CHAPTER 1

General introduction
This thesis focused on sexual dysfunction and socio-economic status (SES) in people with type 2 diabetes. Although these issues may seem unrelated at first, they share the feature of often being neglected, overlooked or disregarded in care for people with type 2 diabetes.

Sexual dysfunction is common among men and women with type 2 diabetes. Unfortunately, it is not ‘a sexy topic’ in research and care for people with type 2 diabetes. Prevalence data from the Dutch population is missing, as is information on the needs and preferences for care for sexual problems among people with type 2 diabetes. Moreover, discussing sexual issues in diabetes care appears to be difficult for both patients and care providers until today. A sexual counseling model, called the PLISSIT model, could improve the discussion of sexual problems in diabetes care. This model offers general practitioners (GPs) tools to discuss sexual issues by using a framework for sexual counseling. The effectiveness of the PLISSIT model in primary care has not been studied so far. To overcome the negligence of sexual dysfunction in people with type 2 diabetes, part A of this thesis aimed to address the aforementioned issues among men and women with type 2 diabetes in primary care.

SES has frequently shown to be inversely related to health outcomes in people with type 2 diabetes. For example, hemoglobin A1c (HbA1c) levels have shown to be worse in people with type 2 diabetes of low SES. Although HbA1c is an important metabolic outcome in the treatment of diabetes, differences in HbA1c levels by SES are rarely taken into account in care for people with type 2 diabetes. To put this topic on the agenda for diabetes care, part B of this thesis focused on the association between SES and HbA1c levels in people with type 2 diabetes.

Diabetes

Diabetes mellitus is a chronic disease characterized by high blood glucose levels (hyperglycemia). It is a major health problem, affecting an estimated 422 million adults worldwide in 2014 (1). In the Netherlands, more than 1 million people have diabetes (2). The majority of these people (90%) are diagnosed with type 2 diabetes, previously known as adult-onset or non-insulin-dependent diabetes. In type 2 diabetes, the body becomes less sensitive to insulin (insulin resistance) in combination with a progressively decreased production of insulin by the pancreas due to progressive beta-cell failure (3). Two main risk factors for developing type 2 diabetes are a sedentary (inactive) lifestyle and obesity.
Diabetes-related complications

Type 2 diabetes can lead to various complications and premature death. Micro- and macrovascular damage due to hyperglycemia is one of the major causes for diabetes-related complications. Commonly known complications include cardiovascular disease, neuropathy, nephropathy, and retinopathy (5). A lesser known complication of type 2 diabetes is sexual dysfunction; with erectile dysfunction (ED) most often studied and discussed within clinical practice.

Although it goes beyond the scope of this thesis, it is worth mentioning that not only physiological factors, such as hyperglycemia and hormonal changes, can lead to sexual dysfunction in people with type 2 diabetes. A complex interplay of factors underlie the association between chronic disease and sexual functioning. The psychological impact of the diagnosis and treatment on individual well-being and relationships should not be underestimated. For example, people with a chronic disease often report negative changes in body image and self-esteem. In addition, a chronic disease can become a source of stress for the partner relationship or, for some, a source of growth (6). Partners may become caretakers, thereby changing the relationship dynamic and testing the interpersonal skills of patients and partners. See also Verschuren et al. (6) for a generic conceptual framework on how chronic disease affects sexual functioning.

It is important to mention here that not every sexual problem that is reported by people with type 2 diabetes is a consequence of the disease. Besides the influence of chronic disease on sexual functioning, other factors, such as ageing, depressive symptoms, anxiety, (a history of) sexual abuse, smoking, substance abuse, and relationship quality, can cause sexual dysfunction regardless of a type 2 diabetes diagnosis (7).

PART A: SEXUAL DYSFUNCTION & TYPE 2 DIABETES

Prevalence of sexual dysfunction

One of the first documentations of sexual dysfunction in people with diabetes was by the Persian polymath Avicenna (980-1037), who described “the abnormal appetite and collapse of sexual functions” in men with diabetes (8). Numerous studies on sexual dysfunction in men with diabetes
have been conducted since the 1950s (9-12). Sexual dysfunction in women with diabetes has received considerably less attention. A handful of studies commenced in the 1970s (13-16), but up until today, they are limited by number. Moreover, the literature on the prevalence of sexual dysfunction in men and women is hampered by methodological issues, such as the classification of sexual dysfunction, methods of diagnosis, and characteristics of the population (17). However, it goes beyond the purpose of this introduction to take these limitations into account when providing an overview of the data.

