associated with latent FC (odds ratio (OR) = 4.125, p = 0.005), while latent FC was the only associated factor of moderate to severe OAB and OAB with urinary incontinence (OR = 4.227, p = 0.005 and OR = 4.753, p = 0.004)	Reverse causality Small sample size Selection bias may have been introduced by investigating patients from the urology department.

		moderate OAB, wet OAB, and dry OAB.		incontinence, and "dry OAB," which was OAB without urinary incontinence. OAB was also classified into three severity categories as follows: mild OAB (scores from 3 to 5), moderate OAB (6 to 11), and severe OAB (12 to 15).	movements, and decrease in stool frequency (<three bowel movements per week). Latent FC was defined by positivity for two or more of the Rome III criteria.				
Moller LA et a. 2000 (55)	Cross sectional study	To assess the association between various risk factors and the prevalence of lower urinary tract symptoms in women 40–60 years old.	2867 women recruited randomly from Danish Civil Registration System and completed a questionnaire on LUTS. 502 women reported LUTS more than weekly and 742 reported no symptoms (controls). Women ages were stratified into 40, 45, 50, 55, and 60 years old.	Self-reported questionnaire. The definitions of stress and urge incontinence were defined by the ICS. Participants were asked to score symptoms on a four-point scale (never, sometimes, often, or weekly, or each time or daily/nightly)	The supplementary questionnaire on associated factors included parity, episiotomy, anal sphincter defect, fetal weight, prior hysterectomy, prior anterior vaginal repair, prior operation for uterine prolapse, weight, height, hormonal status, stool habits, use of diuretics, physical activity, and medication (diuretics,	N/A	Age, BMI, history of physical activity, abortion, parity, fetal weight, history of episiotomy, lesion of anal sphincter, repair of uterine prolapse, constipation , hysterectomy, cystocele repair, straining at stool, hormonal inactivity &	Constipation was inversely associated with lower urinary tract symptoms: Urge UI :aOR 1.6 (95%CI 1.0,2.4) Stress UI: aOR 1.4 (95%CI 1.0,2.1) Stress UI: aOR 1.4 (95%CI 1.0,2.1) Continuous UI: aOR 2.6 (95%CI 1.2,5.6) Urgency: aOR 1.5 (95%CI 1.0,2.2)	Recall bias Reverse causality

					antibiotics for cystitis, and non–antibiotics for non-infectious urinary symptoms).		use of diuretics.		
Coyne et al., 2007(5)	Cross sectional internet-based survey	To examine the prevalence of chronic constipation (CC) and faecal incontinence (FI) in a sample of American men and women aged ≥40 years who report symptoms of OAB.	An internet survey, Epidemiology of Lower Urinary Tract Symptoms II (EpiLUTS II), hosted by YouGov America, was conducted between 8 and 21 September 2008 927 men (mean age 56.1 and SD 10.1) and 1073 women (mean age 56 and SD 10.4) completed a self-administered survey.	The prevalence of OAB was assessed using a definition of presence of urinary urgency and/or urinary urgency incontinence (UUI). Urinary urgency was determined based on the question: 'During the past 4 weeks, how often have you had a sudden need to rush to urinate? UUI was defined as a 'yes' response to a question: 'During the past 4 weeks, did you leak urine in connection with a sudden need to rush to urinate?' OAB with urgency but no UUI was further	Chronic constipation Faecal incontinence	N/A	Age, race, marital status, and education	Men and women with OAB were more likely to report CC (22.3 and 35.9% vs 5.7 and 6.7%, respectively, $P <$ 0.0001). The overall prevalence of FI reported 'rarely' or more was 16.7% of men and 21.9% of women. Men and women with OAB were more likely to report FI than those without OAB.	Self-reported symptom rather than physician diagnosis. Recall bias Reverse causality

				categorized as continent OAB; while incontinent OAB was defined as the presence of UUI with or without urinary urgency					
Zhang et al., 2006 (58)	Cross sectional study	To assess the prevalence and risk factors in Chinese women using the 2002 ICS definition.	Randomly sampled women (n=4684, ages 20 or more) who were registered as a female residents & mailed Bristol Female Lower Urinary Tract Symptoms questionnaire for women self-completion.	Bristol Female Lower Urinary Tract Symptoms questionnaire was self-completed.	Part 1of self - reported questionnaire included questions about participants' age, marital status, employment, weight, body length, menstrual status, number of previous gestations, vaginal deliveries and caesarean sections, child birthweight, constipation etc	N/A	Age, BMI, parity, constipation , episiotomy, menopause, vaginal delivery, caesarean surgery, fetal birth weight and labour worker.	The prevalence of OAB was 8.0%, OAB dry was 2.4%, and OAB wet was 5.6%. Menopause, parity >2, constipation, episiotomy, and higher BMI were potential risk factors for OAB. Constipation increased the occurrence of OAB dry {OR 3.92, 95%CI (2.03,7.58)}.	Reverse causality Recall bias Diagnosis and history of gynaecology were based on anamnestic date thus missing classification might have occurred.
Abreu et al., 2018(59)	Cross sectional study	To assess the prevalence of functional constipation (FC), OAB and the dry and wet subtypes of OAB in women. To assess the association	516 women (mean age of 35.8±6) randomly approached in public spaces in a Northeast Brazilian city.	Self-reported questionnaire on UI and demographic information. The International Consultation on Incontinence Questionnaire - Overactive	Constipation was assessed using the validated Rome IV criteria.	N/A	Age, number of deliveries, schooling, and Roma IV criteria.	Overall, 22.7% of the constipated women were found to have OAB compared to a prevalence of 11.50% in the non-constipated group. Dry OAB was found in 13.7% of the constipated women	Reverse causality Recall bias Sample younger women so results cannot be generalized to older women.

		between FC and OAB.		Bladder (ICIQ-OAB) was used to evaluate symptoms of OAB. OAB was defined as the presence of urgency in the four preceding weeks. The presence of OAB without urinary incontinence was defined as dry OAB, while the presence of urgency associated with urine loss was defined as wet OAB.				compared to 6.5% of the non-constipated women.	
Cameron et al. 2010., (53)	Cross-sectional study	To assess if LUTS are more common in women that report difficult defecation (DD). The LUTS of particular interest included overactive bladder (urgency with or without urgency incontinence, frequency and nocturia) and	2790 black and white community dwelling women from Michigan, aged 35–64, who participated in a telephone interview as part of an epidemiologic study of urinary incontinence.	Participants were interviewed by phone and asked questions on UI. ICS Standardized terminology (number of nocturia episodes, the presence of urgency, and UI), number of daytime voids (frequency), presence of urinary infections in the past year, dysuria, feelings of incomplete	All subjects were asked "When you move your bowels, does the stool come out easily?" Difficult defecation (DD) was considered present in those answering "no	N/A	Age, household income, education, hysterectomy status, previous prolapse surgery, and self-perceived health status	Women with DD were more likely than those without DD to report that they had experienced any urinary incontinence (61.1% v 42.9%, adjusted OR 2.4, 95% CI 1.6–2.7). Women with DD had higher LUTS than those who did not: nocturia (mean 1.8 ± 0.1 vs. 1.3 ± 0.0), urgency (47.6 vs. 29.2%), increased daytime frequency (mean 8.2 ± 0.3 vs.	Outcome measure not validated. Phone interview could have guided participants not to say all answers clearly and openly.

		stress incontinence.		emptying, and the need to locate the nearest toilet as soon as arriving at a new place.				7.2 ± 0.1), dysuria (22.9% vs. 13.7%), and a sensation of incomplete bladder emptying (55.6% vs. 28.2%).	
Carter et al., 2012(51)	Retrospective survey of data from clinic	To examine the correlation between the occurrence of urinary symptoms and chronic constipation and to define possible causes for this correlation	Data collected on patients referred to clinic during 2008–2009 for assessment of chronic constipation,161constipated women and162 healthy female volunteers. Participants mean age 49±13 years.	Birmingham Boweland Urinary Survey Questionnaire (BBUSQ-22) used for measuring urinary and evacuation disorders.	Constipation scoring system was used for assessment of constipation severity and the Rome III module for irritable bowel syndrome (IBS) and chronic constipation.	N/A	Age, BMI, and parity	Demographic data was similar in both groups. LUTS were more common in the constipated group (increased urinary frequency 34 % vs. 14 %, p<0.001, nocturia 31 % vs. 8 %, p<0.001, urinary urgency 53 % vs. 21 %, p< 0.001, incomplete urinary emptying 24 % vs. 9 %, p00.003 and urinary incontinence 21 % vs. 5 %, p<0.0001.	Selection bias is possible due to the retrospective design. Small sample size Reverse causality

2.8.1 Background information on measurement of Constipation

Assessing constipation clinically currently relies on patient's self-report on constipation symptoms without including measures for severity of constipation (60). This means that treatment of constipation is judged by the practitioner based on the magnitude of complaints about constipation symptoms by the patients.

There is no standard instrument that is widely used to measure and evaluate symptoms of constipation. Some health care providers use frequency of bowel movements as a marker to evaluate constipation symptoms (60). Rome Criteria (I, II and III) is the most common instrument used to evaluate constipation (61, 62). It is developed by expert in the fields to help diagnose and treat gastrointestinal disorders including constipation and irritable bowel syndrome. This method is limited by its inability to measure severity of constipations and underestimation of the prevalence of constipation since it is reported by the patients themselves (60).

There are other questionnaires available to assess functional gastrointestinal disorders (such as irritable bowel syndrome) that are also used to measure constipation (63-65). However, these questionnaires measure upper and lower gastrointestinal symptoms making them not ideal measures because they involve questions regarding other gastrointestinal disorders which diminishes specificity for constipation.

ALSPAC does not have a validated questionnaire to assess constipation; however, the cohort have questions on use of medication for constipation which will be explained in detail in the next section. The advantage of measuring constipation by used of medication could be to capture women with severe constipation. As normally women will not take constipation medication unless they are very bothered by constipation symptoms.

2.9 LUTS and quality of life

Table 8 summarises the systematic reviews that have looked at studies investigating associations of LUTS with measures of quality of life (QoL) in women. I identified these systematic reviews using a search in PubMed using the following keywords: ((urinary incontinence) AND (lower urinary tract symptoms)) AND (quality of life)) AND (systematic reviews).

LUTS (By subtypes) were frequently linked to having a particularly negative impact of life(66) (Table 8).UI have been reported as one of the most bothersome diseases affecting physical functioning (67). UI and OAB both have been linked to poor measures of sexual

experience(16). Moreover, LUTS have been reported to be associated with mental health problems including depression and low self-esteem (13, 68).

Measuring QoL in patient suffering from LUTS has been inconsistent in the literature(69). This is because QoL include several different types such mental health or physical function. A systematic review (Table 7) assessed the different measures used to assess QoL in 61 trials from Europe and America(69). The review stated that there measures of QoL included are inconsistent as methods of QoL assessment ranged included incontinence specific QOL measure, generic health outcome only, and a combination of both(69). The review also stated that 10 papers included measures of QoL that were not validated or even referenced, and 10 papers used a non-referenced incontinence specific QOL measure for which there was neither a referenced. Therefore, better evidence is needed that include valid and compatible measures of QoL.

Several studies assessed LUTS and measures of QoL (systematic reviews Table 8). Those studies focus mostly on UI and the impact of other subtypes of LUTS (such as nocturia and urgency) and their impact on QoL. In the systematic reviews, mental health and sexual relationship have been repeatedly reported to be affected by LUTS. However, these two domains of QoL are very difficult to assess as they involve multiple measures which need to be further explored in detail and require very important confounders that need to be assessed for that have not been explained clearly in the systematic reviews. In the next two sections, I present the more in-depth literature reviews I undertook to identify studies that examined associations between LUTS and measures of QoL (quality of sexual experience and depression).

Table 8 Table representing a summary of systematic reviews LUTS and quality of Life (QoL)

Reference	Aim	Years covered, Database searched and Included study Types	Sample	LUTS subtypes	Measure of QoL	Main Findings	Limitation of Study
Pizzol et al. 2020(66)	A systematic review and meta-analysis of existing data to estimate the strength of the association between UI and QoL	MEDLINE/PubMed, Scopus, CINAHL, Embase PsycINFO and Cochrane Library databases from inception until 18th April 2020.was carried out. Meta-analysis of cross-sectional and case–control studies comparing mean values in QoL between patients with UI and controls was performed, reporting random-effects standardized mean differences (SMDs) ± 95% confidence intervals (CIs) as the effect size. Heterogeneity was assessed with the I^2	A total of 24,983 participants, mainly women. The mean age was ≥ 50 years in 12/23 studies.	Stress UI Urgency UI Mixed UI	Physical and social function, mental health and vitality	UI was strongly associated with poor QoL as assessed by the short-form 36 (SF-36) total score ($n = 6$ studies; UI: 473 vs. 2971 controls; SMD = − 0.89; 95% CI − 1.3 to − 0.42; $I^2 = 93.5$) and by the sub-scales of SF-36 and 5/8 of the domains included in the SF-36. Similar results were found using other QoL tools. The risk of bias of the studies included was generally high.	Did not include important factors of quality of such as sexual life. Focused on UI
Bartolie et al. 2010 (67)	A review of evidence on quality of life in patients suffering from UI and OAB.	An electronic search was conducted using Medline and EMBASE was up to January 30, 2009, for studies concerning QoL of patients	82 to 90 538 individuals were included in the studies; 72% were women.	UI OAB	Psychological well-being Physical function Sexual relationship	UI represents one of the most bothersome diseases affecting physical functioning.	Investigates only UI and OAB.

		affected either by UI or OAB. 39 studies were included Surveys (62%), case-control (36%) and cross-sectional studies (41%) are cross-sectional studies.					
Shaw et al.,2002 (16)	To review impact of UI on sexual lives of women	Medline and PsycInfo were searched papers including epidemiology of impact of UI on sex function in women. Search period covered 1980 until December 2001.	Sample ranged from 50-4000 women. Ages ranged from 25-88 years	UI	Dyspareunia, sex avoidance, sexual impairment, desire, arousal and overall satisfaction with sex life.	2 studies reported prevalence (2%) of sexual incontinence in general population. Clinical samples reported prevalence's range from 10 to 56% of sexual impairment due to UI.	Focused on UI only.
Ross et al. 2006(69)	This systematic review examined the use of incontinence-specific quality of life (QOL) measures in clinical trials of female incontinence treatments, and systematically evaluated their quality using a standard checklist.	PubMed was electronically searched between 1966 to March 2004 on articles published in English and that included trials measuring QoL in participants (men, women and children) with UI. 61 trials were included.	Papers from North America and Europe	UI	UI specific QOL measure, generic health outcome or a combination of both..	The majority of trials used (58 papers) used UI specific QOL measure. 8 trials measures of QoL that were not referenced and are not validated. Methods of measuring QoL are inconsistent in trials.	Focused on UI only. Many important measures of QoL were not included.

2.9.1 Measuring constipation by use of medication

Use of medication for constipation was self-reported in two questionnaires at two time points (questionnaire 1: 2001-2003 and questionnaire 2: 2003-2005). At these time points, women were asked to indicate whether they had "used any medicines (pills, syrups, inhalers, drops, sprays, suppositories, pessaries, ointments etc including homeopathic and herbal remedies) in the last 12 months for constipation". Women indicated "yes" in response to this question by checking a box were assumed to have used medication for constipation in the past 12 months. All women who did not respond "yes" were assumed to not have used any medication for constipation in the past 12 months. Responses to using medications for constipation during the two time points were categorised into three categories: none, yes at one of the two timepoints, and yes at both time points. To increase statistical power, the analysis was repeated by collapsing the constipation variable into two categories instead of three: women who reported "no constipation" and women who reported "taking medication for constipation at any time point".

2.10 LUTS and quality of sexual experience

To conduct a literature review for studies on LUTS and quality of sexual experience in women, I searched PubMed and for articles published in English up to the year of 2020. The search conducted including the following search terms: ((Urinary incontinence) AND (lower urinary tract symptoms)) AND (female sexual dysfunction)) AND (quality of sex)

Table 9 is a summary of studies that examined the relationship between LUTS and quality of sexual experience in women. Seven cross-sectional studies suggested that women with LUTS report a higher burden of female sexual dysfunction (FSD). A community-based study (Table 9) reported 34% of women (mean age 43.3 years), who had consulted a physician because of sexual problems in the past, suffered from FSD and urinary incontinence (70). A population-based telephone survey (Table 7) reported 56 % of participants (mean age 53.8 years), suffering from OAB, postmicturition and voiding symptoms reported decreased enjoyment of sexual activity (71).

A systematic review of six cross-sectional studies (sample sizes ranging from 32 to 883) assessed the association between overactive bladder (OAB: urinary urgency accompanied by increased frequency and/or nocturia in the absence of a urinary tract infection or any obvious disease (15) and female sexual dysfunction (e.g., desire, arousal, pain during sex, satisfaction, lubrication, and orgasm (15)). The review found an association between OAB with UI (OAB-

wet) and female sexual dysfunction (15). However, most of the studies had small sample sizes, were limited by potential recall bias (72-74), examined only a few measures of female sexual dysfunction, examined only OAB and did not adjust for some important confounders (e.g., hormone replacement therapy (HRT), anxiety, depression, and alcohol consumption) (72-74).

The evidence on the association of LUTS and quality of sexual experience is inconsistent and has several limitations. Prospective studies are needed to evaluate the relationships between LUTS and women's sexual dysfunction in the longer term, but they were not available in literature. The third aim of my thesis is to assess the association of LUTS (by subtypes) on quality of sexual experience in parous middle-aged women. I examined associations both cross-sectionally and prospectively in a large sample of middle-aged women, with adjustment for several important confounders. Moreover, I examined the relationship of LUTS and a range of quality of sexual experience outcomes including frequency of sex, enjoyment of sex, desire, orgasm, and overall satisfaction with sexual experience.

Table 9 Literature review on the impact of lower urinary tract symptoms (LUTS) on women's quality of sexual experience

Authors	Study Design	Study Aim	Sample	Exposure	Outcome	Follow up period	Confounders	Results	Limitations
Temmi C et al., 2000 (75)	Cross sectional study	To assess the impact of urinary incontinence (UI) on quality of life and sexual function.	2,498 participants were recruited from a voluntary health examination free of charge, which are fully sponsored by the city of Vienna. (332 women: mean age: 54.5±11.9 years and 62 men:56.9±15.8 years; age range: 20–96 years)	UI was assessed using a questionnaire which was adapted from BFLUTS. UI was defined as any involuntary loss of urine within the past 4 weeks.	The impact of urinary incontinence on quality of life and sexual function was assessed using UI questionnaire adapted from BFLUTS.	NA	Age, sex, duration of incontinence.	An impairment of sexual life by UI was stated by 25.1% of women and 30.5% of women.	Recall bias Small sample size Reverse causality Selection bias
Bilgic et al., 2019 (76)	Cross sectional study	To evaluate the relationship between with UI complaints with	436 (49.58 ± 8.65 years (Min: 24-Max: 70) volunteer women	Data were collected through Personal Information	Pelvic Organ Prolapse/Urinary Incontinence Sexual	NA	Age, BMI, pelvic organ prolapses (POP),	47.0% of the incontinent women indicated that they experienced lack of	Recall bias Small sample size

		other LUTS and sexual function in Turkish women.	with UI who were admitted to the urogynaecology department in Istanbul, Turkey.	Form, The Bristol Female Lower Urinary Tract Symptom Questionnaire (BFLUTS).	Questionnaire, (PISQ-12) was used to assess sexual function.		educational level, income status and working status.	sexual arousal, 40.4% had orgasm problems, 44.4% had lack of sexual desire. one-fourth experienced UI in sexual intercourse, and 67.4% had decrease in orgasmic intensity. There was a negative significant correlation between the total PISQ-12 scores and sub-dimension of BFLUTS scores ($p < 0.01$).	Reverse causality
Hansen at al.,2004 (77)	Cross sectional design	This study was conducted to investigate the relationship between LUTS and sexual dysfunction in both men and	In Denmark, questionnaires were mailed to a randomly selected age- and sex-stratified population of 15,000 persons.	Symptoms of LUTS in women were measured using a BFLUTS, self-report questionnaire. To standardise the assessment of	Various aspect of female sexual function was assessed using the PISQ-12, a standardised, validated, and reliable	NA	Age, BMI, alcohol consumption, diabetes, depression, cardiovascular disease, and partner	The PISQ-12 scores were significantly decreasing with age, and overall, 58.2% women reported low (<17) scores.	Recall bias Small sample size Reverse causality Selection bias Response bias, as respondents

		women aged 40–65 years.	A random selection of 7500 women (49:8±10:5 years; range 40–65 years) and 7500 men (49:1±11:0 years; range 40–65 years) were recruited for this study.	LUTS in men a validated symptom scoring system (International Prostate Symptom Score) was used. A total score >1 was defined as LUTS and depending on type of symptoms defined as voiding, storage, or mixed type of LUTS.	instrument developed to evaluate sexual function in women with urinary incontinence. Male sexual function was assessed using standardised, validated questionnaires from the Danish Prostate Symptom Score.		status (partner yes, partner no).	LUTS was strongest predictors of sexual dysfunction in women: Stress UI aOR 0.57 (0.47-0.68), Urgency UI aOR 0.68 (0.51-0.90) and mixed UI aOR 0.36 (0.30-0.43).	may inaccurately report their urinary or sexual dysfunction symptoms.
Field et al. 1993 (78)	Cross sectional. Retrospective study	To investigate the prevalence and nature of sexual dysfunction in women attending for urodynamic investigation, and whether this	100 (women) consecutive new patients referred for urodynamic assessment.	Women filled a standard urodynamic questionnaire includes questions on incontinence during intercourse and dyspareunia.	Women were asked to respond to a further questionnaire relating to various aspects of sexual function. The questionnaire	3 months follow up	NA	Sexual dysfunction was identified in 29% of those with genuine stress incontinence, 71% of those with detrusor instability and 54% of those in whom no urodynamic abnormality was	Small sample size Assessment tool is not validated. Recall bias Reverse causality Study looks at prevalence and

		is related to the urodynamic diagnosis.			was asked by the same individual each time, a gynaecologist with training in psychosexual medicine. Responses related to the preceding 3 months and were scored on a yes/no basis or on a five-point scale relating to degree or frequency.			detected. Bladder symptoms during intercourse were reported by 22 women (38%), particularly those with detrusor instability, and 11 (19%) were incontinent during intercourse.	not associations.
Korda et al., 2007 (70)	Community based study	To evaluate the prevalence of female sexual dysfunction ("FSD") and erectile dysfunction ("ED") in a	Questionnaires were sent to 10,000 women (mean age 43 and men (mean age 53).	UI/LUTS were self-reported through a questionnaire.	The IPSS and KEED (Kölner Erfassungsbogen der erektilen Dysfunktion) were integrated in the male questionnaire	NA	Age	The prevalence of female sexual dysfunction was 38.2%, and it was 19.6% for male sexual dysfunction. 26% of the women and 41.4% of men	Reverse causality Assessment tool is not validated. Recall bias

		community population and the relation to urinary incontinence.			and the FSFI (Female Sexual Function Index) in the female questionnaire.			suffered from UI/ LUTS. 34% of women, who had consulted a physician because of sexual problems in the past, suffered from FSD and urine incontinence.	
Saiki et al., 2019 (79)	Cross sectional design	To examine effects of UI on midlife women's relationships with their intimate partners, from the perspective of both women and their partners.	Participants were 43 community-dwelling midlife couples residing in the southwestern United States; female participants had stress, urgency, or mixed UI by self-report.	Participants completed confidential mailed study packets comprising questionnaires on demographic information and LUTS profile.	Participants completed mailed valid measures of the quality of the relationship, and open-ended questions to explore the effect of UI on the relationship in the participants' own words.	NA	Distress, communication about UI.	Distressed partners had significantly poorer scores on sexual quality of life ($P < .001$), relational ethics ($P = .002$), and communication about UI ($P = .03$).	Recall bias Small sample size Reverse causality
Coyne et al.,	EPIC A population	To examine the effect overactive bladder (OAB)	Sample recruited from 5 countries (Canada, UK,	Participant were asked about presence of UI	Sexual satisfaction was self-reported	NA	Age, marital status,	56 % of participants suffering from OAB, postmicturition and	Recall bias Small sample size

2008 (71)	-based telephone survey Cross sectional design	and other lower urinary tract symptoms (LUTS) on health-related quality of life (HRQoL) in a population sample, as OAB often occurs in conjunction with many other LUTS	Germany, Italy, and Sweden). 1434 identified cases of OAB group and 1434 participants designated as controls. Cases and controls were primarily Caucasian (96.2% and 96.7%, respectively), and most were female (65% in both groups, mean age 53.8 years).	symptoms through a computer assisted telephone interview (CATI). UI questions were adapted from validated IPSS questionnaire. OAB was defined using ICS definitions 2002.	through a computer assisted telephone interview.		education, chronic constipation , high blood pressure, bladder cancer and depression.	voiding symptoms reported decreased enjoyment of sexual activity.	Reverse causality Selection bias
Oh SJ et al., 2008 (80)	Cross-sectional design	Evaluated the impact of stress urinary incontinence (SUI) and overactive bladder (OAB) on health-	245 Korean women with LUTS (SUI; n = 123 and OAB; n = 122; mean age 50.4 years were recruited from individual clinical	BFLUTS questionnaire and frequency volume chart were used to assess LUTS.	The BFLUTS questionnaire was translated to Korean and designed to assess a wide range of symptoms and	NA	NA	The score for 'BFLUTS-sex' was higher in the SUI group than in the OAB group but this was not statistically significant (P =0.096). Of the 169	No adjustment for confounders. Selection bias Reverse causality

		related quality of life (HRQOL) and sexual function	practices at each hospital.		the impact on sexual function and HRQOL.			patients who had a sex life, the SUI group had experienced pain (P =0.033) and leakage (P =0.056) more frequently during intercourse than the OAB group.	
Sako et al., 2011(81)	Cross-sectional study	To assess whether lower urinary tract symptoms (LUTS) affect sexual function in Japanese females.	A multi-component questionnaire was mailed to 576 Japanese women (mean age 32.2 yrs; range 21-56 yrs) working in a hospital.	Self-administered questionnaire pertaining to LUTS (urgency UI, stress UI micturition, nocturia, weak urine flow, sensation of residual urine, bladder pain, and urgency). It is a validated questionnaire that was developed by members of the Japan Neurogenic	Female Sexual Function Index (FSFI)	NA	Age, Desire, arousal, lubrication, orgasm, satisfaction, pain	The mean overall FSFI score was 22.4±9.0. The mean FSFI score was not significantly different between women with LUTS and women without LUTS (23.2±9.3 and 21.6±8.8, respectively; P=0.057). However, the mean FSFI score of women with SUI was significantly lower than that of	Poor inclusion and exclusion criteria. Study included Selection bias Reverse causality

				Bladder Society Committee.				women without it (P=0.04).	
Nilson et al., 2011 (74)	A semi structured questionnaire study. Cross-sectional study	To assess the impact of UI and urgency on women's sexual life and the prevalence of urinary leakage during sexual activity. To explore factors that affect sexual desire and satisfaction with sexual life in these women.	147 women (aged18–74years) with UI and/ or urgency who consulted the Department of Gynaecology, University Hospital, Umea, Sweden and three other outpatient clinics in the same region were, during a period of 2.5years, asked to participate in the study.	Clinical evaluation included medical history, frequency–volume charts, residual urine, urine analysis and vaginal examination. Women completed specific questionnaires (BF-LUTS) concerning urinary problems, present and previous diseases. ICS definitions used to categorize LUTS by subtypes including stress	Women who had a stable partner relationship were also asked to complete a semi-structured questionnaire regarding psychosocial situation, partner relationship and sexuality. The questions about sexuality included sexual desire, vaginal lubrication, painful intercourse, incontinence during sexual activity and	NA	Age, BMI, somatic health, psychological health, attractiveness, quality of partner relationship, vaginal lubrication, painful intercourse, orgasmic ability, partner's health, worry about odour, worry about urinary leakage during	1/3 of the women had urinary leakage during sexual activity. Half reported that sexual life was spoiled due to UI or urgency. Women were worried about having urinary leakage during intercourse. The women's dissatisfaction with sexual life was strongly correlated to unsatisfying psychological health, orgasmic disability and worry about urinary leakage during intercourse.	Small sample size Reverse causation Selection bias Study included

				UI, urgency UI, mixed UI and OAB.	overall satisfaction with sexual life.		sexual activity.		

2.10.1 Background information on measurement of quality of sexual experience

Assessing sexual experience or sexual dysfunction is complicated as it depends on subjective assessment and it has several measures including arousal, desire, frequency of orgasm, frequency of sex and overall satisfaction with sexual experience (82). There are several forms of self-report measures of sexual function including daily diary records, self-administered questionnaires, and event log measures of sexual behaviour (96). Daily diary measures and self -administered questionnaires are the most common methods used to measure sexual behaviour in clinical trials (95).

In the daily diaries, participants will reflect important sexual measures including level of desire, arousal, and satisfaction. Daily diaries are designed to be completed immediately after sexual experience which may result influence completeness. Other major limitations include recall bias and the fact that diaries are mostly designed to give a yes or no answer which does not give details of sexual experience.

Self-administered sexual health questionnaires include different self-reported measures on a variety of measures such as desire, arousal, and satisfaction. They are designed with both ordinal and interval scales and have an advantage of detecting subtle differences at a sophisticated level of sexual experiences (95). Also, these methods have a high degree of reliability and validity in standardized in clinical trials (96). They are inexpensive and easy to use, which make them convenient for larger samples such as in epidemiological studies (83). However, differences in educational, ethnic, or cultural background may influence the validity of the questionnaires (96). Other limitations include reliance on the subject's recall over a period of several weeks and that participant may not want to report accurately their sexual experiences as they do not want to be veridical observer of their own experiences.

Since self-administered questionnaire have evidence of providing more sensitive and accurate information in the measurement of complex and subjective aspects of women's sexual function (96). I decided to use ALSPAC as it has a detailed self-reported questionnaire (2012-2014) on measures of sexual experience including level of arousal, level of desire, frequency of orgasm, frequency of sex and overall satisfaction with sexual experience (Details in next section).

2.11 Depression and LUTS

To conduct a literature review for studies on LUTS and depression, I searched PubMed and Google Scholar for articles published in English up to the year of 2020. The search conducted including the following search terms: ((((lower urinary tract symptoms) AND (urinary incontinence)) AND (depression)) AND (mental health)) AND (anxiety).

Table 10 summarises literature examining the relationship between LUTS and depression. Cross-sectional studies have reported an association between LUTS and depression (84-86), but these studies cannot rule out reverse causality, because there is evidence that depression increase the risk of LUTS (87). These studies are also limited by small sample size and lack of adjustment for important confounders such as body mass index (BMI) and physical activity. Moreover, depression was not measured using validated questionnaires and LUTS were not measured using validated questionnaire or defined by ICS definitions. A population-based study examined whether OAB influences health related quality of life including depression, and reported that women (n=10 584, ages ≥ 40 years) with OAB with bother were more likely to report that their bladder condition caused at least some problems; had worse scores on depression assessments compared to those without OAB bother symptoms(88). A community-based study (Table 9) reported that among Norwegian middle-aged women (n=5321, mean age 40-44 years), with UI, the adjusted OR for depression was 1.64 (95% CI, 1.32–2.04) and compared with women without UI (84).

There are some prospective studies (Table 10) that have examined whether women with LUTS have an increased risk of developing depression, but they focus on postpartum period and not beyond (89, 90). These studies suggest that there is an association between urgency UI, stress UI after delivery and the onset of postpartum depression. However, they have some limitations such as focusing only on postpartum depression, having short follow up period, and not assessing important confounders such as urinary tract infection, physical activity, and alcohol consumption. One of these studies is limited by not using ICS definitions to define UI. Moreover, these studies assessed only UI and no other types of LUTS. It is important to examine subtypes of LUTS prospectively as there is some differential association with depression and other LUTS cross-sectionally.

Although there is some evidence that UI may be associated with depression. Current evidence also suggests possible association in the opposite direction, most likely as depression increases the bother of UI symptoms. A prospective study of aging carried out by University of Alabama

at Birmingham (UAB) reported that after 3 years of follow up women (n=490, age ≥ 65 years) from Medicare beneficiary, baseline depression was weakly associated with incidence of UI (91). A prospective study of health maintenance organization examined the association between medically recognized UI and risk of depression in women (n=3004, age ≥ 65 years)(92). The study reported that depression was associated with incident diagnosed UI (RR=1.60, 95% CI, 1.20–2.00) over 9 years of follow up. Both of the prior studies are limited by focusing on elderly, limited adjustment of confounders and not using validated questionnaires to assess UI or depression. Moreover, the studies focused on incidence of UI and not subtypes of UI.

Understanding whether LUTS are associated with an increased risk of depression has important implications for public health and clinical practice. An increased understanding of whether LUTS are linked to depression will also help clinicians to consider preventing and treating depression in patients with LUTS. Examining LUTS by subtypes will show which subtypes of LUTS are more strongly associated with depression. Therefore, my fourth aim is to assess the association between LUTS (by subtypes) and depression in a large prospective cohort of parous middle-aged women.

Table 10 Literature review on the impact of lower urinary tract symptoms (LUTS) on women's depression

Authors	Study Design	Study Aim	Sample	Outcome measure	Exposure	Follow up period	Confounders	Results	Limitations
Juráško vá et al. 2020 (89)	Prospective cohort study Data for this analysis were derived from initial waves of the Czech part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ).	To identify risk factors related to stress UI and postnatal depression (PND) after birth, and investigate both directions of association between stress UI and PND in population-based sample of Czech mothers.	Czech mothers. 3,701 nulliparous and multiparous women completed the self-reported questionnaires at 6 weeks and 6 months after birth	Edinburgh Postnatal Depression Scale (EPDS) questionnaire related to stress urinary incontinence and depressive symptoms postpartum	Bidirectional stress UI and depression ("Do you experience urinary leakage related to physical activity, coughing and/or sneezing after birth?"). The question is in line with the 2003 International Continence Society (ICS) definition of stress urinary	2 follow up periods:6 wks and 6 months postnatal	age of mother, education, marital status, parity, smoking habits, pre-pregnancy body mass index (BMI), information about back pain, self-reported health, prenatal symptoms, wetting in mother's childhood after age 5 years, prenatal depressive symptoms, depression in mother's family history, birth weight, or mode of delivery.	Initially, SUI at 6 weeks was slightly, but significantly associated with onset of PND at 6 months (OR 1.51, 95% CI 1.02–2.23) while PND at 6 weeks was not significantly related to new cases of SUI at 6 months (OR 1.48, 95% CI 0.91–2.39). After full adjustment these OR reduced to 1.41 and 1.38 (both non-significant), respectively.	Short follow up period. Focus on only stress UI.

Milsom 2012 et al., (88)	A population -based, cross-sectional Internet survey,	To determine the bother associated with overactive bladder (OAB) symptoms and its influence on health-related quality of life (HRQL), anxiety, depression, and treatment seeking in adults in the United States.	Data from 20 000 US participants (9416 men and 10 584 women) aged ≥40 years participating in the Epidemiology of Lower Urinary Tract Symptoms survey.	Health-related quality of life, anxiety and depression measured by a survey completed by participants on internet.	Overactive bladder symptoms (OAB) measured by a survey completed by participants on internet. OAB is a syndrome comprising urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI).	NA	Age, race, sex, marital status, employment, and education.	Men and women with OAB with bother were more likely to report that their bladder condition caused at least some problems; had worse scores on HRQL, anxiety, and depression assessments; and had the greatest number of healthcare visits annually compared with those with OAB without bother and those with no/minimal symptoms. The strongest correlation between bother and symptom frequency was seen for urinary urgency, followed by urgency urinary incontinence and nocturia.	Recall bias Reverse causality Self-reported symptoms not using a validated questionnaire . Limited adjustment confounders.
Hunkaar 2012 et al., (84)	A cross-sectional population -based survey study.	To determine the association between depression and UI and anxiety and UI in	5,321 Norwegian women between 40 and 44 years. Participants lived in the county of Hordaland were	Women self-reported depression and anxiety symptom using a mailed questionnaire.	Women self-reported UI symptom using a mailed questionnaire.	NA	Age, BMI, parity, smoking, marital status, employment, and education.	Among women with UI, the adjusted OR for depression was 1.64 (95% CI, 1.32–2.04) and	Focuses on UI symptoms only. Reverse causality.

		middle-aged women in a large community-based cross-sectional study from Norway, The Hordaland Health Study (HUSK, 1997–1999).	invited by mail to participate and were given questionnaire to complete at home and return through email.		UI include stress UI, urgency UI and Mixed UI.			for anxiety 1.59 (95% CI, 1.36–1.86) compared with women without UI.	Not a validated outcome measure. Recall bias.
Hullfish et al., 2007 (90)	Prospective, cross-sectional study	To determine if there was an association between postpartum depression and symptoms of overactive bladder in postpartum women.	100 patients completed the questionnaires at the University of Michigan Hospital and 46 patients at the University of Virginia Hospital (mean age 29.2±6.1 years; 18–47 years) at their postpartum visit (mean time 45.2± 9.4 days postpartum; 11–79 days)	Depression measured by Edinburgh Postnatal Depression Scale (EPDS)	Overactive bladder and UI Measured by The Urge-Urinary Distress Inventory (URGE-UDI), the Urge-Incontinence Impact Questionnaire (URGE-IIQ)	6 weeks post-partum	Age, race, BMI, smoking Breast feeding, parity, vaginal delivery, and episiotomy.	There was a correlation between the URGE-IIQ score and depression (0.24, p=0.003), but not the URGE-UDI score. There was an association between postpartum depression and symptoms of urge incontinence.	Reverse causality. Focuses on post-partum depression.
Huang et al., 2015 (85)	Cross-sectional Population Based Study.	To test the hypothesis that LUTS are associated with anxiety and depression using a nationwide population-based database in Taiwan.	The study subjects (45906 both genders) were LUTS patients with anxiety or depression who had at least three outpatient service claims in one year, or at least	The records of healthcare seeking for anxiety and depression were collected 2 years before and after the diagnosis of LUTS.	The individuals with LUTS were defined as those who had at least three outpatient service claims in one year, or at least one inpatient hospitalization		Age, gender, hypertension, diabetes mellitus, and CAD, income And urbanization level.	, the odds ratios for anxiety, depression, either anxiety or depression, and both anxiety and depression, were 2.05, 2.19, 2.14, and 2.56, respectively. There was an	Reverse Causality Important confounders have not been adjusted for such as diet, obesity, smoking, psychosocial stressors,

			one inpatient hospitalization claim during 2001–2009.		claim during 2001–2009. LUTS symptoms were classified by storage symptoms, voiding symptoms, and benign prostatic hyperplasia (enlargement).			association between LUTS and the stress-related common mental disorders, and there seemed to be an additive effect of anxiety and depression on the association with LUTS	daily activity, medications.
Huang et al., 2017(86)	Population based cohort study	To further examine the direction and strength of the temporal association between LUTS and anxiety/depression using a representative data set from the Taiwan's National Health Insurance program and using a longitudinal follow-up study design.	Using claims data obtained from the Taiwan National Health Insurance Research Database, 17,489 patients with LUTS and 34,978 non-LUTS matched controls (cohort 1); and 45,707 patients with anxiety, 19,306 patients with depression, 91,414 non-anxiety, and 38,720 non-depression matched controls (cohort 2) were enrolled between 1999 and 2008.	LUTS Patients who had LUTS, anxiety, and depression were defined as having at least three outpatient service claims in one year or at least one inpatient hospitalization claim during the period 1999–2008.	Depression Anxiety	All subjects were followed at least three years or until the date of death or the end of 2011 to estimate the risk of developing anxiety/depression.	Age, gender medical comorbidities including hypertension, diabetes mellitus and coronary artery disease, overweight and obesity urinary tract infection Parkinson's disease multiple sclerosis spinal cord injury and multiple system atrophy.	LUTS patients were 2.12 (95%CI: 1.95–2.30) and 2.03 (95%CI: 1.76–2.33) times more likely to develop anxiety and depression, respectively. Patients with anxiety and depression were 2.01 (95%CI: 1.88–2.14) and 2.37 (95%CI: 2.13–2.65) times more likely to develop LUTS, respectively.	
Goodie et al., 2008 (91)	Prospective cohort study	To determine the incidence and predictors of incident UI	University of Alabama at Birmingham	Depression (self-reported) measured by Geriatric	UI (self-reported) at baseline was	3 years	Age , education, living	Prevalence of UI at baseline was 41% in women.	Important confounders have not been.

		over 3 years in community dwelling older adults.	(UAB) Study of Aging enrolled 490 women and 496 men 65 to 106 years old (mean age 75) from Medicare beneficiary. Participants filled self-reported questionnaires.	Depression Scale score.	determined by the questions “Have you ever leaked even a very small amount of urine?” and “Has this happened in the past year?” At each follow up interview participants were asked, “In the past 6 months, have you leaked even a small amount of urine?”		situation and residence.	Baseline depression was weakly associated with incidence of UI (OR 1.2).	Participants are geriatrics thus results cannot be generalised. Focused on UI in general and not subtypes of UI.
D.Thom et al., 1997 (92)	Prospective cohort design	Examined the association between medically recognized UI and risk of several disease conditions, hospitalization, nursing home admission and mortality.	Review and abstraction of medical records and computerized data bases from n=3004 women aged 65 years and older, of a large health maintenance organization in northern California.	Depression	Incidence of UI	9 years	Age, cohort, dementia, cerebral vascular disease, congestive heart failure, ischaemic heart disease, musculo-skeletal disease, cancer, renal disease and hypertension	Increased risk of newly recognized UI following a diagnosis of depression RR 1.60 (95% CI, 1.20–2.00).	Focused on elderly. Focused on incidence of UI and not subtypes of UI. Important confounders not adjusted for.

