CHAPTER 1

General introduction.
“When I think back, most of my symptoms started when I was in my twenties. Muscle pains, bowel problems, fatigue… I went to the doctor, he did some tests, but all results came back normal. So I moved on and tried to ignore my symptoms. Until they got worse and worse. At the age of 35 I was in so much pain that I was not able to work or to take care of my children anymore. So I resumed my search and tried everything: I visited medical specialists, physiotherapists, psychologists and alternative healers. I spent lots of time and money on offered therapies. But nothing worked. I still did not know what was wrong with me. At a certain point my family even got tired of my quest. I felt hopeless. How to get a grip on this unexplained illness?”

Female MUPS patient, 55 years old

**Medically Unexplained Physical Symptoms**

Our current medical practice is based on a “disease model”: the primary role of the doctor is to determine whether presented symptoms match diagnostic criteria of physical or mental disease, and if so, to offer fitting treatment if needed (Sharpe, 2013). However, in all health care settings patients present with physical symptoms such as fatigue, dizziness and pain, for which no sufficient explanation can be found after thorough medical examination. Such symptoms are called medically unexplained physical symptoms (MUPS). MUPS are very common. In primary care, around 30% of the symptoms that patients present to their general practitioner (GP) are unexplained (Jackson and Passamonti, 2005; Rosendal et al., 2015). In specialist care, up to 70% of the presented symptoms are unexplained, depending on the specialty (Nimnuan et al., 2001; Reid et al., 2002). Most MUPS are transient and mild, with minimal influence on daily life. Of all MUPS presented to the general practitioner, 80% leads to only one consultation (van der Linden et al., 2004). However, up to 20-30% of patients develop persistent symptoms, which can be severe and disabling (Jackson and Passamonti, 2005; Verhaak et al., 2006).

Patients with persistent MUPS have a higher risk of psychosocial disability and experience more psychological distress than patients with explained physical symptoms (de Waal et al., 2004). MUPS patients are often dissatisfied with received medical care, mainly because they have the feeling that doctors do not take them seriously (Malterud, 2000; Page and Wessely, 2003). At the same time, physicians may feel powerless, due to the lack of clear cut explanations for the symptoms (Woivalin et al., 2004). Patients with MUPS are often exposed to unnecessary (and ineffective) diagnostic procedures and medication (Katon and Walker, 1998; Olde Hartman et al., 2004; Smith et al., 1986). Several studies showed that outpatient and inpatient medical care utilization of MUPS patients is at least twice as high, compared to that of patients with explained symptoms.
(Barsky et al., 2005; Hiller et al., 2003). As a consequence, persistent MUPS are associated with high health care costs. Total MUPS related costs are even higher due to work and insurance related costs (Bermingham et al., 2010; Konnopka et al., 2012). It is estimated that 30% of long term absence of work is caused by MUPS (Brenninkmeijer et al., 2006). Summing up, we can conclude that persistent MUPS have extensive personal and societal consequences.

**Classification of MUPS**

As MUPS can be very diverse in nature and severity, there has been a scientific discussion about terminology and classifications for a long time (Barsky and Borus, 1999; Creed et al., 2010; Fink and Schröder, 2010; Sharpe and Carson, 2001; Voigt et al., 2010). Many concepts have been proposed to distinguish the group of patients with problematic MUPS from the greater majority with self-limiting symptoms. In Western medicine symptoms are considered to be caused by either physical or mental pathology (Creed et al., 2010; Mayou et al., 2005). This dualistic thinking is still reflected by current MUPS classifications: in somatic medicine various specialism-specific functional somatic syndromes are described (Wessely and White, 2004), while in psychiatry, classifications such as somatoform disorders (DSM-IV) are used. Both will be discussed below.

**Somatic medicine**

Many medical specialties have their own functional (and thus medically unexplained) somatic syndrome. Examples include Irritable Bowel Syndrome (IBS, Gastroenterology), Chronic Fatigue Syndrome (CFS, Internal Medicine) and Fibromyalgia (FM, Rheumatology). Criteria for these syndromes include organ tract specific symptoms (e.g. abnormal stool passage in IBS or pain at specific tender points in FM), but also a number of general symptoms (e.g. fatigue). The advantage of these organ tract specific diagnoses is that they are compatible with our medical care organisation: the syndromes can be diagnosed and treated by individual medical specialists. However, several researchers have demonstrated considerable overlap between functional syndromes: patients with one syndrome often also meet the criteria for other syndromes (Aaron, Leslie A., Buchwald, 2001; Hamilton et al., 2009; Sullivan et al., 2002; Yunus, 2007). In other words: MUPS may sometimes overarch the level of individual organ tracts.