The Diagnostic and Statistical Manual of Mental Disorders (6th edition: DSM-5) identifies the following types of sexual dysfunction among men: erectile disorder (ED), premature ejaculation disorder (PE), delayed ejaculation (DE) and male hypoactive sexual desire disorder (HSDD) (18). Of these disorders, ED is the most frequently studied sexual dysfunction in literature. It is defined as the marked difficulty in obtaining and/or maintaining an erection during sexual activity (17; 18). The prevalence of ED in the general population has been reported to increase with age: from 1-10% in men younger than 40 years, to 20-40% in men of 60-69 years, to even 50-100% in men of 70 years and older (19). In men with type 2 diabetes, a similar pattern has been observed and ED prevalence estimates of up to 85% have been reported (20-26). A second frequently studied disorder in men is PE, which is a pattern of recurrent or persistent ejaculation within 1 minute after vaginal penetration and before the individual wishes (17; 18). PE has been reported to occur within 32-67% of men with type 2 diabetes (22; 27), compared to 8-30% in men of all ages in the general population (19). Prevalence data on DE, which is the marked delay, infrequency or absence in ejaculation (17; 18), is lacking in men with type 2 diabetes. Studies have estimated the prevalence of DE between 1-10% in the general population (19), and DE has been reported to be comorbid with ED in 32.9% of men with newly diagnosed type 2 diabetes (26). The fourth DSM-5 disorder, HSDD, is defined as “the persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity” (17; 18). HSDD has been reported to range between 25-40% in men with type 2 diabetes (20-22), compared to 15-25% among men in the general population (19).

Among women, the DSM-5 identifies the following types of sexual dysfunction: female sexual interest-arousal disorder, female orgasmic disorder, and genito-pelvic pain-penetration disorder. Most studies, however, only report an overall prevalence of female sexual dysfunction, which has been estimated up to 85% among women with diabetes (28), compared to 40-50% in women of the general
population, regardless of age (19). Importantly, female sexual dysfunction estimates will probably be lower when the clinical distress criterion is included (29), but this is not common in literature and the following estimates are without this criterion. The first DSM-5 disorder, female sexual interest-arousal disorder, is defined as a “lack of, or significantly decreased sexual interest or arousal that is manifested by at least three of the following characteristics”, for example absent or decreased interest in sexual activity, sexual thoughts or fantasies, initiation of sexual activity et cetera (17; 18). Among women with diabetes, low sexual desire has been reported between 50-82% and low arousal between 34-68% (30-32), compared to reports of 40-50% of low desire among women of the general population (19). Second, orgasmic problems, defined as the marked delay, infrequency, or absence of orgasm or orgasmic sensations (17; 18), has been estimated between 36-84% in women with type 2 diabetes (30-32), reflecting the similarly widely ranging prevalence estimates in the general population between 10-80% (19). Finally, the DSM-5 definition of genito-pelvic pain-penetration disorder currently includes the previously separate conditions vaginismus (impossible or painful penetration) and dyspareunia (painful intercourse) (17). Data on genito-pelvic pain-penetration disorder are scarce among women with type 2 diabetes, two studies have reported dyspareunia estimates of 10% (32) and 46% (30), compared to highly ranging prevalence estimates in the general population (19).

