CHAPTER 2

The PROSPECTS study: design of a prospective cohort study on prognosis and perpetuating factors of Medically Unexplained Physical Symptoms (MUPS).

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The PROSPECTS study
Abstract

Objective:
This paper describes the rationale and methodology of the PROSPECTS study, a study which aims to assess the course and prognosis of medically unexplained physical symptoms (MUPS), in terms of symptom severity and physical and social functioning. Additionally, it aims to identify different course types and to determine which factors are associated with these course types. Based on these factors, one or more prediction models will be developed.

Methods
This study is a prospective, multicenter longitudinal cohort study with 1 baseline and 4 follow-up measurements during a 3 year period. 450 MUPS patients (age 18-70 years) will be included, divided over a primary care group, recruited in general practices, and a secondary / tertiary care group, recruited in specialized MUPS care programmes.

Main study parameters/endpoints
Primary outcome measures are severity of symptoms and degree of functional impairment. Secondary outcome measures are health care consumption and level of depressive symptoms and anxiety. Potential predictors are based on current theoretical models describing the perpetuation of MUPS and include somatic, psychological and social factors. Latent class growth mixture modeling will be used to identify distinct course types. Logistic regression analysis will be used to identify risk factors associated with these course types. Finally, one or more multivariate prediction models for the course of MUPS will be developed and tested.

Conclusion
The PROSPECTS study aims to enhance our insight into the course of MUPS, thus contributing to better recognition of future patients at risk for persistent MUPS.
Background
In all health care settings patients present with physical symptoms, such as fatigue, dizziness and pain, for which no sufficient somatic explanation is found after proper medical examination. Such symptoms are called medically unexplained physical symptoms (MUPS). MUPS are very common, especially in primary care. Around 25-50% of the complaints that patients present to their general practitioner (GP) remains unexplained (Barsky and Borus, 1995). Fortunately, almost 80% of these episodes remain restricted to one doctor-patient contact (van der Linden et al., 2004), indicating that most MUPS may be self-limiting. However, around 20-30% of patients develop persisting symptoms, which can be severe and disabling (Jackson and Passamonti, 2005; Verhaak et al., 2006).

Due to the variation in presentation and duration, MUPS can be regarded as a continuum ranging from mild (and often self-limiting) symptoms, to chronic severe symptoms, which are also seen in functional somatic syndromes such as Irritable Bowel Syndrome and Chronic Fatigue Syndrome. At the severe end of the continuum, symptoms are often more numerous and psychiatric co-morbidity often occurs (Landelijke Stuurgroep, 2011). The diversity in the nature and severity of symptoms creates challenges in defining and describing the various forms of MUPS (Carson et al., 2003). In this study we choose to use the term ‘MUPS’ as a general description of the entire spectrum of physical symptoms, which last at least several weeks, and for which no sufficient explanation can be found after proper medical examination. This is in line with the recently published Dutch ‘Multidisciplinary Guideline for MUPS and Somatoform Disorders’ (Landelijke Stuurgroep, 2011) and gives a neutral description of the patient’s symptoms, without suggesting a (physical or psychological) causal explanation.

Costs and societal relevance of MUPS
Patients with persistent MUPS have great risk of functional impairment and experience high levels of psychological distress (Escobar and Burnam, 1987; Gureje et al., 1997; Zoccolillo and Cloninger, 1986). Additionally, persistent MUPS are associated with high costs (Konnopka et al., 2012). It is known that MUPS patients are often exposed to unnecessary diagnostic procedures and may use superfluous medication (Katon and Walker, 1998; Kroenke and Mangelsdorff, 1989; Smith et al., 1986). Outpatient and inpatient medical care utilization is approximately twice as high in patients suffering from severe MUPS, when compared to patients without MUPS (Barsky et al., 2005). Total costs for this patient group are even higher, due to work- and insurance related costs (Bermingham et al., 2010). In the Netherlands, it is estimated that 30% of long term absence of work is caused by MUPS (Brenninkmeijer et al., 2006).

Mechanisms contributing to MUPS
Several theories are available for the mechanisms that play a role in the development and persistence of MUPS. The cognitive behavioural model is seen as a meta-model, incorporating many of these theories (Deary et al., 2007; van Ravenzwaaij et al., 2010). It provides explanations for
physical symptoms in different domains, including somatic causes, illness perceptions, illness behaviour and illness predispositions.