2.11.1 Background information on measuring depression

There is no extant procedure considered ideal to measure depression due to the complexity and nature of depression symptoms. However, a combination of interviews and self-reported questionnaires are considered the most suitable assessments for depression. According to research, an evidence-based assessment tool for measuring depression should include several important parameters. These parameters include an adequate coverage of depression symptoms and adequate psychometric properties measures. Moreover, assessment tools should measure anhedonia (inability to feel pleasure), depressed moods, suicidal thoughts. There should also be an approach to measure if suicidal thoughts plans are resolved or there are new preparation plans for suicide. Other important assessment parameters include melancholic (suffering from severe depression or sadness) subtypes, comorbidity, and bipolarity. Since epidemiological research involve large sample, it is more convenient to use validated self-reported questionnaires. There are several depression questionnaires used to measure depression in adults such as Beck Depression Inventory (screens depression and measures behaviour manifestation and severity of depression) and Centre for Epidemiologic Studies Depression Scale (designed to measure depression in general population and primary care).

ALSPAC uses self -reported validated depression scale (EPDS) to measure depression symptom. I combined EPDS and intake of antidepressants to measure depression for my analysis (further on that in the next section).

2.12 Summary of Introduction

From the literature reviews conducted in my thesis, there was gap in literature in examining prospective associations between physical activity and LUTS by subtypes. Moreover, there was conflicting evidence with regards to this association as some studies suggest that exercise might cause more leakage during the exercise while other studies suggest that more exercise might be protective against LUTS in later life. Therefore, the first aim of this thesis is to examine the prospective association between physical activity and LUTS (by subtypes) in parous middle-aged women.

Although it has been established in literature that constipation and LUTS my co-occur in women. Examining whether currently having constipation might increase risk of LUTS in later life is still not clear. Therefore, the second aim of my thesis is to disentangle the temporal relationship between constipation and LUTS (by subtypes) in parous middle-aged women.

Although there was good evidence in literature that LUTS may affect the quality of sex for women when examined cross-sectionally. There were gaps in literature on the long-term effect of LUTS (by subtypes) on measures for quality of sexual experience in women. Therefore, the third aim of my thesis examined the prospective association between LUTS (by subtypes) and multiple measures for quality of sexual experience in parous middle-aged women.

Finally, depression symptoms and LUTS cooccur but the direction association is not established clearly. Therefore, the fourth aim of my thesis examines if depression is associated with LUTS (by subtypes) in parous middle-aged women.

The next chapter of my theses involves methods (Chapter 3) used to achieve my aims. Then results of analyses for each aim (Chapters 4-7) will be presented. Followed by an overall discussion of thesis (Chapter 8) including strength and limitations of studies, mechanisms explaining associations, comparison of my results to previous literature, mechanisms explain associations, finally future recommendation, and conclusion.

3 Chapter 3. Methods

In this chapter, I will describe design and methods of each study carried out in the thesis including:

1. Examining prospective association between physical activity and risk of LUTS (by subtypes) in parous middle-aged women. (Published in Journal of Urology)

2. Examining prospective association between constipation and the risk of developing LUTS (by subtypes) in parous middle-aged women. (Published in Journal of Women's Health)

3 a) To assess the cross-sectional and prospective association of stress UI with frequency and satisfaction with sex.

b) To assess the prospective associations of LUTS (by subtypes) on quality of sexual experience in parous middle-aged women.

4. Examining prospective association between LUTS (by subtypes) and depression (measured by Edinburgh Post Natal Depression Scale and/or antidepressant intake) in parous middle-aged women.

I will give an overview of the ALSPAC mothers' cohort and methods of measurement of subtypes of LUTS.I will also explain participant exclusion/ inclusion criteria, measurement of outcome/exposure, confounders and statistical method used for the results chapters (4-7). Each section will end with a summary table of the methods that are used for the results chapters (4-7).

3.1 Overview of the Avon Longitudinal Study of Parents and Children Mothers' Cohort, measurement of lower urinary tract symptoms and dealing with missing data in thesis

3.1.1 The Avon Longitudinal Study of Parents and Children (ALSPAC) mother's cohort

All analyses carried out in this thesis used data from the ALSPAC mothers' cohort. ALSPAC is a prospective population-based birth cohort study which recruited pregnant women residing in the former Avon Health Authority in England with an estimated date of delivery between 1st of April 1991 and 31st of December 1992 (93). A sample of 20,248 women were eligible for the recruitment campaign carried out between 1990 and 1992. Only 14,541 pregnant women were enrolled because they had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99. There was an attempt to bolster original sample with eligible sample that did not joint originally the study when the oldest children were approx. 7 years. This resulted in a total sample of 15,454 pregnancies from original sample. Detailed information on the cohort description and the eligible sample available in cohort profile (http://www.bristol.ac.uk/alspac/researchers/cohort-profile/). Mothers were followed up extensively using up to 24 questionnaires and were asked to self-report data on range of characteristics including demographic, psychological and health related behaviours such as alcohol consumption and physical activity. Detailed information on ALSPAC is available on the cohort website (http://www.bristol.ac.uk/alspac), which includes a fully searchable data-dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). ALSPAC has a general ethical approval which was used to carry studies included in thesis. The approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Details about the number of women participated in each analysis will be explained later under each section.

3.1.2 Measuring lower urinary tract symptoms (LUTS)

Two validated questionnaires were used to assess LUTS in the ALSPAC mothers' cohort at two different timepoints. The first time point was in 2002-2004 when LUTS were measured using a validated British Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire (33). The second time point was in 2011-2012 when LUTS was measured using an International Consultation on Incontinence Questionnaire Female Lower Urinary Tract

Symptoms (ICIQ-FLUTS). The ICIQ-FLUTS evaluates female LUTS and impact on quality of life in research and clinical practice across the world. The ICIQ-FLUTS is derived from the fully validated BFLUTS questionnaire (28). It involves the exact same questions of BFLUTS with additional questions asking women about how bothersome their symptoms are. Details on content, development, and validation of BFLUTS and ICIQ FLUTS questionnaires are published (33).

Table 11 lists the questions available on ALSPAC related to LUTS in both questionnaires. Based on the International Continence Society (ICS) definitions, responses to these questions were used to categorise different types of LUTS. LUTS were considered present if symptoms were reported to occur at least "sometimes" for all subtypes except for increase daytime frequency (≥ 9 times) and nocturia (≥ 2 times nightly). LUTS investigated in the thesis include stress UI, urgency UI, mixed UI, urgency, nocturia, increased daytime frequency, hesitancy, and intermittency. I chose those LUTS due to evidence for their greater impact on women's quality of life (94).Ideally, other important subtypes of LUTS including post-micturition dribble should be investigated but there were no data available in ALSPAC on those types of LUTS.

Table 11 Represents the International Continence Society definitions and ALSPAC questions used to measure LUTS (by subtypes)

International Continence Society definitions and ALSPAC questions used to measure subtypes of LUTS					
LUTS subtypes	***Definitions**	**BFLUTS (2002-2004)**	**Response option**	**ICIQ-FLUTS (2011-2012)**	**Response option**
Stress urinary incontinence (stress UI)	Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.	In the past month, how often have you had any of the following: problem holding urine when you jump, sneeze etc.	**1-Almost all the time** **2-Sometimes** 3-Not at all	Does urine leak when you are physically active, exert yourself, cough or sneeze?	1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time**
Urgency urinary incontinence (urgency UI)	Complaint of involuntary loss of urine associated with urgency.	Does urine leak before you can get to the toilet? AND How often do you have to rush to the toilet to urinate?	1-Never 2-Ocassionally **3-Sometimes** **4-Most times** **5-Every time** 1-Never 2-Occasionally **3-Sometimes** **4-More often than not** **5-Every time**	Does urine leak before you can get to the toilet? AND Do you have a sudden need to rush to the toilet to urinate?	1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time** 1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time**

Mixed urinary incontinence (mixed UI)	Complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing, or coughing.	Does urine leak before you can get to the toilet? AND How often do you have to rush to the toilet to urinate? AND In the past month, how often have you had any of the following: problem holding urine when you jump, sneeze etc.	1-Never 2-Ocassionally **3-Sometimes** **4-Most times** **5-Every time** 1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time** **1-Almost all the time** **2-Sometimes** 3-Not at all	Does urine leak before you can get to the toilet? AND Do you have a sudden need to rush to the toilet to urinate? AND Does urine leak when you are physically active, exert yourself, cough or sneeze?	1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time** 1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time** 1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time**
Nocturia	Waking to pass urine during the main sleep period.	During the night, how many times do you have to get up to urinate, on average?	1-none 2-one **3-two** **4-three** **5-four or more**	During the night, how many times do you have to get up to urinate, on average?	1-none 2-one **3-two** **4-three** **5-four or more**
Urgency	Complaint of a sudden compelling desire to pass urine, which is difficult to defer.	How often do you have to rush to the toilet to urinate?	1-Never 2-Occasionally **3-Sometimes** **4-More often than not** **5-Everytime**	Do you have a sudden need to rush to the toilet to urinate?	1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time**

Increased Daytime Frequency (IDF)	Complaint that micturition occurs more frequently during waking hours than previously deemed normal.	During the day, how many times do you urinate (pass water or have a wee) on average?	1 - 6 times 7 - 8 times **9 - 10 times** **11 – 12 times** **13 or more times**	During the day, how many times do you urinate (pass water or have a wee) on average?	1 - 6 times 7 - 8 times **9 - 10 times** **11 – 12 times** **13 or more times**
Hesitancy	Complaint of a delay in initiating micturition.	How often is there a delay before you can start to urinate?	1-Never 2-Occasionally **3-Sometimes** **4-Most times** **5-Every time**	Is there a delay before you can start to urinate?	1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time**
Intermittency	Intermittent stream (Intermittency)is the term used when the individual describes urine flow, which stops and starts on one or more occasions, during micturition	Do you stop and start more than once while you urinate without meaning to?	1-Never 2-Occasionally **3-Sometimes** **4-Most times** **5-Every time**	Do you stop and start more than once while you urinate?	1-Never 2-Occasionally **3-Sometimes** **4-Most of the time** **5-All of the time**
Answers marked as **bold** were considered positive when defining the types of urinary incontinence. Urgency UI and mixed UI were identified only if women have responded positively to all relevant questions *All definitions are taken from ICS standardised definition of LUTS (20)					

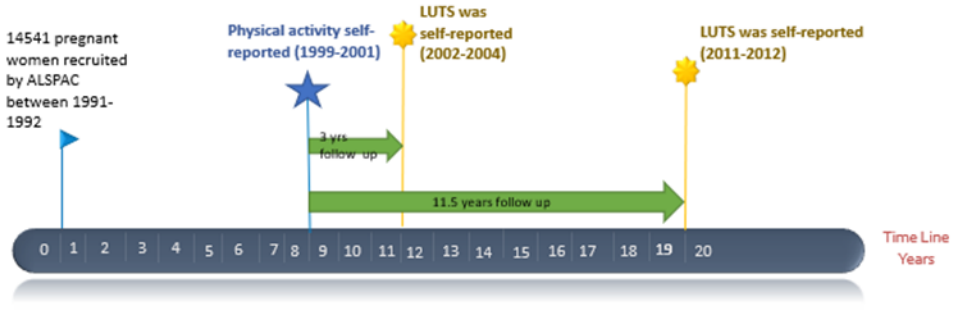
3.1.3 Dealing with missing data

In this thesis, analyses were carried out using logistic regression to estimate associations between our exposures and outcomes. However, there was missing data for some of the exposures, outcomes and confounders used in the analyses of the theses. Details of missing data of variables used in this thesis are available in each result chapter (chapters 4-7); these include a description of the percentage of missing data for each variable, the use of multiple imputation to mitigate bias due to missing data, and the distribution of covariates in the imputed and observed datasets. Multiple imputation was used to impute missing data on potential confounders for all eligible participants. All analyses were repeated on a complete case sample to give comparison to multiple imputation results and to assess bias to missing data. Complete case analysis includes sample restricted to participants with information on exposure, outcome, and confounders. Multiple imputation models included the exposure, outcome, and confounders. Twenty imputed data sets were generated using multiple imputation by fully conditional specification (chained equations). Main analysis results were obtained by averaging the results of 20 data sets using the Rubin rules(95), where the estimation of the 95% confidence intervals and p values considers the uncertainty in the imputations as well as uncertainty in the estimate. All analysis was carried out suing STATA/MP™ 15. Detailed descriptions of the statistical analysis for each research study are provided in the following sections.

3.2 Methods of Physical activity and LUTS Analysis

Aim: To examine the prospective association between physical activity and risk of LUTS (by subtypes) in parous middle-aged women.

The timeline below (Figure 5) demonstrates the timepoint were ALSPAC recruited pregnant women (1991-1992). It also represents the time points were physical activity (exposure) was measured and the follow up timepoints were LUTS (outcome) were measured. At 3 years of follow up, women's mean age was 40.5 years; SD 4.5. At 11.5 years of follow up, women's mean age was 49.3 years; SD 4.4.



Symbol	Resembles
	Time point ALSPAC recruited pregnant women
	Exposure: Physical activity (self reported)
	Outcome: LUTS (by subtypes) self-reported
	Prospective follow up from measuring exposure

Figure 5 Timeline for physical activity and LUTS analysis

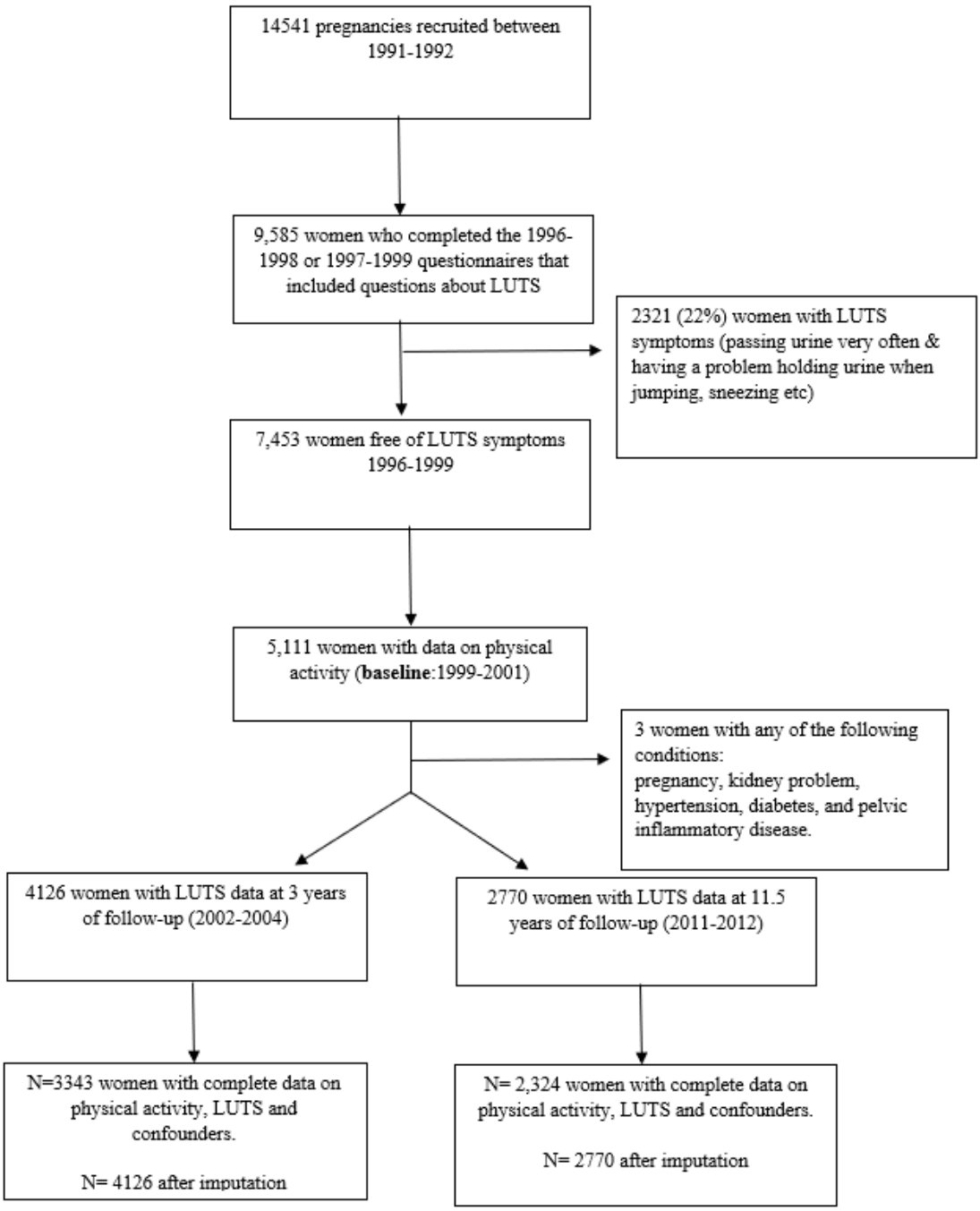
3.2.1 Participants

In 1991-1992, ALSPAC recruited 14,541 pregnant women (Details section 3.1.1) (73). In 1996-1998 questionnaire and 1997-1999 questionnaire 9,585 women completed questions on LUTS. Among these women, 2,321 reported having LUTS and were excluded before baseline of physical activity and LUTS analysis (Figure 6) resulting in 7,453 participants who were free of LUTS. At baseline, 5,111 of these women completed a self-reported questionnaire on physical activity at 1999-2001. I further excluded 3 women as they fit exclusion criteria (details in next section).

Women were eligible for inclusion in the imputation datasets if they had data on physical activity and LUTS, were free of LUTS symptoms in 2002-2004 and did not meet my exclusion

criteria. This analysis included two follow up points were LUTS were measured (3 and 11.5 years from baseline). At 3 years from baseline, eligible sample of 4,126 of these women completed BFLUTS questionnaire that measures LUTS. At 11.5 years from baseline, eligible sample of 2,770 women completed ICIQ-FLUTS questionnaire to measure LUTS. Details of participants flow chart is available in Figure 6.

Figure 6 Flow chart showing the women included in the prospective study of Physical activity and LUTS



Notes:

Physical activity (exposure) measured between 1999-2001

LUTS (outcome) measured between 2011-2012

All confounders were measured between 1991-1992

3.2.2 Exclusion Criteria

Table 12 shows ALSPAC questions (self-reported), and the time points used to exclude women with the following conditions: pregnancy, kidney disease, hypertension, diabetes and/or pelvic inflammatory disease. These conditions were chosen to be excluded because these are physical conditions/diseases that could cause LUTS, whilst I am interested in women with functional incontinence rather than due to organic causes (i.e., due to illness / anatomical or neurological problems). Excluding participants means that my findings will not be generalisable to women with these conditions. Women with LUTS symptoms (stress UI and frequency) at baseline (1999-2001) were also excluded because I wanted to study whether physical activity influenced the risk of developing LUTS.

Table 12 shows the ALSPAC questions used for Exclusion Criteria

Exclusion Criteria		
Excluded conditions (Year of exclusion)	**Question**	**Response Option**
Hypertension (1997-1999)	Have you had (or continued to have) any of the following since your study child's 5th birthday: Hypertension	**1-Yes, consulted a doctor** **2-Yes, not consulted a doctor** 3-No
Diabetes (1997-1999)	Have you had (or continued to have) any of the following since your study child's 5th birthday: Diabetes	**1-Yes, consulted a doctor** **2-Yes, not consulted a doctor** 3-No
Pregnancy (1999-2001)	If you have no periods now, is this because:	**1-You are pregnant** 2-You have had a hysterectomy 3-You are menopausal (going through the change) 4-don't know
Pelvic inflammatory disease (1999-2001)	Have you ever had any of the following problems: Pelvic inflammatory disease	**1-Yes, had it recently in the past year** **2-Yes in past not recently** 3- No never
Kidney disease (1999-2001)	Have you ever had any of the following problems: Kidney Disease	**1-Yes, had it recently in the past year** **2-Yes in past not recently** 3- No never
Women with stress UI symptoms	Problem holding urine when you jump sneeze etc?	1-Not at all **2- Sometimes**

(1996-1998)		**3- Almost all the time**
Women with frequency LUTS symptoms (1997-1999)	Passing urine very often	1-Not at all **2-Sometimes** **3-Almost all the time**
Women responding in **bold** were excluded.		

In next two sections, I will give an introduction on methods of measurement of physical activity in literature. Then I will explain methods used in ALSPAC to measure physical activity.

3.2.3 Measurement of Physical Activity (MET-hours/week)

Women self-reported average hours in a typical week (>6 hrs, 2-6 hrs, < 2hrs, never) of diverse types of physical activity in 1999-2001. Physical activities included were jogging, aerobics, squash, yoga, tennis/badminton, swimming, brisk walking, cycling, weight training, keep fit exercises and other exercises. I translated the self-reported physical activity measures into metabolic equivalents scores (METs). One MET is defined as the energy you use when you are resting or sitting still. I estimated the metabolic equivalents scores (METs) of these different measures using the estimated energy costs of different types of physical activity in the Compendium of Physical Activity; details are found it the website below:

(https://sites.google.com/site/compendiumofphysicalactivities/). I excluded keep fit exercises and other exercises as I could not assign them METs with confidence.

I calculated activity specific MET-hours per week by the following equation:

MET-hours per week = activity assigned METs × the time spent doing an activity × frequency

Response options of the time spent doing an activity (hrs/week) were categorial, therefore, I estimated hrs/week as follows: 6 for '≥ 6hrs', 4 for '2– 6hrs', 1 for '< 2hrs' and 0 for 'never'. I derived the total activity score for each participant by summing up MET-hours per week (MET hours/week) for the different types of physical activity. I divided the MET hours/week into quartiles (excluding those women who reported no activity) to obtain five categories of physical activity levels: zero was the reference group, 0.1-17.2, 17.3-29.2, 29.3-43.2 and ≥43.2 MET hours/week. The reason for converting continuous physical activity (MET hours/week) variable into quartiles was to assess if the relationship between physical activity and LUTS is non-linear (U-shaped). For example, to test whether there are higher odds of LUTS in the lowest and highest physical activity groups.

3.2.4 Measurement of LUTS

In this analysis, LUTS was measured at 3 years of follow up (from baseline) using an adapted version of the BFLUTS questionnaire (96). At 11.5 years after baseline (2011-2012), women completed an adapted version of ICIQ-FLUTS (28). Further details on measuring LUTS are available in section 3.1.2.

3.2.5 Confounders

All confounders in this thesis are included if they might be a risk factor of LUTS (discussed in Chapter 2, section 2.6) and other exposures or outcomes.

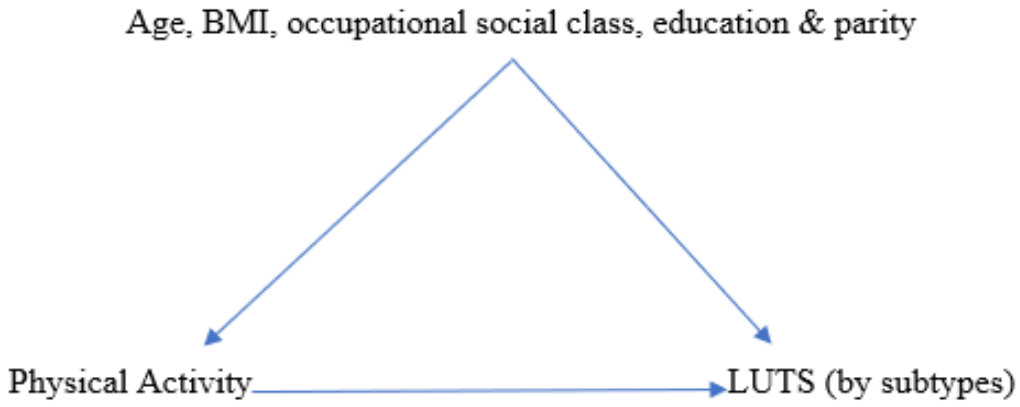
Confounders (Figure 6) were included in this analysis if they might be associated with physical activity and risk factors for LUTS. Age, BMI, occupational social class, education & parity have all been previously reported as risk factors for LUTS (13, 14, 97, 98). A detailed literature review on risk factors for LUTS are available in Chapter 2, section 2.6.

The above potential confounders are also associated with physical activity. For example, functional limitations have been reported to become more prevalent with age (99). It is important to adjust for BMI because studies have shown correlation between high physical and a low body fat (100). Parity is another important confounder because physical function may reduce with rise in parity status; the mother will be busy with the children thus have less time to be physically active (101). Adjusting for occupational social class and education is also important, as individuals how a higher socio-economic class perform more leisure-time activity (i.e. moderate-vigorous intensity physical activity) than those at the bottom (102). There was consistent evidence of a higher prevalence or higher levels of leisure-time or moderate-vigorous intensity physical activity in those at the top of the socio-economic strata compared with those at the bottom (84).

Originally, I considered adjusting for mode of delivery (i.e., vaginal, or caesarean delivery) because it is an important risk factor of LUTS especially UI (12), but a confounder should affect both physical activity and LUTS. While, searching the literature there was no convincing evidence that mode of delivery is associated with physical activity over an extended period of time. Since women included in our analysis had delivered their child at least 5 years prior to the baseline for the analysis, and this is a long period of time for mode of delivery to affect physical activity, I did not adjust for mode of delivery in this analysis. Although hysterectomy is a plausible confounder as it associated with both physical activity and LUTS. Hysterectomy

would only affect physical activity post operative and not over an extended period. Therefore, I decided not to adjust for it.

Figure 7: Potential confounders that could influence physical activity and LUTS



Women's age, occupational social class, education, parity, weight, and height were self-reported at recruitment (1991-1992). Weight and height were used to calculate BMI (weight in kg / height in meters squared). I categorised occupational social class according to the 1991 British Office of Population and Census Statistics and then binarized into manual and non-manual occupational social class. I categorised women's education into university level degree vs other degree (Certificate of Secondary Education, Vocational, Ordinary level, Advanced level). Although, it is better to leave occupational social class and women's education variables categorial to have a better adjustment for confounders, frequencies across categories of each variable were small. Therefore, I had to binarize the variables to ensure model convergence.

3.2.6 Statistical Analysis used to examine physical activity and LUTS

Examining physical activity (MET hours/week) as an exposure, the variable was continuous, but I transformed it into categorial variable of four levels which was represented in results section as percentages. LUTS variables (outcomes) examined were binarized (details in Table 11) and represented as percentages and frequencies.

I used logistic regression to estimate the association between physical activity and subtypes of LUTS. Evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS was tested by comparing a model where physical activity categories were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

Due to studies reporting that high-impact physical activity might increase the risk of developing UI (75, 76), I wanted to further explore this association. Therefore, I repeated all analyses with

restricting activities to those classified as high intensity (METs ≥ 6 or more). These included cycling, aerobics, swimming, jogging, tennis/badminton, and squash.

To minimise selection bias due to including only those participants with complete data (on all of exposure, outcomes and covariables), and to increase statistical power, we used multiple imputation to impute missing covariate information for women considered to be eligible for the analysis (i.e., women who provided data on physical activity and LUTS). We generated 20 datasets using multiple imputation by fully conditional specification (chained equations). The imputation model included physical activity, all LUTS outcomes and the covariates mentioned above.

3.2.7 Summary Table: Methods of physical activity and LUTS analysis

Table 13 is a summary table of the methods used for physical activity and LUTS analysis. It includes summary on participants exclusion and inclusion criteria, measurement of physical activity, measurement of LUTS, potential confounders and method of statistical analysis.

Table 13 Summary Table of Method for Physical Activity and LUTS Analysis

Summary Table for Methods of Physical activity and LUTS	
Participants	After 3 years of follow up (n=4126; mean age=40.5 years) After 11.5 years of follow-up (n=2770; mean age=49.3 years)
Exclusion Criteria	Pregnancy, heart disease, diabetes and/or pelvic inflammatory disease. Women with LUTS symptoms at baseline (1991-2001) were also excluded.
Physical Activity (Measured at baseline:1999-2001)	Physical activity levels were self-reported at baseline and translated into metabolic-equivalents hours per week (MET hours/week).
Measuring LUTS (Measured at 2011-2012)	Self-reported LUTS using validated questionnaire BFLUTS at ≈3 years of follow up and ICIQ-FLUTS at ≈11.5 years of follow up. LUTS (subtypes) were categorised using ICS definitions.
Confounders (Measured at 1991-1992)	Age, BMI, occupational social class, education & parity
Statistical Analysis	Logistic regression and multiple imputation.

3.3 Methods of Constipation and LUTS Analysis

Aim: Examining prospective association between constipation and the risk of developing LUTS (by subtypes) in parous middle-aged women.

The timeline below (Figure 8) demonstrates the timepoint were ALSPAC recruited pregnant women (1991-1992). It also represents the time points were constipation (exposure) was measured and the follow up timepoints were LUTS (outcome) were measured. At 10 years of follow up, women's mean age was 43.3 years and SD 4.5.

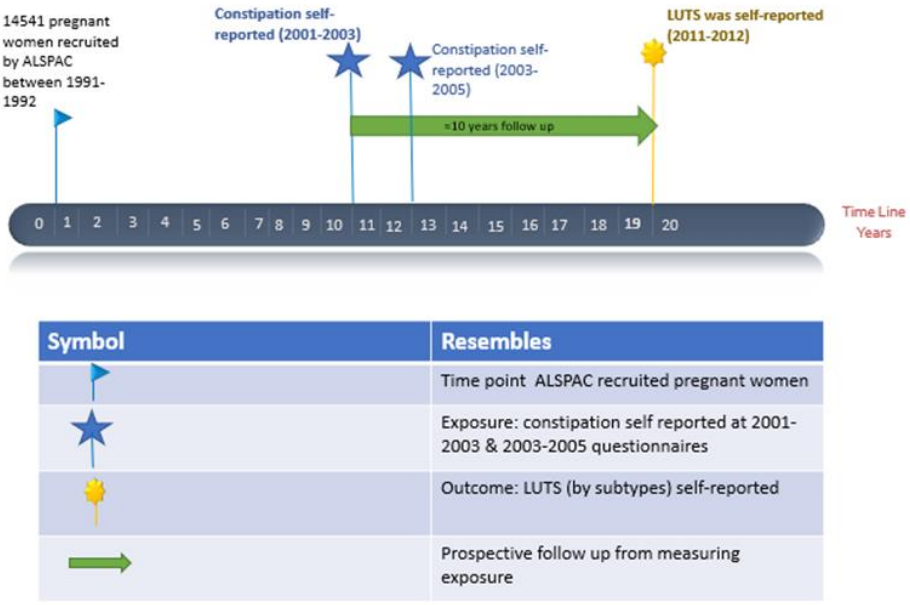


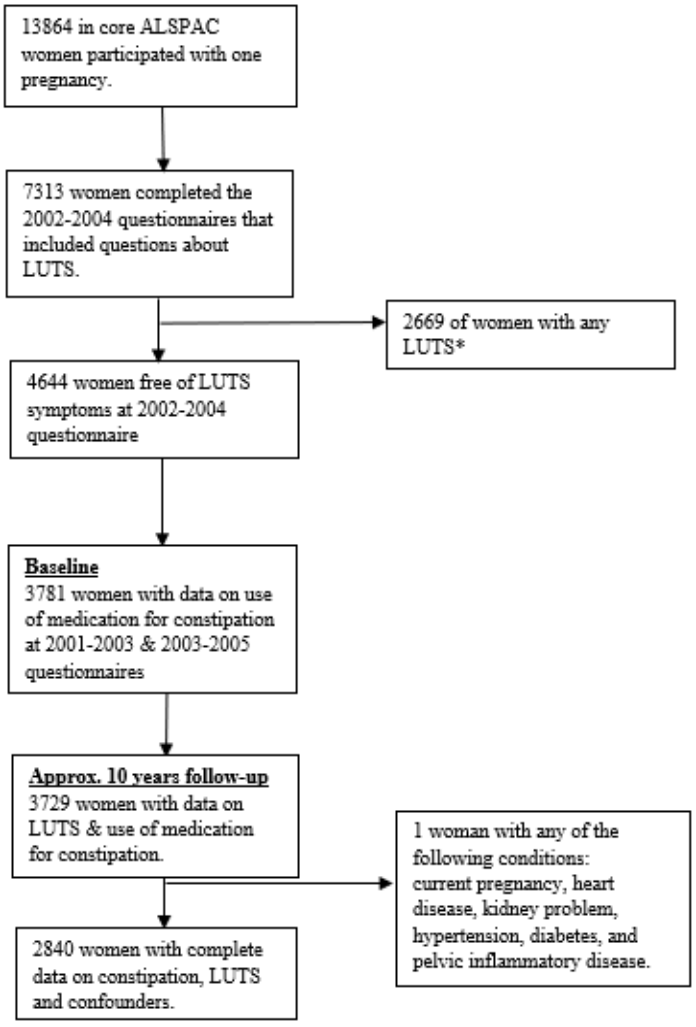
Figure 8 Timeline for constipation and LUTS analysis

3.3.1 Participants

14,541 pregnant women (Details section 3.1.1) were recruited by ALSPAC from former Avon Health Authority in England (73). 13,864 of these ALSPAC women participated with one pregnancy. In 2002-2004 questionnaire, 7,313 women completed BFLUTS questionnaire on LUTS. From these women, 2,669 reported having LUTS (stress UI, mixed UI, urgency UI, urgency, nocturia, increased daytime frequency, hesitancy, and intermittency) and were excluded before baseline of use of constipation medication and LUTS analysis (Figure 9) resulting in 4,644 eligible participants who were free of LUTS at baseline. Women with LUTS

were excluded at baseline because I wanted to focus only on studying new onsets of LUTS. Baseline of the current study was between 2001 and 2005, at which time a total of 3922 women without LUTS provided information on use of medication for constipation (Figure 9). After approximately 10 years of follow up , 3729 of these women self-reported LUTS by completing ICIQ-FLUTS questionnaire from ALSPAC (2011-2012). Therefore, eligible sample (n=3729) included in the imputation datasets if they had data on constipation (measured by medication intake) and LUTS, were free of LUTS symptoms in 2002-2004 and did not meet my exclusion criteria. Details of participants flow chart on constipation (measured by medication intake) and LUTS analysis is available in Figure 9.

Figure 9 : A sample flow chart use of medication for constipation and LUTS analysis



Notes:

Constipation (exposure) measured at baseline (timepoints 2001-2003 and 2003-2005).

LUTS (outcome) measured at approx. 10 years follow up from baseline (2011-2012).

Confounders including age, education, social class, and parity were measured at 1991-1992. BMI, physical activity and hysterectomy were measured at 2002-2004.

Any LUTS includes storage symptoms (stress UI, mixed UI, urgency UI, urgency, nocturia, increased daytime frequency) and voiding symptoms (hesitancy and intermittency).

3.3.2 Exclusion Criteria

Exclusion criteria is the same as the physical activity and LUTS analysis. It is explained in detail in Table 11 (section 3.2.2).

I will now give an introduction on methods of measurement of constipation in literature. Then I will explain methods used in ALSPAC to measure constipation.

3.3.3 Measurement of LUTS

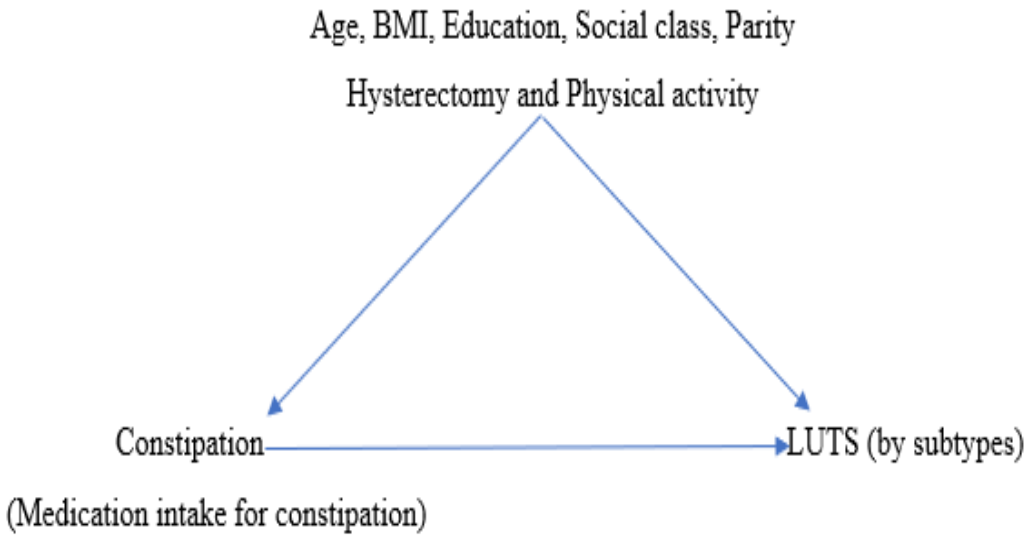
In this analysis, LUTS was self-reported in ALSPAC by women using the ICIQ-FLUTS (details in section 3.1.2, Table 11) after 10 years of follow up (2011-2012). Responses to questions were categorized using the ICS definitions (Table 11) into stress UI, mixed UI, urgency UI, urgency, nocturia, increased daytime frequency, hesitancy, and intermittency.