Consequences of sexual dysfunction

Sexual dysfunction negatively affects the quality of life of people with type 2 diabetes. First of all, people with diabetes have reported to be less satisfied about their sex life than people without diabetes. The prevalence of low sexual satisfaction has been estimated between 27-54% for men (20; 33; 34) and 18-49% for women (33-36). Moreover, men with type 2 diabetes who have ED compared to men without ED: 1) have reported significantly worse health-related quality of life (HRQOL) (37; 38); 2) have reported worse psychological adaption to the diabetes diagnosis (39); 3) more often reported diabetes-specific health-related distress (39); 4) more often reported depressive symptoms (38; 39); and 5) more often reported a decreased quality of sexual life (38). Research on the effects of sexual dysfunction on the HRQOL of women with type 2 diabetes is lacking at the moment. Nonetheless, the high prevalence and negative effects of sexual dysfunction on the HRQOL of people with type 2 diabetes warrant clinical attention.
Talking about sexual dysfunction in primary care

In the Netherlands, diabetes care is predominantly organized in primary care. People with type 2 diabetes generally have three-monthly control visits with the practice nurse and a yearly consultation with their GP. According to the diabetes treatment guideline of the Dutch Society of General Practitioners (NHG), sexual issues should be addressed during this yearly appointment with the GP (40). The GP should explicitly inquire whether the patient experiences sexual problems, including ED, loss of sexual desire, and decreased vaginal lubrication. In addition, the GP should discuss possible treatment options, such as medication adjustment (40).

Despite the instructions in the NHG guidelines, sexual problems appear to be one of the most frequently neglected complications in diabetes care (6). Literature reports to substantiate this are scarce. Two studies have reported that only 8–10% of men with type 2 diabetes had been asked by their doctor about sexual problems (39; 41). Data on women with diabetes are missing, but a global study among 27,500 participants paints a similar picture: only 9% of men and women reported to have been asked by a doctor about sexual health during a routine visit in the last 3 years (42). Interestingly, diabetes has been mentioned by GPs as a main reason or opportunity to discuss sexual issues in primary care (43; 44).

One of the main reasons that sexual problems are often neglected in diabetes care is that both GPs and patients experience difficulties with discussing sexual problems. A survey among GPs identified the following most frequently reported barriers: 1) a lack of training, education, and/or knowledge to discuss sexual issues; 2) difficulty discussing sexual issues when the patient has a different gender than the GP; 3) the patient’s reluctance, reticence, and/or embarrassment to discuss sexual issues; and 4) a lack of time to discuss sexual issues in daily primary care (45). A qualitative study among GPs and practice nurses confirmed these findings, and added that it was also more difficult to discuss sexual issues when patients are of older age, of different ethnicity, and non-heterosexual (46).

On the other hand, it seems that people with type 2 diabetes often do not seek help for their sexual problems (21; 41; 47), even though more than half of men with ED reported a need to discuss sexual issues with their doctor (41). Feelings of embarrassment and being unaware of effective treatment options for ED have been mentioned as barriers to seek help among men with type 2 diabetes (41). Among women, the care provider’s characteristics, such as age, sex, years of
experience, medical specialty, and time and privacy constraints, have been reported as barriers (47). Further, it seemed in one study that men prefer doctors to take initiative to discuss sexual issues (41), while women in one qualitative study were divided about this (47). Importantly, it should be noted that these data on the patient-perspective come from a study in Taiwanese men (41) and a study in Swedish women with type 2 diabetes (47). Data are currently missing on the needs and preferences for care for sexual problems among men and women with type 2 diabetes in the Netherlands.

**Screening**

The discussion of sexual problems and possible care needs seems to be insufficient in diabetes care. It seems to occur infrequently and is hindered by various barriers. It is therefore important that this is overcome, as negligence of sexual problems may only further decrease a person’s quality of life (48). In addition, it is important that people in need for help are identified in time, in order for the treatment of sexual problems to be effective. The use of a screening instrument could facilitate this identification, while simultaneously lowering the threshold for both patients and care professionals to discuss sexual issues in daily practice.

Figure 1 shows the model of the proposed inverse funnel of sexual care needs in (primary) care (49). It is suggested in this figure that not every person with a sexual complaint will also have a DSM-5 or other diagnosable type of sexual dysfunction; and that not every person with a sexual dysfunction will also be dissatisfied about his or her sexual life et cetera. With regard to screening, it would therefore be most effective to screen among sexually dissatisfied people in primary care to quickly identify those people in need for help.
PLISSIT