**Psychiatry**

In psychiatry, mental disorders are categorized using the Diagnostic and Statistical Manual of Mental Disorders (DSM). In the DSM-IV TR (the second last edition) MUPS were described in the somatoform disorder section (American Psychiatric Association, 2000). The most prevalent somatoform disorder was the undifferentiated somatoform disorder. This disorder category included all patients with one or more impairing physical symptoms lasting longer than 6 months. Critics stated that the diagnosis was useless due to the lack of psychological criteria. They believed that a psychiatric diagnosis could only be justified if the diagnostic criteria would include psychological symptoms (Rief and Isaac, 2007).
In 2013 the DSM 5 was introduced (American Psychiatric Association, 2013). In this new edition, the somatoform disorders are replaced by the somatic symptom disorder, consisting of a new set of criteria including psychological ones (namely health related anxiety, excessive thoughts about symptoms and/or excessive time and energy devoted to them). Impairing physical symptoms are still part of the core criteria, however, they no longer have to be medically unexplained. Although the new criteria may seem to be an improvement, they have also been criticised as being clinically unhelpful (Mayou, 2014). As symptoms no longer have to be unexplained, the disorder may cover an extremely heterogeneous group of patients, including patients with health anxiety or illness thoughts due to explained diseases (Rief and Martin, 2014). In addition, it may be rather difficult to objectively determine when illness thoughts or behaviours can be labelled as “excessive”. In order to evaluate whether the critics are right, it is necessary to apply the old and new diagnostic criteria in relevant populations and to compare them.

**Research question**

What is the clinical value of the newly introduced DSM 5 diagnostic criteria (including psychological symptoms), compared to the old DSM IV criteria, in a MUPS population?

**This thesis**

We choose to use the term ‘MUPS’ throughout this thesis, as it is the most neutral description of the entire spectrum of unexplained physical symptoms. This choice is in line with the Dutch ‘Multi-disciplinary Guideline for MUPS and Somatoform Disorders’ and the Dutch national guideline for GPs about MUPS (Landelijke Stuurgroep, 2011; Dutch College of GPs, 2013).

**Course of MUPS**

As clinical uncertainty and body-mind dualism in Western medicine create challenges in classification of MUPS based on symptom characteristics, more recently an alternative classification method has been proposed: classification based on prognosis. Prognosis-based classification aims to categorise the patient’s risk of ongoing symptoms, complications, increased healthcare use or disability because of the symptoms (Rosendal et al., 2017). It can improve decision making in clinical practice as it supports clinicians in offering treatment to those patients at risk for an adverse course (and not to those patients with self-limiting symptoms), regardless of the presence or absence of symptom explanations. However, for this prognosis-based classification, the identification of evidence-based prognostic subgroups (course trajectories) is essential.

In a systematic review, Olde Hartman et al. summarized six cohort studies assessing the course of MUPS in several health care settings (Olde Hartman et al., 2009). They found that although approximately 50% of patients improve or recover completely, the symptoms of 10-30% of patients with MUPS deteriorate or become chronic. However, heterogeneity and methodological flaws of the
included studies hampered the reliability of their findings. Duration of follow-up was generally short (6 to 15 months) and duration of symptoms at baseline was often unknown. Since the publication of this systematic review several additional studies have been performed, both in general populations as in primary care (Budtz-Lilly et al., 2015; Creed et al., 2012; Koch et al., 2009; Steinbrecher and Hiller, 2011). Results differed from Olde Hartman’s, as in these studies even 43 to 68% of participants had persistent symptoms after 1 year (Creed et al., 2012; Koch et al., 2009; Steinbrecher and Hiller, 2011) or 2 years (Budtz-Lilly et al., 2015) of follow-up.