3.3.4 Potential Confounders

Potential confounders (Figure 8) were included in this analysis if they might be associated with constipation and risk factors for LUTS as identified by a detailed search of the literature and clinical knowledge (Chapter 2). Age, BMI, education level, social class, parity, hysterectomy, and physical activity are all risk factors LUTS (Figure 8).

The above risk factors are also associated with constipation making them potential confounders that should be adjusted for in my analysis that examines the association between constipation (measured by medication) and LUTS.As a person age bowel movement slows down which hardens the stool thus constipation may occur (103). Increased BMI have been linked to constipation through poor diet that is low in fibre and fluids intake (104). Physical inactivity has been associated with increased odd of constipation as being inactive slows down bowel movement (93). Lower socioeconomic class (105) higher parity and hysterectomy (105, 106) have also been linked with constipation in previous research. Therefore, I decided to adjust for all the previous potential confounders.

Figure 10 Illustrates possible confounders influencing Constipation and LUTS



Based on the above evidence, I adjusted for age (self-reported between year of 1991-1992), educational qualifications categorized as university degree vs no degree (Certificate of Secondary Education, Vocational, Ordinary level, Advanced level), occupational social class (1991 British Office of Population and Census Statistics - dichotomised into manual and non-

manual), body mass index (BMI: calculated from self-reported height and weight at 2002-2004), parity (self-reported by women between year of 1991-1992 and categorized into 1,2,3 or more births), hysterectomy (self-reported by women at 2002-2004 and categorized into yes/no) and physical activity (self-reported at 2002-2004 and translated into total metabolic equivalents minutes per week (MET min/week) and categorized into five categories: 0 , 0.1-17.2, 17.3-29.2, 29.3-43.2 and greater than 43.2 MET hours/week).

3.3.5 Statistical Analysis

Constipation (measured by medication intake) was generated as a categorial variable and represented as frequencies and percentages. Log-binomial multivariable regression was used to estimate the association between constipation (none/at one time point/at both time points) and subtypes of LUTS, reporting relative risks (RRs) and 95% confidence intervals (CIs). This is because prevalence rate of LUTS was more than 10%, so it was better to report results in risk ratios as opposed to odds ratios. Multiple imputation was used to impute missing covariate information for women considered to be eligible for the analysis (i.e., women who provided data on constipation and LUTS).

3.3.6 Summary Table: Methods of constipation (measured by medication intake) and LUTS analysis

Table 14 is a summary table of the methods used for constipation (measured by medication intake) and LUTS analysis.

Table 14 Summary Table for methods of constipation and LUTS

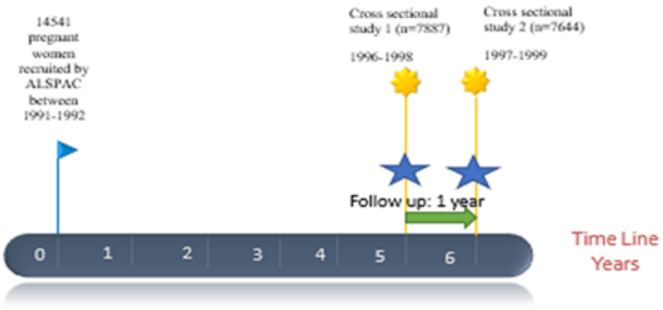
Summary Table for methods of constipation and LUTS	
Participants	N=3729 women mean age 43.3 years, SD 0.5) recruited from ALSPAC
Exclusion Criteria	Any LUTS, pregnancy, kidney problem, hypertension, diabetes, and pelvic inflammatory disease.
Constipation measured at baseline (timepoints 2001-2003 and 2003-2005).	Self-reports of medication intake for constipation at two timepoints (Baseline):2001-2003 and 2003-2005.
Measuring LUTS measured after ≈10 years (2011-2012) of follow up from baseline.	Self-reported LUTS using validated questionnaire ICIQ-FLUTS at ≈10 years of follow up. LUTS (sub types) were categorised using ICS definitions.
Confounders	Age, education, social class, and parity were measured at 1991-1992. BMI, physical activity and hysterectomy were measured at 2002-2004.
Statistical Analysis	Log-binomial multivariable regression and multiple imputation.

3.4 Method of measuring stress UI and quality of sexual experience (measured by frequency and satisfaction with sex)

I wanted to examine the concurrent association between LUTS and quality of sexual experience (i.e., cross-sectionally). However, ALSPAC relevant data on LUTS and sexual experiences was collected in questionnaires administered at two time points (1996-1998 and 1997-1999). These two timepoints were limited by only assessing one type of LUTS which is stress UI and two measures of quality of sexual experience (frequency and satisfaction with sex). Stress UI is linked to poor quality of sexual experience as urinary leakage could occur during sexual intercourse and may disturb the quality of sexual experience for women and may even cause women to avoid sexual intercourse (Chapter 2, 2.10)(107). Therefore, I decided to explore that association (stress UI with frequency and satisfaction with sex) further by performing two cross-sectional studies approx. one year apart as consistency of findings will strengthen evidence. Since it is plausible that LUTS may also have a lasting effect on the quality of sexual experience, I decided to examine the association using prospective analyses. This section will explain the method of the cross-sectional and prospective analysis to examine the associations between LUTS and quality of sexual experience.

Aim: To assess the cross-sectional association of stress UI with quality of sexual experience (measured by frequency and satisfaction with sex).

The timeline below (Figure 11) demonstrates the timepoint were ALSPAC recruited pregnant women (1991-1992). It also represents the time point of cross-sectional study 1 (1996-1998) were stress UI (exposure) and quality of sexual experience (outcome) were measured. At cross-sectional study 1, mean age of women (SD) of 34.9 (0.12) years. The timeline also represents the time point of cross-sectional study 2 (1997-1999) were stress UI (exposure) and quality of sexual experience (outcome) were measured. At cross-sectional study 2, mean age of women (SD) of 35.9 (0.10) years.



Symbol	Resembles
	Exposure: Stress UI (self reported)
	Outcome: Frequency & satisfaction of sex (self reported)
	Prospective 1 year follow up of changes in stress UI (None, Improved, worsened and persistent). Re-ran analysis at cross-sectional study 2
Exclusion Criteria	No partner, cancer, multiple sclerosis, pelvic inflammatory disease and physical disabilities

Figure 11 Timeline for stress UI and quality of sexual experience analysis

3.4.1 Participants

I performed two cross-sectional studies to assess association of stress UI with frequency and satisfaction with sex in parous middle-aged women. The first cross-sectional study was between years of 1996-1998 and the second cross-sectional study was between years of 1997-1999. I then performed a prospective analysis with the exposure measured at time point 2 (1997-1999) and the outcome at time point 1(1996-1999).

This section will discuss participants included in cross sectional study 1 and 2 and the prospective analysis that have been conducted between the two time points of the cross-sectional studies.

3.4.1.1 Participants at cross sectional study 1 (1996-1998)

14,541 pregnant women (Details section 3.1.1) were recruited by ALSPAC from former Avon Health Authority in England (73). Of these women, 7887 parous women (mean age= 34.9 years, SE= 0.12) had data on stress UI and quality of sexual experience (frequency and satisfaction with sex) approx. 5 years after recruitment into the cohort (1996-1998).

3.4.1.2 Participants at cross sectional study 2 (1997-1999)

As mentioned before, ALSPAC recruited 14541 pregnant women from former Avon Health Authority in England (73). Of these women, 7644 parous women (mean age= 35.9 years, SE= 0.10) had information on stress UI and quality of sexual experience (frequency and satisfaction with sex) from the questionnaire administered (1997-1999).

3.4.2 Exclusion criteria

Exclusion criteria involved having cancer, multiple sclerosis, pelvic inflammatory disease, physical disabilities and having no partner.

3.4.3 Measuring stress UI, frequency, and satisfaction with sex in both cross-sectional studies

Self-reported stress UI, frequency of sex and satisfaction with sex were measured using similar ALSPAC questions measured at cross-sectional study 1 and cross-sectional study 2 (

Table 15)

Table 15 : ALSPAC questions used to measure stress UI, frequency of sex and satisfaction with sex at cross-sectional study 1 and 2.

Measuring Stress UI	**ALSPAC Questions and Responses**
ALSPAC question used to measure *stress UI	In the past month, how often have you had problem holding urine when you jump sneeze etc? **Almost all the time** **Sometimes** Not at all
Measuring Frequency of Sex	
ALSPAC question used to measure frequency of sex	How often are you having sex? Not at all less than once a month 1-3 times a month, about once a week 2-4 times a week 5 or more times a week
Measuring Satisfaction with Sex	
ALSPAC question used to measure satisfaction with sex	In general, do you enjoy it? Yes, very much Yes, somewhat No, not a lot No, not at all Doesn't happen
***Women with stress UI must respond with sometimes and/ or all the time** **Each question was asked twice once in questionnaire 1996-1998 and one in 1997-1999**	

Aim: To examine the prospective association between changes in stress UI symptoms and quality of sexual experience (measured by frequency and satisfaction with sex) in parous women.

3.4.4 Prospective follow up (1 year) between from cross-sectional study 1 (1996-1998):

I created 'change in stress UI' variable to follow up (1 year of follow-up) women prospectively between cross-sectional study 1 and cross-sectional study 2. This variable was categorised into none, improved, worsened and persistent stress UI symptoms. Women who had no stress UI at both timepoint were considered as not having stress UI symptoms (none); women with stress UI at time point 1 and none at time point 2 were considered improved; women who had no stress UI at time point 1 but at timepoint 2 were considered as having worsened; and women who had stress UI at both timepoints were considered persistent. We re-ran the analysis of change in Stress UI variable' with frequency and satisfaction with sex at time point 2.

3.4.5 Potential Confounders

Background characteristics were defined as confounders if they could influence both stress UI (Chapter2, section 2.6) and frequency or satisfaction with sex. These include age, BMI, antidepressant, alcohol consumption, depression, and anxiety.

The prevalence of sexual dysfunction in women have been reported to increase with age as biological changes occur with aging might disturb or inhibits measures of sexual experience such as orgasm and desire(108). There is furthermore evidence that BMI is associated with poor sexual measures including orgasmic disorders (109). Use of antidepressants is higher among women with LUTS, and has also been linked to induce sexual dysfunction and affect the ability to experience an orgasm (110, 111). Increased alcohol consumption has been linked to reduced lubrication in women making it difficult to orgasm (112). Sexual distress is linked to be associated with psychological conditions including depression and anxiety as having low moods and fear might reduce sexual desire and arousal (108, 113).

Potential confounders were all self-reported including age (measured at 1991-1992), and antidepressant (measured at 1991-1993). Alcohol consumption (never drink alcohol, monthly or less, 2-4 times a month, 2-3 times a week, ≥ 4 or more times a week) was measured at 1992-1993. Anxiety (measured by crown crisp), BMI (calculated as self-reported weight divided by height in meters squared) and depression (measured by EPDS) all measured at 1996-1998. Confounders were the same for both cross-sectional studies and the prospective follow up study (section 3.5.6).

3.4.6 Statistical Analysis

Frequency and satisfaction with sexual experience were both generated as a categorial variables and represented as frequencies and percentages. For both cross-sectional studies, multinomial logistic regression was used to estimate the association between stress UI and frequency (not at all, less than once a month, 1-3 times a month, about once a week, 2-4 times a week, 5 or more times a week) and satisfaction with sex (Yes, very much/ yes, somewhat /no, not a lot/ no, not at all) for both cross sectional studies. For the prospective study, multinomial logistic regression was used to estimate the association between changes in stress UI (none, improved, worsened and persistent stress UI symptoms) and categories of frequency and satisfaction with sexual experience (see above). All associations were reported as prevalence rates ratios (PRR) and 95% confidence intervals (CIs). Information on PRR can be found here https://www.stata.com/manuals/rmlogit.pdf. Multiple imputation was used to impute missing covariate information for women considered to be eligible for the analysis (i.e., women who provided data on stress UI and measures of quality of sexual experience).

3.5 Methods of measuring LUTS (by subtypes) and quality of sexual experience

Aim: To assess the prospective associations of LUTS (by subtypes) and quality of sexual experience in parous middle-aged women.

The timeline below (Figure 12) demonstrates the timepoint were ALSPAC recruited pregnant women (1991-1992). It also represents the time points were LUTS (exposure) were measured and the follow up timepoint were quality of sexual experience (outcome) were measured. At approx. 2 years of follow up, women's mean age 49.3 years and SD 0.5.

Symbol	Resembles
	Time point ALSPAC recruited pregnant women
	Exposure: LUTS (by subtypes) self-reported (2011-2012)
	Outcome: Quality of sexual experience self-reported (2012-2014)
	Prospective follow up from measuring exposure

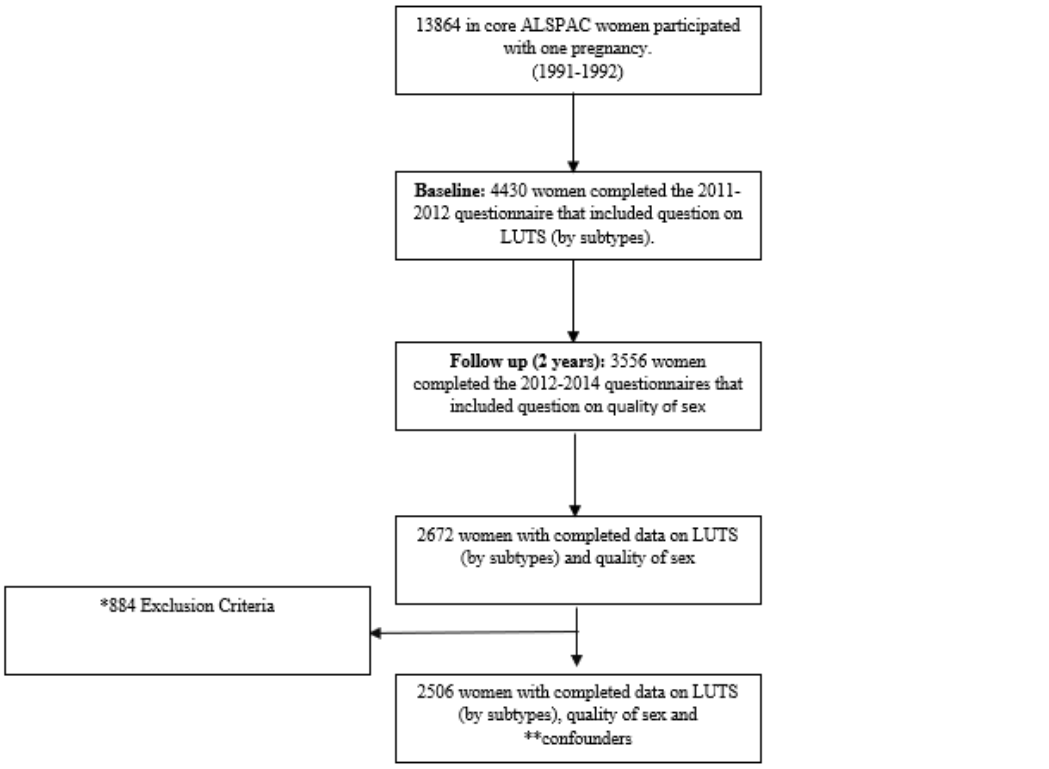
Figure 12 Timeline for LUTS and quality of sexual experience analysis

3.5.1 Participants

Among the women originally recruited into core sample of ALSPAC (n=13864), 4430 had information on LUTS from the questionnaire administer at 2011-2012 defined as our baseline. Of these women, 3556 women completed the 2012-2014 questionnaires that included question on quality of sexual experience, at approx. two years of follow up. Of these women, a total of 884 women were excluded because they did not have a partner or because they had underlying health conditions (see Table 16 for details), resulting in a final eligible sample of 2672 women

with LUTS and information on their sexual experience after two years of follow-up (2012-2014).

Figure 9: Sample flow chart of LUTS and quality of sexual experience



Notes:

Confounders including age, menopausal status and UTI measured at baseline 2011-2012.Depression, use of antidepressants, hormone replacement therapy and hysterectomy were measured at 2010-2011.

3.5.2 Exclusion Criteria

Exclusion criteria (Table 16) involved currently having no partner, cancer diagnosis, heart failure, pelvic inflammatory disease and or physical disabilities. Women were excluded if they have any disease or condition that might interfere with the quality of sexual experience.

Table 16: Exclusion criteria for LUTS and quality of sexual experience analysis

Exclusion criteria For LUTS and quality of sexual experience analysis		
Excluded conditions	**ALSPAC Question for Exclusion Criteria (Year of questionnaire)**	**Response Option**
Currently have no partner	Did you have a sexual partner in the last month? (2013)	1-Yes **2-No**

Physical disabilities	Are you/your partner currently unable to work through sickness/disability (2013)	**1-Yourself** **2-Partner**
Heart Failure	Have you ever been told that you have had any of the following conditions? Heart Failure (2010)	**1-Yes** 2-No
Cancer	Have you had any of the following in the last 2 years (since your study child's 10th birthday)? Cancer (2003-2005)	**1-Yes, consulted a doctor** **2-Yes, not consulted a doctor** 3-No
Pelvic inflammatory disease	Have you ever had any of the following problems? Pelvic inflammatory disease (2002-2004)	**1-Yes, had it recently in the past year** **2-Yes in past not recently** 3- No never
Women responding in **bold** were excluded.		

3.5.3 Measuring LUTS

LUTS were measured using a validated self-reported ICIQ-FLUTS questionnaire at baseline (2011-2012) and subtypes of LUTS were categorised based on the ICS definitions (details in box 9).

3.5.4 Measuring quality of sexual experience

After approx. 2 years of follow up (2012-2014) from baseline, women participating in ALSPAC completed a detailed questionnaire on their sexual experience including questions on frequency of sexual activities, frequency of orgasm, level of worry/distress about their level of desire, sexual activities, experiencing an orgasm, and overall sex life. The questions used to define these outcomes are shown in Table 17. There were 5 responses alternatives for levels of worry/distress: *1-not at all worried or distressed; 2- a little bit worried or distressed; 3-moderately worried, or distressed; 4-very worried or distressed; and 5- extremely worried or distressed.* These responses were further categorised into three categories: *not worried (response 1), moderately worried (responses 2 & 3) and very worried (response 4 & 5).* There were eight responses alternatives for frequency of sexual activity which were further categorised into five categories: *not at all; once in the last month; 2-3 times in the last month; once a week; and ≥2 times a week*. Responses for frequency of orgasm were *almost never/never, a few times (much less than half the time), sometimes (about half the time), most of the time (much more than half & almost always/always.* I was particularly interested in women's level of worry/distress as women could have infrequent sex but still be satisfied and vice versa.

Table 17 : Measurement of female quality of sexual experience in ALSPAC after two years of follow up (2012-2014)

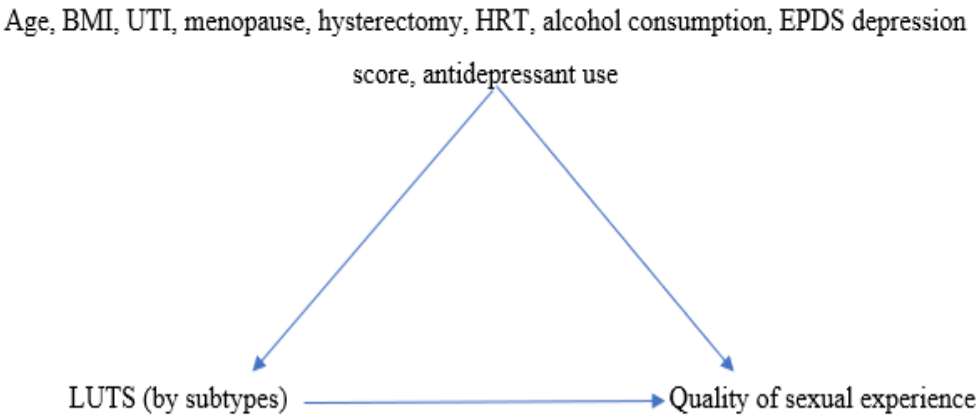
Measurement of quality of sexual experience	ALSPAC questionnaire (2012-2014)	Responses	Reponses categories
Frequency of sex	In the last month, how many times have you attempted sexual intercourse?	1- Not at all 2- Once in the last month 3- 2-3 times in the last month 4- Once a week 5- 2-3 times a week 6- 4-6 times a week 7- Once a day 8- More than once a day	Responses were further categorised into: 1- Not at all 2- Once in the last month 3- 2-3 times in the last month 4- Once a week 5- ≥2 times a week (responses 5,6 &7)
Frequency of orgasm	When you have sexual stimulation, how often do you have the feeling of orgasm or climax?	1-Almost never/never 2-A few times (much less than half the time) 3- Sometimes (about half the time) 4- Most of the time (much more than half the time) 5- Almost always/always	N/A
Level of worry/distress of desire	Are you worried or distressed by your current level of sexual drive/desire?	1- Not at all worried or distressed 2- A little bit worried or distressed 3- Moderately worried or distressed 4- Very worried or distressed 5 Extremely worried or distressed	Responses were further categorised into: 1-Less worried (response 1 & 2) 2-Moderately worried (response 3) 3-Very worried response (4 & 5)
Level of worry/distress of orgasmic experience	Are you worried or distressed by your current orgasmic experience?	1-Not at all worried or distressed 2- A little bit worried or distressed 3- Moderately worried or distressed 4- Very worried or distressed 5- Extremely worried or distressed	Responses were further categorised into: 1-Not worried (response 1) 2-Moderately worried (response 2 & 3) 3-Very worried response (4 & 5)
Level of worry/distress of frequency of sex activities	Are you worried or distressed by the overall frequency of your sexual activities (including intercourse, kissing and satisfaction)	1-Not at all worried or distressed 2-A little bit worried or distressed 3-Moderately worried or distressed 4-Very worried or distressed 5- Extremely worried or distressed	Responses were further categorised into: 1-Not worried (response 1) 2-Moderately worried (response 2 & 3) 3-Very worried response (4 & 5)
Satisfaction with sex	How satisfied are you with your overall sex life?	1-Very satisfied 2- Moderately satisfied 3- About equally satisfied and dissatisfied 4- Moderately dissatisfied 5- Very dissatisfied	Responses were further categorised into: 1-Very Satisfied (response 1) 2-Moderately satisfied (response 2) 3-About equally satisfied and dissatisfied (response 3) 4-Dissatisfied (responses 4 & 5)

3.5.5 Potential Confounders

Potential confounders (Figure 13) included background characteristics which could influence both LUTS (discussed earlier, section 2.6, Chapter 2) and quality of sexual experience and were identified based on established literature and clinical experience.

The association between age, BMI, antidepressant, alcohol consumption, depression, anxiety, and poor sexual experience have been explained in in this chapter (section 3.4.5). Other risk factors that may influence quality of sexual experience include menopause, hormone replacement therapy (HRT) hysterectomy and UTI (114-116). Moreover, decreased blood flow has been linked to vaginal dryness and reduced arousal. HRT have been linked to positively improve sexual function in women as it increases oestrogen level thus improving sexual arousal and desire(115). Hysterectomy had been associated with poor sexual function including reduced lubrication and difficulty in reaching orgasm (114).

Figure 13 Illustrates potential confounders for LUTS and quality of sexual experience analysis



All confounders were self-reported by women in questionnaires either at baseline or one year before baseline depending on availability of data. Confounders measured at baseline (2011-2012) include women's age, menopausal status (yes, no), and number of times they had experienced a UTI in the past month (almost all the time, sometimes, not at all). Confounders obtained one year before baseline (2010-2011) include depressive symptoms (measured using the Edinburgh Postnatal Depression Scale), use of antidepressants (yes, no), body mass index (BMI: calculated as self-reported weight divided by height in meters squared), alcohol

consumption (never drink alcohol, monthly or less, 2-4 times a month, 2-3 times a week, ≥ 4 or more times a week), hysterectomy (yes, no) and hormone replacement therapy (yes, no).

3.5.6 Statistical Analysis

Sexual measures (measured by frequency, satisfaction and level of worry or distress about desire, frequency of sex, orgasm) were all categorial and were described as frequencies and percentages. Analyses were carried out using ordinal logistic regression analysis to estimate associations between the LUTS subtypes and indicators of quality of sexual experience. Ordinal regression is used to predict an ordinal dependent variable given one or more independent variables. I first ran an unadjusted model (Model 1), and subsequently a model adjusted (Model 2) adjusted for age, BMI, UTI, menopause status, hysterectomy, HRT, alcohol consumption. I conducted a separate analysis further adjusting for EPDS depression score and antidepressant use (Model 3), because it is possible that the association between LUTS and sexual health could be partially mediated by depression symptoms.

3.5.7 Summary Table: Methods of LUTS and quality of sexual experience analysis

Table 18 below describes briefly the method used to measure participants, exposure, outcome, potential confounders, and statistical analysis used for LUTS and quality of sexual experience analysis.

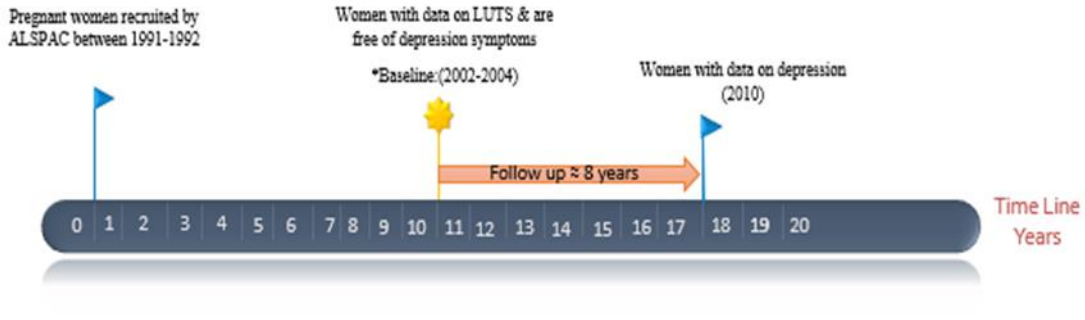
Table 18: Summary Table for methods of LUTS and quality of sexual experience

Participants	2672 women (mean age=37.8 years, range 24.3-52.1 years, SD 4.27) recruited from ALSPAC
Exclusion Criteria	No partners, cancer, heart failure, pelvic inflammatory disease &/or physical disabilities.
Measuring LUTS (Baseline:2011-2012)	Self-reported LUTS using validated questionnaire ICIQ-FLUTS. LUTS (storage) were categorised using ICS definitions.
Quality of sexual experience (≈2 years follow up period:2012-2014)	Self-reported quality of sexual experience symptoms: 1- Frequency of sex and orgasm. 2- Level of worry/distress about desire, sexual activities, experiencing an orgasm. 3- Overall satisfaction with sex life.
Confounders	Age, menopausal status and UTI measured at baseline 2011-2012.Depression, use of antidepressants, hormone replacement therapy and hysterectomy were measured at 2010-2011.
Statistical Analysis	Ordinal regression and multiple imputation.

3.6 Methods of measuring LUTS and depression (measured by EPDS and antidepressant intake)

Aim: Examining prospective association between LUTS (by subtypes) and depression (measured by Edinburgh Post Natal Depression Scale and/or antidepressant intake) in parous middle-aged women.

The timeline below (Figure 14) demonstrates the timepoint were ALSPAC recruited pregnant women (1991-1992). It also represents the time points were LUTS (exposure) were measured and the follow up timepoint were depression (outcome) was measured. At approx. 8 years of follow up, women's mean age 43.3 years at baseline, SD 0.5.



Symbol	Resembles
	Exposure: LUTS (Subtypes) measured by BF-LUTS questionnaire and categorized using ICS definition
	Outcome: Depression measured by Edinburgh Post-natal Depression Scale (EPDS) and use of antidepressants.
*Exclusion Criteria at baseline	Reporting depression symptoms on *EPDS >12, taking antidepressants, cancer, multiple sclerosis, pelvic inflammatory disease, physical disabilities

Figure 14 Timeline for LUTS and depression analysis

3.6.1 Participants

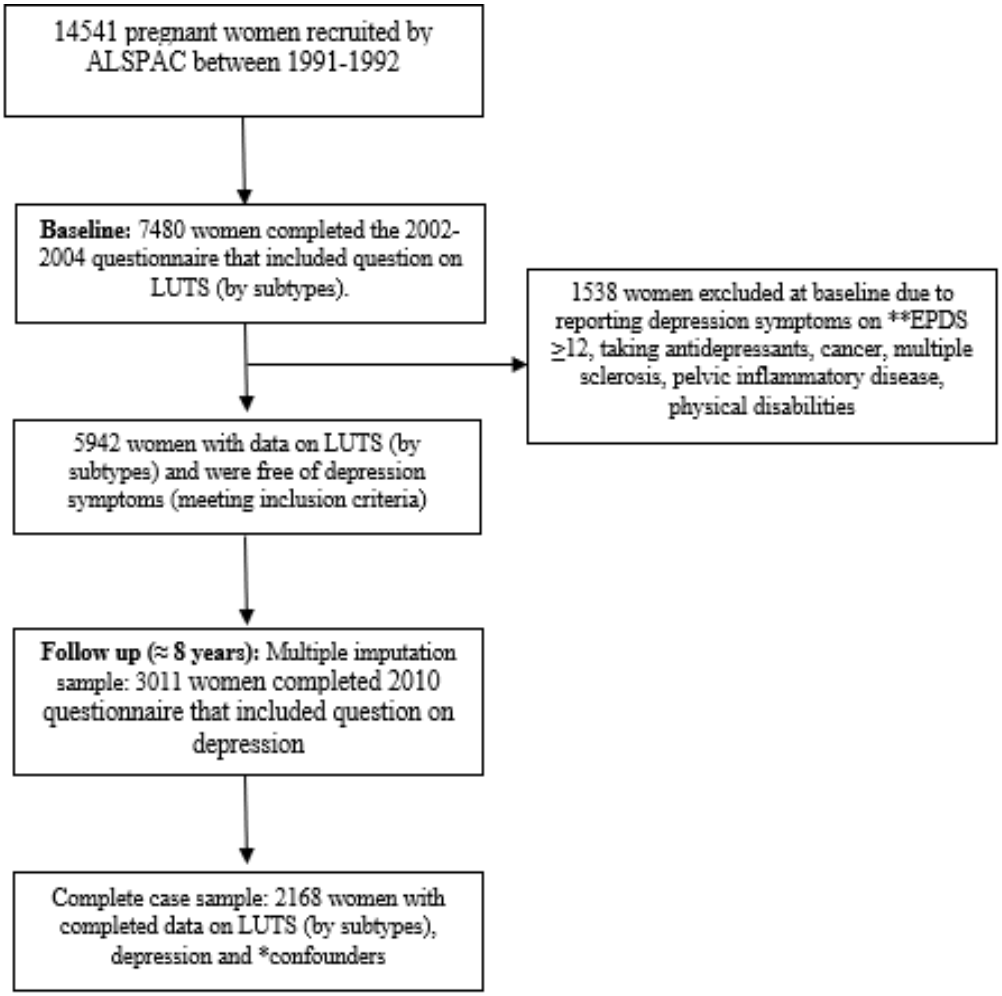
Between 1991-1992, ALSPAC recruited 14,541 pregnant women (Details section 3.1.1) from former Avon Health Authority in England (73). The baseline of this study was at 2002-2004 questionnaire, during that time 7480 women self -reported LUTS using an adapted version of BFLUTS questionnaire. Of these women, 1538 women were excluded because they reported depression symptoms (≥12), were taking antidepressants, and fitted exclusion criteria (see next section) resulting in 5492 women (figure 9)(117). After eight years of follow up (2010), 3011 of these women provided data on depression (measured by EPDS and use of antidepressants). Therefore, eligible sample included in the multiple imputation data sets included women with

data on LUTS and depression (measured by EPDS and use of antidepressants) were free of depression at baseline (2002-2004) and did not meet my exclusion criteria. Details of flow chart in Figure 15.

3.6.2 Exclusion Criteria

Women were excluded at baseline (2002-2004) if they had depression symptoms on **EPDS ≥12, were taking antidepressants, or had cancer, pelvic inflammatory disease and or physical disabilities.

Figure 15 Participant flow chart for LUTS and depression analysis



Notes:

LUTS (exposure) measured at 2002-2004.

Depression (outcome) measured at approx. 8 years of follow up from baseline (2010).

Confounders including age, parity, menopausal status, anxiety and UTI were measured at baseline 2011-2012. Hysterectomy, hormone replacement therapy, BMI, alcohol consumption and depression (measured by EPDS and use of antidepressants) were measured at 2010-2011.

3.6.3 Measuring LUTS

At baseline (2002-2004), self-reported LUTS were measured using the BFLUTS (Table 11, section 3.1.2). LUTS were categorized according to ICS definitions as stress UI, urgency UI, mixed UI, urgency, nocturia and increased daytime frequency.

3.6.4 Measuring depression

After 8 years of follow up from baseline, self-reported depression was measured using EPDS and self-reported use of antidepressants. Use of antidepressants was self-reported using ALSPAC question: “In the last 2 years how often have you taken pills for depression?”. Response options were every day, often, sometimes, and not at all. I categorised this information into a binary variable: not on antidepressants (not at all) and using antidepressants (everyday, often, and sometimes). Women were classified as depressed if they scored ≥12 on the EPDS and/or were using antidepressants (117).

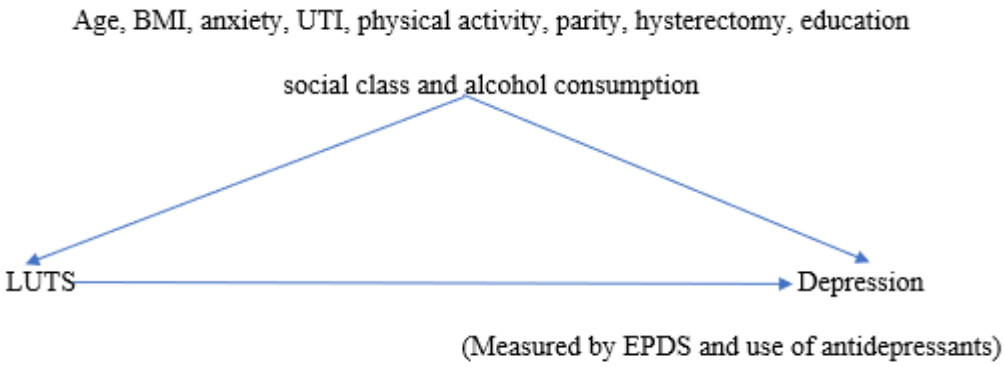
I also wanted to assess how LUTS are associated with different scores of EPDS. Therefore, I re-ran the analysis using a categorial variable of self-reported EPDS which involved none or minimal depression (scores 0-6), mild depression (scores7-13) and moderate to severe depression (scores 14-30)(118).Please note that established categories for EPDS involves none or minimal depression (0–6), mild depression (7–13), moderate depression (14–19), and severe depression (19–30) (118).However, due to the small number of women in the severe depression score, I had to combine the last two categories (mild-moderate) and name it moderate to severe.

3.6.5 Potential Confounders and Mediators

Background characteristics were defined as confounders (Figure 16) if they might influence LUTS (by subtypes) and depression (measured by EPDS and use of antidepressants). This includes age, BMI, anxiety, UTI, physical activity, parity hysterectomy, education level, social class, and alcohol consumption. Evidence showed that prevalence of depression symptoms increases with age (119). Prevalence of depression symptoms also increases with obesity (107), as obesity is linked to poor self-image and low self-esteem which are contributors for depression. History of hysterectomy is also linked to depression as removing uterus means loss of fertility to women and it triggers sadness(120). Experiencing recurrent UTI is associated with multiple urinary tract symptoms and could affect the patient's quality of life and might

relate depression(121). Increase in alcohol consumption has been associated with depression as they might impact neurotransmitters of the brain making depressive symptoms worse (122). Poor socioeconomic status have been associated with a higher prevalence of depression; this might be due to job insecurities or poor health care that my enhance depression symptoms (123). Since all the previous confounders are linked to depression and LUTS, I adjusted for all of them in my analysis. Anxiety is intricately linked to depression and often appear as comorbid conditions (124), and I therefore evaluated anxiety as a potential mediator of the relationship between LUTS and depression.

Figure 16 Potential confounders that may influence LUTS and depression



Confounders measured at baseline include women's age, BMI (calculated as self-reported weight divided by height in meters squared), anxiety (measured by crown crisp), number of times they had experienced a UTI in the past month (almost all the time, sometimes, not at all), hysterectomy (self-reported by women at baseline and categorized into yes/no), physical activity (self-reported at baseline and translated into total metabolic equivalents minutes per week (MET min/week) and categorized into five categories: 0 , 0.1-17.2, 17.3-29.2, 29.3-43.2 and greater than 43.2 MET hours/week) and parity (self-reported by women between years of 1991-1992 and categorized into 1,2,3 or more births). Confounders obtained ≈3 years before baseline include educational qualifications categorized as university degree vs no degree (Certificate of Secondary Education, Vocational, Ordinary level, Advanced level), occupational social class (1991 British Office of Population and Census Statistics - dichotomised into manual and non-manual). Alcohol consumption (never drink alcohol, <1 a week, at least once a week,1-2 units every day and ≥ 3 units every day) was self-reported ≈5 years before baseline.

3.6.6 Statistical Analysis

Depression (measured by EPDS ≥12 or use of antidepressants) was a binary variable and was described using frequencies. Analyses were carried out using log-binomial regression to estimate the association between LUTS (by subtypes) and depression, reporting relative risks (RRs) and 95% confidence intervals (CIs). I first estimated an unadjusted model (Model 1), and subsequently estimated a model adjusted for age, BMI, socioeconomic status, education, hysterectomy, physical activity, parity UTI and alcohol consumption (Model 2). Finally, I re-ran the analysis with an additional adjustment for anxiety (Model 3). This is because it is possible that the association between LUTS and depression could be partially mediated by anxiety symptoms.

3.6.7 Summary Table: Methods of LUTS and Depression Analysis

Below is a summary table of methods used to measure LUTS and depression.

Table 19: Summary Table of Methods of LUTS and Depression Analysis

Participants	3011 women (mean age 43.3years, SD 0.5) recruited from ALSPAC
Exclusion Criteria	Reporting depression symptoms on EPDS ≥12, taking antidepressants, cancer, multiple sclerosis, pelvic inflammatory disease &/or physical disabilities.
Measuring LUTS (Baseline:2002-2004)	Self-reported LUTS using validated questionnaire BFLUTS LUTS (storage) were categorised using ICS definitions.
Measuring Depression (≈8 years follow up period:2010)	1-Self-reported depression symptoms using EPDS 2-Use of antidepressants
Confounders	Age, anxiety, menopausal status and UTI were measured at baseline 2011-2012.Hysterectomy, HRT, BMI, alcohol consumption and depression (measured by EPDS and use of antidepressants) were measured at 2010-2011.

Statistical Analysis	log-binomial multivariable regression and multiple imputation.

4 Chapter 4: Physical Activity and Risk of LUTS

This chapter will present the results and summary of my analysis examining the association between physical activity and risk of LUTS. The results from the multiple imputation analysis are presented first followed by the complete case analysis.