The use of a sexual counselling model could aid GPs with the discussion of sexual issues with their patients. Over the past few decades, several counseling models have been developed, such as ALARM (50), BETTER (51), and PLISSIT (52). The ALARM model has been designed for interviewing cancer patients about sexual dysfunction. ALARM stands for: Activity (sexual), Libido, Arousal, Resolution and Medical history (50; 53). The BETTER model was also developed for the assessment of sexuality in patients with cancer. BETTER stands for: Bringing up the topic of sexuality, Explaining that sex is an important part of life, Telling patients about, Timing of intervention, Education on side effects of treatment, and Recording discussion content (51; 54). The effectiveness of the ALARM model or the BETTER model has not been studied. The PLISSIT model, however, has shown promising features in women with sexual problems (55-57), stoma patients (58), women with multiple sclerosis (59), and women with cancer (60-62). Moreover, the model has been frequently recommended for health care professionals and for diabetes care professionals specifically (48).
The PLISSIT model was developed by Annon in 1976 as a framework for care providers to assist in the ordering and treatment of sexual problems (52). PLISSIT is an acronym for the four stages of the model: Permission, Limited Information, Specific Suggestions, and Intensive Therapy. The first two steps of the PLISSIT model focus on the invitation to the patient to talk about sexuality and on the normalization of the sexual problem (63). During the first step of the model, Permission, the care provider invites the patient to talk about sexual issues. For example by asking: ‘People with diabetes often experience sexual problems, would it be okay for you if I ask you some questions about this?’ On the one hand, permission refers to explicit permission-giving by the patient to talk about this (yes/no) with the GP. On the other hand, it also refers to implicit permission-giving through the normalization of sexual problems by the care provider (64). The second step, Limited Information, concerns providing general information, for example on the effects of diabetes on sexual function.

Compared to the previous steps, the care provider needs additional skill and knowledge to carry out the third step of the model, Specific Suggestions. In order to provide relevant suggestions, the care provider needs to understand the patient’s particular complaint, which may include taking a sexual history (63). Examples of specific suggestions may include the use of lubricants, lifestyle changes, or medication adjustment. These suggestions are aimed to directly help the patient within a relatively short period of time (63). Since most GPs will not be skilled enough to perform the fourth step of the model, Intensive Therapy, this step will almost always include referring the patient to specialized care. Step four may be applied to complex sexual problems or problems that were not sufficiently helped in the previous steps.

The PLISSIT model thus provides a framework for when referral is appropriate, but most importantly, the model aids the GP with the discrimination between problems for which brief therapy will suffice (step 1–3) and problems needing intensive therapy (step 4) (63). Notably, the use of the model is geared to the GP’s competence, hence allowing the GP to refer patients to other care providers for further treatment during each step.

**Aim of part A of this thesis**

It can generally be concluded from the literature that men and women with type 2 diabetes are often affected by sexual dysfunction and that these problems can have negative consequences for their quality of life. It seemed, however, that most studies so far have been conducted in men with diabetes,
and these studies predominantly focused on erectile dysfunction. Data on the prevalence and effects of sexual problems in women with type 2 diabetes are scarce. Moreover, even though the high prevalence of sexual dysfunction among men and women with type 2 diabetes warrants clinical attention, sexual problems are currently inadequately addressed in primary care. Certain barriers that impede this discussion have been identified, but data on the needs and preferences for care for sexual problems among men and women with type 2 diabetes in the Netherlands are lacking at the moment.

It is important that people with a sexual problem and a need for help are identified in diabetes care. The use of a routine screening instrument might facilitate this, whereby screening among sexually dissatisfied people seems most effective. Yet, data are currently lacking on the prevalence of care needs among sexually dissatisfied people with type 2 diabetes in primary care. After having successfully identified people with type 2 diabetes with a need for help, the use of a sexual counseling model, such as the PLISSIT model, could improve the discussion of sexual issues in diabetes care. Nevertheless, the effectiveness of the PLISSIT model in improving self-reported sexual functioning and quality of life outcomes has not been studied in people with type 2 diabetes in primary care. Therefore, the following research objectives for part A of this thesis were formulated:

1. To study the prevalence and correlates of sexual dysfunction among men and women with type 2 diabetes in the Netherlands.
2. To study the needs and preferences for care for sexual problems among men and women with type 2 diabetes in the Netherlands.
3. To screen for sexual dissatisfaction among men and women with type 2 diabetes in Dutch primary care.
4. To examine the effectiveness of the PLISSIT model in improving sexual functioning, satisfaction with sexual function, and quality of life in men and women with type 2 diabetes in Dutch primary care.
PART B: SOCIO-ECONOMIC STATUS & TYPE 2 DIABETES