Although the described studies provide some information about the course of MUPS, several aspects still need to be elucidated. First, very little is known about the course of MUPS related disability, which is a very important aspect of MUPS prognosis. Out of all studies mentioned above, only 1 study assessed the course of physical and mental functioning in a population of patients with various forms of MUPS (showing slight improvement in both physical and mental functioning over 1 year of follow-up) (Creed et al., 2012). Secondly, all mentioned studies only assessed outcomes at baseline and at one single follow-up moment, therefore knowledge about stability of improvements or deteriorations is currently lacking.

We can conclude that the body of high quality evidence about the long term course of MUPS is very small. In order to make the proposed prognosis based categorisation possible, it is necessary to expand knowledge about the course of symptoms and functional status in MUPS populations.

**Research question**

Can we identify (demographic, psychological, behavioural and biological) factors, which are related to the course of MUPS?

**Predictors of the course of MUPS**

As we know very little about the course of MUPS, it may come as no surprise that there is also limited evidence about factors that predict or influence this course. Several studies aimed to identify factors that predict an adverse course of MUPS. A higher number and a longer duration of symptoms at baseline repeatedly emerged as predictors (de Gucht et al., 2004; Kooiman et al., 2004; Speckens et al., 1996b). Female sex was also reported as a predictor in some studies (Leiknes et al., 2006; Speckens et al., 1996b), but others did not confirm these findings (Carson et al., 2003). Studies evaluating the role of affective disorders showed conflicting results (de Gucht et al., 2004; Kooiman et al., 2004; Speckens et al., 1996b; Steinbrecher and Hiller, 2011). Olde Hartman concluded that the body of evidence is currently too small to draw conclusions about relevant predicting factors (Olde Hartman et al., 2009).
**General introduction**

**Theoretical models of MUPS**

In addition to the described empirical studies (mainly assessing the predictive value of demographic and symptom-related factors), literature provides a wide range of theoretical models aiming to explain which factors influence the development and persistence of MUPS. The cognitive behavioural model (which forms the basis of CBT) is seen as a meta-model, incorporating many of these theories (Deary et al., 2007; van Ravenzwaaij et al., 2010). It embodies various elements, including somatic causes, illness predispositions, illness perceptions and illness behaviours.

One of the theories within the cognitive behavioural model is the ‘sensitivity theory’. This theory assumes that some individuals are more vulnerable to develop or maintain physical symptoms than others. Factors that have been found to be related to this vulnerability are personality traits, such as neuroticism, catastrophic thinking and traumatic experiences in early childhood (van Ravenzwaaij et al., 2010). A second theory is the ‘somatosensory amplification theory’, which states that a physical sensation can lead to increased attention to this sensation, which in turn can lead to (faulty) attributions and cognitions about it. This creates a vicious circle, as it amplifies the symptom perception (Barsky and Wyshak, 1990). A third theory is the ‘response to illness theory’, which states that one’s response to symptoms influences their course and that ‘all or nothing’-coping strategies and avoidance behaviours may play an important role in the onset and perpetuation of MUPS (Deary et al., 2007). A final example of a theory is based on the fact that stress (physical or psychological) influences the bodily hormonal stress system: the hypothalamic pituitary adrenal axis (HPA axis). Prolonged stress may lead to HPA axis down regulation and reduced production of cortisol, a stress hormone. As a result stress sensitivity increases (Fries and Hesse, 2005), which may lead to persistence of symptom. This last theory reflects the interplay between body and mind and may therefore provide a concrete link between psychological burden and physical symptoms.

Although the cognitive behavioural model forms the basis for various MUPS therapies, it is unknown which of the incorporated theoretical elements are actually related to persistence or recovery of MUPS. Identification of relevant theoretical elements that predict the course of MUPS would create possibilities to strengthen prognostic categorisation. Additionally, it would also identify possible effective treatment elements.

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**Research question**

What is the effectiveness of currently available non-pharmacological treatments of MUPS? And what is optimal clinical practice in MUPS management based on current literature?
MUPS treatment
Both Dutch national MUPS guidelines provide concise recommendations for the management of patients with MUPS (Landelijke Stuurgroep, 2011; Dutch College of GPs, 2013). They suggest a tailored approach: treatment choices depend on the severity of MUPS. The GP should manage mild MUPS, with a favourable prognosis, by providing patient education and addressing somatic, cognitive, emotional, behavioural and social factors that may inhibit symptom recovery. Moderate MUPS, with a more adverse prognosis, should be treated in collaboration with other health care workers in primary care, such as psychologists or physiotherapists. Patients with severe MUPS, who are at great risk for chronicity, should be referred to multidisciplinary treatment settings in secondary and tertiary care. This tailored approach is based on recommendations by experts in the field of MUPS (Henningsen et al., 2007).