4.1 Physical Activity and risk of LUTS (main analysis using multiple imputation datasets)

Table 20 shows the distribution of women's characteristics in the two samples used for this analysis (Chapter 3 and Figure 6). Eligible sample involved women with self-reported data on physical activity, LUTS by subtypes and imputed confounders. Further details below.

In 2002-2004 (mean age 40.5 years; SD 4.5), 3 years after physical activity levels were ascertained, 16% of a sample of 4126 women reported any LUTS symptoms with urgency (9%) and stress UI (9%) as the most common type of LUTS. In 2011-2012 (mean age 49.3 years; SD 4.4), after 11.5 years of follow up, 23% of a sample of 2770 women reported any LUTS symptoms and stress UI (13%) was the most common type of LUTS.

Table 20. Characteristics of women included in analyses

	2002-2004 (3 years follow up) N=4126	**2011-2012 (11.5 years follow up) N=2770**
Age, Mean (SE)	40.5 (0.1)	49.3 (0.1)
BMI, Mean (SE)	24.6 (0.1)	24.3 (0.1)
Parity, %		
1	48	48
2	36	37
3+	16	15
Occupational Social Class, %		
Non-manual	84	82
Manual	16	18
University Degree, %		
Yes	73	91
No	27	9
Physical activity (MET hours/week), %		
0	14	12
0.1-17.2,	24	23
17.3-29.2,	23	23
29.3-43.2	19	21
≥43.2	20	21
Stress UI, %		
Yes	9	13
No	91	87
Urgency UI, %		
Yes	3	4
No	97	96
Mixed UI, %		
Yes	3	6
No	97	94
Urgency, %		
Yes	9	3
No	91	97
Nocturia, %		
Yes	3	1
No	97	99
Any type of LUTS, %		
Yes	16	23
No	84	77

Table 21 and Table 22 compare the distribution of characteristics in women with complete case and in those women included in the imputed datasets (i.e., women with data on physical activity and LUTS) for analysis of LUTS, at 3 years and 11.5 years of follow up, respectively. There was a higher proportion of women in non-manual occupational social class, and in the group with a university degree in multiple imputation analyses compared to complete case analysis at both time points. There was a lower percentage of women suffering from stress UI at the two follow up time points (3 years and 11.5 years). However, percentage of women suffering from stress UI was higher at 11.5 years of follow up compared to 3 years of follow up; this may be because prevalence of stress UI increases with age (125). Proportion of women across categories of parity were similar in both (complete case and MI) at both follow up time points. There was also similar proportion of women with urgency UI at 11.5 years of follow up in the multiple imputation data sets.

Table 21. Distribution of characteristics of women included in analysis of LUTS at 3 years of follow up in complete case and imputed datasets

Variables with missing values	Observed values Mean (SE) or %	Imputed values Mean (SE) or % (N=4126)
BMI (kg/m^2)	24.7 (0.1)	24.6 (0.1)
Stress UI (%)		
Yes	9	8
No	91	92
Parity (%)		
1	47	48
2	36	36
3+	16	16
Occupational Social Class (%)		
Non-manual	80	84
Manual	20	16
University Degree (%)		
Yes	89	73
No	12	27

Table 22 Distribution of characteristics of women included in analysis of LUTS at 11.5 years of follow up in complete case and imputed datasets

Variables with missing values	**Observed values Mean (SE) or %**	**Imputed values Mean (SE) or % (N=2770)**
BMI (kg/m^2)	24.7 (0.1)	24.3 (0.1)
Stress UI (%)		
Yes	33	13
No	77	87
Urgency UI (%)		
Yes	5	4
No	95	96
Parity (%)		
1	47	48
2	36	37
3+	16	15
Occupational Social Class (%)		
Non-Manual	75	82
Manual	25	18
University Degree (%)		
Yes	80	91
No	20	9

Table 23 and 24 show the distribution of women's characteristics across categories of physical activity at 3 and 11.5 years of follow up. Older women had higher mean physical activity levels at both 3 and 11.5 years of follow up, while mean BMI decreased across increasing levels of physical activity at both time points. The proportion of women with university degree decreased with increasing levels of physical activity at both follow up time points. Proportion of women decreased across-categories of parity as levels of physical activity increased.

Table 23. Characteristics of women with data on confounders and physical activity at 3 years of follow up

	*Categories of physical activity (MET hours/week) N=4126					
	First (Lowest) (n= 577)	Second (n=956)	Third (n=955)	Fourth (n=803)	Fifth (Highest) (n=835)	P-value
Age, years (Mean (SD))	36.5 (4.9)	37.1 (4.5)	37.1 (4.5)	37.4 (4.2)	37.7 (4.2)	<0.001
BMI, kg/m^2 (Mean (SD))	25.0 (5.1)	25.1 (4.7)	25.0 (4.7)	24.2 (4.0)	23.7 (3.4)	<0.001
Occupational Social Class, %						0.669
Non-manual	79	80	80	80	82	
Manual	21	20	20	20	18	
University Degree %						<0.001
Yes	17	14	12	8	8	
No	83	86	88	92	92	
Parity %						0.009
1	51	48	46	49	46	
2	31	33	38	37	39	
3+	18	19	16	14	15	

* Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

Table 24. Characteristics of women with data on confounders and physical activity at 11.5 years of follow up

	*Categories of physical activity (MET hours/week) N=2770					
	First (Lowest) (n= 343)	Second (n=633)	Third (n=637)	Fourth (n=574)	Fifth (Highest) (n=583)	P-value
Age, years (Mean (SD))	48.3 (4.8)	48.9 (4.4)	49.2 (4.2)	49.5 (4.1)	49.8 (4.5)	<0.001
BMI (kg/m^2) (Mean (SD))	24.7 (5.2)	24.9 (4.7)	24.6 (4.3)	23.9 (3.5)	23.6 (3.4)	<0.001
Occupational Social Class, %						0.309
Non-manual	81	81	81	81	84	
Manual	19	19	19	19	16	
University Degree %						0.023
Yes	27	26	21	19	23	
No	73	74	79	81	77	
Parity %						0.069
1	51	50	46	52	46	
2	34	33	39	34	40	
3+	15	17	15	14	14	

* Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

4.1.1 Physical activity and subtypes of LUTS after 3 years of follow up

The associations between physical activity (in quintiles of MET scores) and LUTS at 3 years after baseline are presented in Table 25. There was evidence of a non-linear relationship between physical activity and risk of stress UI, nocturia and any type of LUTS, as assessed using a likelihood ratio test comparing a model in which quintiles of physical activity levels were entered as a continuous variable to a model as four dummy variables. No evidence of departure from linearity was noted for urgency, urgency UI or mixed UI. However, I present results from the model using four dummy variables for physical activity, for all outcomes, for consistency.

In the unadjusted model, women in the highest category of physical activity (≥43.2 MET hours/week) reported lower odds of stress UI, mixed UI or any LUTS at 3 years of follow-up compared to inactive women. Despite collapsing the top two physical activity categories, this group included only 8 women with nocturia. Women in this category (≥29.3 MET hours/week) were less likely to report having nocturia compared to women reporting zero MET hours/week. There was no evidence for an association of categories of physical activity (MET hours/week) with urgency and urgency UI.

The results of the confounder adjusted model were similar to the unadjusted model. Women in the highest category of physical activity had lower odds of reporting stress UI or mixed UI at 3 years of follow-up compared to inactive women. Nocturia was also less frequent in women in the highest category of physical activity (≥29.3 MET hours/week) compared to women reporting zero MET hours/week, though the confidence interval was wide. Women in the highest category of MET hours/week also had reduced odds of reporting any LUTS (adjusted at 3 years of follow-up compared to women with zero MET hours/week. Similar to the unadjusted model, no evidence of associations was observed between physical activity and urgency UI or urgency at 3 years of follow up.

For all examined LUTS, point estimates for the intermediate categories (i.e., category 2: 0.1-17.2 MET hours/week, category 3: 17.3-29.2 MET) were also smaller than one, but confidence intervals included the null value in both models (unadjusted and adjusted).

Table 25. Association of physical activity with risk of LUTS at 3 years of follow up

Outcome	Physical activity Categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR** (95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	577	47 (8)	Ref	Ref	0.010
	2	955	61 (6)	0.83 (0.59, 1.16)	0.80 (0.54, 1.18)	
	3	955	62 (6)	0.74 (0.53, 1.05)	0.72 (0.48, 1.07)	
	4	803	51 (8)	0.72 (0.50, 1.03)	0.80 (0.53, 1.21)	
	5	835	34 (4)	0.50 (0.34, 0.74)	0.51 (0.32, 0.80)	
Urgency						
	1	577	58 (10)	Ref	Ref	0.899
	2	956	83 (9)	0.85 (0.60, 1.21)	0.90 (0.63, 1.30)	
	3	955	91 (10)	0.94 (0.66, 1.33)	0.96 (0.72, 1.47)	
	4	803	71 (9)	0.87 (0.60, 1.24)	0.98 (0.67, 1.43)	
	5	835	60 (7)	0.69 (0.47, 1.01)	0.80 (0.54, 1.18)	
	per category			0.93 (0.86, 1.01)	0.97 (0.88, 1.04)	
Nocturia						
	1	577	13 (2)	Ref	Ref	0.007
	2	956	15 (2)	0.69 (0.33, 1.46)	0.81 (0.36, 1.86)	
	3	955	14 (1)	0.65 (0.30, 1.38)	0.54 (0.22, 1.35)	
	*4+5	1683	8 (1)	0.21 (0.10, 0.52)	0.26 (0.10, 0.72)	
Urgency UI						
	1	577	23 (4)	Ref	Ref	0.382
	2	956	25 (3)	0.65 (0.36, 1.15)	0.63 (0.34, 1.14)	
	3	955	25 (3)	0.65 (0.36, 1.15)	0.70 (0.40, 1.27)	
	4	803	20 (2)	0.62 (0.33, 1.13)	0.70 (0.38, 1.30)	
	5	835	20 (2)	0.59 (0.32, 1.08)	0.67 (0.35, 1.25)	
	per category			0.90 (0.78, 1.03)	0.94 (0.81, 1.08)	
Mixed UI						
	1	557	27 (5)	Ref	Ref	0.386
	2	956	26 (3)	0.57 (0.33, 0.99)	0.38 (0.19, 0.76)	
	3	955	23 (2)	0.50 (0.29, 0.89)	0.50 (0.26, 0.94)	
	4	803	24 (3)	0.63 (0.36, 1.10)	0.78 (0.42, 1.46)	
	5	835	16 (2)	0.40 (0.21, 0.75)	0.48 (0.24, 0.99)	
	per category			0.84 (0.73, 1.00)	0.93 (0.79, 1.10)	
Any type of LUTS						
	1	577	113 (20)	Ref	Ref	0.049
	2	956	166 (17)	0.86 (0.66, 1.12)	0.86 (0.63, 1.17)	
	3	954	163 (17)	0.85 (0.65, 1.10)	0.85 (0.63, 1.16)	
	4	803	128 (16)	0.78 (0.59, 1.03)	0.95 (0.69, 1.31)	
	5	834	105 (13)	0.59 (0.44, 0.79)	0.64 (0.46, 0.90)	
	per category			0.89 (0.84, 0.95)	0.93 (0.87, 1.00)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week
****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.
Note:
Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

Since some studies reported that high-impact physical activity might increase the risk of developing UI (75, 76), I further explored this association by restricting physical activities to those classified as high intensity (METs ≥ 6 or more). Findings for the analyses limited to high intensity physical activities are presented in Table 26.

Women in the highest category of physical activity (≥43.2 MET hours/week) had lower odds of reporting stress UI and any LUTS compared to women reporting zero MET hours/week. After adjustment for confounders, women in the highest category of physical activity (compared to women reporting zero MET hours/week) had lower odds of stress UI, while the association with any LUTS was attenuated to the null. There was no evidence of an association between high intensity physical activity and other types of LUTS (mixed UI, urgency UI and urgency) in both unadjusted and adjusted models. Nocturia was not studied here due to the insufficient number of women reporting nocturia in this sample (n<5).

Table 26. Associations of high intensity physical activity with risk of LUTS at 3 years of follow up

Outcome	Physical activity Categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted** OR (95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	1557	148 (10)	Ref	Ref	0.027
	2	669	68 (10)	1.07 (0.79, 1.45)	1.10 (0.81, 1.51)	
	3	1020	79 (8)	0.80 (0.60, 1.06)	0.87 (0.64, 1.17)	
	4	286	21 (7)	0.75 (0.47, 1.21)	0.87 (0.54, 1.40)	
	5	594	33 (6)	0.56 (0.38, 0.82)	0.65 (0.44, 0.97)	
Urgency						
	1	1557	182 (12)	Ref	Ref	0.042
	2	669	81 (12)	1.04 (0.79, 1.38)	1.13 (0.84, 1.50)	
	3	1020	102 (10)	0.84 (0.65, 1.08)	0.93 (0.71, 1.21)	
	4	286	27 (9)	0.79 (0.51, 1.21)	0.86 (0.55, 1.33)	
	5	594	55 (9)	0.77 (0.56, 1.06)	0.91 (0.65, 1.25)	
	per category			0.93 (0.86, 1.00)	0.97 (0.90, 1.04)	
Urgency UI						
	1	1557	48 (3)	Ref	Ref	0.524
	2	669	16 (2)	0.79 (0.44, 1.40)	0.86 (0.48, 1.54)	
	3	631	17 (3)	0.87 (0.50, 1.53)	1.00 (0.56, 1.76)	
	4	675	17 (3)	0.80 (0.46, 1.40)	0.90 (0.51, 1.60)	
	5	594	15 (3)	0.81 (0.45, 1.45)	0.93 (0.51, 1.70)	
	per category			0.93 (0.82, 1.04)	0.97 (0.86, 1.86)	
Mixed UI						
	1	1557	54 (3)	Ref	Ref	0.493
	2	669	18 (3)	0.78 (0.45, 1.32)	0.77 (0.45, 1.32)	
	3	1020	22 (2)	0.61 (0.37, 1.01)	0.61 (0.37, 1.01)	
	4	286	8 (3)	0.80 (0.38, 1.70)	0.80 (0.38, 1.70)	
	5	594	14 (2)	0.67 (0.37, 1.22)	0.67 (0.37, 1.21)	
	per category			0.89 (0.78, 1.02)	0.95 (0.83, 1.10)	
Any type of LUTS						
	1	1557	278 (18)	Ref	Ref	0.019
	2	669	128 (19)	1.09 (0.86, 1.38)	1.15 (0.90, 1.46)	
	3	1020	153 (15)	0.81 (0.65, 1.00)	0.87 (0.70, 1.09)	
	4	286	41 (14)	0.77 (0.54, 1.10)	0.84 (0.59, 1.21)	
	5	595	75 (16)	0.66 (0.50, 0.87)	0.75 (0.57, 1.00)	
	per category			0.90 (0.84, 0.96)	0.93 (0.87, 0.98)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

4.1.2 Physical activity and subtypes of LUTS at 11.5 years of follow up

The associations between physical activity levels and LUTS 11.5 years after baseline are presented in Table 27. Before adjusting for confounders, women in the highest category of physical activity had reduced odds of reporting stress UI, urgency, urgency UI, mixed UI, and any type of LUTS compared to women with zero MET hours/week. Lower odds of stress UI were found for all levels of physical activity (compared to inactive women), but confidence intervals excluded the null only for women with 17.3-29.2 MET hours/week of physical activity.

Lower odds of urgency UI were observed among women with both 0.1-17.2 MET hours/week and 17.3-29.2 MET hours/week, but for 29.3-43.2 MET hours/week, despite the lower odds, confidence intervals spanned the null. Women in all categories of MET hours/week of physical activity had lower odds of mixed UI compared to inactive women. When I examined any type of LUTS, odds ratios were all less than one, but 95% confidence intervals spanned the null for all but the highest level of PA (as noted above).

I was not able to evaluate nocturia at 11.5 years of follow-up because of the small number of women who experienced this outcome (n<5).

After adjusting for confounders, women in the highest category of physical activity level had reduced odds of reporting stress UI, urgency, urgency UI, mixed UI, and any type of LUTS compared to women with zero MET hours/week.

For the intermediate physical activity levels ORs were all <1 but results did not follow a dose response, for example, ORs across increasing levels of physical activity were 0.78 (95%CI: 0.55, 1.11), 0.65 (0.45, 0.93), 0.89 (0.62, 1.26) and 0.56, (0.39, 0.82).

Table 27. Associations of physical activity with risk of LUTS at 11.5 years of follow up

Outcome	Physical activity categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)**	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	275	58 (21)	Ref	Ref	0.026
	2	494	86 (17)	0.79 (0.57, 1.09)	0.78 (0.55, 1.11)	
	3	530	78 (15)	0.66 (0.47, 0.92)	0.65 (0.45, 0.93)	
	4	477	84 (18)	0.80 (0.57, 1.12)	0.89 (0.62, 1.26)	
	5	474	59 (12)	0.51 (0.35, 0.72)	0.56 (0.39, 0.82)	
Urgency						
	1	272	14 (5)	Ref	Ref	0.042
	2	490	15 (3)	0.67 (0.47, 1.00)	0.64 (0.45, 0.93)	
	3	531	19 (4)	0.84 (0.60, 1.19)	0.87 (0.61, 1.24)	
	4	477	20 (4)	0.89 (0.63, 1.26)	0.98 (0.68, 1.39)	
	5	472	11 (2)	0.44 (0.30, 0.65)	0.47 (0.31, 0.70)	
Urgency UI						
	1	343	37 (11)	Ref	Ref	0.027
	2	633	44 (7)	0.61 (0.38, 0.96)	0.55 (0.33, 0.92)	
	3	637	38 (6)	0.53 (0.33, 0.86)	0.54 (0.32, 0.90)	
	4	574	41 (7)	0.65 (0.40, 1.04)	0.78 (0.47, 1.30)	
	5	583	23 (4)	0.33 (0.19, 0.56)	0.34 (0.20, 0.67)	
Mixed UI						
	1	274	25 (10)	Ref	Ref	0.006
	2	492	29 (6)	0.58 (0.36, 0.94)	0.55 (0.33, 0.91)	
	3	530	31 (6)	0.56 (0.34, 0.91)	0.55 (0.33, 0.92)	
	4	477	27 (6)	0.57 (0.35, 0.93)	0.63 (0.38, 1.07)	
	5	473	15 (3)	0.32 (0.18, 0.57)	0.34 (0.19, 0.63)	
Any type of LUTS						
	1	339	97 (29)	Ref	Ref	0.007
	2	626	144 (23)	0.75 (0.55, 1.00)	0.72 (0.52, 1.00)	
	3	636	146 (23)	0.74 (0.55, 1.00)	0.71 (0.52, 0.98)	
	4	574	140 (24)	0.80 (0.59, 1.09)	0.88 (0.64, 1.20)	
	5	579	93 (16)	0.48 (0.35, 0.66)	0.52 (0.37, 0.73)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

Table 28 represents findings for the analyses limited to high intensity physical activities at 11.5 years of follow up from baseline. In both models, women in the highest category of physical activity had lower odds of reporting stress incontinence, urgency and any LUTS compared to women reporting zero MET hours/week. Nocturia was not examined due to the insufficient sample number to give a meaningful analysis. There was no evidence of association between categories of physical activities and mixed UI or urgency UI.

Table 28. Associations of high intensity physical activity with Risk of LUTS at 11.5 Years of follow up

Outcome	Physical activity categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR**(95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	429	47 (11)	Ref	Ref	0.073
	2	717	61 (9)	0.80 (0.59, 1.08)	0.83 (0.62, 1.13)	
	3	772	62 (8)	0.84 (0.65, 1.10)	0.90 (0.69, 1.17)	
	4	633	51 (8)	0.90 (0.60, 1.34)	0.97 (0.65, 1.46)	
	5	659	34 (5)	0.60 (0.43, 0.85)	0.68 (0.48, 0.96)	
Urgency						
	1	961	146 (15)	Ref	Ref	0.099
	2	475	73 (15)	1.01 (0.74, 1.37)	1.08 (0.79, 1.47)	
	3	717	111 (15)	1.02 (0.78, 1.34)	1.11 (0.84, 1.46)	
	4	206	27(13)	0.84 (0.54, 1.31)	0.92 (0.59, 1.45)	
	5	411	39 (9)	0.58 (0.40, 0.85)	0.66 (0.44, 0.96)	
	per category			0.94 (0.82, 1.09)	0.94 (0.86, 1.01)	
Urgency UI						
	1	961	77 (8)	Ref	Ref	0.251
	2	475	29 (6)	0.76 (0.49, 1.19)	0.78 (0.50, 1.23)	
	3	717	46 (6)	0.80 (0.55, 1.17)	0.88 (0.60, 1.29)	
	4	206	11 (5)	0.65 (0.34, 1.24)	0.73 (0.38, 1.42)	
	5	411	20 (5)	0.56 (0.34, 1.94)	0.67 (0.40, 1.12)	
	per category			0.90 (0.79, 1.02)	0.94 (0.81, 1.06)	
Mixed UI						
	1	429	22 (5)	Ref	Ref	0.121
	2	718	12 (2)	0.81 (0.52, 1.28)	0.83 (0.53, 1.32)	
	3	772	19 (2)	0.72 (0.48, 1.08)	0.77 (0.51, 1.17)	
	4	633	20 (3)	0.66 (0.33, 1.30)	0.73 (0.37, 1.46)	
	5	660	13 (2)	0.59 (0.35, 1.01)	0.70 (0.41, 1.20)	
	per category			0.84 (0.73, 1.00)	0.93 (0.79, 1.10)	
Any type of LUTS						
	1	963	239 (25)	Ref	Ref	0.027
	2	476	103 (22)	0.83 (0.64, 1.08)	0.83 (0.63, 1.11)	
	3	717	169 (24)	0.93 (0.74, 1.16)	0.93 (0.73, 1.19)	
	4	205	44 (21)	0.82 (0.57, 1.18)	0.99 (0.67, 1.44)	
	5	409	65 (16)	0.56 (0.42, 0.76)	0.62 (0.45, 0.87)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

4.2 Complete case analysis results for physical activity and LUTS

In this section, I will briefly explain the results of the complete case analysis examining the association between physical activity and LUTS.

4.2.1 Physical activity and subtypes of LUTS after 3 years of follow up (Complete case analysis results)

Results of the complete case analysis for LUTS at 3.5 years of follow-up (Table 29) were similar to the multiple imputation results. Compared to lower categories of physical activity (zero MET hours/week), higher categories of physical activity (≥43.2 MET hours/week) were strongly associated with lower odds of stress UI, mixed UI and any LUTS in main analysis and adjusted analysis for confounders. Women in lower categories of physical activity (0.1-17.2 and 17.3-29.2 MET hours/week) were also associated with lower odds of mixed UI compared to the zero MET hours/week category. Women in the category of ≥ 29.3 MET hours/week were less likely to report having nocturia compared to women reporting zero MET hours/week, though the confidence interval was wide. There was evidence of association detected between 0.1-17.2 MET hours/week and urgency (adjusted OR=0.35; 95% CI 0.14, 0.90) only in the adjusted model. There was no evidence of association detected between categories of physical activity and urgency in the unadjusted model. However, in the unadjusted model, evidence of association was observed between 0.1- 17.2 MET hours/week and urgency UI.

Table 29. Associations between physical activity and LUTS at 3 years of follow up

Outcome	Physical activity Categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR** (95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	449	49 (11)	Ref	Ref	0.011
	2	748	65 (9)	0.78 (0.53, 1.15)	0.79 (0.53, 1.17)	
	3	801	63 (8)	0.70 (0.47, 1.03)	0.72 (0.48, 1.07)	
	4	657	54 (8)	0.73 (0.49, 1.09)	0.80 (0.53, 1.21)	
	5	685	36 (5)	0.45 (0.29, 0.71)	0.51 (0.32, 0.80)	
Urgency						
	1	449	52 (12)	Ref	Ref	0.948
	2	749	68 (9)	0.71 (0.46, 1.12)	0.70 (0.43, 1.01)	
	3	802	84(10)	0.88 (0.56, 1.36)	0.94 (0.61, 1.46)	
	4	657	77(12)	1.01 (0.65, 1.54)	1.05 (0.67, 1.66)	
	5	686	57 (8)	0.71 (0.47, 1.11)	0.76 (0.48, 1.22)	
	per category			1.00 (0.89, 1.10)	0.97 (0.88, 1.07)	
Nocturia						
	1	449	9 (2)	Ref	Ref	0.007
	2	749	13(2)	0.86 (0.37, 2.04)	0.84 (0.35, 1.98)	
	3	802	13(1)	0.81 (0.34, 1.90)	0.79 (0.33, 1.87)	
	4+5	1343	7 (1)	0.26 (0.09, 0.69)	0.26 (0.10, 0.72)	
Urgency UI						
	1	449	15 (3)	Ref	Ref	0.489
	2	749	12 (2)	0.42 (0.17, 1.00)	0.35 (0.14, 0.90)	
	3	802	20 (3)	0.67 (0.32, 1.42)	0.72 (0.33, 1.55)	
	4	657	19 (3)	0.84 (0.40, 1.77)	0.88 (0.40, 1.93)	
	5	686	15 (2)	0.75 (0.35, 1.60)	0.83 (0.38, 1.83)	
	per category			1.02 (0.86, 1.22)	1.07 (0.88, 1.29)	
Mixed incontinence						
	1	449	22 (5)	Ref	Ref	0.386
	2	749	14 (2)	0.37 (0.19, 0.73)	0.38 (0.19, 0.76)	
	3	802	19 (2)	0.47 (0.25, 0.87)	0.50 (0.26, 0.94)	
	4	657	21 (3)	0.64 (0.35, 1.18)	0.78 (0.42, 1.45)	
	5	686	13 (2)	0.37 (0.19, 0.75)	0.18 (0.24, 0.99)	
	per category			0.88 (0.81, 0.97)	0.94 (0.85, 1.05)	
Any type of LUTS						
	1	782	82 (18)	Ref	Ref	0.049
	2	1355	120 (16)	0.85 (0.63, 1.16)	0.86 (0.63, 1.17)	
	3	1318	126 (16)	0.84 (0.62, 1.13)	0.85 (0.63, 1.16)	
	4	1078	108 (16)	0.88 (0.64, 1.21)	0.95 (0.69, 1.31)	
	5	1200	80 (12)	0.59 (0.42, 0.83)	0.64 (0.46, 0.90)	

Footnote

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

After restricting analysis to high physical activity (Table 30), 17.3-29.2 MET hours/week category of physical activity was associated with lower odds of stress UI and mixed UI in main analysis and adjusted for confounders analysis. Interestingly, 29.3-43.2 MET hours/week category of physical activity was associated with higher odds of reporting urgency UI in main analysis and adjusted analysis. However, this association is based on a small sample number and was not detected in the multiple imputation analysis (Table 28). There was no evidence of association detected between categories of physical activity and other examined LUTS (urgency and any LUTS).

Table 30. Associations between high intensity physical activity with risk of LUTS at 3 years of follow up

Outcome	Physical activity categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR**(95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	1205	112 (9)	Ref	Ref	0.675
	2	557	51 (9)	0.93 (0.76, 1.15)	0.85 (0.67, 1.09)	
	3	859	63 (7)	0.77 (0.64, 0.93)	0.77 (0.62, 0.96)	
	4	239	18 (8)	0.74 (0.54, 1.01)	0.79 (0.55, 1.12)	
	5	480	23 (5)	0.82 (0.66, 1.03)	0.83 (0.64, 1.08)	
	Per category			0.93 (0.89, 0.98)	0.98 (0.87, 1.09)	
Urgency						
	1	1206	122 (10)	Ref	Ref	0.766
	2	558	61(11)	1.30 (0.89, 1.91)	1.40 (0.94, 2.06)	
	3	859	88 (10)	1.00 (0.70, 1.41)	1.11 (0.77, 1.60)	
	4	240	23 (9)	1.05 (0.60, 1.80)	1.12 (0.64, 1.97)	
	5	480	44 (9)	0.98 (0.65, 1.50)	1.09 (0.71, 1.68)	
	per category			0.99 (0.90, 1.00)	1.01 (0.92, 1.09)	
Urgency UI						
	1	1206	29 (2)	Ref	Ref	0.178
	2	558	11 (2)	0.93 (0.42, 1.99)	0.84 (0.37, 1.93)	
	3	859	22 (3)	1.07 (0.57, 2.04)	1.10 (0.61, 2.30)	
	4	240	9 (4)	2.35 (1.09, 1.34)	2.41 (1.08, 1.56)	
	5	480	10 (2)	1.11 (0.52, 2.37)	1.26 (0.58, 1.74)	
	per category			0.91 (0.42, 1.99)	1.13 (0.95, 1.34)	
Mixed UI						
	1	1206	40 (3)	Ref	Ref	0.731
	2	558	13 (2)	0.99 (0.71, 1.38)	0.94 (0.63, 1.39)	
	3	859	18 (2)	0.54 (0.38, 0.77)	0.59 (0.40, 0.88)	
	4	240	7 (3)	0.74 (0.44, 1.24)	0.92 (0.52, 1.62)	
	5	48	11 (2)	0.97 (0.69, 1.37)	1.07 (0.71, 0.60)	
	per category			0.93 (0.86, 1.00)	1.02 (0.84, 1.23)	
Any type of LUTS						
	1	1206	199 (17)	Ref	Ref	0.723
	2	557	98 (18)	1.08 (0.83, 1.41)	1.09 (0.76, 1.56)	
	3	859	128 (15)	0.89 (0.70, 1.13)	1.03 (0.74, 1.41)	
	4	239	35(15)	0.87 (0.59, 1.28)	1.18 (0.73, 1.93)	
	5	480	56(12)	0.67 (0.49, 0.92)	0.87 (0.58, 1.31)	
	per category			0.91 (0.85, 0.98)	0.98 (0.90, 1.08)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

4.2.2 Physical activity and subtypes of LUTS after 11.5 years of follow up (Complete case analysis results)

At 11.5 years of follow up (Table 31), higher physical activity categories (≥43.2 MET hours/week) were associated with lower odds of stress UI, urgency UI, mixed UI and any LUTS in main and adjusted analysis. 17.3-29.2 MET hours/week category was also associated with lower odds of any LUTS compared to the zero MET hours/week physical activity category. There was evidence of inverse association between ≥43.2 MET hours/week (highest category) and urgency in both models (unadjusted and adjusted).

Table 31. Association between physical activity and LUTS at 11.5 years of follow up

Outcome	Physical activity Categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR** (95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	289	61 (21)	Ref	Ref	0.044
	2	510	87 (17)	0.77 (0.53, 1.11)	0.79 (0.55, 1.15)	
	3	543	82 (15)	0.66 (0.46, 0.96)	0.69 (0.47, 1.00)	
	4	493	88 (18)	0.81 (0.56, 1.17)	0.89 (0.62, 1.29)	
	5	487	60 (12)	0.53 (0.36, 0.78)	0.58 (0.39, 0.86)	
Urgency						
	1	286	16 (6)	Ref	Ref	0.069
	2	506	16 (3)	0.66 (0.42, 1.04)	0.69 (0.43, 1.09)	
	3	544	20 (4)	0.93 (0.61, 1.42)	0.90 (0.58, 1.39)	
	4	493	22 (5)	0.92(0.60, 1.41)	0.98 (0.62, 1.51)	
	5	485	11 (2)	0.75 (0.29, 0.86)	0.48 (0.29, 0.79)	
Urgency UI						
	1	289	30 (10)	Ref	Ref	0.057
	2	510	34 (7)	0.60 (0.37, 1.08)	0.64 (0.35, 1.18)	
	3	544	31 (6)	0.60 (0.34, 1.07)	0.61 (0.34, 1.11)	
	4	493	35 (7)	0.74 (0.42, 1.30)	0.81 (0.44, 1.45)	
	5	488	17 (3)	0.39 (0.20, 0.75)	0.40 (0.20, 0.80)	
Mixed incontinence						
	1	288	27 (9)	Ref	Ref	0.022
	2	508	29 (6)	0.59 (0.34, 1.01)	0.59 (0.34, 1.03)	
	3	543	32 (6)	0.61 (0.36, 1.03)	0.63 (0.36, 1.07)	
	4	493	31 (6)	0.65 (0.38, 1.11)	0.74 (0.43, 1.28)	
	5	486	15 (3)	0.31 (0.16, 0.59)	0.35 (0.18, 0.73)	
Any type of LUTS						
	1	204	82 (29)	Ref	Ref	0.007
	2	391	114 (23)	0.73 (0.52, 1.01)	0.74 (0.53, 1.03)	
	3	427	116 (21)	0.68 (0.49, 0.94)	0.69 (0.50, 0.96)	
	4	374	119 (24)	0.79 (0.57, 1.10)	0.86 (0.62, 1.20)	
	5	407	78 (16)	0.48 (0.34, 0.68)	0.52 (0.36, 0.74)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

After restricting analysis to high intensity physical activity (Table 32), higher physical activity categories (≥43.2 MET hours/week) were associated with lower odds of stress UI, any LUTS in main and adjusted analysis and lower odd of urgency UI in the adjusted model. There was no evidence of association observed between categories of physical activity and other examined LUTS in both unadjusted and adjusted analysis.

Table 32 Associations between high intensity physical activity with risk of LUTS at 11.5 years of follow Up

Outcome	Physical activity categories MET hours/week*	N	N cases (%)	Unadjusted OR (95% CI)	Adjusted OR**(95% CI)	Non-Linearity Test P -value
Stress UI						
	1 (0 MET hours/week)	786	112 (9)	Ref	Ref	0.039
	2	397	51 (9)	0.86 (0.62, 1.19)	0.89 (0.64, 1.23)	
	3	623	63 (7)	0.89 (0.67, 1.17)	0.93 (0.70, 1.23)	
	4	176	18 (8)	1.06 (0.69, 1.60)	1.13 (0.74, 1.72)	
	5	340	23 (5)	0.61 (0.42, 0.89)	0.67 (0.46, 0.98)	
	Per category			0.93 (0.89, 0.98)	0.94 (0.87, 1.02)	
Urgency						
	1	782	122 (10)	Ref	Ref	0.173
	2	397	61 (11)	1.20 (0.82, 1.72)	1.21 (0.85, 1.81)	
	3	620	88 (10)	1.00 (0.71, 1.40)	1.05 (0.74, 1.48)	
	4	175	23 (9)	0.90 (0.52, 1.54)	0.91 (0.52, 1.60)	
	5	340	44 (9)	0.70 (0.45, 1.09)	0.72 (0.46, 1.14)	
	per category			0.93 (0.84, 1.01)	0.93 (0.85, 1.03)	
Urgency UI						
	1	786	59 (8)	Ref	Ref	0.351
	2	398	25 (6)	0.89 (0.52, 1.52)	0.86 (0.50, 1.50)	
	3	623	38 (6)	0.88 (0.55, 1.40)	0.92 (0.58, 1.48)	
	4	176	10 (6)	1.00 (0.49, 2.03)	0.98 (0.47, 2.08)	
	5	341	15 (4)	0.70 (0.39, 1.29)	0.68 (0.36, 1.30)	
	per category			0.89 (0.52, 1.52)	0.94 (0.81, 1.08)	
Mixed UI						
	1	784	40 (3)	Ref	Ref	0.137
	2	396	13 (2)	0.93 (0.57, 1.52)	0.95 (0.58, 1.57)	
	3	623	18 (2)	0.82 (0.53, 1.28)	0.89 (0.57, 1.40)	
	4	176	7 (3)	0.66 (0.31, 1.41)	0.75 (0.35, 1.62)	
	5	339	11 (2)	0.55 (0.30, 1.02)	0.63 (0.34, 1.18)	
	per category			0.93 (0.86, 1.00)	0.90 (0.79, 1.03)	
Any type of LUTS						
	1	781	191 (24)	Ref	Ref	0.034
	2	396	85 (22)	0.84 (0.63, 1.13)	0.87 (0.65, 1.16)	
	3	620	138 (22)	0.88 (0.69, 1.14)	0.93 (0.72, 1.19)	
	4	175	41 (23)	0.95 (0.64, 1.39)	1.00 (0.68, 1.48)	
	5	340	54 (16)	0.58 (0.42, 0.81)	0.63 (0.45, 0.88)	
	per category			0.91 (0.84, 0.97)	0.92 (0.86, 1.00)	

***** Category 1: 0 MET hours/week, Category 2: 0.1- 17.2 MET hours/week, Category 3: 17.3-29.2 MET hours/week, Category 4: 29.3-43.2 MET hours/week, Category 5: ≥43.2 MET hours/week

****** Confounders included for the adjusted models are age, parity, BMI, university degree and social status.

Note:

Per category: examines evidence of departure from linearity in the relationship between physical activity (MET hours/week) and LUTS subtypes by comparing a model where categories of physical activity were entered as a continuous variable to a model including four dummy variables using a likelihood ratio test.

4.3 Summary

Women in the highest category of physical activity (≥43.2 MET hours/week) had lower odds of stress UI, mixed UI and any LUTS compared to women in the lowest category (0 MET hours/week) after 3 and 11.5 years of follow-up from baseline. There was also evidence of lower odds of nocturia at 3 years of follow up and lower odds of urgency UI after 11.5 years of follow-up in these women. Intermediate levels of physical activity were also associated with reduced odds of LUTS at 3 and 11.5 years of follow up but often confidence intervals crossed the null value and the associations between levels of physical activity and LUTS did not follow a dose-response relationship.

5 Chapter 5 Constipation and Risk of LUTS

This chapter will present the results of the analysis examining the association between constipation (as proxied by medication use) and risk of LUTS. I present the results from the multiple imputation analysis first, followed by the complete case analysis.

5.1 Results of constipation and risk of LUTS multiple imputation analysis

3729 women, free of LUTS symptoms in 2002-2004, provided information on use of medication for constipation between 2001-2005 (baseline), and information on LUTS in 2011-2012 (after approx. 10 years of follow up); these women were eligible for inclusion in analyses. 40% of these women reported any LUTS at follow-up (mean age 43.3 years; SD 4.5), with stress UI (23%) being the most common type of LUTS.

Table 33 presents the distribution of background characteristics in the complete-case and the multiple-imputation datasets for women included in analyses. The distribution of background characteristics was very similar before and after imputation. 6% of women reported taking constipation medication at either questionnaires and 2% of women reported taking medication at both time points (questionnaire 1: 2001-2003 and questionnaire 2: 2003-2005).