Socio-economic status

Socio-economic status (SES) is a commonly studied factor in health research. Extensive research has shown that people of low SES generally have worse health outcomes than people of high SES. For example, differences in health by SES are frequently observed for chronic conditions with high morbidity and mortality rates, such as cancer, diabetes, cardiovascular conditions, and arthritis (65; 66). Though it should be mentioned that this inverse association is not exclusively reported: the burden of disease has also reported to be evenly distributed among SES groups, for example for leukemia (67); or even the other way around: where people of high SES were at higher risk of melanoma carcinoma compared to people of low SES (68).

SES is ideally studied as composite measure that includes a person’s social status, economic status, and work status, for example by measuring level of education, income and occupation (65; 69). It can be a measure of childhood, adolescent, adult, or life course SES, assessed on an individual, household or regional level. SES indicators are interrelated and can overlap to a certain extent, for example a person’s educational level (partially) determines his level of occupation and income (70; 71). Importantly, SES indicators are not completely interchangeable. It is therefore recommended to study various SES indicators as each indicator may provide specific insight into the effects of SES on health (67). Yet, most studies on differences in health outcomes by SES often study just one or two SES indicators, such as individual level of education and income. SES indicators that are measured on other levels than individual level, such as partner SES, or indicators representing a different SES status, such as occupation, are less often studied. As SES is a complex construct and its association with health is not yet fully understood, research on the association between SES and health outcomes could be improved by taking into account other aspects of SES, such as partner SES and occupational status.

SES & type 2 diabetes

Differences in health outcomes by SES in people with type 2 diabetes have been identified in all stages of the disease: from pre-diabetes to disease progression to death. It was shown in a meta-analysis from 2011 that three indicators of low versus high SES were associated with an overall increased risk of type 2 diabetes, respectively education (41%), income (40%), and occupation (31%)
Low SES has also been associated with inequalities in diabetes care: important metabolic parameters were less often assessed, and metabolic targets seem to be less often achieved in people with type 2 diabetes of low SES, compared to those of high SES (73). Furthermore, low SES has been associated with an increased risk of both diabetes-related and all-cause mortality in people with type 2 diabetes (74).

The exact pathways through which SES affects health outcomes in people with type 2 diabetes are yet to be elucidated. Brown et al. developed a conceptual framework that might aid with this (see Figure 2) (71). According to this framework, low SES may affect diabetes-related health outcomes via certain factors that can act as moderators and/or mediators in the association between SES and health. These factors are distinguished between proximal and distal factors. Proximal factors include individual health behaviors, access to care, and processes of care. For example, people of low SES with type 2 diabetes monitor their blood glucose less frequently, more often smoke, and less often exercise than people of high SES (71). Distal factors include characteristics of the individual, care provider, health care system, and neighborhood. For example, people of low SES with type 2 diabetes are more often health illiterate\(^1\), have poor patient-provider communication skills, and are more often experiencing stress than people of high SES (71). It is recommended by Brown et al. that critical covariates, such as age, sex, and ethnicity, are taken into account when studying this association (71).

Importantly, this framework provides insight for clinical practice into which factors could be targeted in health interventions that pay attention to SES differences in people with type 2 diabetes. As SES itself is rather static and robust to directly intervene on, an intervention could be tailored to low SES groups by focusing on moderating and mediating factors that seem susceptible to change, for example individual health behaviors, such as glucose monitoring, smoking, and physical activity, or individual characteristics, such as patient-provider communication, mental health, social support, and health literacy (71).

\(^1\) health literacy= “the ability to perform basic reading and numerical tasks required to function in the health care environment” 75. Association M: Health Literacy: Report of the Council on Scientific Affairs. JAMA 1999;281
Hemoglobin A1c (HbA1c) is an important metabolic parameter in diabetes care. It reflects the average blood glucose concentration over the past 2-3 months (1). Since fasting and 2-hour glucose measurements of the blood are variable, HbA1c is used in diabetes care as a target for treatment and to monitor disease status. According to the diabetes treatment guideline by the Dutch Society of General Practitioners (NHG), good glycemic control is defined as an HbA1c below 7.0% or 53 mmol/mol. In people of older age and/or with a longer diabetes duration, this target is advised to be less stringent (40).