Although the guidelines provide clear recommendations about the choice of therapists, recommendations about the type of treatment are ill-defined. This is due to the limited body of evidence about effective MUPS treatments. Pharmacological treatments are currently not recommended as only low to very low quality evidence is available for the effectivity of new generation antidepressants (such as selective serotonin reuptake inhibitors) and natural products (such as St. John's worth), while side effects of these agents are common (Kleinstäuber et al., 2014). When it comes to specific non-pharmacological therapies, several literature reviews have been performed (Edwards et al., 2010; Kleinstäuber et al., 2011; Rosendal et al., 2013; Sumathipala, 2007). They showed effectiveness of some specific interventions, especially of Cognitive Behavioural Therapy (CBT), which focuses on addressing or changing cognitions and behaviours related to the symptoms that people experience. However, characteristics of populations (e.g. duration, type and severity of symptoms) and characteristics of investigated treatments (e.g. content and duration of treatment sessions and performing therapists) varied widely in the investigated studies. In addition, as the described reviews only concerned specific of interventions or specific MUPS subgroups, a complete overview of all non-pharmacological interventions within MUPS populations is lacking.

The PROSPECTS study
We started a prospective cohort study on course and prognosis of MUPS: the PROSPECTS study. In this study, we defined MUPS as physical symptoms, which had lasted at least several weeks and for which no sufficient explanation was found after proper medical examination. MUPS patients (18-70 years old) from various health care settings (primary, secondary and tertiary care) were included and monitored at predefined intervals. Patients received questionnaires in order to evaluate the course of their physical symptoms and functional status. Additionally, they completed questionnaires about potential predictors of the course of MUPS, based on the mechanisms suggested in theoretical literature. Examples of these potential predictors are (health) anxiety, depression, illness thoughts and behaviours, coping style, life events, personality, positive affect and physical activity. In order to assess the relation between MUPS and bodily stress, saliva samples were collected in order to assess cortisol levels. We used data collected at baseline, and at 6, 12 months and 24 months of follow-up to answer most of the research questions as described below.
Outline of this thesis
In line with the text boxes in the introduction, we aimed to answer the following research questions:

1. What is the clinical value of the newly introduced DSM 5 classification criteria (including psychological symptoms), compared to the old DSM IV criteria, in a MUPS population?
2. What is the course of MUPS in terms of severity of symptoms and functional status? Can we identify different course types (trajectories)?
3. Can we identify (demographic, psychological, behavioural and biological) factors, which are associated to MUPS severity and course of MUPS?
4. What is the effectiveness of currently available non-pharmacological treatments of MUPS?
5. What is optimal clinical practice in MUPS management based on current literature?

Figure 1 summarizes the outline of this thesis. In chapter 2 the study design of the PROSPECTS study is presented; our prospective cohort study on course and influencing factors of MUPS. In the subsequent chapters data of the PROSPECTS study are used to answer the research questions. In chapter 3 we assess the clinical value of the newly introduced DSM 5 classification criteria (including psychological symptoms), compared to the old DSM IV criteria, using baseline data of the PROSPECTS study. In chapter 4 we study the course of symptoms in terms of symptom severity and functional impairment, by identifying various course types. In chapter 5 we assess the relation of a biological factor, salivary cortisol, with the severity of MUPS and functional impairment. Chapter 6 provides results of a qualitative analysis of patients’ views on factors contributing to MUPS improvement. In chapter 7 prediction models for the course of MUPS are developed and tested in order to identify demographic, psychological and behavioural factors related to favourable an adverse course types. Chapter 8 is a condensed version of a Cochrane systematic review of non-pharmacological treatments of MUPS and somatoform disorders in adults. In chapter 9 the results of this review and reviews of other MUPS treatments (e.g. pharmacological interventions) are summarized in order to provide clinicians with an overview of the most optimal treatment options. The final chapter, chapter 10, discusses the main findings of this thesis and gives an overview of the clinical and scientific consequences of our study results.
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**General discussion: chapter 10**

*Figure 1: Outline of this thesis.*