Table 33. Distribution of characteristics of women included in analyses of LUTS in complete case, observed and imputed datasets

	Missing (n)	Observed data	Imputed data sets (%) n=3729
Age, Mean (SE)	95	43.3 (0.08)	43.3 (0.01)
BMI, Mean (SE)	369	24.3 (4.3)	24.3 (0.07)
Parity, n (%)	83		
1		546 (15)	559 (15)
2		1776 (49)	1827 (49)
3+		1324 (36)	1343 (36)
Hysterectomy n (%)	95		
Yes		122 (3)	112 (3)
No		3512 (97)	3617 (97)
Occupational Social Class, n (%)	372		
Manual			
Non-manual		564 (15)	634 (17)
		2793 (85)	3095 (83)
Physical activity (MET hours/week), n (%)	0		
0		472 (13)	485 (13)
0.1-17.2,		733 (20)	709 (19)
17.3-29.2,		813 (22)	820 (22)
29.3-43.2		907 (24)	895 (24)
≥43.2		804 (21)	820 (22)
University Degree, n (%)	310		
Yes		261(8)	299 (8)
No		3158 (92)	3430 (92)
Constipation medication, n (%)	0		
None		3415 (92)	3431(92)
Only one timepoint		227 (6)	224 (6)
Both timepoints		87 (2)	74 (2)
Constipation medication, n (%)	0		
None		3415 (92)	3430 (92)
Any timepoint		314 (8)	299 (8)

Stress UI, n (%)	8		
Yes		844 (23)	858 (23)
No		2877 (77)	2871 (77)
Urgency UI, n (%)	13		
Yes		318 (9)	336 (9)
No		3398 (91)	3393 (91)
Mixed UI, n (%)	15		
Yes		304 (9)	299 (8)
No		3410 (91)	3430 (92)
Increased daytime frequency, n (%)	7		
Yes		531 (14)	552 (14)
No		3191 (86)	3207 (86)
Nocturia, n (%)	7		
Yes		330 (9)	336 (9)
No		3392 (91)	3393 (91)
Urgency, n (%)	6		
Yes		657 (18)	671 (18)
No		3066 (82)	3058 (82)
Any type of LUTS, n (%)	165		
Yes		1443 (40)	1492 (40)
No		2121 (60)	2237 (60)
Hesitancy n (%)	52		
Yes		181 (6)	186 (5)
No		3496 (94)	3543 (95)
Intermittency n (%)	15		
Yes		341 (9)	336 (9)
No		3373 (91)	3393 (91)

Table 34 shows the distribution of characteristics of women according to use of medication for constipation. There was no convincing evidence of differences in the examined characteristics across categories of constipation medication use, other than for the proportion of women who underwent hysterectomy. The proportion of women who underwent hysterectomy was slightly higher amongst women who reporting taking medication for constipation at only one time point (4%) compared to women not taking medication (3%). None of the women who reported taking constipation medication at both time points reported having a hysterectomy.

Table 34. Characteristics of women according to use of medication for constipation

	Constipation Medication			
Confounder	None at both time points. (n= 3415)	Only one timepoint (n=227)	Both timepoints (n=87)	P-value
Age, years (Mean (SD))	43.3 (0.5)	43.2 (0.5)	43.3 (0.5)	0.125
BMI (kg/m^2) (Mean (SD))	24.3 (4.3)	24.8 (4.2)	24.1 (3.9)	0.262
Hysterectomy, % Yes	 3	 4	 0	0.005
Physical activity (MET hours/week), % 0 0.1-17.2, 17.3-29.2, 29.3-43.2 ≥43.2	 13 20 22 24 21	 13 21 19 25 22	 12 15 23 26 24	0.590
Occupational Social Class % Manual Non-Manual	 17 83	 14 86	 17 83	0.559
University Degree % Yes	 8	 8	 9	0.932
Parity % 1 2 3+	 15 49 36	 15 52 33	 16 47 37	0.538

5.1.1 Self-reported constipation (measured by medication intake) and LUTS

Table 35 shows the findings comparing women who reported using medications for constipation at ‘only one time point’ and at ‘both time points’ compared to women who reported not using any medication for constipation at either time point.

Before adjusting for confounders, women who used medication for constipation at one time point had an increased risk of urgency and hesitancy compared to women who did not use constipation medication. This association remained after adjustment for confounders. A greater risk of urgency and hesitancy was seen for women who reported using medication at both timepoints both before and after adjustment for confounders and the point estimates were larger than those observed for women reporting medication use at a single timepoint only. Estimates for urgency and hesitancy were larger for using medications for constipation at two timepoints versus one timepoint suggesting a dose response effect.

There was no convincing evidence of an association between use of medication for constipation and any other examined types of LUTS (any LUTS, stress UI, urgency UI, mixed UI, increase daytime frequency and nocturia).

Table 35. Associations of use of constipation medication (at only one time point and at both time points) with LUTS at 10 years of follow up:

Outcome	Constipation Medication	N	N cases (%)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Stress UI					
	None	3409	762 (22)	Ref	Ref
	Only one time points	225	56 (25)	1.15 (0.84, 1.57)	1.17 (0.82, 1.65)
	Both time points	87	26 (30)	1.48 (0.92, 2.36)	1.37 (0.80, 2.31)
Increased daytime frequency					
	None	3408	483 (14)	Ref	Ref
	Only one time points	227	32 (14)	0.99 (0.68, 1.46)	0.90 (0.58, 1.40)
	Both time points	87	16 (18)	1.36 (0.79, 2.37)	1.46 (0.81, 2.64)
Nocturia					
	None	3408	302 (9)	Ref	Ref
	Only one time points	227	17 (7)	0.83 (0.50, 1.38)	0.68 (0.37, 1.25)
	Both time points	87	11 (13)	1.49 (0.79, 2.83)	1.37 (0.65, 2.91)
Urgency UI					
	None	3404	288 (8)	Ref	Ref
	Only one time points	225	22 (10)	1.17 (0.74, 1.85)	0.99 (0.58, 1.69)
	Both time points	87	8 (9)	1.10 (0.52, 2.29)	1.17 (0.53, 2.60)
Urgency					
	None	3411	584 (17)	Ref	Ref
	Only one time points	225	51 (23)	1.42 (1.03, 1.96)	1.35 (1.04, 1.95)
	Both time points	87	22 (25)	1.64 (1.00, 2.68)	1.94 (1.15, 3.29)
Mixed UI					
	None	3402	274 (8)	Ref	Ref
	Only one time points	225	21 (9)	1.18 (0.74, 1.87)	1.07 (0.63, 1.84)
	Both time points	87	9 (10)	1.32 (0.65, 2.66)	1.29 (0.58, 2.87)
Hesitancy					
	None	3369	155 (5)	Ref	Ref
	Only one time points	222	17 (8)	1.72 (1.02, 2.89)	1.72 (1.04, 3.01)
	Both time points	86	9 (10)	2.42 (1.19, 4.92)	1.78 (1.03, 4.19)
Intermittency					
	None	3403	301 (9)	Ref	Ref
	Only one time points	224	28 (13)	1.47 (0.97, 2.22)	1.18 (0.72, 1.94)
	Both time points	87	12 (14)	1.65 (0.89, 2.89)	1.49 (0.73, 2.98)
Any type of LUTS					
	None	3268	1310 (40)	Ref	Ref
	Only one time points	214	92 (43)	1.13 (0.85, 1.49)	1.07 (0.78, 1.46)
	Both time points	82	41 (50)	1.49 (0.96, 2.32)	1.54 (0.95, 2.51)

Footnote
***** Confounders included for the adjusted models are age, parity, BMI, university degree and social status, physical activity, and hysterectomy.

Table 36 shows the results of the analysis comparing women who reported using medications for constipation at ‘any time point’, i.e., collapsing the categories of medication use at one and at both timepoints, compared to women who reported not using medication for constipation at either time point. Findings were similar to the main results in both models (unadjusted and adjusted for confounders). In the unadjusted model, women who reported using constipation medication had increased risks of hesitancy and urgency compared to women who did not use constipation medication and these associations remained in the adjusted model. There was no strong evidence of an association with other examined LUTS subtypes.

Table 36. Associations of medication intake for constipation at any time point and LUTS at approx. 10 years of follow up

Outcome	Constipation Medication	N	N cases (%)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Stress UI					
	None	3409	76 (22)	Ref	Ref
	Any time point	312	82 (26)	1.24 (0.95, 1.61)	1.22 (0.91, 1.64)
Frequency					
	None	3408	483 (14)	Ref	Ref
	Any time point	314	48 (15)	1.09 (0,80, 1.51)	1.05 (0.73, 1.50)
Nocturia					
	None	3408	302 (9)	Ref	Ref
	Any time point	314	28 (9)	1.00 (0.80, 1.51)	0.85 (0.53, 1.38)
Urgency UI					
	None	3404	288 (8)	Ref	Ref
	Any time point	312	30 (10)	1.15 (0.78, 1.71)	1.04 (0.66, 1.63)
Urgency					
	None	3411	584 (17)	Ref	Ref
	Any time point	312	73 (23)	1.48 (1.12, 1.95)	1.51 (1.10, 2.05)
Mixed UI					
	None	3402	274 (8)	Ref	Ref
	Any time point	312	30 (10)	1.21 (0.78, 1.71)	1.13 (0.72, 1.28)
Hesitancy					
	None	3369	155 (5)	Ref	Ref
	Any time point	308	26 (8)	1.91 (1.24, 2.94)	1.88 (1.16, 3.04)
Intermittency					
	None	3403	301 (9)	Ref	Ref
	Any time point	311	40 (13)	1.52 (1.07, 2.16)	1.26 (0.83, 1.91)
Any type of LUTS					
	None	3268	1310 (40)	Ref	Ref
	Any time point	296	133 (45)	1.22 (0.95, 1.61)	1.18 (0.91, 1.55)

Footnote
***** Confounders included for the adjusted models are age, parity, BMI, university degree and social status, physical activity, and hysterectomy.

5.2 Constipation and LUTS complete case analysis results

This section will present the results of the complete case analysis carried out to assess associations between constipation (measured by medication intake) and LUTS. The results will be described briefly as in this thesis because multiple imputation results are presented as my main findings as it reduces bias due to missing data.

5.2.1 Results of constipation (measured by medication intake) and risk of LUTS complete case analysis

Table 37 shows the findings comparing women who reported using medications for constipation at 'only one time point' and at 'both time points' compared to women who reported not using any medication for constipation at either time point. There was evidence of an association between constipation medication intake at either time points compared to no medication intake with urgency and hesitancy. There was no strong evidence of an association with other examined LUTS subtypes (any LUTS, stress UI, urgency UI, mixed UI, increase daytime frequency and nocturia).

Table 37. Associations of constipation medication intake (at none, only onetime point and both time points) and LUTS at 10 years of follow up

Outcome	Constipation Medication	N	N cases (%)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Stress UI					
	None	2606	578 (22)	Ref	Ref
	Only one time points	165	40 (24)	1.09 (0.83, 1.44)	1.07 (0.81, 1.42)
	Both time points	62	14 (23)	1.02 (0.64, 1.62)	1.06 (0.68, 1.68)
Frequency					
	None	2606	375 (14)	Ref	Ref
	Only one time points	167	23 (14)	0.95 (0.64, 1.41)	0.95 (0.64, 1.40)
	Both time points	62	10 (15)	1.05 (0.57, 1.92)	1.15 (0.64, 2.04)
Nocturia					
	None	2608	224 (9)	Ref	Ref
	Only one time points	167	12 (7)	0.84 (0.48, 1.46)	0.77 (0.45, 1.34)
	Both time points	62	7 (11)	1.31 (0.65, 2.67)	1.37 (0.67, 2.79)
Urgency UI					
	None	2604	218 (8)	Ref	Ref
	Only one time points	165	15 (9)	1.09 (0.66, 1.79)	1.07 (0.66, 1.75)
	Both time points	62	6 (10)	1.16 (0.53, 2.50)	1.21 (0.57, 2.61)
Urgency					
	None	2608	428 (16)	Ref	Ref
	Only one time points	165	37 (22)	1.37 (1.01, 1.84)	1.35 (1.00, 1.81)
	Both time points	62	15 (24)	1.47 (0.94, 2.31)	1.49 (0.95, 2.33)
Mixed UI					
	None	2602	205 (8)	Ref	Ref
	Only one time points	165	14 (9)	1.08 (0.64, 1.81)	1.06 (0.63, 1.76)
	Both time points	62	5 (8)	1.02 (0.44, 2.40)	1.09 (0.47, 2.53)
Any type of LUTS					
	None	2501	995 (40)	Ref	Ref
	Only one time points	157	66 (42)	1.06 (0.87, 1.28)	1.04 (0.86, 1.25)
	Both time points	55	27 (47)	1.19 (0.90, 1.57)	1.20 (0.92, 1.59)
Hesitancy					
	None	2577	125 (5)	Ref	Ref
	Only one time points	162	14 (9)	1.66 (1.03, 2.70)	1.75 (1.03, 2.96)
	Both time points	62	5 (8)	2.27 (1.20, 4.30)	1.76 (0.75, 4.14)
Intermittency					
	None	2603	233 (9)	Ref	Ref
	Only one time points	164	18 (11)	1.41 (0.98, 2.03)	1.18 (0.75, 1.85)
	Both time points	62	6 (10)	1.56 (0.91, 2.67)	1.10 (0.51, 2.31)

Footnote
***** Confounders included for the adjusted models are age, parity, BMI, university degree and social status, physical activity, and hysterectomy.

Table 38 shows the findings comparing women who reported using medications for constipation at ‘any time point’ (i.e., collapsing the categories of medication use at one and at both timepoints) compared to women who reported not using any medication for constipation at either time point. In both examined models (unadjusted and adjusted), the risk of constipation medication intake at any timepoint compared to women who reported not using medication for constipation at either time point is directly associated with urgency and hesitancy. There is no evidence of association observed between use of medication for constipation and other examined LUTS.

Table 38. Associations of constipation medication intake (none versus anytime point) and LUTS at 10 years of follow up

Outcome	Constipation Medication	N	N cases (%)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
Stress UI					
	None	2606	578 (22)	Ref	Ref
	Any time point	227	54 (24)	1.07 (0.84, 1.37)	1.08 (0.84, 1.38)
Increased Daytime Frequency					
	None	2606	375 (14)	Ref	Ref
	Any time point	229	33 (14)	1.01 (0.72, 1.39)	1.00 (0.70, 1.39)
Nocturia					
	None	2608	224 (9)	Ref	Ref
	Any time point	229	19 (8)	0.97 (0.62, 1.51)	0.92 (0.59, 1.43)
Urgency UI					
	None	2604	218 (8)	Ref	Ref
	Any time point	227	21 (9)	1.11 (0.72, 1.69)	1.12 (0.73, 1.69)
Urgency					
	None	2608	428 (16)	Ref	Ref
	Any time point	227	52 (23)	1.40 (1.08, 1.80)	1.39 (1.08, 1.78)
Mixed UI					
	None	2602	205 (8)	Ref	Ref
	Any time point	227	19 (8)	1.06 (0.68, 1.67)	1.06 (0.70, 1.66)
Any type of LUTS					
	None	2501	995 (40)	Ref	Ref
	Any time point	214	93 (44)	1.09 (0.93, 1.28)	1.08 (0.92, 1.27)
Hesitancy					
	None	2577	125 (5)	Ref	Ref
	Any time point	224	19 (9)	1.83 (1.23, 2.73)	1.75 (1.10, 2.78)
Intermittency					
	None	2603	233 (9)	Ref	Ref
	Any time point	226	24 (11)	1.45 (1.07, 1.98)	1.16 (0.78, 1.72)

Footnote
***** Confounders included for the adjusted models are age, parity, BMI, university degree and social status, physical activity, and hysterectomy.

5.3 Summary

There was evidence of an increased risk of LUTS among women (mean age 43.3 years, SD 0.5) who reported using medication for constipation compared to women who did not use constipation medication. Women who took medication for constipation at either time point had increased risks of urinary urgency and hesitancy compared with women who reported not using medication for constipation at either time points. The risk of urgency and hesitancy was also greater among women who took medication for constipation at both time points. Point estimates for urgency and hesitancy were larger for using medications for constipation at two timepoints versus one timepoint suggesting a dose response. There was no evidence of an association between constipation and other types of examined LUTS. Multiple imputation and complete case analysis showed similar results.

6 Chapter 6: Results and summary of LUTS and Measures of Quality of Sexual Experience

The third aim of my thesis was to investigate the relationship between LUTS and quality of sexual experience in parous middle-aged women using both a cross-sectional and prospective designs. This chapter will present the results and summary of analyses carried out to achieve my third aim. The chapter is divided into three sections. The first section will represent the results of two cross-sectional analyses conducted using data collected at two different time points (1996-1998 and 1997-1999) examining the association between stress UI and concurrent quality of sexual experience (frequency and overall satisfaction with sex). The second part will present the results of a prospective analysis examining the association of changes in stress UI symptoms (no onset of stress UI, new onset of stress UI, resolved and persistent stress UI symptoms) and quality of sexual experience (frequency and overall satisfaction with sex) at 1 year of follow up. This analysis was limited to stress UI because it was frequently reported as among the most common bothersome symptoms associated with poor sexual experience (105, 125).” Repetition of assessment (i.e., on association between stress UI and measures of sexual experience) on a large sample of women that ALSPAC provide will strengthen the available evidence. Examining the association cross-sectionally is important to understand if stress UI have concurrent association with poor sexual experience. The third section will present the results of the analysis examining the prospective associations between LUTS and measures of quality of sexual experience (frequency of sex and orgasm; level of worry or distress about level of desire, orgasmic experience, and frequency of sex; overall satisfaction with sexual experience) assessed at one year of follow up. The rationale behind the multiple analyses presented in this chapter is that it is plausible that LUTS affects the quality of concurrent sexual behaviours and experience, whilst affects might also be lasting and hence the prospective analyses. The results from the multiple imputation analysis are presented first followed by the complete case analysis.

6.1 Multiple Imputation results of cross-sectional studies 1 (1996-1998) and 2 (1997-1999) on stress UI and quality of sexual experience

This section will present the multiple imputation results from the two cross-sectional studies examining the association of stress UI with quality of sexual experience measures (frequency and satisfaction with sex).

6.1.1 Characteristics of women with and without stress UI at cross-sectional study 1 (1996-1998) and cross-sectional study 2 (1997-1999)

Table 39 shows characteristics of women with and without stress UI included in cross-sectional study 1 and cross-sectional study 2. At a mean age (SD) of 34.9 (0.12) years (1996-1998), prevalence of stress UI was 22% and at mean age (SD) 35.9 (0.10) years (1997-1999), prevalence of stress UI was 23%. Mean of age, anxiety and depression was slightly higher among women with stress UI at both time points compared to women with no symptoms of stress UI. At both time points, a higher proportion of women suffering from stress UI were taking antidepressants compared to women without stress UI. Moreover, women with stress UI were consuming more alcohol (everyday, often, or sometimes) compared to women with no stress UI; while proportions of women with stress UI who were not consuming alcohol (not at all) decreased compared to women without stress UI. Women with stress UI also reported a lower frequency of sex and were less satisfied about overall sex life compared to women without stress UI.

Table 39. Characteristics of women with and without stress UI at cross-sectional study 1 (1996-1998) and cross-sectional study 2 (1997-1999)

	Cross-sectional study 1		**Cross-sectional study 2**	
	Stress UI (Total n=7887) at		**Stress UI (Total n=7644) at**	
	No (n=6073)	**Yes (n=1814)**	**No (n=5503)**	**Yes (n=2141)**
Age, Mean (SE)	33.8 (0.06)	34.9 (0.12)	34.5 (0.06)	35.9 (0.10)
BMI, Mean (SE)	24.1 (0.05)	24.7 (0.10)	24.0 (0.05)	24.7 (0.09)
Anxiety, Mean (SE)	5.21 (0.04)	6.50 (0.04)	6.20 (0.04)	6.21 (0.04)
Depression, mean (SE)	5.43 (0.06)	6.90 (0.13)	5.47 (0.06)	6.78 (0.11)
Antidepressants (%)				
Everyday	2	3	3	4
Often	1	2	2	2
Sometimes	2	4	3	3
Not at all	94	91	93	91
Alcohol consumption (%)				
Never drink alcohol	7	7	8	7
<once a week	38	37	39	37
At least once a week	37	37	37	38
1-2 units nearly everyday	15	18	15	16
≥ 3 everyday	3	1	1	2
Frequency of sex %				
Not at all	2	3	2	2
< once a month	10	13	11	16
1-3 times a month	28	32	26	29
About once a week	27	26	27	26
2-4 times a week	30	24	31	25
5+ times a week	3	2	3	2
Overall satisfaction of sex %				
No	8	11	8	12
Yes	92	89	92	88

6.1.1.1 Stress UI and self-reported frequency of sex

Table 40 shows the associations between stress UI and frequency of sex (not at all, < once a month, 1-3 times a month, about once a week, 2-4 times a week or 5 +time a week). Multinomial logistic regression was used to estimate the association between stress UI and

frequency and results were presented as prevalence rate ratios (PRR) and 95% confidence intervals. In study 1, stress UI was associated with a greater prevalence of not having sex, having sex less than once a month, having sex 1-3 times a month and about once a week, as compared to having sex 2-4 times (reference group as it is the largest group) a week in unadjusted and adjusted analyses, with increasing prevalence ratios across decreasing categories of frequency. There were no association detected between stress UI and the prevalence of having sex 5 +time a week, though the point estimate indicated a reduced probability of having sex 5+ times compared to 2-4 times per week.

In study 2, in the unadjusted model, stress UI was associated with increased odds of reduced frequency of sex, though CI is for not having any sex crossed the null value. However, this association was weakened after adjusting for confounders as stress UI was associated with increased odds of reduced frequencies of sex (having sex less than once per month and 1-3 times a month). Stress UI showed no association with other categories of frequencies of having sex (not at all and 5 +time a week) in the analysis that involved adjustment of confounders.

Table 40. Frequency of sex according to the presence of stress UI in participants at cross-sectional study 1 (1996-1998) and cross-sectional study 2 (1997-1999)

	Frequency of sex											
	Not at all		**< once a month**		**1-3 times a month**		**About once a week**		**2-4 times A week (Ref)**	**5+ times a week**		
	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	P-value
Women with Stress UI (at 1996-1998 Questionnaire)	2.10 (1.49, 2.94)	2.34 (1.57, 3.48)	1.68 (1.40, 2.01)	1.34 (1.08, 1.68)	1.47 (1.28, 1.70)	1.30 (1.10, 1.54)	1.47 (1.28, 1.70)	1.26 (1.07, 1.50)	1	0.68 (0.44, 1.05)	0.89 (0.54, 1.44)	0.00
Women with Stress UI (at 1997-1999 Questionnaire)	1.10 (0.78, 1.56)	0.87 (0.60, 1.27)	1.67 (1.41, 1.97)	1.32 (1.10, 1.57)	1.34 (1.17, 1.53)	1.16 (1.00, 1.35)	1.16 (1.02, 1.34)	1.09 (0.94, 1.26)	1	0.86 (0.60, 1.22)	0.90 (0.61, 1.37)	0.00
Footnote ***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, and alcohol consumption												

6.1.1.2 Stress UI and self-reported overall satisfaction with sex

Table 41 shows participants overall satisfaction with sex according to the presence of stress UI at cross-sectional study 1 and cross-sectional study 2. Overall satisfaction with sex (binarized variable yes, no) was reported as prevalence rate ratios (95% CI) with a higher score indicating poorer satisfaction. In cross-sectional study 1 (Mean age (SD): 34.9 (0.12) years), stress UI was associated with a poorer overall sexual satisfaction experience. Although after adjustment for confounders, stress UI continued to be associated with poorer over all sexual satisfaction experience confidence intervals were narrower and started at the null. In cross-sectional study 2 (mean age (SD): 35.9 (0.10) years), main analysis and adjusted analysis showed direct association between stress UI and poorer overall sexual satisfaction experience.

Table 41 Overall satisfaction with sex according to the presence of stress UI at cross-sectional study 1 (1996-1998) and cross-sectional study 2 (1997-1999)

	Unadjusted PRR (95 % CI)	***Adjusted PRR (95% CI)**	**P-value**
Stress UI at approx. 5 years (1996-1998)			
No (Ref)	**1**	**1**	0.06
Yes	1.51 (1.27, 1.80)	1.21 (1.00, 1.50)	
Stress UI at approx. 6 years (1997-1998)			
No (Ref)	**1**	**1**	0.01
Yes	1.62 (1.38, 1.92)	1.29 (1.08, 1.54)	
Footnote ***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, and alcohol consumption Outcome: overall satisfaction of sex (yes/no)			

6.1.2 Complete case analysis results of cross-sectional analysis on stress UI and quality of sexual experience (measured by frequency and satisfaction with sex)

Tables 42 and 43 presents the results of the complete case analysis which were similar to the multiple imputation results. The analysis using multiple imputation strengthened associations between stress UI and our examined measures of quality of sexual experience. Further details are explained below.

6.1.2.1 Stress UI and self-reported frequency of sex (complete case analysis results)

Table 42 presents frequency of sex according to the presence of stress UI at cross-sectional study 1 (1996-1998) and cross-sectional study 2 (1997-1999). At mean age 34.9 years, 5996 women (eligible sample) had complete data on stress UI, frequency of sex, satisfaction with sex and confounders. Most women (31%) with stress UI reported frequency of sex 1-3 times a month, while only 2% of women (with stress UI) reported frequency of sex 5+ times a week. Stress UI was associated with greater prevalence ratios of reduced frequencies of sex (not at all, < once a month, 1-3 times a month and about once a week) compared to frequency of sex (2-4 times a week). There was no evidence of association between stress UI and prevalence of frequency of sex 5+ times a week. Similar results were observed in study 2.

Table 42 Frequency of sex according to the presence of stress UI at cross-sectional study 1 (n=5996) and cross-sectional study 2 (n=5479)

	Frequency of sex										
	2-4 times a week	**Not at all**		**< once a month**		**1-3 times a month**		**About once a week**		**5+ times a week**	
	N (%)	N (%)	*Adjusted PRR (95% CI)	N	Adjusted PRR (95% CI)	N	Adjusted PRR (95% CI)	N	Adjusted PRR (95% CI)	N	Adjusted PRR (95% CI)
Stress UI at Time point 1											
No	1438 (31)	73 (1)	**Ref**	472 (10)	**Ref**	1281 (28)	**Ref**	1254 (27)	**Ref**	115 (2)	**Ref**
Yes	317 (23)	47 (4)	2.35 (1.57, 3.50)	179 (13)	1.35 (1.09, 1.68)	428 (31)	1.31 (1.11, 1.55)	371 (27)	1.27 (1.01, 1.51)	21 (2)	0.90 (0.55, 1.47)
Stress UI at Time point 2											
No	1196 (30)	85 (2)	**Ref**	432 (11)	**Ref**	1062 (27)	**Ref**	1089 (28)	**Ref**	91 (2)	**Ref**
Yes	391 (26)	34 (2)	0.95 (0.62, 1.45)	243 (16)	1.31 (1.07, 1.60)	424 (28)	1.06 (0.90, 1.25)	407 (27)	1.05 (0.89, 1.24)	25 (1)	0.85 (0.53, 1.36)

Footnote

***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, and alcohol consumption

6.1.2.2 Stress UI and self-reported overall satisfaction with sex (complete case results)

Table 43 present the results of overall satisfaction with sexual experience according to the presence of stress UI at both cross-sectional studies. In study 1 (1996-1998), stress UI was associated with poorer overall satisfaction with sexual experience in both the unadjusted and adjusted. Similar results were observed in cross-sectional study 2 (1997-1998).

Table 43 Satisfaction with overall sexual experience according to the presence of stress UI at cross-sectional study 1 (1996-1998) and cross-sectional study 2 (1997-1999)

	Enjoys Sex N (%)	**Do not Enjoy Sex N (%)**	**Unadjusted PRR (95 % CI)**	***Adjusted PRR (95% CI)**
Stress UI at time point 1				
No	4276 (92)	357 (8)	**Ref**	**Ref**
Yes	1207 (89)	156 (11)	1.49 (1.24, 1.77)	1.19 (1.01, 1.42)
Stress UI at time point 2				
No	3651 (92)	304 (7)	**Ref**	**Ref**
Yes	1344 (88)	180 (12)	1.53 (1.29, 1.83)	1.24 (1.04, 1.48)
Footnote ***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, and alcohol consumption				

6.1.3 Summary of stress UI and quality of sexual experience cross-sectional studies results (measured by frequency and satisfaction with sex)

At a mean age (SD) of 34.9 (0.12) years, stress UI was associated with a higher prevalence of lower frequencies of sex (not having sex, having less than once a month, and having sex 1-3 times a month as compared to having sex 2-4 times a week. While at mean age (SD) 35.9 (0.10) years, stress UI was associated with lower prevalence of having sex less than once per month and 1-3 times a month. At both timepoints, stress UI was associated with a poorer overall sexual satisfaction experience.

6.2 Summary and results of changes in stress UI and quality of sexual experience prospective analysis

I found evidence that stress UI is associated cross-sectionally with measures of quality sexual experience (frequency and satisfaction with sex). I therefore examined whether stress UI symptoms could have an association with poorer quality of sexual experience overtime. Therefore, I conducted a prospective study examining the association between changes in stress UI symptoms (no onset of stress UI, resolved stress UI, new onset stress UI and persistent stress UI) and measures of quality of sexual experience (frequency and satisfaction with sex) at one year follow up (1997-1999) from baseline (1996-1998). I will first present the results of the multiple imputation results followed by the complete case analysis.

6.2.1 Multiple imputation results of examining prospective association between changes of stress UI and quality of sexual experience

This section will present the multiple imputation results of the prospective analysis examining the association between changes in stress UI and quality of sexual experience measures (frequency and satisfaction with sex).

6.2.1.1 Characteristics of women with changes in stress UI at follow up (1997-1999)

Table 44 shows characteristics of women with change in stress UI at one year of follow up from baseline (1996-1998). Women with new-onset or persistent stress UI were older and had greater scores for anxiety and depression compared to women with no stress UI and women with resolved stress UI symptoms. Mean BMI, use of antidepressants and alcohol consumption were similar across categories of change in stress UI. Proportions of women having higher frequencies of sex (about once a week, 2-4 times a week ,5+ times a week) were higher in women with no stress UI compared to women with other examined categories of stress UI. A higher proportion of women with resolved stress UI reported frequencies of sex of < once a month,1-3 times a month and about once a week compared to other stress UI categories. Finally, proportions of women enjoying sex were lower in women with persistent stress UI and new onset of stress UI compared to the other categories of stress UI.

Table 44 Characteristics of women with changes in stress UI at one year of follow up from baseline (1996-1998)

	Change in stress UI symptoms (Total n=7021) at follow up (1997-1999)			
	No onset of stress UI symptoms (n=4656)	**Resolved stress UI symptoms (n=430)**	**New onset of stress UI symptoms (n=788)**	**Persistent stress UI symptoms (n=1147)**
Age, Mean (SE)	34.6 (0.07)	34.8 (0.21)	35.5 (0.16)	36.4 (0.14)
BMI, Mean (SE)	24.0 (0.06)	24.5 (0.20)	24.5 (0.15)	24.8 (0.13)
Anxiety, Mean (SE)	5.75 (0.05)	6.66 (0.17)	6.83 (0.12)	7.21 (0.10)
Depression, mean (SE)	5.36 (0.07)	6.45 (0.25)	6.32 (0.17)	7.09 (0.15)
Antidepressants (%)				
Everyday	3	3	2	4
Often	1	1	2	1
Sometimes	3	4	3	3
Not at all	93	92	93	92
Alcohol consumption (%)				
Never drink alcohol	8	9	7	7
<once a week	39	37	37	37
At least once a week	37	37	39	38
1-2 units nearly everyday	15	16	15	16
≥3 units everyday	1	1	2	2
Frequency of Sex at 1997-1999 (%)				
Not at all	2	3	2	2
< once a month	16	17	15	17
1-3 times a month	26	30	29	29

About once a week	27	22	26	26
2-4 times a week	30	25	26	24
5+ times a week	3	3	2	2
Satisfaction with sex at 1997-1999 (%)				
Yes	92	91	89	88
No	8	9	11	12

6.2.1.2 Changes in stress UI and self-reported frequency of sex

Table 45 shows the associations between frequency of sex (Not at all, < once a month, 1-3 times a month, about once a week, 2-4 times a week and 5+ times a week) and changes of stress UI (no onset of stress UI, resolved stress UI, new onset of stress UI, persistent stress UI symptoms) between the two time-points. Multinomial logistic regression was used to estimate the association between stress UI and frequency and results were presented as prevalence rate ratios (PRR) and 95% confidence intervals.

In the main analysis (unadjusted), resolved stress UI (i.e., women with no stress UI symptoms at follow up but had symptoms at baseline) was associated with a lower prevalence of having sex less than once a month and 1-3 times a month compared to having sex 2-4 times a week. Similar results were detected after adjustment for confounders. In both analysis (unadjusted and adjusted), new onset of stress UI and persistent stress UI were associated with a greater prevalence of having sex less than once a month. There were no associations detected with other categories of stress UI and frequency of sex.

Table 45. Frequency of sex according to the change of stress UI after one year of follow up from baseline (1996-1998)

	Frequency of sex										
	Not at all vs. 2-4 times a week		**< once a month vs. 2-4 times a week**		**1-3 times a month vs. 2-4 times a week**		**About once a week vs. 2-4 times a week**		**5+ times a week vs. 2-4 times a week**		P-value
	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	Unadjusted PRR (95% CI)	*Adjusted PRR (95% CI)	0.037
No onset of stress UI symptoms (Reference group)	1	1	1	1	1	1	1	1	1	1	0.037
Resolved stress UI symptoms	1.57 (0.85, 2.89)	1.40 (0.75,1.89)	1.95 (1.43, 2.67)	1.75 (1.27,2.38)	1.41 (1.08, 1.84)	1.35 (1.03,1.76)	0.96 (0.72, 1.28)	0.94 (0.70,1.25)	1.14 (0.60, 2.18)	1.15 (0.60,2.20)	
New onset of stress UI symptoms	0.89 (0.50,1.58)	0.76 (0.43,1.36)	1.61 (1.25, 2.06)	1.33 (1.03,1.71)	1.29 (1.05, 1.57)	1.17 (0.95,1.44)	1.11 (0.91, 1.38)	1.03 (0.84,1.28)	0.98 (0.59, 1.64)	1.04 (0.61,1.73)	
Persistent stress UI symptoms	1.34 (0.87,2.07)	0.97 (0.62,1.53)	2.01 (1.43, 2.67)	1.44 (1.15,1.79)	1.43 (1.19, 1.70)	1.19 (0.98,1.43)	1.24 (1.36, 1.49)	1.10 (0.91,1.32)	0.70 (0.42, 1.18)	0.75 (0.44,1.28)	

6.2.1.3 Changes in stress UI and self-reported overall satisfaction with sex

Table 46 shows participants overall satisfaction with sex according to the change of stress UI at one year of follow up. In both models (adjusted and unadjusted) new onset stress UI and persistent stress UI were both associated with a poorer overall sexual satisfaction experience. There were no associations between resolved stress UI category and overall satisfaction experience in both models.

Table 46. Overall satisfaction with sex according to the change of stress UI at one year of follow up from baseline (1996-1998)

	Unadjusted PR (95 % CI)	***Adjusted PR (95% CI)**	**p-value**
No onset of Stress UI symptoms (Reference group)	1	1	0.912
Resolved Stress UI symptoms	1.26 (0.89, 1.77)	1.11 (0.78, 1.51)	
New onset of Stress UI symptoms	1.53 (1.19, 1.96)	1.34 (1.04, 1.72)	
Persistent Stress UI symptoms	1.71 (1.39, 2.11)	1.30 (1.05, 1.62)	
Footnote ***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, alcohol consumption and Stress UI at questionnaire 1 (1996-1998) Outcome: overall satisfaction of sex (yes/no)			

6.2.2 Complete case analysis main finding of prospective study examining stress UI with frequency and satisfaction with sex

This section will present the results of the compete case analysis of the prospective study examining the association between changes in stress UI and self-reported frequency and satisfaction with sex.

6.2.2.1 Changes in stress UI and self-reported frequency of sex (complete case analysis results)

Table 47 presents frequency of sex according to the presence of stress UI at one year of follow up from baseline (1996-1998). Women with resolved stress UI symptoms were more likely to report a lower prevalence ratio of having sex less than once a month. Women with new onset of stress UI symptoms reported positive association with prevalence ratio of frequencies of sex including 1-3 times a month. Women with persistent stress UI symptoms were positively associated with prevalence ratios of having sex less than once a month.

Table 47 Frequency of sex at one year of follow up according to categories of change in stress UI from baseline (1996-1998)

		Frequency of sex										
	Total N	**2-4 times a week**	**Not at all**		**< once a month**		**1-3 times a month**		**About once a week**		**5+ times a week**	
		N (%)	N (%)	*Adjusted PR (95% CI)	N	Adjusted PR (95% CI)	N	Adjusted PR (95% CI)	N	Adjusted PR (95% CI)	N	Adjusted PR (95% CI)
No onset of Stress UI symptoms (Reference group)	3591	1096 (30)	74 (2)	**Ref**	376 (10)	**Ref**	952 (27)	**Ref**	1011 (28)	**Ref**	83 (3)	**Ref**
Resolved Stress UI symptoms	331	85 (26)	11 (3)	1.23 (0.82, 1.88)	54 (17)	1.64 (1.14, 2.38)	102 (31)	1.31 (0.97, 1.77)	71 (21)	0.88 (0.64, 1.22)	8 (2)	1.25 (0.58, 2.68)
New onset of Stress UI symptoms	619	167 (27)	13 (2)	0.88 (0.63, 1.23)	93 (15)	1.31 (0.99, 1.74)	175 (28)	1.10 (0.87, 1.38)	158 (26)	0.96 (0.76, 1.22)	13 (2)	1.05 (0.56, 1.93)
Persistent Stress UI symptoms	898	221 (25)	21 (2)	1.07 (0.81, 1.40)	149 (17)	1.39 (1.09, 1.78)	248 (28)	1.07 (0.87, 1.33)	247 (27)	1.10 (0.90, 1.35)	12 (1)	0.72 (0.38, 1.35)
Footnote ***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, and alcohol consumption												

6.2.2.2 Changes in stress UI and self-reported frequency of sex (complete case analysis results)

Table 48 presents associations between categories of change in stress UI and overall satisfaction with sexual experience at approx. one year follow up from baseline (1996-1998). The highest proportion (92%) of women enjoying sex was observed in the no onset of stress UI symptoms group (reference group). While the lowest proportion of women reported enjoying sex was in persistent stress UI symptoms group.

In the unadjusted analysis, there was weak evidence of association between resolved stress UI symptoms and overall satisfaction with sex. Point estimates were more than one but confidence intervals crossed the null. Women reporting new onset of stress UI symptoms and persistent stress UI symptoms were had lower overall satisfaction with sexual experience.

After adjustment for confounders, resolved stress UI symptoms were not associated with overall satisfaction experience. While new onset of stress UI symptoms showed weak evidence of association with overall satisfaction experience. Persistent stress UI symptoms were associated with worse overall satisfaction with sex.

Table 48 Enjoyment of sex according to the presence of stress UI at one year of follow up from baseline (1996-1998)

	Total N	Enjoys Sex N (%)	Do not Enjoy Sex N (%)	Unadjusted PR (95 % CI)	*Adjusted PR (95% CI)
Stress UI at 1 year of follow up					
No onset of stress UI symptoms (Reference group)	3591	3139 (92)	272 (8)	**Ref**	**Ref**
Resolved stress UI symptoms	331	303 (91)	28 (9)	1.13 (0.75, 1.69)	1.00 (0.66, 1.51)
New onset of stress UI symptoms	619	550 (89)	69 (11)	1.53 (1.16, 1.89)	1.32 (1.00, 1.75)
Persistent stress UI symptoms	898	788 (88)	110 (12)	1.70 (1.34, 1.99)	1.29 (1.01, 1.64)
Footnote ***** Confounders included for the adjusted models are age, BMI, anxiety, depression, antidepressant, and alcohol consumption					

6.2.3 Summary of changes in stress UI and quality of sexual experience prospective analysis results

After 1 year follow up, resolved stress UI compared to no stress UI was associated with a lower prevalence rate of having sex less than once a month compared to having sex 2-4 times a week. Both new onset of stress UI and persistent stress UI were associated with a greater prevalence of having sex less than once a month. New onset of stress UI and persistent stress UI were both associated with a poorer overall sexual satisfaction experience.