For people with type 2 diabetes, achieving good glycemic control is important for the prevention of micro- and macrovascular diabetes-related complications (76). However, there appears to be an inverse association between SES and HbA1c levels in people with type 2 diabetes: people of low SES seem to have significantly higher HbA1c levels than people of high SES. This warrants attention in clinical practice, but SES is often not taken into account or overlooked in interventions that aim to improve glycemic outcomes, or other diabetes-related outcomes for that matter. Yet, interventions that
do take SES into account, seem to be more effective than usual care. For example a recent meta-analysis by Kim et al., showed that diabetes self-management interventions that took the health literacy of patients into account, resulted in significantly lower HbA1c levels compared to usual care (77).

So far, the literature on SES and HbA1c levels in people with type 2 diabetes has not been pooled or weighted for risk of bias. Moreover, reviews that have been conducted on this association included people with both type 1 and type 2 diabetes (73; 78), while the effects of SES in people with type 1 diabetes may be different from people with type 2 diabetes, as this is a different disease and a different patient population. To put SES as a topic on the agenda of diabetes care, it is important that the evidence on the association between SES and HbA1c levels is systematically summarized among people with type 2 diabetes.

**Aim of part B of the thesis**

Differences in HbA1c levels by SES have been identified among people with type 2 diabetes. So far, these differences have not been quantified, nor weighted for risk of bias. Although the reported differences in HbA1c levels between people of high and low SES warrant clinical attention, SES is not a hot topic on the agenda of diabetes care. Moreover, other SES indicators than individual level of education or income, are infrequently studied. It is important to study various SES indicators, as each indicator can provide a specific insight into the association between SES and health. Therefore, the following **research objectives for part B of this thesis** were formulated:

1. To systematically summarize the difference in HbA1c levels between people with type 2 diabetes of high and low SES in a systematic review.
2. To quantify the difference in HbA1c levels between people with type 2 diabetes of high and low SES in a meta-analysis.
3. To study the effects of individual level and partner’s level of occupation on HbA1c levels in people with type 2 diabetes.

**Outline of the thesis**

Following this general introduction (Chapter 1), **part A of this thesis will describe the results of the studies that focused on sexual dysfunction in people with type 2 diabetes. Chapter 2 will describe the**
results from a cross-sectional survey on the prevalence and correlates of sexual dysfunction in people with type 2 diabetes in the Netherlands. **Chapter 3** focuses on the results that were retrieved from a cross-sectional survey and qualitative interviews that were conducted to study the needs and preferences for care for sexual problems among men and women with type 2 diabetes in the Netherlands. **Chapter 4** describes the design of the RCT that was conducted to study the effectiveness of the PLISSIT model in improving sexual functioning, sexual satisfaction, and quality of life in people with type 2 diabetes in Dutch primary care. In **Chapter 5**, the results from the routine screening for sexual dissatisfaction in people with type 2 diabetes in Dutch primary care are reported. Finally, the results from the RCT on the effectiveness of the PLISSIT model are reported in **Chapter 6**.

**Part B** of this thesis will describe the results of the studies that focused on SES in people with type 2 diabetes. **Chapter 7** describes the results from a systematic review and meta-analysis that were conducted to study the association between SES and HbA1c levels in people with type 2 diabetes. In **Chapter 8**, the results are reported from a cross-sectional study in the Dutch Diabetes Pearl cohort on the association between individual level and partner’s level of occupation on HbA1c levels in people with type 2 diabetes. Finally, in **Chapter 9**, the main results of thesis are summarized and discussed in a broader perspective.
REFERENCES

29. Hayes RD, Dennerstein L, Bennett CM, Fairley CK: What is the “true” prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? J Sex Med 2008;5:777-787
60. Chun N: [Effectiveness of PLISSIT model sexual program on female sexual function for women with gynecologic cancer]. J Korean Acad Nurs 2011;41:471-480