6.3 Summary and results of LUTS (by subtypes) and quality of sexual experience analysis

After finding evidence that stress UI is prospectively associated with quality of sexual experience (frequency and satisfaction with sex), I wanted to explore the prospective association with other LUTS and more measures of sexual experience including worry or distress about sexual desire, orgasmic experience, and frequency of sex. Therefore, I conducted an analysis examining association between LUTS (by subtypes) and multiple measures of quality of sexual experience. This analysis will add to the limited prospective evidence that explores the association between subtypes of LUTS and measures of quality of sexual experience. I will first present the multiple imputation analysis results followed by complete case analysis results.

6.3.1 Multiple imputation results for LUTS and quality of sexual experience measures

This section presents results of LUTS and quality of sexual experience multiple imputation analysis (i.e., data on stress UI, sexual experience measures and imputed confounders).

6.3.1.1 Characteristics of women with LUTS at 2 years of follow up from baseline (2011-2012)

Table 49 shows the characteristics of women with LUTS measured at mean age 49.3 years in the analysis with the complete case sample and in the multiple imputed data (see Chapter 3 and Figure 6). 2672 women with data on LUTS and quality of sexual experience were eligible for inclusion in this study and were included in the multiple imputation analysis., 43% of these women (mean age 49.3 years at baseline, SD 0.5) reported symptoms of 'any LUTS' with stress UI (23%) being the most common. The distribution of background characteristics was very similar before and after imputation. However, mean depression, proportions of menopause and hormone replacement therapy were slightly higher in women in the multiply imputed data compared to the complete case analysis. Percentages of women who reported poor measures of sexual experience were similar between multiply imputed and complete case data; except for overall sexual satisfaction for which the proportions were slightly different. Proportion of women in the "equally satisfied and dissatisfied" group increased in the multiple imputation analysis while proportion of women in the "very satisfied" and "moderately satisfied" groups have decreased.

Table 49: Characteristics of women with LUTS at 2 years of follow up from baseline (2011-2012)

	Missing (N)	Observed Data	Imputed datasets (N=2672)
Confounders			
Age, Mean (SE)	186	49.2 (0.08)	49.3 (0.08)
BMI, Mean (SE)	300	24.1 (0.09)	24.2 (0.09)
Depression, mean (SE)	436	6.83 (0.11)	7.04 (0.11)
UTI in past month (%)	41		
Almost all the time		9 (1)	2
Sometimes		88 (4)	3
Not at all		2368 (95)	95
Antidepressants (%)	552		
Everyday		94 (5)	5
Often		19 (1)	1
Sometimes		57 (3)	3
Not at all		1814 (91)	91
Alcohol consumption (%)	409		
Never drink alcohol		177 (8)	9
Monthly or less		311 (15)	15
2-4 times a month		395 (19)	19
2-3 times a week		756 (36)	35
≥ 4 or more times a week		458 (22)	23
Hysterectomy (%)	456		
Yes		42 (2)	2
No		2008 (98)	98
Menopause	239		
Yes		735 (32)	36
No		1532 (68)	64
HRT (%)	413		
Yes		167 (8)	10
No		1926 (92)	90
Exposure			
Stress UI (%)	0		
Yes		569 (23)	23
No		1937 (77)	77
Urgency UI (%)	0		
Yes		203 (8)	9
No		2303 (92)	91
Mixed UI (%)	0		
Yes		192 (8)	9
No		2314 (92)	91
Urgency (%)	0		

Yes		421 (17)	18
No		2085 (83)	82
Nocturia (%)	0		
Yes		209 (8)	9
No		2297 (92)	91
Increased daytime Frequency (%)	0		
Yes		371 (15)	15
No		2135 (85)	85
Any LUTS	0		
Yes		1064 (42)	43
No		1442 (58)	57
Outcomes			
Worried about level of desire	14		
Not worried		1771 (71)	68
A little bit worried		526 (21)	23
Very Worried		195 (8)	9
Frequency of orgasm in sexual stimulation	108		
Almost never/never		144 (7)	7
A few times (< half the time)		211 (10)	9
Sometimes (about half the time)		467 (19)	19
Most of the time (> half the time)		427 (17)	17
Almost always/always		1149 (47)	48
	71		
Bothersome of orgasmic experience			
Not worried		2116 (87)	86
A little bit		213 (9)	9
Very Worried		98 (4)	5
Frequency intercourse	74		
Not at All		181 (8)	9
Once in the last month		370 (17)	16
2-3 times in the last month		749 (30)	30
Once a week		483 (19)	19
≥2 a week		634 (26)	25
Worried of overall frequency of sexual activity			
1-Not at all worried or distressed	89	1772 (73)	69
2-A little bit worried or distressed		469 (19)	21
3-Moderately worried or distressed		191 (8)	10
Satisfaction	71		
Very satisfied		899 (37)	34
Moderately satisfied		656 (27)	25

Equally satisfied and dissatisfied		465 (19)	20
Dissatisfied		415 (17)	22

Table 50 shows the characteristics of women with and without any LUTS at baseline (2011-2012). Mean age, percentages of use of HRT or history of hysterectomy were similar between women with or without LUTS at baseline. Proportions of women who were consuming less alcohol (never drink alcohol and monthly or less alcohol consumption) was higher among women with any LUTS compared to those without; while proportions of women with higher levels of alcohol consumption was lower among women with any LUTS compared to those without. This is interesting as in previous research it has been reported that women who consume more alcohol are at higher risk of LUTS (1). This may indicate that women with LUTS reduced their alcohol consumption. Women with LUTS had a higher mean BMI, higher mean depression score, higher proportion of antidepressant use, were more likely to have experienced menopause or have a history of UTIs, compared to women without LUTS.

Table 50: Distribution of background characteristics among women with and without a history of any LUTS in the multiple imputation datasets

	Any LUTS Total N=2672		
	No (57% of Total N)	**Yes (43% of Total N)**	**P-value**
Confounders			
Age, Mean (SE)	37.7 (0.11)	37.8 (0.13)	0.34
BMI, Mean (SE)	23.9 (0.10)	24.5 (0.15)	<0.001
Depression, mean (SE)	6.44 (0.15)	7.87 (0.17)	<0.001
UTI in past month			<0.001
Almost all the time	1	1	
Sometimes	3	4	
Not at all	96	95	
Antidepressants (%)			<0.001
Everyday	4	7	
Often	1	1	
Sometimes	3	4	
Not at all	92	88	
Alcohol consumption (%)			0.03
Never drink alcohol	8	10	
Monthly or less	13	17	
2-4 times a month	20	17	
2-3 times a week	36	33	
≥ 4 or more times a week	23	23	
Hysterectomy (%)			0.98
Yes	2	2	
No	98	98	

Menopause			0.37
Yes	36	37	
No	64	63	
HRT (%)			0.98
Yes	10	10	
No	90	90	

6.3.1.2 LUTS and self-reported frequency of sex and orgasm

Table 51 shows the association of LUTS with frequency of sex (not at all, once in the last month, 2-3 times in the last month, once a week and ≥2 times a week) and orgasm (almost never/never, a few times (< half the time), sometimes (about half the time), most of the time (> half the time) and almost always/always) at approx. 2 years of follow up. Results were obtained using ordinal logistic regression (2).

In the main unadjusted analysis, there was an inverse association between any LUTS, stress UI, urgency UI, mixed UI, nocturia and frequency of sex. Point estimates for urgency were also less than one but confidence intervals included the null value. After adjusting for confounders (model 2), stress UI showed an inverse association with frequency of sex. Other LUTS (any LUTS, urgency UI, mixed UI and nocturia) point estimates were also smaller than one but confidence intervals included the null value (model 2). There was no evidence of associations between urgency, frequency of daytime urination and frequency of sex in after adjustment for confounders. After adjustment for depressive symptoms and use of antidepressants (model 3), there was still evidence of an association of stress UI and any LUTS with reduced frequency of sex. Adjustment for depression and antidepressants (Model 3) had little impact on effect estimates, but the confidence interval for the association between stress UI and any LUTS with reduced frequency of sex was more precise and excluded the null value. Urgency UI, mixed UI, urgency and nocturia point estimates were also smaller than one but confidence intervals included the null value. There was no evidence of associations between increased daytime urination and frequency of sex in any of the models.

I also examined the association between LUTS and frequency of orgasm (Table 51). There was an inverse association between stress UI, mixed UI, and frequency of orgasm (model 1). Other LUTS (any LUTS, urgency UI, mixed UI, urgency, and increased daytime frequency) point estimates were also smaller than one but confidence intervals included the null value. Nocturia showed no evidence of association with frequency of orgasm (model 1). After adjustment for potential confounders (model 2), stress UI and mixed UI continued to show inverse association with frequency of orgasm. Other measured LUTS (except for nocturia) had small point estimates but confidence intervals crossed the null. Results were similar after adjusting for depressive symptoms and use of antidepressants (model 3), but confidence interval crossed the null.

Table 51: Association of LUTS with frequency of sex and frequency of orgasm

	Frequency of Sex In the last month, how many times have you attempted sexual intercourse?		
Subtypes of LUTS	Model 1: unadjusted OR (95% CI)	Model 2: adjusted* OR (95% CI)	Model 3: adjusted** OR (95% CI)
Any LUTS	0.74 (0.62, 0.87)	0.86 (0.71, 1.01)	0.84 (0.72, 0.98)
Stress UI	0.74 (0.62, 0.87)	0.80 (0.65, 0.98)	0.78 (0.63, 0.95)
Urgency UI	0.72 (0.55, 0.94)	0.91 (0.66, 1.28)	0.86 (0.64, 1.17)
Mixed UI	0.71 (0.54, 0.93)	0.76 (0.54, 1.07)	0.73 (0.52, 1.00)
Urgency	0.85 (0.70, 1.26)	1.06 (0.83, 1.35)	0.99 (0.79, 1.24)
Increased Daytime Frequency	1.00 (0.82, 1.24)	1.08 (0.80, 1.37)	1.03 (0.82, 1.30)
Nocturia	0.68 (0.52, 0.89)	0.78 (0.56, 1.05)	0.80 (0.58, 1.18)
	Frequency of Orgasm When you have sexual stimulation, how often do you have the feeling of orgasm or climax?		
Subtypes of LUTS	Model 1: unadjusted OR (95% CI)	Model 2: adjusted* OR (95% CI)	Model 3: adjusted** OR (95% CI)
Any LUTS	0.92 (0.80, 1.07)	0.92 (0.76, 1.09)	0.92 (0.80, 1.10)
Stress UI	0.83 (0.70, 0.98)	0.80 (0.64, 0.98)	0.77 (0.64, 0.96)
Urgency UI	0.85 (0.65, 1.10)	0.89 (0.65, 1.01)	0.85 (0.62, 1.16)
Mixed UI	0.72 (0.55, 0.93)	0.67 (0.48, 0.94)	0.64 (0.46, 0.90)
Urgency	0.93 (0.77, 1.13)	0.97 (0.77, 1.22)	0.93 (0.74, 1.17)
Increased Daytime Frequency	0.89 (0.72, 1.08)	0.91 (0.72, 1.15)	0.90 (0.70, 1.13)
Nocturia	1.01 (0.78, 1.31)	1.07 (0.78, 1.48)	0.90 (0.75, 1.07)

Higher levels indicate greater worry and distress.

*Model 2: adjusted for age, BMI, UTI, menopause, hysterectomy, HRT, alcohol consumption

**Model 3: adjusted for age, BMI, UTI, menopause, hysterectomy, HRT, alcohol consumption, EPDS depression score, antidepressant use

Note: Women with LUTS (by subtypes) are compared to reference group (women without LUTS).

Missing information is imputed using multiple imputation with chained equations.

6.3.1.3 LUTS and level of worry or distress about sexual desire, orgasmic experience, frequency of sex and overall satisfaction about sex life.

In the main unadjusted analysis (model 1), any LUTS, stress UI, urgency UI, mixed UI and urgency were all associated with a higher level of worry or distress about level of sexual desire (Table 52). Nocturia had point estimates more than one showing some association with a higher level of worry or distress about level of sexual desire, but confidence intervals crossed the null. Increased day time frequency showed no association with measures of sexual desire. After adjustment for confounders (model 2), any LUTS, stress UI, urgency UI, mixed UI and urgency were still associated with higher levels of worry or distress about level of sexual desire. Confidence intervals for nocturia and increased daytime frequency now crossed the null. However, after adjustment for symptoms of depression and use of antidepressants (model 3), there was evidence of associations between urgency UI and urgency with greater worry or distress about level of sexual desire, while there was no strong evidence of associations with other examined LUTS including any LUTS, stress UI, and mixed UI as their estimates crossed the null. Increased day time frequency and nocturia showed no evidence of association with worry or distress about level of sexual desire after adjustment for depression and use of antidepressants.

All models showed evidence of associations of any LUTS, stress UI, urgency UI, mixed UI, and urgency with higher level of worry or distress about orgasmic experience. However, increased daytime frequency and nocturia showed no strong evidence of association with levels of worry or distress about orgasmic experience (Table 52).

In model 1 and after adjustment of confounders (model 2), any LUTS, stress UI, urgency UI, mixed UI and urgency were associated with higher levels of worrying or distress related to frequency of sexual activity (Table 52). Nocturia had estimates above one showing some positive association with level of worry or distress with frequency of sexual activity but confidence intervals crossed the null. Increased daytime frequency showed no associations with level of worry or distress with frequency of sexual activity. After adjustment for symptoms of depression and use of antidepressants (model 3), associations were attenuated for all subtypes of LUTS except for urgency UI and mixed UI. Any LUTS, stress UI, and urgency estimates were greater than one but confidence intervals crossed the null. There was no strong

evidence of associations between increased daytime frequency and worrying or distress about frequency of sexual activity (model 3).

Examining the association between LUTS and overall satisfaction with sex life (Table 52, model 1) showed evidence of direct association between any LUTS, stress UI, urgency UI, mixed UI, and urgency with lower overall satisfaction with sex life (model 1). After adjusting for confounders (model 2), only stress UI, urgency UI and mixed UI were associated with lower overall satisfaction with sex life while other LUTS showed no association (Table 52). After additional adjustment for depression and antidepressants, associations with stress UI, urgency UI, mixed UI were more pronounced, and we also observed an association with any LUTS. There was no strong evidence of associations with urgency (in model 2 and 3), increased daytime frequency or nocturia with satisfaction with overall sex life as the point estimates were greater than one but confidence intervals crossed the null.

Table 52. Associations of LUTS with worrying or distress related to levels of sexual desire, orgasmic experience, frequency of sex and overall satisfaction about sex life.

	Level of sexual desire Are you worried or distressed about your level of desire?			**Orgasmic experience** Are you worried or distressed by your current orgasmic experience?			**Frequency of sex** Are you worried or distressed by the overall frequency of your sexual activities?			**Sexual satisfaction** How satisfied are you with your overall sex life?		
*Subtypes of LUTS	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**
Any LUTS	1.20 (1.01, 1.43)	1.27 (1.02, 1.57)	1.16 (0.94, 1.45)	1.42 (1.13, 1.79)	1.59 (1.20, 2.11)	1.49 (1.11, 1.97)	1.23 (1.03, 1.45)	1.28 (1.04, 1.60)	1.18 (0.96, 1.46)	1.25 (1.09, 1.44)	1.11 (0.93, 1.31)	1.21 (1.02, 1.43)
Stress UI	1.21 (1.00, 1.50)	1.31 (1.03, 1.67)	1.21 (0.94, 1.54)	1.40 (1.07, 1.82)	1.82 (1.31, 2.51)	1.68 (1.20, 2.34)	1.24 (1.01, 1.51)	1.33 (1.04, 1.70)	1.21 (0.95, 1.56)	1.26 (1.07, 1.49)	1.16 (1.06, 1.42)	1.27 (1.04, 1.52)
Urgency UI	1.70 (1.28, 2.25)	1.90 (1.35, 2.69)	1.65 (1.16, 2.35)	1.80 (1.28, 2.52)	1.87 (1.17, 2.98)	1.56 (1.00, 2.42)	1.86 (1.39, 2.49)	2.07 (1.47, 2.92)	1.76 (1.22, 2.52)	1.71 (1.34, 2.18)	1.48 (1.09, 2.00)	1.70 (1.26, 2.30)
Mixed UI	1.37 (1.02, 1.85)	1.64 (1.13, 2.39)	1.42 (0.98, 2.08)	1.87 (1.32, 2.64)	2.27 (1.38, 3.07)	1.96 (1.23, 3.09)	1.70 (1.26, 2.28)	1.81 (1.25, 2.62)	1.60 (1.09, 2.35)	1.74 (1.36, 2.23)	1.64 (1.18, 2.27)	1.86 (1.35, 2.57)
Urgency	1.42 (1.14, 1.77)	1.33 (1.20, 1.97)	1.33 (1.00, 1.75)	1.64 (1.24, 2.16)	1.70 (1.20, 2.40)	1.51 (1.07, 2.15)	1.46 (1.17, 1.83)	1.51 (1.16, 1.98)	1.31 (1.00, 1.72)	1.30 (1.08, 1.55)	1.08 (0.86, 1.35)	1.22 (0.97, 1.52)
Increased Daytime Frequency	0.97 (0.76, 1.24)	1.05 (0.78, 1.40)	0.98 (0.73, 1.32)	1.81 (0.76, 1.46)	1.04 (0.69, 1.52)	0.99 (0.68, 1.46)	0.95 (0.74, 1.21)	0.98 (0.73, 1.32)	0.93 (0.70, 1.25)	1.15 (0.95, 1.39)	1.10 (0.87, 1.37)	1.17 (0.93, 1.46)
Nocturia	1.07 (0.78, 1.46)	1.08 (0.72, 1.59)	0.98 (0.65, 1.46)	1.42 (0.97, 2.08)	1.15 (0.67, 1.94)	1.08 (0.64, 1.82)	1.19 (0.88, 0.91)	1.10 (0.74, 1.63)	1.03 (0.70, 1.53)	1.24 (0.97, 1.58)	1.02 (0.74, 1.40)	1.11 (0.81, 1.52)

Higher levels indicate greater worry and distress.

*Model 2: adjusted for age, BMI, UTI, menopause, hysterectomy, HRT, alcohol consumption

**Model 3: adjusted for age, BMI, UTI, menopause, hysterectomy, HRT, alcohol consumption, EPDS depression score, antidepressant use

Note: Women with LUTS (by subtypes) are compared to reference group (women without LUTS).

Missing information is imputed using multiple imputation with chained equations.

6.3.2 Complete case analysis results of LUTS and quality of sexual experience

This section presents results of LUTS and quality of sexual experience complete case analysis (i.e., data on LUTS, quality of sexual experience measures and confounders). Table 53, Table 54, and Table 55 shows the results of the complete case analysis which were similar to the main results of the imputed data.

6.3.2.1 LUTS and self-reported frequency of orgasm and frequency of sex (Complete case analysis results)

Examining the association between LUTS and self-reported frequency of sex (Table 53), showed inverse association with any LUTS, stress UI, urgency UI, mixed UI, nocturia with frequency of sex. Urgency point estimates were lower than one but confidence interval crossed the null showing week inverse association with frequency of sex. After adjustment of confounders (model 2), any LUTS, stress UI and urgency UI continued to be inversely associated with frequency of sex. Urgency UI, urgency and nocturia point estimates were also smaller than one but confidence intervals included the null value (model 2). After further adjustment for depression (model 3), similar results to model 2 were detected.

Any LUTS, stress UI, urgency UI, mixed UI, urgency, nocturia, showed week evidence of association with frequency of orgasm (Table 53); point estimates were less than one but confidence interval crossed null. Model 2 and 3 showed similar results to the main unadjusted analysis (model 1).

Increased daytime frequency point estimates were more than one with confidence intervals crossing the null in all examined models for both frequency of sex and frequency of orgasm; this means there might be a weak direct association between increased daytime frequency and frequency of orgasm.

Table 53 Associations of LUTS with frequency of orgasm and frequency of sex

	Frequency of Sex In the last month, how many times have you attempted sexual intercourse?		
Subtypes of LUTS	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
Any LUTS	0.79 (0.69, 0.91)	0.80 (0.66, 0.95)	0.81 (0.67, 0.98)
Stress UI	0.72 (0.61, 0.86)	0.70 (0.56, 0.87)	0.75 (0.60, 0.94)
Urgency UI	0.74 (0.56, 0.95)	0.83 (0.60, 1.17)	0.92 (0.65, 1.29)
Mixed UI	0.71 (0.54, 0.93)	0.65 (0.45, 0.94)	0.68 (0.47, 0.99)
Urgency	0.87 (0.72, 1.06)	0.97 (0.76, 1.24)	1.07 (0.83, 1.38)
Increased Daytime Frequency	1.01 (0.82, 1.24)	1.08 (0.80, 1.37)	1.11 (0.86, 1.44)
Nocturia	0.70 (0.54, 0.91)	0.80 (0.57, 1.12)	0.84 (0.59, 1.19)
	Frequency of Orgasm When you have sexual stimulation, how often do you have the feeling of orgasm or climax?		
Subtypes of LUTS	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
Any LUTS	0.90 (0.88, 1.11)	0.96 (0.81, 1.14)	0.97 (0.83, 1.13)
Stress UI	0.91 (0.80, 1.04)	0.95 (0.79, 1.06)	0.90 (0.75, 1.07)
Urgency UI	0.87 (0.71, 1.07)	0.98 (0.74, 1.29)	0.84 (0.65, 1.10)
Mixed UI	0.83 (0.67, 1.01)	0.93 (0.70, 1.24)	0.85 (0.64, 1.13)
Urgency	0.87 (0.74, 1.00)	0.98 (0.79, 1.21)	0.87 (0.71, 1.06)
Increased Daytime Frequency	1.07 (0.91, 1.25)	1.09 (0.87, 1.35)	1.06 (0.87, 1.32)
Nocturia	0.91 (0.75, 1.11)	0.93 (0.70, 1.23)	0.94 (0.71, 1.22)

*Model 1 involves Unadjusted OR (95% CI)

**Model 2 involves Adjusted OR (95% CI) without depression (age, BMI, UTI, menopause, hysterectomy, HRT, alcohol consumption)

***Model 3 involves Adjusted OR (95% CI) with depression (age, BMI, depression, UTI, menopause, hysterectomy, HRT, alcohol consumption and antidepressants)

Note: Women with LUTS (by subtypes) are compared to reference group (women without LUTS)

6.3.2.2 LUTS and level of worry or distress about sexual desire, orgasmic experience, frequency of sex and overall satisfaction about sex life (complete case analysis)

Any LUTS, stress UI, urgency UI, mixed UI and urgency were all associated with a higher level of worry or distress about level of sexual desire in the main multivariable analysis (Table 54). Similar results were observed after adjustment for confounders (model 2) and adjustment for depression and use of antidepressants (model 3).

All models showed evidence of associations of any LUTS, stress UI, urgency UI, mixed UI, and urgency with higher level of worry or distress about frequency of sex (Table 54). However, increased daytime frequency and nocturia showed no strong evidence of association with levels of worry or distress about frequency of sex (Table 54).

Table 54. Association of LUTS with worrying or distress of desire level, orgasmic experience, frequency of sex and overall satisfaction with sex life

	Level of sexual desire Are you worried or distressed about your level of desire?			**Orgasmic experience** Are you worried or distressed by your current orgasmic experience?			**Frequency of sex** Are you worried or distressed by the overall frequency of your sexual activities?			**Sexual satisfaction** How satisfied are you with your overall sex life?		
*Subtypes of LUTS	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**	Model 1: unadjusted	Model 2: adjusted*	Model 3: adjusted**
Any LUTS	1.23 (1.03, 1.45)	1.29 (1.04, 1.61)	1.14 (0.94, 1.42)	0.92 (0.80, 1.07)	1.75 (1.30, 2.37)	0.91 (0.75, 1.09)	1.23 (1.03, 1.45)	1.47 (1.13, 1.60)	1.19 (0.98, 1.51)	1.10 (0.93, 1.29)	1.22 (1.01, 1.47)	1.11 (0.90, 1.36)
Stress UI	1.28 (1.05, 1.56)	1.40 (1.09, 1.82)	1.19 (1.12, 1.55)	0.95 (0.77, 1.08)	2.05 (1.47, 2.84)	0.88 (0.70, 1.10)	1.27 (1.04, 1.57)	1.47 (1.13, 1.60)	1.27 (0.96, 1.65)	1.13 (0.93, 1.38)	1.42 (1.14, 1.77)	1.15 (0.89, 1.49)
Urgency UI	1.68 (1.25, 2.25)	1.67 (1.14, 2.42)	1.53 (1.04, 2.24)	0.95 (0.72, 1.23)	1.69 (1.05, 2.74)	1.00 (0.71, 1.42)	1.93 (1.44, 2.60)	1.96 (1.35, 2.86)	1.83 (1.24, 2.69)	1.56 (1.15, 2.11)	1.61 (1.15, 2.27)	1.56 (1.15, 2.11)
Mixed UI	1.47 (1.09, 1.99)	1.57 (1.03, 2.38)	1.38 (1.10, 1.71)	0.84 (0.64, 1.10)	2.40 (1.45, 3.97)	0.82 (0.56, 1.17)	1.80 (1.32, 2.44)	1.82 (1.20, 2.76)	1.52 (1.10, 2.32)	1.41 (1.03, 1.93)	1.92 (1.32, 2.79)	1.49 (0.97, 2.29)
Urgency	1.38 (1.10, 1.71)	1.44 (1.09, 1.91)	1.31 (1.00, 1.75)	0.97 (0.79, 1.17)	1.64 (1.14, 2.37)	0.99 (0.76, 1.27)	1.47 (1.18, 1.85)	1.50 (1.13, 2.00)	1.42 (1.05, 1.91)	1.22 (0.98, 1.52)	1.19 (0.93, 1.52)	1.31 (0.98, 1.74)
Increased Daytime Frequency	1.05 (0.82, 1.33)	1.06 (0.79, 1.43)	1.04 (0.73, 1.35)	0.84 (0.69, 1.03)	1.09 (0.73, 1.64)	0.84 (0.64, 1.08)	0.99 (0.88, 1.25)	0.93 (0.67, 1.27)	0.85 (0.61, 1.18)	1.04 (0.83, 1.31)	1.11 (0.87, 1.42)	0.89 (0.66, 1.19)
Nocturia	1.02 (0.74, 1.39)	1.00 (0.66, 1.52)	0.85 (0.54, 1.34)	1.08 (0.83, 1.40)	1.18 (0.68, 2.01)	1.08 (0.77, 1.55)	1.14 (0.83, 1.56)	1.07 (0.70, 1.63)	0.91 (0.57, 1.41)	1.00 (0.74, 1.34)	0.96 (0.68, 1.36)	1.07 (0.72, 1.58)

*Model 1 involves Unadjusted OR (95% CI)

**Model 2 involves Adjusted OR (95% CI) without depression (age, BMI, UTI, menopause, hysterectomy, HRT, alcohol consumption)

***Model 3 involves Adjusted OR (95% CI) with depression (age, BMI, depression, UTI, menopause, hysterectomy, HRT, alcohol consumption and antidepressants)

Note: Women with LUTS (by subtypes) are compared to reference group (women without LUTS)

6.3.3 Summary of LUTS and quality of sexual experience results

There was strong evidence of associations between any LUTS, stress UI, mixed UI with reduced frequency of sex and orgasm assessed two years from baseline. Furthermore, women with any LUTS, stress UI, mixed UI and urgency also had higher levels of worry and distress related to their sexual desire, orgasm experience and frequency of sex. Stress UI, urgency UI and mixed UI were all associated with a lower overall satisfaction with sex life.

There was no evidence of associations between urgency and frequency of urination during daytime with frequency of orgasm or frequency of sex. Any LUTS, urgency UI and nocturia were not associated with frequency of orgasm. Increased day time frequency showed no strong evidence of association with level of worry or distress of sexual desire, orgasmic experience, and frequency of sex.

7 Results of LUTS and measures of depression multiple imputation analysis

Table 55 shows the distribution of characteristics among women in the complete case analysis and multiple imputation analysis (see section 3.5.1 in Chapter 3 and Figure 15). In 2002-2004 (baseline), 31% women (mean age 43.3 years at baseline, SD 0.5) of a total sample of 3011 eligible women (i.e., with data on LUTS, depression and imputed confounders) reported symptoms of any LUTS. Increased daytime frequency was the most common LUTS among women with a prevalence of 15%.

Table 55 Distribution of background characteristics among women in complete case and multiple imputation analysis

	Missing (N)	Observed Data	Imputed (N=3011)
Confounders			
Age, Mean (SD)	0	43.3 (0.5)	43.3 (0.5)
BMI, Mean (SD)	296	24.3 (0.9)	24.4 (0.8)
Anxiety, mean (SD)	166	5.52 (0.1)	5.56 (0.1)
UTI in past month	14		
Almost all the time		0 (0)	1
Sometimes		63 (3)	3
Not at all		2105 (97)	96
Alcohol consumption (%)	143		
Never drink alcohol		137 (6)	7
Less than once a week		759 (35)	36
At least once a week		893 (41)	40
1-2 units nearly everyday		354 (16)	16
≥ 3 units everyday		25 (2)	1
Hysterectomy (%)	0		
Yes		62 (3)	3
No		2106 (97)	97
Parity	86		
1		290 (13)	15
2		1065 (49)	48
3+		813 (38)	37
Social Class	324		
Non-Manual		1813 (84)	83
Manual		355 (16)	17
University degree	244		

No Yes		1203 (56) 965 (44)	56 44
Physical activity (MET hours/week), n (%) 0 0.1-17.2, 17.3-29.2, 29.3-43.2 ≥43.2	0	 185 (9) 407 (19) 509 (23) 564 (26) 503 (23)	 10 20 23 24 23
Antidepressants Yes No	0	 151 (6) 2017(94)	 7 93
Exposure			
Stress UI (%) Yes No	0	 242 (12) 1926 (88)	 12 88
Urgency UI (%) Yes No	0	 229 (11) 1939 (89)	 11 89
Mixed UI (%) Yes No	0	 71 (3) 2097 (97)	 3 97
Urgency (%) Yes No	0	 180 (8) 1988 (92)	 8 92
Nocturia (%) Yes No	0	 88 (4) 2080 (96)	 4 96
Increased daytime Frequency (%) Yes No	0	 323 (15) 1845 (85)	 15 85
Any LUTS Yes No	0	 663 (31) 1505 (69)	 31 69
Outcomes			
EPDS < 12 & not taking antidepressants EPDS >12 & taking antidepressant	0	1786 (82) 382 (18)	81 19
EPDS Score (%)	0		

None or minimal depression (0-6) Mild depression (7-12) Moderate to severe depression (13-30)		1228 (57) 702 (32) 238 (11)	56 32 12

Table 56 shows the distribution of characteristics of women with and without any LUTS at baseline (2002-2004). There was a higher proportion of women with a history of UTI and an increased proportion of women across number of parities among women with LUTS compared to women without LUTS. Moreover, women with any LUTS were more likely to have a slightly higher mean BMI, higher mean of anxiety scores compared to women without any LUTS. There was no difference in mean age or proportion of women with history of hysterectomy between women with or without any LUTS. Proportion of women across levels of physical activity (0, 0.1-17.2,17.3-29.2 MET hours/week) were similar in both groups. Proportion of women in alcohol consumption, educational attainment and social class are similar in women with without any LUTS.

Table 56 Distribution of background characteristics among women with and without history of any LUTS

	Any LUTS **Total N=3011**		
	No (57% of Total N)	**Yes (43% of Total N)**	**P-value**
Confounders			
Age, Mean (SD)	43.3 (0.49)	43.3 (0.48)	0.62
BMI, Mean (SD)	24.4 (4.05)	24.8 (4.79)	<0.001
Anxiety, mean (SD)	5.44 (3.08)	5.90 (3.12)	<0.001
UTI in past month (%)			<0.001
Almost all the time	1	5	
Sometimes	1	1	
Not at all	98	94	
University degree (%)			0.39
No	55	57	
Yes	45	43	
Social Class (%)			0.50
Non-Manual	84	83	
Manual	16	17	
Physical activity (MET hours/week), (%)			0.75
0	10	10	
0.1-17.2,	20	20	
17.3-29.2,	23	23	
29.3-43.2	24	25	

≥43.2	23	22	
Alcohol consumption (%)			0.06
Never drink alcohol	7	8	
Monthly or less	36	37	
2-4 times a month	40	39	
2-3 times a week	16	15	
≥ 4 or more times a week	1	1	
Hysterectomy (%)			0.76
Yes	3	3	
No	97	97	
Parity (%)			0.12
1	14	18	
2	50	45	
3+	36	37	

7.1 LUTS and self-reported depression (measured by EPDS and/or antidepressant intake)

Table 57 shows the associations of LUTS (by subtypes) with depression (measured by EPDS and/or use of antidepressants) after 8 years of follow-up.

Before adjusting for confounders (model 1), stress UI, urgency UI, mixed UI, urgency, nocturia and any LUTS were associated with greater risk of depression. There was a weak association between increased daytime frequency and risk of depression as point estimates were greater than one, but confidence intervals crossed the null.

After adjusting for confounders (model 2), stress UI, urgency UI, urgency and any LUTS remained associated with greater risk of depression (model 2). Mixed UI point estimates were higher than one, but confidence intervals started at the null. Moreover, nocturia and increased daytime frequency showed no strong evidence of association with risk of depression as their point estimates more than one but crossed the null.

After further adjusting for anxiety as a confounder (model 3), the association between urgency UI, mixed UI, urgency, any LUTS with depression strengthened. Stress UI was associated with depression in the unadjusted model and main adjusted model accounting for potential confounders (model 2), but after adjusting for anxiety (model 3) the confidence interval crossed the null value. Nocturia and increased daytime frequency continued to show no strong evidence of association with risk of depression as their point estimates more than one but crossed the null.

Table 57 Associations of LUTS with depression measured by EPDS and/or antidepressant intake at 8 years of follow up

	Depression Measured by EPDS (>12) and/or use of Antidepressant **Note: Reference group is Depression Measured by EPDS (<12) and/or not taking Antidepressant**		
Subtypes of LUTS	**Model 1: unadjusted** **(95% CI)**	**Model 2: adjusted*** **(95% CI)**	**Model 3**** **(95% CI)**
Stress UI	1.45 (1.17, 1.80)	1.35 (1.05, 1.73)	1.34 (0.95, 1.70)
Urgency UI	1.68 (1.36, 2.10)	1.49 (1.15, 1.92)	1.59 (1.24, 2.00)
Mixed UI	1.53 (1.02, 2.30)	1.59 (1.00, 2.52)	1.70 (1.08, 2.65)
Urgency	1.55 (1.19, 2.00)	1.44 (1.01, 1.95)	1.51 (1.13, 2.01)
Increased Daytime Frequency	1.22 (0.99, 1.50)	1.20 (0.95, 1.51)	1.27 (0.81, 2.00)
Nocturia	1.57 (1.07, 2.29)	1.26 (0.78, 2.00)	1.16 (0.70, 1.92)
Any LUTS	1.34 (1.18, 1.51)	1.29 (1.03, 1.34)	1.25 (1.10, 1.43)

Model 2 involves Adjusted OR (95% CI) without anxiety (age, BMI, antidepressants, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

Model 3 involves Adjusted OR (95% CI) with anxiety (age, BMI, antidepressants, anxiety, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

7.2 LUTS and self-reported depression (measured by EPDS)

Table 58 shows the associations of LUTS with self-reported depression measured by EPDS and categorised into none (0-6), mild (7-12) and moderate to severe (13-30) depression. I analysed this outcome using multinomial logistic regression.

When examining the association between LUTS and mild depression (scores 7-12), stress UI and any LUTS was associated with mild depression scores before adjusting for confounders (model 1). Urgency UI, mixed UI and urgency showed weak association with mild depression as point estimates were greater than 1 but confidence intervals crossed the null. There was no evidence of association observed between nocturia, increased daytime frequency and risk of mild depression (model 1). Similar results were observed after adjusting for confounders (model 2). After adjustment for anxiety (model 3), only stress UI was positively associated with mild depression scores. While, urgency UI, mixed UI, urgency, any LUTS showed weak evidence of association with risk of mild depression. Nocturia and increased daytime frequency showed no association with mild depression.

Examining the association of LUTS with moderate to severe depression (scores 13-30), stress UI, urgency UI, nocturia and any LUTS were positively associated with risk of moderate to severe depression (model 1). Other examined LUTS showed no strong evidence of association with risk of moderate to severe depression. Similar results were observed after adjustment for confounders (model 2) but the association with urgency and risk of moderate to severe depression weakened. After adjusting for anxiety (model 3), stress UI and any LUTS continued to be positively associated with risk of moderate to severe depression. Oher examined LUTS were not strongly associated with highest category of depression as confidence intervals crossed the null.

Interestingly, stress UI showed evidence of associations with all categories of depression scores after adjusting for anxiety whilst associations for other LUTS (except for any LUTS) were attenuated. This could be because stress UI was more common (see Table 55) than other LUTS as reflected in the confidence intervals.

Table 58. Associations of LUTS and depression (Measured by EPDS) at 8 Years of Follow Up

	Depression measured by EPDS (scores 0-30)						
	None or minimal depression (0-6)	Mild depression (7-12)			Moderate to severe depression (13-30)		
Subtypes of LUTS	**Reference Group**	**Model 1: unadjusted (95% CI)**	**Model 2: adjusted* (95% CI)**	**Model 3** (95% CI)**	**Model 1: unadjusted (95% CI)**	**Model 2: adjusted* (95% CI)**	**Model 3** (95% CI)**
Stress UI	1	1.30 (1.05, 1.59)	1.29 (1.04, 1.59)	1.22 (1.16, 1.48)	1.49 (1.14, 1.96)	1.42 (1.08, 1.94)	1.34 (1.07, 1.53)
Urgency UI	1	1.17 (0.93, 1.47)	1.10 (0.87, 1.41)	1.04 (0.81, 1.34)	1.51 (1.14, 2.01)	1.32 (0.96, 1.84)	1.19 (0.81, 1.67)
Mixed UI	1	1.26 (0.85, 1.87)	1.24 (0.80, 1.91)	1.16 (0.61, 2.07)	1.22 (0.70, 2.14)	1.30 (0.70, 2.42)	1.16 (0.61, 2.10)
Urgency	1	1.17 (0.90, 1.51)	1.12 (0.85, 1.48)	1.08 (0.81, 1.44)	1.36 (0.97, 1.91)	1.23 (0.83, 1.82)	1.15 (0.76, 1.71)
Increased Daytime Frequency	1	0.94 (0.77, 1.15)	0.89 (0.71, 1.11)	0.84 (0.67, 1.05)	1.24 (0.96, 1.59)	1.26 (0.96, 1.66)	1.13 (0.85, 1.50)
Nocturia	1	0.95 (0.64, 1.42)	0.97 (0.62, 1.49)	0.92 (0.65, 1.05)	1.89 (1.23, 2.93)	1.68 (1.12, 2.70)	1.67 (0.98, 2.85)
Any LUTS	1	1.16 (1.04, 1.19)	1.08 (1.03, 1.45)	1.02 (0.98, 1.10)	1.33 (1.15, 1.54)	1.29 (1.09, 1.48)	1.13 (1.08, 1.40)

*Model 2 involves Adjusted OR (95% CI) without anxiety (age, BMI, antidepressants, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

**Model 3 involves Adjusted OR (95% CI) with anxiety (age, BMI, antidepressants, anxiety, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

7.3 LUTS and Depression Complete Case Analysis Results

Table 59 and Table 60 presents results of complete case analysis i.e., sample with data on all LUTS, depression and confounders). Details about the complete case sample can be found in Table 1.

7.4 LUTS with depression measured by EPDS and/or antidepressant

Table 59 presents the results from examining the association of LUTS with depression (measured by EPDS and/or antidepressants intake) at approx. 8 years of follow up. In the unadjusted analysis (model 1), there was a direct association between stress UI, urgency UI, any LUTS and risk of depression. Mixed UI, urgency, increased daytime frequency and nocturia showed week association with risk of depression; point estimates were more than one but confidence intervals crossed the null. After adjusting for confounders (model 2), urgency UI and any LUTS were positively associated with risk of depression at approx..8 years of follow up. While other examined LUTS had weak evidence of association with risk of depression. Similar result to model were observed after adjustment for anxiety in model 3.

Table 59 Association of LUTS with depression measured by EPDS and/or antidepressant intake at 8 years of follow up

	Depression Measured by EPDS (>12) &/or use of Antidepressant Note: Reference group is Depression Measured by EPDS (<12) & not taking Antidepressant		
Subtypes of LUTS	**Model 1: unadjusted (95% CI)**	**Model 2: adjusted* (95% CI)**	**Model 3** (95% CI)**
Stress UI	1.34 (1.01, 1.77)	1.34 (0.95, 1.70)	1.27 (0.95, 1.70)
Urgency UI	1.51 (1.14, 2.00)	1.49 (1.13, 1.97)	1.41 (1.06, 1.89)
Mixed UI	1.25 (0.72, 2.19)	1.26 (0.72, 2.21)	1.19 (0.67, 2.11)
Urgency	1.37 (1.00, 1.91)	1.37 (0.99, 1.91)	1.33 (0.98, 1.87)
Increased Daytime Frequency	1.13 (0.88, 1.46)	1.05 (0.14, 1.46)	1.05 (0.81, 1.36)
Nocturia	1.20 (0.72, 1.99)	1.16 (0.70, 1.92)	1.13 (0.67, 1.89)
Any LUTS	1.25 (1.08, 1.45)	1.25 (1.08, 1.44)	1.19 (1.02, 1.34)

Model 2 involves Adjusted OR (95% CI) without anxiety (age, BMI, antidepressants, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

Model 3 involves Adjusted OR (95% CI) with anxiety (age, BMI, antidepressants, anxiety, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

7.5 LUTS with depression (measured by EPDS)

Table 60 presents the results of examining association of LUTS (by subtypes) and categories of depression (non or minimal, mild, moderate to severe) at approx. 8 years of follow up.

There was weak evidence of positive associations of stress UI, urgency UI, mixed UI, urgency, and risk of depression in the main unadjusted analysis (model 1). However, no association was observed between nocturia, increased daytime frequency, any LUTS and risk of depression. After adjustment for confounders (model 2 and 3), results continued to be similar to the main unadjusted analysis (model 1).

There was weak evidence of association between all LUTS (except for mixed UI) and risk of moderate to severe depression in the unadjusted and adjusted analysis (model 1 and 2). Mixed UI was not associated with risk of moderate to severe depression (model 1 and 2). None of the LUTS were associated with risk of moderate to severe depression.

Table 60. Association of LUTS (by subtypes) and depression (measured by EPDS) at ≈8 years of follow up

	Depression measured by EPDS (scores 0-30)						
	None or minimal depression (0-6)	Mild depression (7-12)			Moderate to severe depression (13-30)		
Subtypes of LUTS	**Reference Group**	**Model 1: unadjusted (95% CI)**	**Model 2: adjusted* (95% CI)**	**Model 3** (95% CI)**	**Model 1: unadjusted (95% CI)**	**Model 2: adjusted* (95% CI)**	**Model 3** (95% CI)**
Stress UI	1	1.23 (0.92, 1.64)	1.19 (0.92, 1.54)	1.13 (0.87, 1.48)	1.32 (0.87, 2.00)	1.28 (0.90, 1.84)	1.20 (0.82, 1.74)
Urgency UI	1	1.14 (0.87, 1.49)	1.13 (0.86, 1.48)	1.08 (0.81, 1.45)	1.32 (0.92, 1.92)	1.30 (0.89, 1.88)	1.20 (0.81, 1.78)
Mixed UI	1	1.41 (0.87, 2.27)	1.34 (0.84, 2.17)	1.27 (0.76, 2.07)	0.86 (0.36, 2.01)	0.85 (0.36, 2.00)	0.78 (0.34, 1.87)
Urgency	1	1.12 (0.82, 1.53)	1.11 (0.82, 1.52)	1.08 (0.79, 1.48)	1.32 (0.85, 1.99)	1.28 (0.84, 1.97)	1.22 (0.79, 1.90)
Increased Daytime Frequency	1	0.88 (0.70, 1.11)	0.88 (0.69, 1.10)	0.81 (0.64, 1.03)	1.10 (0.80, 1.49)	1.09 (0.80, 1.49)	0.96 (0.70, 1.32)
Nocturia	1	0.97 (0.60, 1.54)	0.91 (0.57, 1.45)	0.89 (0.55, 1.44)	1.64 (0.93, 2.89)	1.52 (0.86, 2.67)	1.47 (0.82, 2.65)
Any LUTS	1	1.00 (0.87, 1.15)	0.99 (0.86, 1.41)	0.95 (0.82, 1.10)	1.20 (1.00, 1.46)	1.19 (0.99, 1.42)	1.11 (0.92, 1.34)

*Model 2 involves Adjusted OR (95% CI) without anxiety (age, BMI, antidepressants, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

**Model 3 involves Adjusted OR (95% CI) with anxiety (age, BMI, antidepressants, anxiety, socioeconomic status, education, hysterectomy, physical activity, parity, UTI, alcohol consumption)

7.6 Summary of LUTS and Depression Results

The prevalence of LUTS in women was 31%, with increased daytime frequency (15%) being the most common. There was evidence of an association between urgency UI, mixed UI, urgency, any LUTS and depression (measured by EPDS and/ or use of antidepressants) assessed after eight years of follow-up. There was strong evidence that stress UI was associated with depression but after adjusting for anxiety this association was weakened and the confidence interval crossed the null.

Depression was also assessed using EPDS and categorised into none or minimal depression, mild depression, moderate and severe depression. Stress UI was associated with mild depression and moderate to severe depression compared to the non-minimal depression. There was strong evidence that any LUTS was associated with mild and moderate to severe depression. However, after adjusting for anxiety, there were no association detected between any LUTS and mild depression. Urgency UI was only associated with moderate to severe depression before adjusting for confounders. Nocturia was also associated with moderate to severe depression but after adjusting for anxiety the association was weakened. There was no evidence of association between increased daytime frequency and depression.

8 Chapter 8: Discussion

This thesis included four prospective studies examining the association between risk factors and LUTS in middle-aged parous women participating in ALSPAC. I examined the prospective association between constipation, physical activity and LUTS. I also examined the association of LUTS with two outcomes - sexual experience and depression.

In this chapter, I will begin by summarising the main findings of the thesis. I will then describe the overall strengths and limitations of the thesis. I will then go on to discuss unique aspects of the four results sections separately.

Each results section will discuss the following:

- Main findings
- Individual strengths and limitations for each study
- Comparison to previous studies
- Potential mechanisms explaining the findings

Then, I will describe the implications of these findings, the clinical message, future directions, and recommendations with respect to genetic epidemiology and causal inference, potential for randomised control trials (RCT), and replication of results. Finally, I will draw my overall thesis conclusions.

8.1 Summary of the main findings for risk factors (physical activity and constipation) of LUTS

For my first study, I (Chapter 4) examined the prospective association between self-reported physical activity, translated into metabolic equivalents scores (MET-hours/week), and subtypes of LUTS (stress UI, urgency UI, mixed UI, urgency, nocturia and any LUTS) in parous middle-aged women. Findings from this study add to the limited evidence base on the association between physical activity and LUTS. Greater physical activity is associated with reduced odds of LUTS (stress UI, mixed UI and any LUTS) in middle-aged parous women in the ALSPAC cohort. There was evidence of an association between greater physical activity and lower odds of urgency UI, but the association should be further investigated in a large independent sample, because the confidence intervals were wide due to the small number of cases in each of LUTS subgroups. This study suggests that women performing higher physical activity have lower odds of developing LUTS.

The second prospective study (Chapter 5) explored the association between constipation (measured by self-reported intake of constipation medication) and LUTS in the same cohort of parous middle-aged women (ALSPAC). The study added to the evidence that constipation is prospectively associated with an increased risk of urinary urgency and hesitancy among parous middle-aged women.

8.2 Summary of main findings of LUTS outcomes (quality of sexual experience and depression)

In Chapter 6, I conducted two cross-sectional studies examining the association between stress UI and measures on quality of sexual experience (frequency and satisfaction with sex). Both studies suggest that stress UI is associated with higher prevalence of lower frequencies of sex and poorer satisfaction with sexual experience.

I also conducted a prospective analysis that assesses the association between changes in stress UI and quality of sexual experience (measured by frequency and satisfaction with sex) in parous women. After 1 year of follow up, resolved stress UI compared to no stress UI was associated with a lower prevalence rate of having sex less than once a month compared to having sex 2-4 times a week. Both new onset of stress UI and persistent stress UI were associated with a greater prevalence of having sex less than once a month. New onset of stress

UI and persistent stress UI were both associated with a poorer overall sexual satisfaction experience.

I conduct the third prospective study of the thesis to examine the association between LUTS and self-reported measures of female sexual dysfunction in parous middle-aged women. The study suggested that storage LUTS (any LUTS, stress UI, mixed UI, and urgency) in women are prospectively associated with greater levels of worry or distress about sexual desire, frequency of sex and orgasmic experience. Storage LUTS were also associated with a lower frequency of sex and orgasm. Subtypes of UI (stress, urgency or mixed) were associated with lower overall satisfaction with women's sex life.

In Chapter 7, I perform the fourth prospective study examining the association between LUTS and self-reported depression (measured by the Edinburgh Postnatal Depression Score; EPDS) and use of medication (antidepressants) in women. The study added to the evidence that storage LUTS (urgency UI, mixed UI, urgency and any LUTS) in women are prospectively associated with increased depression. The study also reported weak evidence of an association between nocturia and depression.

I will now discuss the overall strengths and limitations of the thesis.

8.3 Strengths the thesis

Major strengths of the studies I conducted include the use of a large representative cohort of parous middle-aged women, validated measures of LUTS, investigations of several subtypes of LUTS, the wide range of available data on relevant confounders and the long follow up period and the use of MI to reduce selection bias and increase statistical power which are a result of missing data. Each strength will be discussed in detail below.

In terms of strengths, I was able to investigate multiple subtypes of LUTS using International Continence Society (ICS) definitions and measured by validated questionnaires British Female Lower Urinary Tract Symptoms and/or International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms (BF-LUTS and/or ICIQ-FLUTS). This enabled me to examine whether associations were specific by subtypes or common to all, LUTS. ALSPAC also have multiple measures of LUTS at different ages/time points which helped me to assess associations with a different range of follow up periods. For example, stress UI was inversely associated with highest category of physical activity (≥43.2 MET hours/week) as compared to those in the lowest category (zero MET hours/week), at two follow-up periods

with 8.5 years apart (3 and 11.5 years). The repeated measures give certainty of the magnitude of association over time.

One of the advantages of prospective study is that it helps to disentangle the temporal direction of association between exposure and outcome of interest (1). It helps to reduce the chance of reverse causation, which is a limitation if associations are examined cross-sectionally (2). In my thesis, I was able to assess all associations prospectively as opposed to examining association between variables at the same time (a cross-sectional analysis). For the constipation (measured by use of medication) and LUTS analysis (Chapter 5), I was able to exclude all subtypes of LUTS at baseline (2002-2004) using the BFLUTS questionnaire and then re-assess LUTS at follow up. This means the temporal direction between constipation (measured by use of medication) and LUTS is clear. Similarly, for the LUTS and depression (measured by EPDS an use of antidepressants) analysis (Chapter 7), I excluded women with depression symptoms at baseline (were LUTS was assessed) and then re-assessed depression at follow-up. This helps understand whether LUTS influenced the risk of developing depression which eliminates reverse causation. However, for the physical activity and LUTS analysis (Chapter 4), I was able to exclude only stress UI and frequency of urination making it difficult to eliminate reverse causation (more on that in limitations section). Finally, for the LUTS and quality of sexual experience (Chapter 6), I was unable to exclude data on measures of sexual experience at baseline as information was unavailable therefore the temporal direction between examined association is less certain.

It was important to exclude women with LUTS at baseline from the analysis of determinants of LUTS to minimise reverse causation for example, when assessing association between constipation and LUTS excluding LUTS at baseline made us establish that constipation is associated with increased risk of LUTS prospectively. If this step was not performed, then I would not be able to establish if constipation increased risk of LUTS or vice versa especially that they co-occur. Therefore, the result can be generalised confidently.

Whilst for the physical activity as a determinant for LUTS, I did not have data to exclude subtypes of LUTS at baseline except for stress UI. Therefore, I cannot completely establish if physical activity is associated with increased risk of LUTS or vice versa. The only result I can generalise is that increased physical activity is associated with reduced odds of stress UI in parous middle-aged women.

In this thesis, I focused on studying LUTS in a cohort of parous women because parous women could be more prone to LUTS as they undergo pregnancy and childbirth which affects pelvic floor muscles thus leading to LUTS. However, the result of my analysis cannot be generalised to nulliparous women. Therefore, future studies are recommended to conduct similar analysis on parous and nulliparous women.

Finally, all analyses included adjustment for multiple relevant potential confounders, such as parity and hysterectomy which are both known risk factors for LUTS (126). The individual confounders were selected as appropriate for each results chapter based on literature review and clinical knowledge.

These strengths are especially important as they addressed the limitations from previous studies (see literature review, Chapter 2) in literature which included smaller samples, shorter follow up periods, limited adjustment of important confounders. Other limitations of previous studied include studies mostly designed cross-sectionally, examined fewer subtypes of LUTS as they mostly focused on UI and not using a validated questionnaire or standard definitions for measuring LUTS.

8.4 Limitations of thesis

There are also limitations to consider in this thesis that could affect the interpretation of results. It is important to take in consideration that a major limitation of observational studies is the inability to be certain about the mechanism driving observed association between outcome and exposure. This is because observed associations could result from selection bias, incomplete adjustment of important confounders (residual confounding), reverse causation or chance. Therefore, results may not reflect true causal relationship between the examined exposure and outcome. Below I will discuss how these limitations might have affected studies carried out in my thesis. Moreover, I will explain what methods I have done to reduce the likelihood these being potential explanations of the associations observed in analysis carried out in this thesis.

My thesis includes prospective studies using multivariable analysis to control for potential confounders. Study attrition is a limitation of this thesis, whereby women leaving the study or missing certain questions can lead to missing data. Multivariate and longitudinal research are limited by sample loss and missing data which decreases statistical power and can increase selection bias (127). The most common method to deal with missing data is to exclude participant who have missing values (128). This is called complete case analysis, as noted above, complete case analysis can suffer from selection bias as participants who have complete

data may be different to those with missing data and lower statistical power (128). It is therefore recommended to perform multiple imputation analysis. Multiple imputation has several advantages including reducing selection bias and increasing precision(127). Therefore, I presented the multiple imputation results as my main findings. I also included the complete case analysis because there is debate in literature that multiple imputation is recommended to be a sensitivity analysis surrounding the robustness of the results of the missing data (129).

Although this thesis uses multivariable regression methods, adjusting for a range of relevant confounders, residual confounding is a potential limitation. Residual (unmeasured) confounding is a potential limitation of all observational studies, which means that it is not possible to infer causal relationships.

Despite using a prospective design, I could not always exclude the chance of reverse causation. For example, in the physical activity and LUTS analysis (Chapter 4), there is a limitation that only stress UI and frequency items were excluded at baseline to rule out LUTS. However, these two items are not enough to rule out all subtypes of LUTS at baseline were not excluded at baseline which makes it difficult to eliminate reverse causation affecting estimated associations between LUTS (other than stress UI and frequency) and physical activity. It would have been better if ALSPAC had the ICIQ-LUTS or BFLUTS at baseline so that I could be more certain that all LUTS were excluded.

Finally, a limitation with this thesis is that women participating in ALSPAC are parous and predominantly white; therefore, the results might not be generalizable to other ethnicities and to nulliparous women. Moreover, there could be differences in the socioeconomic status in ALSPAC women compared to general population of other countries making it difficult to generalise results to women with different socioeconomic status than UK. All these findings should be further evaluated in a larger and more diverse sample of women.

These were the major strengths and limitations that applied to all my studies. I will now go on to discuss each study in more detail. I will discuss the main findings, individual strength, and limitations for that study, compare the findings to previous relevant studies and discuss potential mechanisms which may explain or underpin the findings.

8.4.1 Section 1: Physical activity and LUTS

Section 1 discusses the first aim of my thesis which was assessing the prospective association between physical activity and risk of LUTS (by subtypes) in parous middle-aged women.

8.4.2 Main findings

There was evidence of a decreased risk of LUTS at 3 and 11.5 years of follow-up among middle-aged parous women who reported higher levels of physical activity compared to those with lower level of physical activity. The odds of stress UI, mixed UI and any LUTS were lower among women in the highest category of physical activity (≥43.2 MET hours/week) as compared to those in the lowest category (zero MET hours/week), after both 3 and 11.5 years of follow-up. There was also evidence of lower odds of nocturia at 3 years of follow up and lower odds of urgency UI after 11.5 years of follow-up among those in the highest category of physical activity.

8.4.3 Limitations

The unavailability of information on some types of LUTS (urgency UI and nocturia) meant that I was unable to exclude women with these LUTS types at baseline. Therefore, I cannot exclude the possibility of reverse causation affecting estimated associations between physical activity and LUTS. This means that reverse causation could be an alternative explanation for the association between physical activity and LUTS. Moreover, physical activity (as well as potential confounders) was only assessed once and levels may have changed during follow-up periods (3 and 11.5 years) i.e., between baseline and outcome assessment.

Several studies have compared measuring physical activity by self-reported questionnaires and objective measurements using an accelerometer. These studies reported that participants using self-reported questionnaires may over-report their physical activity and under-report the amount of sedentary time (130). In my study, self-reported physical activity was used to estimate MET-hours of physical activity per week which might have introduced misclassification in the exposure, resulting in biased estimates. Due to social desirability, women may over-report time spent being physically active due to the tendency to present themselves in a generally favourable fashion by seeming more physically active (5). Since it's a prospective study, the measurement error due to social desirability can't be associated with the outcome, hence any misreporting will likely result in an underestimate.

8.4.4 Comparison with previous studies

Findings of my study show that higher physical activity is prospectively associated with reduced odds of LUTS; especially stress UI, mixed UI and any LUTS. This is similar to the findings of a prospective study of women (aged 54-79 years) which reported an inverse association between levels of physical activity and UI incidence after two years of follow up (131). In another prospective study of middle-aged women (n=30,135; mean age 46 years) based on data from the Nurses' Health Study II, results indicated a decrease in risk of urgency and stress UI among women with higher physical activity after 12 years of follow-up (132). Findings from the Leicestershire MRC study (n= 6424; median age 21 years) also reported lower risk of wet overactive bladder (OAB), dry OAB and stress UI among more physically active women (133).

When restricting the analysis to high-intensity physical activity, my results were not altered. In contrast, results from findings from a previous systematic review of studies in female athletes, indicated that women who performed high-impact physical activity were more likely to report UI (134) compared with women in the community. The review explained that athletes exercise for long periods engaging in strenuous activities, which might damage pelvic floor muscles. High-impact physical activity including trampolining and gymnastics, may also increase the risk of developing UI due to strain on pelvic floor muscles (135, 136). The discrepancy might be explained by the fact that I examined high intensity and not high-impact physical activity and from the different populations studied. My work is based on a general population of women that are unlikely to be exercising to the same intensity as athletes.

Cross-sectional studies provided conflicting evidence with regards to the association between exercise and LUTS(135, 137, 138).A cross-sectional study reported that women suffering from UI especially stress UI may avoid engaging in sports(139).Other cross-sectional studies reported that high impact exercises might be harmful to the pelvic floor and could increase UI symptoms in women(135, 136, 140).While some cross-sectional studies reported that low impact exercise have a protective mechanism and a therapeutic effect against UI(141). However, findings from my study shows that higher physical activity is prospectively associated with reduced odds of LUTS; especially stress UI, mixed UI and any LUTS. When restricting the analysis to high intensity physical activity, findings from my study showed that high intensity exercise is associated with reduced odds of LUTS especially stress UI. The difference in results could be because I used high intensity exercise which depends on

frequency of exercise while previous studies examined high impact exercises such as trampoline that put pressure directly on pelvic floor resulting in increased stress UI.

8.4.5 Potential mechanisms explaining findings

There are various mechanisms that might explain the association between higher physical activity and lower risk of LUTS. Health literacy is an important explanation for the observed association as women who have higher levels of physical activity might have greater health literacy than those with lower physical activity. Women with higher physical activity could be more aware of their overall health; therefore, they might perform Kegel pelvic floor exercises which could directly decrease the risk of LUTS by strengthening of the muscles (129), as part of their routine work out. Unfortunately, information on pelvic floor exercises were not obtained through the ALSPAC questionnaires to explore this in more detail. Physical activity may also reduce the risk of developing LUTS by lowering BMI which in turn is associated with lower intra-abdominal pressure (130). However, after adjusting for BMI measured concurrently to the assessment of outcomes, results in my study were similar, suggesting that mediation by BMI did not account for associations between physical activity and LUTS.

Prolonged exercise may cause fluids to be over consumed due to sweating resulting in a reduced ability to produce urine to excrete the excess volume thus less risk of LUTS especially UI (131).

8.5 Section 2: Constipation and LUTS

Section 2 discusses the second aim of the thesis which was studying the prospective association between constipation and the risk of developing LUTS (by subtypes) in parous middle-aged women.

8.5.1 Main findings

Use of medications for constipation was prospectively associated with an increased risk of LUTS (urgency and hesitancy) after 10 years of follow up among middle-aged parous women. There was no evidence of an association between medication intake for constipation and other LUTS (stress UI, urgency UI, mixed UI, nocturia, increase daytime frequency, intermittency and any LUTS)

8.5.2 Limitations

Limitations of this study include the use of medication for constipation as a proxy to measure constipation. This was because I did not have access to direct self-report or questionnaires about prevalence of constipation. Therefore, this does not give information on severity and duration of constipation. Although assessing constipation using treatment may capture more severe cases, I am still concerned that this included many women with very mild constipation. For example, it is unclear how mild constipation such as having a laxative once a month could result in chronic constipation that might increase risk of LUTS. Therefore, constipation treatment assessed as yes/no for any use of medication/supplement for constipation in past 12 months is a limitation, as this includes a wide range of women who had very mild constipation (used a laxative once) to very severe (used daily laxatives). It is unfortunate that I was unable to study the most severe group with highest risk of LUTS however this could be a recommendation for future research.

Other limitations include power, only a small number of women were reported as taking medication for constipation. This resulted in wide confidence intervals thus a lack of precision in my results. Constipation was categorised as either medication used “none, yes at one of the two timepoints, and yes at both time points”. I classed women who used medication at both time points have the most severe (chronic) constipation. However, these categories could include women who had mild constipation (e.g., used a laxative once) to severe (e.g., used daily laxatives) so I may have lost a lot of information by using this classification.

8.5.3 Comparison with previous studies

One prior prospective study (n=234 pregnant women) examined the association between constipation and UI. This study reported that chronic constipation (women scoring ≥9 using the Sandwell Incontinence Following Childbirth Risk Assessment Tool (SIFCRAT) risk scale) was associated with an increased risk of stress UI 6 months after delivery (46). However, in my study using a larger number of middle-aged women, I did not find an association between constipation and stress UI. It is unexpected that I did not find an association between constipation (measured by medication intake) and stress UI because the straining due to constipation and pressure on the pelvic floor could potentially lead to stress UI. However, it is important to note that the prior sample study included women who were 6 months post-natal which means the pelvic floor muscles have been through labour recently making them still weak and may have acted as a mediator to have stress UI. On the other hand, stress UI in my study sample was assessed approx. 10 years from measuring constipation and women included were not post-natal which might mean that pelvic floor muscles may have fully recovered and strengthened during that period. It is important to note that I included a larger sample (n=3729) of women which increases statistical power to detect an effect (or no effect).

A retrospective cohort study (over12 years period) was conducted at a pelvic floor disorder centre in a tertiary healthcare facility to characterize urogenital symptoms in women with and without constipation (142). 875 women (mean age 57.0 ± 16.9 years) were asked to self-report urinary symptoms using The Urinary Distress Inventory (UDI-6). Women with constipation completed the Constipation Severity Instrument (CSI) to assess constipation. The study reported that women with chronic constipation were more likely to report symptoms of urinary hesitancy (27.0% vs.17.0%, $p < 0.001$). This result aligns with the findings of my analysis, constipation was associated with increased risks hesitancy among parous middle-aged women.

A systematic review (including animal studies and human studies: men and women, ages ≥23, sample range 23-4684), examined the relationship between bowel and bladder function and its implications for managing coexisting constipation and OAB, including urgency UI, nocturia, increased daytime frequency of urination and urgency (41). The review concluded that constipation may contribute to the development of OAB symptoms, including urgency and frequency. This was supported by my findings that constipation is positively associated with urgency.

Further evidence of a link between constipation and LUTS comes from an intervention study that examined the effect of alleviating constipation on LUTS, including urgency and frequency. Participants (42 men and 10 women; ages 65-89) with chronic constipation and LUTS completed self-reported questionnaire on constipation and LUTS monthly for four months. Constipation was treated using medication including Paraffin, Benzalkonium, Senokot, Lactulose or Cisapride. The study reported that by treating constipation, urgency and urinary frequency symptoms decreased (143). This gives insight for potential clinical translation of my findings, supported by real world evidence. Further and larger studies such as these should be performed to see if these associations still exist in larger samples (and samples of just women).

The studies mentioned above have reported an increased risk of urgency in constipated patients (46, 143) similar to what I observed in my study of ALSPAC participants. However, the confidence intervals in my study were wide and crossed the null value due to the small number of women who were taking medication for constipation. Therefore, these must be interpreted with caution.

8.5.4 Potential mechanisms explaining findings

There are several plausible mechanisms that could explain the association between constipation and LUTS. Chronic constipation without treatment could cause changes in the pelvic floor structure through several mechanisms which may result in an increased risk of developing LUTS. The rectum and the bladder are anatomically aligned close to each other and share the muscular structure of the pelvic floor. The cumulative effect of chronic constipation on pelvic floor musculature could increase muscle tone which may cause dysfunctional elimination of urine (41, 50). Constipation may cause strain for women while emptying the bowel. This could put pressure on the pelvic floor muscles which would be expected to lead to stress UI. Although I did not find association with constipation and stress UI, the previous mechanism could explain why other studies detected an association between constipation and stress UI. Moreover, this continuous straining due to constipation over long period of time may weaken the pelvic floor muscles resulting in pelvic organ prolapse which could increase risk of developing LUTS (41, 50). Unfortunately, there were no data on pelvic organ prolapse available from the ALSPAC questionnaires to explore this mechanism. Having a full rectum may press the bladder wall which could result either in increased spasm or outflow obstruction. This mechanism could explain the association between constipation and hesitancy. Since the bladder is anatomically in front of the rectum, enlarged stool (due to constipation) may press on the bladder resulting in impaired emptying (144).

It is also possible that there is a common underlying cause of constipation and LUTS such as inflammation, or high levels of stress reactivity that I have not accounted for in analyses. Constipation and LUTS might both be part of a phenotype associated with susceptibility to stress that affects the bladder (e.g., overactive bladder) and bowel (e.g. irritable bowel syndrome). Future research should focus on exploring possible underlying common causes of constipation and LUTS.

The next part of this chapter (sections 3 and 4) discusses the findings of the studies included in my thesis that examined outcomes associated with LUTS. These outcomes included several measures of sexual experience and measures of depression (EPDS and use of antidepressants).

8.6 Section 3a: Cross-sectional association between stress UI and concurrent quality of sexual experience (Measured by frequency and satisfaction with sex)

8.6.1 Strengths and limitations

A unique strength of this analysis was that the association between stress UI and quality of sex (measured by frequency and satisfaction) was measured cross-sectionally and prospectively with 1 year of follow up. Due to the nature of the analysis, the limitations are the same as in Chapter 6, section 3b.

8.6.2 Main findings

Since stress UI is linked to poor quality of sexual experience (145), I carried out two cross-sectional studies (with one year apart between mean ages 34.9 years (SD: 0.12) and 35.9 years (SD: 0.10) assessing the association between stress UI and frequency and satisfaction with sex. Findings of both studies (Chapter 6) showed that stress UI was associated with a greater likelihood of lower frequencies of sex and a poorer overall sexual satisfaction experience. I also examined whether changes in stress UI symptoms between the two time points (one year apart) influenced women's frequency and satisfaction with their sex life (Chapter 6). I found that women with resolved stress UI reported a higher frequency of sex compared to women with no onset of stress UI symptoms. Both worsened stress UI and persistent stress UI was associated with a greater likelihood of having sex less than once a month. Worse stress UI and persistent stress UI were also both associated with a poorer overall sexual satisfaction experience.

8.6.3 Potential mechanisms explaining findings

Women suffering from stress UI have reported that they might leak urine during intercourse. This might cause women to avoid sexual intercourse due to embarrassment thus reducing overall frequency and satisfaction with sex life (146). When leakage occurs during intimate moments, women might become more anxious resulting in reduced overall sexual satisfaction. Symptoms of urinary incontinence have also been linked to poorer self-image which could decrease confidence of women to engage in sexual activities (146). Women suffering from stress UI reported several factors that contribute to a decreased frequency in sexual intercourse including loss of spontaneity, the general feeling of unattractiveness from wearing pads in bed and worry over odour (147). Therefore, a woman's perception of her own sexuality is affected, leading to sexual inhibition. These findings should be further investigated in both qualitative and quantitative studies. If these relationships are found to be reported in larger samples of women, then I should encourage clinicians to ask women about these topics to create a better dialogue and reduce women feeling stigmatised. Clinicians should be aware of the effects of LUTS and UI on women's physical and mental health and quality of life.

8.7 Section 3b: LUTS and Female Sexual Dysfunction

After finding evidence that stress UI is associated with poor measures of sexual experience (frequency and satisfaction with sex). I further explored prospectively the association between other subtypes of LUTS and multiple measures of quality sexual experience in parous middle-aged women (Chapter 6, section 6.3). Below are my main findings.

8.7.1 Main findings

There was evidence that any LUTS, stress UI, mixed UI and urgency were associated with greater levels of worry or distress about sexual desire, frequency of sex and orgasmic experience. At mean age 49.3 years, any LUTS, stress UI and mixed UI were also associated with a lower frequency of sex and orgasm. Subtypes of UI (stress, urgency or mixed) were further associated with women's lower overall satisfaction with their sex life. After adjusting for depression and use of antidepressants, I observed an attenuation of the relationships with measures of worrying or distress about sexual desire, orgasmic experience, and frequency of sex, and an increase in the magnitude of the association with lower overall satisfaction with own sex life.

8.7.2 Strengths and limitations

A unique strength of this analysis is that I was able to examine multiple measures of quality of sexual experience such as level of desire or orgasm, frequency of sex and satisfaction with sex. As my literature review shows, this is an improvement on previously published papers which did not have this depth of data (literature review Table 8).

However, information on sexual function at baseline were not available therefore I could not examine how it might have changed between baseline and outcome assessment. Also, it is possible that due to social desirability or embarrassment, women with LUTS might have underreported their levels of worrying and distress related to their sexual dysfunction, and overreported their overall satisfaction with their sexual life, which may have resulted in an underestimation of the true relationships.

Although I adjusted for parity, it is important to consider adjusting for age of youngest child. Several of women recruited by ALSPAC may still have a young child. Women with young children might be busier thus overwhelmed and might have less desire to engage in sexual activity or might reduce frequency of sexual activities. Future studies should consider adjusting for age of youngest child and not just parity like I did in my thesis.

In order to examine whether LUTS may affect sexual experience in women who are sexually active, I excluded women who do not have partners at baseline. However, I might be removing women who are still engaging in sexual activity randomly instead with a specific partner; this might affect the power of the analysis due to loss of number of women. Moreover, this will make the results of the analysis not generalisable for women with no sexual partners.

8.7.3 Comparison of findings with previous studies

The results of my study showed a prospective association between stress UI, urgency UI, mixed UI and measures of quality sexual experience including levels of worry and distress related to women's sexual desire, orgasm experience and frequency of sex. A systematic review and meta-analysis (15) reported similar findings that OAB-wet (defined as urinary urgency accompanied by increased frequency and/or nocturia, with UI, in the absence of a UTI or any obvious disease) had the strongest association with female sexual dysfunction. This could be because women are worried about urinary leakage during sexual intercourse or orgasm.

I also found evidence of associations between stress UI and mixed UI with more adverse levels of all measures used to assess quality of sexual experience. These findings are similar with a small retrospective study that examined the associations subtypes of UI (stress UI, urgency UI and mixed UI) with female sexual dysfunction (n=93, mean age 53.4 ± 4) and quality of sex life (73) measured using self-administered Female Sexual Function Index (FSFI) and Female Sexual Distress Scale (FSDS) questionnaires. The study reported that women with mixed UI and stress UI had lower sexual desire than those with urgency UI (73). Also, women with mixed UI showed greater sexual dysfunction compared with other women (73). Although, this retrospective study reported that women with mixed UI and urgency UI had more orgasmic disorders than those with stress UI, I only found associations of mixed UI and stress UI with orgasmic disorders and weak evidence of associations with urgency UI.

8.7.4 Possible mechanisms explaining findings

This study showed evidence that symptoms of depression and use of antidepressants before the assessment of LUTS might explain some of the association between LUTS and measures of sexual dysfunction at/or after baseline. After adjusting for depression and antidepressants (measured one year before baseline), the association between LUTS and poorer sexual satisfaction was strengthened, which might reflect that women might be dissatisfied with their overall sex life due to psychological health, failure to achieve orgasm and worry about urinary leakage during intercourse (148, 149). LUTS may not directly affect women's ability to have

sex but psychological fear of having urinary leakage during sex can cause women to avoid sexual intimacy (148, 150). Urgency or urinary leakage could also reduce sexual desire and satisfaction as women may feel unattractive (151).

Depression might be on the causal pathway between LUTS and measures of quality sexual experience, but there was no data on depression at or after baseline and before sexual satisfaction was assessed to allow us to directly explore this. Future studies are recommended to explore if depression is a mediator between the association of LUTS and measures of poor sexual experience. However, adjusting for depression before baseline did strengthen the association between LUTS and measures of sexual dysfunction which indicates that depression might be an underlying cause for both. Further studies are recommended to examine mechanisms, such as depression, which might explain the relationship between LUTS and poor sexual experience to identify modifiable factors that could be targeted in interventions.

There was evidence of inverse associations of stress UI, mixed UI with frequencies of orgasm and sex. Stress UI occurs in the presence of increased intra-abdominal pressure without perception of previous micturition desire. Sexual intercourse can cause pressure on pelvic floor muscles which may cause urinary leakage during sex. Therefore, women might avoid future sexual activity due to worries about incontinence (107, 152).

8.8 Section 4: Depression and LUTS

Section 4 addresses the fourth aim of the thesis which assesses the prospective association between LUTS (by subtypes) and depression (measured by EPDS and use of antidepressants) among parous middle-aged women.

8.8.1 Main Findings

This study provides evidence that storage LUTS in women are prospectively associated with depression. After approx. eight years of follow up from baseline (2002-2004, mean age (SD): 43.3(0.8), stress UI, urgency UI, mixed UI, urgency, any LUTS were associated with depression (measured by EPDS and/ or use of antidepressants). Weak evidence of an association between nocturia and depression was detected. There were no association between increased daytime frequency and depression.

8.8.2 Strengths and limitations

A strength of this study is that it used validated questionnaires (EPDS) to measure depression (153). Women with depression at baseline were excluded which helps us minimise the risk of reverse causation. The study was also able to examine associations of different subtypes defined using ICS definitions of LUTS with measures of depression.

A limitation of this study is that there were no measures of anxiety after LUTS at baseline. This is important to examine whether there was a mediating effect of anxiety on the relationship between LUTS and depression.

Although the relationship between anxiety and depression is complicated. It was important to adjust for anxiety when examining the association between LUTS and depression. This is because anxiety symptoms and depression symptoms usually co-occur. The chance of acquiring depression is much higher when an anxiety disorder already exists. People who are depressed often feel anxious and worried. However, adjusting for anxiety did not make a difference in the results which could be because women with baseline depression were excluded from the analysis. Therefore, adjusting for anxiety in this analysis could potentially be over adjustment.

Another limitation of this study was not adjusting for menopause. Menopause is associated with both LUTS and depression. This is because depressive symptoms have been reported more in menopausal women compared to premenopausal women(154). Menopause is also associated

with decreased oestrogen level that cause pelvic floor muscles week resulting increased risk of LUTS(155). Therefore, future studies are recommended to adjust for menopause when examining the association between LUTS and depression.

8.8.3 Comparison of findings with previous studies

There are some prospective studies that have examined whether women with LUTS have an increased risk of developing depression, but they all focused on the postpartum period with smaller sample sizes (89, 90). These studies suggest that there is association between urgency UI, stress UI and the onset of postpartum depression.

A prospective cohort study from the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ) aimed to identify risk factors related to stress UI and postnatal depression (PND) (89). The study investigated both possible directions of association between stress UI (self-reported and defined by ICS) and PND (measured by EPDS) in population-based sample of Czech mothers (n=3721). Stress UI at 6 weeks postpartum was associated with an increased risk of PND six months after delivery. However, there was no association between PND at 6 weeks after delivery and new onset of stress UI cases after 6 months.

A population-based cohort study aimed to examine the direction and strength of the temporal association between LUTS (n=34978) and anxiety/depression using data from the Taiwan's National Health Insurance program(86). After three years of follow up, the study reported a greater risk of anxiety/depression among those with LUTS.

A prospective cross-sectional study examined an association between postpartum depression (measured by EPDS) and symptoms of OAB (self-reported using URGE-UDI or URGE-IIQ score questionnaire) in postpartum women (n=100, mean age 29.2±6.1 years; 18–47 years) (90). This study reported an increased risk of postpartum depression 6 weeks after delivery among women with urgency UI.

These studies results are in line with my study results, as I also found associations of urgency UI, stress UI and other LUTS with depression.

8.8.4 Possible mechanisms explaining findings

Several mechanisms might explain the association between LUTS (especially urgency UI, mixed UI, urgency and any LUTS) and depression. LUTS may impact daily activities which negatively affect self-esteem thus consequently leading to depression (94, 156). LUTS can also cause embarrassment which discourage women to participate in socially thus may lead to

isolation and depression. Urgency and nocturia also could affect women's mood indirectly by its negative impact on the quality of sleep (157) and sex life, as discussed above in sections 3a and 3b. The association between urgency UI and anxiety or depression, may further be explained by the fact that these syndromes share common biological pathways for example stress reactivity, HPA axis, neurological basis of LUTS and depression, low grade inflammation (86). Systemic inflammation is an established risk factor for LUTS and depression and could partially mediates the prior association (158). Increases levels of proinflammatory cytokines often occurs before a depressive episode and could last after the remission of depression which may be associated with subsequent mental illness such as dementia (158). Neurotransmitters are also involved in the physiological process of both LUTS and depression (34). There are experiment that suggest serotonin has a central nervous system effect that could impair lower urinary tract function which could be a possible explanation for the association observed between LUTS and depression(159). It has been shown that urgency UI was associated with global hypoperfusion of the frontal areas of the brain in geriatric patients (160) and reduced anterior cingulate cortex activity accompanied by failure of inhibition of detrusor overactive contractions (161). Moreover, it has been reported that dysfunction of the limbic system and hypoperfusion, especially in the anterior cingulate cortex, may result in late-life depression in women (162).

It is plausible that there is a hormonal mechanism explaining the association between LUTS and depression. Some studies have shown that serotonin and norepinephrine are involved in the pathophysiology of depression (163, 164). A neuro-endocrine explanation for association of OAB symptoms with depression and anxiety may be found in shared dysregulation of the hypothalamic–pituitary-adrenal axis, which plays a role in depression disorders (165).

8.9 Patterns of LUTS across examined risk factors and outcomes

This section will explain the patterns of examined LUTS with examined risk factors (physical activity and use of medication) and outcomes (quality of sexual experience and depression).

It was interesting to notice that increased day time frequency was the least type of LUTS to be associated with any of the examined risk factors or outcomes. However, in the LUTS and depression analysis (Chapter 7) increased daytime frequency was the most highly prevalent (15 %) LUTS among eligible sample. Nocturia was the least prevalent LUTS among women in all analyses carried out in this thesis with percentage ranging from 1 to 9%. Followed by mixed UI with prevalence range between 3% to 9%.

Stress UI, urgency UI and mixed UI were the most common LUTS symptoms associated with the examined risk factors and outcomes in this thesis. It was also noticeable that stress UI was highly prevalent in all eligible sample included in thesis analyses with percentage ranging between 12 to 23.

8.10 Section 5 Implication of findings and clinical message of the theses

In this section I will discuss the potential clinical implications of my findings. Firstly, findings from physical activity and LUTS study (Chapter 4) provide evidence that middle aged parous women who engage in a higher level of physical activity are at lower risk of LUTS. If causal, this suggests that performing high intensity exercises including jogging or swimming equivalent to 6 hours or more throughout the week (equivalent to ≥43.2 MET-hrs/week) may help reduce the risk of women developing stress UI by 49% (95% CI: 20%, 68%) compared to women who do not exercise at all. This could be recommended to women to see if this has a positive effect on their symptoms. Further research, e.g., an RCT, would need to be done to establish whether the association is indeed causal. If there is a causal relationship, interventions could recommend increasing physical activity to avoid LUTS. I discuss the possibility of randomised control trials (RCT) to study these effects in Section 6, below.

According to the results of the constipation and LUTS study (Chapter 5), constipation was prospectively associated with increased risks of urgency and hesitancy among parous middle-aged women. Constipation may result in increased risk of developing LUTS in parous middle-aged women. If further research supports this evidence and can establish a causal effect between constipation and LUTS, women should be advised to seek treatment to alleviate constipation and reduce their consequent risk of developing these LUTS. Furthermore, this should be an active conversation between clinicians and women to reduce stigma.

Findings from the LUTS and measures of quality sexual experience study (Chapter 6) showed that there is a prospective association between storage LUTS and measures of poorer sexual function in parous middle-aged women. Therefore, it is important to increase awareness among health care providers and women of the increased risk of sexual dysfunction among women with LUTS. Also, it is an added incentive to seek treatment for LUTS. Similarly, findings from this study showed associations of stress UI with frequency and satisfaction with sex in parous middle-aged women. Therefore, women suffering from LUTS (especially stress UI) are advised to seek early treatment to avoid it from interfering with their sex life.

Finally, findings from my study showed that there is a prospective association between storage LUTS and measures of depression in parous middle-aged women. Therefore, it is important to increase awareness among health care providers and women of the increased risk of mental health problems among women with LUTS. Women suffering from LUTS are advised to seek early treatment before symptoms worsen and potentially interfere with mental well-being.

Even if the associations found here, between physical activity, constipation and LUTS and between LUTS and quality of sexual experience and depression, are not causal, they still suggest that it is important to screen for these measures.

To my knowledge, the National Institute for Health and Care Excellence (NICE) only has guidelines for management of LUTS in men. Unfortunately, NICE guidelines on LUTS for women only covers urinary incontinence and not other LUTS. Therefore, it is important to have clear guidelines for diagnosis and management of LUTS in women as this field is neglected. Moreover, there is a lack of training of health professional in incontinence especially in Kuwait where I come from. This lack of training means fewer health professionals are available to deliver the proper assessment and treatment for LUTS in women, despite the prevalence of LUTS in women being high. It is important to fund and invest in educating women about the importance of early treatment for LUTS to prevent the symptoms from interfering with their quality of life - such as developing depression or abstaining from sex. Ways to educate women about LUTS could be through short advertisement on social media or in clinics by performing anti-natal and postnatal classes, as pregnancy and delivery is associated with an increased LUTS risk and women are already in contact with health providers, with group session on LUTS.

8.11 Section 6 Future directions and recommendations

8.11.1 Genetic epidemiology

In my thesis I reported results from observational epidemiology. Whilst genetic epidemiology has attempted to find genetic markers for risk of LUTS, the underlying genetics of LUTS is still unclear. Previously reported genome-wide association studies (GWAS) have identified genetic associations with UI but there are mixed results, and the papers conclude more research to be done (166). However, a recent 2021 GWAS reported two genes (*EDN1* and *MARCO*) that may be associated with UI. These genes have been previously associated with muscle contractions(167). Therefore, these could be important in future causal work, and development of potential targeted therapeutic treatments, which I discuss in the section below. However, it

is important future research explores other subtypes of LUTS other than UI, as I have done in this thesis. Future work is needed in this area to establish whether these genes are important in LUTS in women.

8.11.2 Causal inference and Mendelian Randomization (MR)

Causal inference techniques, such as Mendelian Randomization (MR), use genes as proxies or instruments for exposures of interests. These methods can help us understand whether associations are likely to reflect causal relationships as the genetic instruments should not be associated with confounders due to their random allocation at a population level.

Future work could leverage causal inference techniques such as MR to try and understand more about the nature of the relationship between risk factors and LUTS and between LUTS and outcomes. However, if causality is not detected, clinicians are still advised to screen for examined risk factors (physical activity and constipation) and outcomes (female sexual dysfunction and depression) because they may help with risk stratification. This can help improve identification of high-risk women of LUTS. Importantly, MR analysis must be significantly powered to detect these effects and I would require a larger sample than ALSPAC.

8.11.3 Replication of results

This work was conducted in ALSPAC a large cohort of women in the southwest of England. Whilst this is a large, prospective cohort, most of the women are of white ethnicity and above average socioeconomic status(168). Future work should attempt to replicate these findings on women with non-white ethnicities and those with different socioeconomic statuses such as the Born in Bradford cohort (169).

8.11.4 Randomised control trial

As has been discussed throughout this thesis, I have reported associations, but not examined causality, or whether clinical interventions based on targeting these exposures/outcomes would have translational benefit for women. To help clinical practitioners understand more about these associations, future work could undertake randomised controlled trials (RCT) to try and establish which women are more at risk of LUTS. For example, my work has suggested that physical activity could be associated with a reduction in the incidence of LUTS. Therefore, an RCT could be designed which randomly allocated physical activity to one group of women and compare the incidence of LUTS to a control group of women who were not assigned physical activity intervention. However, this would require large samples sizes. Alternative approaches

could be undertaking an RCT of women with LUTS to see if exercise improved their symptoms.

For examining the outcomes of LUTS in women, an intervention could compare the prevalence of outcomes (e.g., depression, sex quality) before/after treatment for LUTS, and compare different treatments to see which had the most beneficial reduction in LUTS outcomes.

However, these are recommended interventions to be undertaken further down the translational pipeline, for which my work provides good quality evidence for.

8.12 Thesis Conclusion

In my thesis, I met the aims and objectives of my study, outlined in the Introduction. In this thesis, I carried out four prospective studies investigating different associations with LUTS in a sample of parous middle-aged women. Overall, this thesis adds to the literature that constipation and physical activity are prospectively associated with LUTS in parous middle-aged women. The thesis also added to the evidence that LUTS are associated with poorer measures of female sexual dysfunction and higher depression scores. Studying associations with LUTS are only the first step, future recommendations of studying causality with LUTS is important to understand underlying mechanisms and support clinical translation.

9 References

1. Alhababi N, Magnus MC, Joinson C, Fraser A. A prospective study of the association between physical activity and lower urinary tract symptoms in parous middle-aged women: results from the Avon Longitudinal Study of Parents and Children. The Journal of urology. 2019;202(4):779-86.
2. Alhababi N, Magnus MC, Drake MJ, Fraser A, Joinson C. The Association Between Constipation and Lower Urinary Tract Symptoms in Parous Middle-Aged Women: A Prospective Cohort Study. Journal of Women's Health. 2021.
3. Haylen BT, De Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. 2010;29(1):4-20.
4. Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs F, Fourcade R, et al. The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. BJU international. 2003;92(4):409-14.
5. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I. National community prevalence of overactive bladder in the United States stratified by sex and age. Urology. 2011;77(5):1081-7.
6. Coyne KS, Sexton CC, Thompson CL, Milsom I, Irwin D, Kopp ZS, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. 2009;104(3):352-60.
7. Chapple C, Castro-Diaz D, Chuang Y-C, Lee K-S, Liao L, Liu S-P, et al. Prevalence of lower urinary tract symptoms in China, Taiwan, and South Korea: results from a cross-sectional, population-based study. 2017;34(8):1953-65.
8. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU international. 2011;108(7):1132-8.
9. Soler R, Gomes CM, Averbeck MA, Koyama MJN, Urodynamics. The prevalence of lower urinary tract symptoms (LUTS) in Brazil: Results from the epidemiology of LUTS (Brazil LUTS) study. 2018;37(4):1356-64.
10. Hunskaar S, Lose G, Sykes D, Voss SJBi. The prevalence of urinary incontinence in women in four European countries. 2004;93(3):324-30.
11. Coyne KS, Sexton CC, Bell JA, Thompson CL, Dmochowski R, Bavendam T, et al. The prevalence of lower urinary tract symptoms (LUTS) and overactive bladder (OAB) by racial/ethnic group and age: results from OAB-POLL. 2013;32(3):230-7.
12. Tähtinen RM, Cartwright R, Tsui JF, Aaltonen RL, Aoki Y, Cardenas JL, et al. Long-term impact of mode of delivery on stress urinary incontinence and urgency urinary incontinence: a systematic review and meta-analysis. European urology. 2016;70(1):148-58.
13. Troko J, Bach F, Toozs-Hobson P. Predicting urinary incontinence in women in later life: A systematic review. Maturitas. 2016;94:110-6.
14. Hunskaar S. A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women. Neurourology and Urodynamics: Official Journal of the International Continence Society. 2008;27(8):749-57.
15. Balzarro M, Rubilotta E, Mancini V, Trabacchin N, Oppezzi L, Marzi VL, et al. Impact of Overactive Bladder-Wet Syndrome on Female Sexual Function: A Systematic Review and Meta-Analysis. 2019.
16. Shaw CJEu. A systematic review of the literature on the prevalence of sexual impairment in women with urinary incontinence and the prevalence of urinary leakage during sexual activity. 2002;42(5):432-40.
17. Pereira MG, Lynch B, Hall-Faul M, Pedras S. Quality of life of women with urinary incontinence in rehabilitation treatment. Journal of Health Psychology. 2019;24(2):254-63.
18. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. International journal of epidemiology. 2013;42(1):97-110.

19. Fall M, Abrams P, Griffiths D, Victor AJN, urodynamics. The standardisation of terminology of lower urinary tract function: Report from the standardisation sub-committe. 2002;21:167-78.
20. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. American Journal of Obstetrics & Gynecology. 2002;187(1):116-26.
21. Hashim H, Blanker MH, Drake MJ, Djurhuus JC, Meijlink J, Morris V, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. 2019;38(2):499-508.
22. Mahadevan VJS. Anatomy of the lower urinary tract. 2016;34(7):318-25.
23. Raizada V, Mittal RKJGCoNA. Pelvic floor anatomy and applied physiology. 2008;37(3):493-509.
24. Lopes LG, Vasconcelos CTM, Neto JAV, Oriá MOB, Saboia DM, Gomes MLS, et al. A systematic review of the prevalence, risk factors, and impact of pelvic floor dysfunctions in nurses. 2019;38(6):1492-503.
25. de Groat WC, Yoshimura NJHocn. Anatomy and physiology of the lower urinary tract. 2015;130:61-108.
26. Wei JT, De Lancey JOJCo, gynecology. Functional anatomy of the pelvic floor and lower urinary tract. 2004;47(1):3-17.
27. Roosen A, Chapple CR, Dmochowski RR, Fowler CJ, Gratzke C, Roehrborn CG, et al. A refocus on the bladder as the originator of storage lower urinary tract symptoms: a systematic review of the latest literature. 2009;56(5):810-20.
28. Murphy AM, Bethoux F, Stough D, Goldman HBJInj. Prevalence of stress urinary incontinence in women with multiple sclerosis. 2012;16(2):86.
29. Hubeaux K, Deffieux X, Ismael SS, Raibaut P, Amarenco GJTJou. Autonomic nervous system activity during bladder filling assessed by heart rate variability analysis in women with idiopathic overactive bladder syndrome or stress urinary incontinence. 2007;178(6):2483-7.
30. Fantl J, Wyman J, Wilson M, Elswick R, Bump R, Wein A. Diuretics and urinary incontinence in community-dwelling women. Neurourology and Urodynamics. 1990;9(1):25-34.
31. Finkelstein MMJCFP. Medical conditions, medications, and urinary incontinence. Analysis of a population-based survey. 2002;48(1):96-101.
32. Smith A, Bevan D, Douglas HR, James DJB. Management of urinary incontinence in women: summary of updated NICE guidance. 2013;347.
33. Jackson S, Donovan J, Brookes S, Eckford S, Swithinbank L, Abrams PJBjou. The Bristol female lower urinary tract symptoms questionnaire: development and psychometric testing. 1996;77(6):805-12.
34. Schou J, Poulsen AL, Nordling JJSjou, nephrology. The value of a new symptom score (DAN-PSS) in diagnosing uro-dynamic infravesical obstruction in BPH. 1993;27(4):489-92.
35. Kelleher C, Cardozo L, Khullar V, Salvatore SJBAIJoO, Gynaecology. A new questionnaire to assess the quality of life of urinary incontinent women. 1997;104(12):1374-9.
36. Morton S, Berg A, Levit L, Eden J. Finding what works in health care: standards for systematic reviews. 2011.
37. Wennberg A-L, Molander U, Fall M, Edlund C, Peeker R, Milsom IJEu. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. 2009;55(4):783-91.
38. Coyne KS, Margolis MK, Kopp ZS, Kaplan SAJU. Racial differences in the prevalence of overactive bladder in the United States from the epidemiology of LUTS (EpiLUTS) study. 2012;79(1):95-101.
39. Offermans MP, Du Moulin MF, Hamers JP, Dassen T, Halfens RJJN, Society UOJotIC. Prevalence of urinary incontinence and associated risk factors in nursing home residents: a systematic review. 2009;28(4):288-94.

40. Almousa S, van Loon ABJM. The prevalence of urinary incontinence in nulliparous adolescent and middle-aged women and the associated risk factors: A systematic review. 2018;107:78-83.
41. Kaplan S, Dmochowski R, Cash B, Kopp Z, Berriman S, Khullar V. Systematic review of the relationship between bladder and bowel function: implications for patient management. International journal of clinical practice. 2013;67(3):205-16.
42. de Mattos Lourenco TR, Matsuoka PK, Baracat EC, Haddad JMJIuj. Urinary incontinence in female athletes: a systematic review. 2018;29(12):1757-63.
43. Danforth KN, Shah AD, Townsend MK, Lifford KL, Curhan GC, Resnick NM, et al. Physical activity and urinary incontinence among healthy, older women. 2007;109(3):721-7.
44. Nygaard I, Girts T, Fultz NH, Kinchen K, Pohl G, Sternfeld BJO, et al. Is urinary incontinence a barrier to exercise in women? 2005;106(2):307-14.
45. Dallosso H, McGrother C, Matthews R, Donaldson M, international LMISGJB. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. 2003;92(1):69-77.
46. Ewings P, Spencer S, Marsh H, O'Sullivan M. Obstetric risk factors for urinary incontinence and preventative pelvic floor exercises: cohort study and nested randomized controlled trial. Journal of obstetrics and gynaecology. 2005;25(6):558-64.
47. Townsend MK, Danforth KN, Rosner B, Curhan GC, Resnick NM, Grodstein FJTJou. Physical activity and incident urinary incontinence in middle-aged women. 2008;179(3):1012-7.
48. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. Cmaj. 2006;174(6):801-9.
49. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. Applied physiology, nutrition, and metabolism. 2010;35(6):725-40.
50. Averbeck MA, Madersbacher H. Constipation and LUTS - how do they affect each other? Int Braz J Urol. 2011;37(1):16-28.
51. Carter D, Beer-Gabel MJIuj. Lower urinary tract symptoms in chronically constipated women. 2012;23(12):1785-9.
52. Maeda T, Tomita M, Nakazawa A, Sakai G, Funakoshi S, Komatsuda A, et al. Female functional constipation is associated with overactive bladder symptoms and urinary incontinence. BioMed Research International. 2017;2017.
53. Cameron A, Fenner DE, DeLancey JO, Morgan DM. Self-report of difficult defecation is associated with overactive bladder symptoms. Neurourology and urodynamics. 2010;29(7):1290-4.
54. Varma MG, Hart SL, Brown JS, Creasman JM, Van Den Eeden SK, Thom DH. Obstructive defecation in middle-aged women. Digestive diseases and sciences. 2008;53(10):2702-9.
55. Møller LA, Lose G, Jørgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. Obstetrics & Gynecology. 2000;96(3):446-51.
56. Soligo M, Salvatore S, Emmanuel AV, De Ponti E, Zoccatelli M, Cortese M, et al. Patterns of constipation in urogynecology: clinical importance and pathophysiologic insights. 2006;195(1):50-5.
57. Ng SC, Chen YC, Lin LY, Chen GDJIJoG, Obstetrics. Anorectal dysfunction in women with urinary incontinence or lower urinary tract symptoms. 2002;77(2):139-45.
58. Zhang W, Song Y, He X, Huang H, Xu B, Song JJN, et al. Prevalence and risk factors of overactive bladder syndrome in Fuzhou Chinese women. 2006;25(7):717-21.
59. ABREU GEd, DOURADO ER, ALVES DdN, ARAUJO MQd, MENDONÇA NSP, BARROSO JUNIOR UJAdg. Functional constipation and overactive bladder in women: a population-based study. 2018;55:35-40.
60. Varma MG, Wang JY, Berian JR, Patterson TR, McCrea GL, Hart SL. The constipation severity instrument: a validated measure. Diseases of the colon & rectum. 2008;51(2):162-72.
61. Thompson WG. The road to Rome. Gastroenterology. 2006;130(5):1552-6.
62. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. Journal of gastrointestinal and liver diseases. 2006;15(3):237.

63. Mouzas IA, Fragkiadakis N, Moschandreas J, Karachristos A, Skordilis P, Kouroumalis E, et al. Validation and results of a questionnaire for functional bowel disease in out-patients. BMC Public Health. 2002;2(1):1-8.
64. Shaw M, Talley N, Adlis S, Beebe T, Tomshine P, Healey M. Development of a digestive health status instrument: tests of scaling assumptions, structure and reliability in a primary care population. Alimentary pharmacology & therapeutics. 1998;12(11):1067-78.
65. Drossman DA, Li Z, Toner BB, Diamant NE, Creed FH, Thompson D, et al. Functional bowel disorders. Digestive diseases and sciences. 1995;40(5):986-95.
66. Pizzol D, Demurtas J, Celotto S, Maggi S, Smith L, Angiolelli G, et al. Urinary incontinence and quality of life: a systematic review and meta-analysis. Aging clinical and experimental research. 2020:1-11.
67. Bartoli S, Aguzzi G, Tarricone R. Impact on quality of life of urinary incontinence and overactive bladder: a systematic literature review. Urology. 2010;75(3):491-500.
68. Abrams P, Smith AP, Cotterill NJBi. The impact of urinary incontinence on health-related quality of life (HRQoL) in a real-world population of women aged 45–60 years: results from a survey in F rance, G ermany, the UK and the USA. 2015;115(1):143-52.
69. Ross S, Soroka D, Karahalios A, Glazener CM, Hay-Smith EJC, Drutz HP. Incontinence-specific quality of life measures used in trials of treatments for female urinary incontinence: a systematic review. International Urogynecology Journal. 2006;17(3):272-85.
70. Korda J, Braun M, Engelmann UJDUAA. Sexual dysfunction at urinary incontinence. 2007;46(9):1058-65.
71. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU international. 2008;101(11):1388-95.
72. Patel AS, O'leary ML, Stein RJ, Leng WW, Chancellor MB, Patel SG, et al. The relationship between overactive bladder and sexual activity in women. 2006;32(1):77-87.
73. Caruso S, Brescia R, Matarazzo MG, Giunta G, Rapisarda AMC, Cianci AJU. Effects of urinary incontinence subtypes on women's sexual function and quality of life. 2017;108:59-64.
74. Nilsson M, Lalos O, Lindkvist H, Lalos AJAoegS. How do urinary incontinence and urgency affect women's sexual life? 2011;90(6):621-8.
75. Temml C, Haidinger G, Schmidbauer J, Schatzl G, Madersbacher S. Urinary incontinence in both sexes: prevalence rates and impact on quality of life and sexual life. Neurourology and Urodynamics: Official Journal of the International Continence Society. 2000;19(3):259-71.
76. Bilgic D, Gokyıldız Surucu S, Kizilkaya Beji N, Yalcin O. Sexual function and urinary incontinence complaints and other urinary tract symptoms of perimenopausal Turkish women. Psychology, health & medicine. 2019:1-12.
77. Hansen BL. Lower urinary tract symptoms (LUTS) and sexual function in both sexes. European Urology. 2004;46(2):229-34.
78. Field S, Hilton P. The prevalence of sexual problems in women attending for urodynamic investigation. International Urogynecology Journal. 1993;4(4):212-5.
79. Saiki LS, Meize-Grochowski RJJoWO, Nursing C. Relationship Satisfaction of Intimate Partners of Persons Living With Urinary Incontinence. 2019;46(3):228-34.
80. Oh SJ, Ku JH, Choo MS, Yun JM, Kim DY, Park WHJIJoU. Health-related quality of life and sexual function in women with stress urinary incontinence and overactive bladder. 2008;15(1):62-7.
81. Sako T, Inoue M, Watanabe T, Ishii A, Yokoyama T, Kumon HJIuj. Impact of overactive bladder and lower urinary tract symptoms on sexual health in Japanese women. 2011;22(2):165-9.
82. Althof SE, Rosen RC, ROGATIS LD, Corty E, Quirk F, Symonds T. Outcome measurement in female sexual dysfunction clinical trials. Journal of sex & marital therapy. 2005;31(2):153-66.
83. Rosen RC. Assessment of female sexual dysfunction: review of validated methods. Fertility and sterility. 2002;77:89-93.

84. Felde G, Bjelland I, Hunskaar SJIuj. Anxiety and depression associated with incontinence in middle-aged women: a large Norwegian cross-sectional study. 2012;23(3):299-306.
85. Huang CL-C, Ho C-H, Weng S-F, Hsu Y-W, Wang J-J, Wu M-PJPr. The association of healthcare seeking behavior for anxiety and depression among patients with lower urinary tract symptoms: a nationwide population-based study. 2015;226(1):247-51.
86. Huang CL-C, Wu M-P, Ho C-H, Wang J-JJJoPR. The bidirectional relationship between anxiety, depression, and lower urinary track symptoms: a nationwide population-based cohort study. 2017;100:77-82.
87. Sakakibara R, Ito T, Yamamoto T, Uchiyama T, Yamanishi T, Kishi M, et al. Depression, anxiety and the bladder. 2013;5(3):109-20.
88. Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZSJU. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. 2012;80(1):90-6.
89. Jurášková M, Piler P, Kukla L, Švancara J, Daňsová P, Hruban L, et al. Association between Stress Urinary incontinence and Depressive Symptoms after Birth: the czech eLSpAc Study. 2020;10(1):1-7.
90. Hullfish KL, Fenner DE, Sorser SA, Visger J, Clayton A, Steers WDJIUJ. Postpartum depression, urge urinary incontinence, and overactive bladder syndrome: is there an association? 2007;18(10):1121-6.
91. Goode PS, Burgio KL, Redden DT, Markland A, Richter HE, Sawyer P, et al. Population based study of incidence and predictors of urinary incontinence in black and white older adults. The Journal of urology. 2008;179(4):1449-54.
92. Thom DH, Haan MN, Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age and ageing. 1997;26(5):367-74.
93. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. 2013;42(1):97-110.
94. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom IJBi. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. 2008;101(11):1388-95.
95. Royston P. Multiple imputation of missing values. The Stata Journal. 2004;4(3):227-41.
96. Jackson S, Donovan J, Brookes S, Eckford S, Swithinbank L, Abrams P. The Bristol female lower urinary tract symptoms questionnaire: development and psychometric testing. British journal of urology. 1996;77(6):805-12.
97. Markland A, Chu H, Epperson CN, Nodora J, Shoham D, Smith A, et al. Occupation and lower urinary tract symptoms in women: a rapid review and meta-analysis from the PLUS research consortium. Neurourology and urodynamics. 2018;37(8):2881-92.
98. Foldspang A, Mommsen S, Lam GW, Elving L. Parity as a correlate of adult female urinary incontinence prevalence. Journal of Epidemiology & Community Health. 1992;46(6):595-600.
99. Brown RT, Diaz-Ramirez LG, Boscardin WJ, Lee SJ, Steinman MA. Functional impairment and decline in middle age: a cohort study. Annals of internal medicine. 2017;167(11):761-8.
100. Rowland TW. Effects of obesity on aerobic fitness in adolescent females. American Journal of Diseases of Children. 1991;145(7):757-62.
101. Singh S, Kaur R, Singh S. Relationship of parity and health related quality of life among women. Human Biology Review. 2015;4(2):159-66.
102. Gidlow C, Johnston LH, Crone D, Ellis N, James D. A systematic review of the relationship between socio-economic position and physical activity. Health education journal. 2006;65(4):338-67.
103. Gallagher P, O'Mahony D. Constipation in old age. Best Practice & Research Clinical Gastroenterology. 2009;23(6):875-87.

104. Silveira EA, Ribeiro JN, Noll M, dos Santos Rodrigues AP, de Oliveira C. Prevalence of constipation in adults with obesity class II and III and associated factors. BMC gastroenterology. 2021;21(1):1-10.
105. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC gastroenterology. 2008;8(1):1-7.
106. Kepenekci I, Keskinkilic B, Akinsu F, Cakir P, Elhan AH, Erkek AB, et al. Prevalence of pelvic floor disorders in the female population and the impact of age, mode of delivery, and parity. Diseases of the Colon & Rectum. 2011;54(1):85-94.
107. Fatton B, De Tayrac R, Costa PJNRU. Stress urinary incontinence and LUTS in women—effects on sexual function. 2014;11(10):565.
108. Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lizza E, et al. Epidemiology/risk factors of sexual dysfunction. The journal of sexual medicine. 2004;1(1):35-9.
109. Rabiepoor S, Khalkhali H, Sadeghi E. What kind of sexual dysfunction is most common among overweight and obese women in reproductive age? International Journal of Impotence Research. 2017;29(2):61-4.
110. Luft MJ, Dobson ET, Levine A, Croarkin PE, Strawn JR. Pharmacologic interventions for antidepressant-induced sexual dysfunction: A systematic review and network meta-analysis of trials using the Arizona sexual experience scale. CNS spectrums. 2021:1-43.
111. Rhee SJ, Kim EY, Kim SW, Kim SH, Lee HJ, Yoon DH, et al. Longitudinal study of the relationship between lower urinary tract symptoms and depressive symptoms. Journal of Psychosomatic Research. 2019;116:100-5.
112. McCool ME, Zuelke A, Theurich MA, Knuettel H, Ricci C, Apfelbacher CJSmr. Prevalence of female sexual dysfunction among premenopausal women: a systematic review and meta-analysis of observational studies. 2016;4(3):197-212.
113. Hayes RD, Dennerstein L, Bennett CM, Sidat M, Gurrin LC, Fairley CK. Risk factors for female sexual dysfunction in the general population: Exploring factors associated with low sexual function and sexual distress. The journal of sexual medicine. 2008;5(7):1681-93.
114. Mokate T, Wright C, Mander T. Hysterectomy and sexual function. British Menopause Society Journal. 2006;12(4):153-7.
115. Castelo-Branco C, Blumel J, Araya H, Riquelme R, Castro G, Haya J, et al. Prevalence of sexual dysfunction in a cohort of middle-aged women: influences of menopause and hormone replacement therapy. Journal of Obstetrics and Gynaecology. 2003;23(4):426-30.
116. Sobczak JA. Alcohol use and sexual function in women: A literature review. Journal of Addictions Nursing. 2009;20(2):71-85.
117. Garcia-Esteve Ls, Ascaso C, Ojuel J, Navarro P. Validation of the Edinburgh postnatal depression scale (EPDS) in Spanish mothers. Journal of affective disorders. 2003;75(1):71-6.
118. McCabe-Beane JE, Segre LS, Perkhounkova Y, Stuart S, O'Hara MW. The identification of severity ranges for the Edinburgh Postnatal Depression Scale. Journal of Reproductive and Infant Psychology. 2016;34(3):293-303.
119. Anthony JC, Petronis KR. Suspected risk factors for depression among adults 18–44 years old. Epidemiology. 1991:123-32.
120. Choi HG, Rhim CC, Yoon JY, Lee SW. Association between hysterectomy and depression: a longitudinal follow-up study using a national sample cohort. Menopause. 2020;27(5):543-9.
121. Renard J, Ballarini S, Mascarenhas T, Zahran M, Quimper E, Choucair J, et al. Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: a prospective, observational study. Infectious diseases and therapy. 2015;4(1):125-35.
122. Dixit AR, Crum RM. Prospective study of depression and the risk of heavy alcohol use in women. American Journal of Psychiatry. 2000;157(5):751-8.
123. Kessler RC, de Jonge P, Shahly V, van Loo HM, Wang PS-E, Wilcox MA. Epidemiology of depression. 2014.

124. Beuke CJ, Fischer R, McDowall J. Anxiety and depression: Why and how to measure their separate effects. Clinical Psychology Review. 2003;23(6):831-48.
125. Reynolds WS, Dmochowski RR, Penson DF. Epidemiology of stress urinary incontinence in women. Current urology reports. 2011;12(5):370.
126. Minassian VA, Stewart WF, Wood GCJO, Gynecology. Urinary incontinence in women: variation in prevalence estimates and risk factors. 2008;111(2):324-31.
127. McCleary L. Using multiple imputation for analysis of incomplete data in clinical research. Nursing Research. 2002;51(5):339-43.
128. Lee KJ, Simpson JA. Introduction to multiple imputation for dealing with missing data. Respirology. 2014;19(2):162-7.
129. Lee KJ, Tilling KM, Cornish RP, Little RJ, Bell ML, Goetghebeur E, et al. Framework for the treatment and reporting of missing data in observational studies: The Treatment And Reporting of Missing data in Observational Studies framework. Journal of clinical epidemiology. 2021;134:79-88.
130. Dyrstad SM, Hansen BH, Holme IM, Anderssen SAJMSSE. Comparison of self-reported versus accelerometer-measured physical activity. 2014;46(1):99-106.
131. Danforth KN, Shah AD, Townsend MK, Lifford KL, Curhan GC, Resnick NM, et al. Physical Activity and Urinary Incontinence Among Healthy, Older Women. Obstetrics & Gynecology. 2007;109(3):721-7.
132. Townsend MK, Danforth KN, Rosner B, Curhan GC, Resnick NM, Grodstein F. Physical activity and incident urinary incontinence in middle-aged women. The Journal of urology. 2008;179(3):1012-7.
133. Dallosso H, McGrother C, Matthews RJ, Donaldson M, Group LMIS. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. BJU international. 2003;92(1):69-77.
134. de Mattos Lourenco TR, Matsuoka PK, Baracat EC, Haddad JM. Urinary incontinence in female athletes: a systematic review. International urogynecology journal. 2018:1-7.
135. Eliasson K, Edner A, Mattsson E. Urinary incontinence in very young and mostly nulliparous women with a history of regular organised high-impact trampoline training: occurrence and risk factors. International Urogynecology Journal. 2008;19(5):687-96.
136. Nygaard IE, Thompson FL, Svengalis SL, Albright JP. Urinary incontinence in elite nulliparous athletes. Obstetrics and Gynecology. 1994;84(2):183-7.
137. Tennstedt SL, Link CL, Steers WD, McKinlay JB. Prevalence of and risk factors for urine leakage in a racially and ethnically diverse population of adults: the Boston Area Community Health (BACH) Survey. American journal of epidemiology. 2008;167(4):390-9.
138. Zhu L, Lang J, Wang H, Han S, Huang J. The prevalence of and potential risk factors for female urinary incontinence in Beijing, China. Menopause. 2008;15(3):566-9.
139. Nygaard I, Girts T, Fultz NH, Kinchen K, Pohl G, Sternfeld B. Is urinary incontinence a barrier to exercise in women? Obstetrics & Gynecology. 2005;106(2):307-14.
140. Almeida M, Barra A, Saltiel F, Silva-Filho A, Fonseca A, Figueiredo E. Urinary incontinence and other pelvic floor dysfunctions in female athletes in B razil: A cross-sectional study. Scandinavian Journal of Medicine & Science in Sports. 2016;26(9):1109-16.
141. Bø K, Mørkved S, Frawley H, Sherburn M. Evidence for benefit of transversus abdominis training alone or in combination with pelvic floor muscle training to treat female urinary incontinence: a systematic review. Neurourology and Urodynamics: Official Journal of the International Continence Society. 2009;28(5):368-73.
142. Ortega M, Kim Y, Hung K, James K, Savitt L, Von Bargen E, et al. Women with chronic constipation have more bothersome urogenital symptoms. Techniques in Coloproctology. 2022;26(1):29-34.
143. Charach G, Greenstein A, Rabinovich P, Groskopf I, Weintraub M. Alleviating constipation in the elderly improves lower urinary tract symptoms. Gerontology. 2001;47(2):72-6.

144. Chase J, Homsy Y, Siggaard C, Sit F, Bower W. Functional constipation in children. The Journal of urology. 2004;171(6 Part 2):2641-3.
145. Oh SJ, Ku JH, Choo MS, Yun JM, Kim DY, Park WH. Health-related quality of life and sexual function in women with stress urinary incontinence and overactive bladder. International Journal of Urology. 2008;15(1):62-7.
146. Duralde ER, Rowen TSJSmr. Urinary incontinence and associated female sexual dysfunction. 2017;5(4):470-85.
147. Barber MD, MULLEN KJJCCjom. The impact of stress urinary incontinenceonsexualactivityinwomen. 2005;72(3):225.
148. Asoglu MR, Selcuk S, Cam C, Cogendez E, Karateke AJEJoO, Gynecology, et al. Effects of urinary incontinence subtypes on women's quality of life (including sexual life) and psychosocial state. 2014;176:187-90.
149. Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen C-I, Wein AJJEu. Global prevalence and economic burden of urgency urinary incontinence: a systematic review. 2014;65(1):79-95.
150. Sinclair AJ, Ramsay INJTO, Gynaecologist. The psychosocial impact of urinary incontinence in women. 2011;13(3):143-8.
151. Jha S, Ammenbal M, Metwally MJTjosm. Impact of incontinence surgery on sexual function: A systematic review and meta-analysis. 2012;9(1):34-43.
152. Su CC, Sun BYC, Jiann BPJIJoU. Association of urinary incontinence and sexual function in women. 2015;22(1):109-13.
153. Cox JL, Chapman G, Murray D, Jones PJJoad. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. 1996;39(3):185-9.
154. Timur S, Sahin NH. The prevalence of depression symptoms and influencing factors among perimenopausal and postmenopausal women. Menopause. 2010;17(3):545-51.
155. Bruce D, Rymer J. Symptoms of the menopause. Best practice & research Clinical obstetrics & gynaecology. 2009;23(1):25-32.
156. Nicolson P, Kopp Z, Chapple C, Kelleher CJBjohp. It's just the worry about not being able to control it! A qualitative study of living with overactive bladder. 2008;13(2):343-59.
157. Krystal AD, Preud'homme XA, Amundsen CL, Webster GDJTJou. Detrusor overactivity persisting at night and preceding nocturia in patients with overactive bladder syndrome: a nocturnal cystometrogram and polysomnogram study. 2010;184(2):623-8.
158. Ou M-J, Huang C-C, Wang Y-C, Chen Y-L, Ho C-H, Wu M-P, et al. Depression is a major risk factor for the development of dementia in people with lower urinary tract symptoms: A nationwide population-based study. PloS one. 2019;14(6):e0217984.
159. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas. 2014;79(2):184-90.
160. Awata S, Ito H, Konno M, Ono S, Kawashima R, Fukuda H, et al. Regional cerebral blood flow abnormalities in late-life depression: relation to refractoriness and chronification. 1998;52(1):97-105.
161. Blok BF, Willemsen AT, Holstege GJBajon. A PET study on brain control of micturition in humans. 1997;120(1):111-21.
162. Griffiths DJBbr. Clinical studies of cerebral and urinary tract function in elderly people with urinary incontinence. 1998;92(2):151-5.
163. Holmes AJN, Reviews B. Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. 2008;32(7):1293-314.
164. Griebling TLJTJou. Re: Risk Factors for New-Onset Overactive Bladder in Older Subjects: Results of the Fujiwara-kyo Study. 2013;189(5):1820-.
165. Arborelius L, Owens M, Plotsky P, Nemeroff CBJTJoe. The role of corticotropin-releasing factor in depression and anxiety disorders. 1999;160(1):1-12.
166. Penney KL, Townsend MK, Turman C, Glass K, Staller K, Kraft P, et al. Genome-Wide Association Study for Urinary and Fecal Incontinence in Women. J Urol. 2020;203(5):978-83.

167. Cartwright R, Franklin L, Tikkinen KA, Kalliala I, Miotla P, Rechberger T, et al. Genome-Wide Association Study Identifies Two Novel Loci Associated with Female Stress and Urgency Urinary Incontinence. J Urol. 2021;206(3):679-87.
168. Golding J, Pembrey M, Jones RJP, epidemiology p. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. 2001;15(1):74-87.
169. Wright J, Small N, Raynor P, Tuffnell D, Bhopal R, Cameron N, et al. Cohort Profile: The Born in Bradford multi-ethnic family cohort study. International Journal of Epidemiology. 2012;42(4):978-91.