One of the theories incorporated in the model is the sensitivity theory. This theory suggests that some individuals are more vulnerable for developing or maintaining 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 incorporated in the model is the somatosensory amplification theory, which suggests that a physical sensation leads to increased attention to this sensation, which in turn leads 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 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 cortisol production. As a result stress sensitivity increases (Fries and Hesse, 2005). This theory reflects the interplay between body and mind and may therefore provide a concrete link between psychological burden and physical symptoms.

A narrative review showed some evidence for the influence of these and other theoretical elements on MUPS (Deary et al., 2007). However, it is unknown which elements play the most important role in the persistence of MUPS. Better insight in these contributing factors might provide clues for treatment of MUPS.

**Prognosis and treatment of MUPS**

Little is known about the course of MUPS. In a recent review, Olde Hartman et al. summarised cohort studies about the course and prognosis of MUPS (Olde Hartman et al., 2009). They found that very few, highly heterogenic, studies have been performed. Additionally, included studies had methodological flaws. Baseline duration of symptoms was often unknown, possible treatments were not described and duration of follow-up was generally short (6 to 15 months). They concluded that although 50% of patients improve or recover completely, the symptoms of 10-30% of patients with MUPS deteriorate or become chronic. Due to the heterogeneity in the studies, they could not identify prognostic factors for the course of MUPS. Due to the short follow-up, no conclusions could be drawn about the stability of the short term outcomes (e.g. the long term symptom recurrence rate after an initial recovery is currently unknown).

Interventions used to treat persistent MUPS have shown disappointingly little effect. For cognitive behavioural therapy (CBT) empirical support has been found in some studies, but effect sizes were small. A possible explanation could be the lack of focus on a well-defined target population.
Identification of prognostic subgroups would make it possible to offer CBT to those patients who actually need and may benefit from it. Additionally, it is unclear which components of CBT are effective. This may be caused by the lack of knowledge about factors playing the most important role in influencing the course of MUPS (Kleinstäuber et al., 2011; Kroenke, 2007b; Sumathipala, 2007).

Based on current knowledge, we can say that MUPS is mostly self-limiting, but when MUPS persist, they have a great personal and societal impact. We know very little about the long-term course of MUPS. It is unclear which percentage of patients develops persistent MUPS in different health care settings and which factors contribute to the persistence of MUPS. Given these gaps in current knowledge, the PROSPECTS study has 3 main study objectives:

**Aims of this study**
1. To assess the long-term course of MUPS presented in different settings (primary care and secondary/tertiary care) in terms of severity of symptoms and functional impairment.
2. To identify different course types, based on the course of symptom severity and functional impairment.
3. To determine which baseline characteristics are associated with favourable and adverse course types and to develop a multivariate prediction model for the course of MUPS

**Methods**

**Study design**
This is a prospective cohort study of patients with MUPS in multiple health care settings. The duration of follow-up will be 3 years. After baseline measurement, follow-up measurements will take place after 6, 12, 24 and 36 months. Information will be collected through questionnaires and saliva samples. The Medical Ethics Committee of the VU University Medical Center approved the study protocol (May 10th 2013). Written informed consent will be obtained from all study participants.

**Health care settings**
In primary care, the study will be carried out in general practices linked to the VU University Medical Center. These practices are located in urban as well as rural areas across the Netherlands. Approximately 50 general practitioners will be included, who have experience with the electronic ICPC (International Classification of Primary Care) coding system (Lamberts et al., 1987). The structure of the ICPC coding system is, though less detailed, comparable with the ICD classification (the International Classification of Diseases, www.who.int/en/).

In secondary and tertiary care the study will be conducted in organizations, which are participating in an integrated care program for MUPS patients in greater Amsterdam. These are the psychiatric department of the VU University Medical Center (VUmc); GGZ Ingeest, a secondary mental health care organization; and Reade, a centre for rehabilitation medicine.
Patients

Inclusion criteria

The study population will consist of patients between 18-70 years old, suffering from MUPS. We define MUPS as the presence of physical symptoms, which have lasted at least several weeks and for which no sufficient explanation has been found after proper medical examination by a physician. Additionally, the patient has to have a score of 2 for at least one symptom of the PHQ-15 questionnaire (indicating that the symptom is bothering a lot).

The PHQ-15 (Kroenke et al., 2002; van Ravesteijn et al., 2009) is a frequently used and validated questionnaire about physical symptoms. In the original validation study, cut-offs of 5 and 10 were suggested, based on the correlation of these scores with the presence of a somatoform disorder according to the PRIME-MD diagnostic interview for common mental disorders (Spitzer and Williams, 1994). However, as our definition of MUPS only requires the existence of at least one bothering symptom as a criterion, a lower cut off score of 2 for at least one symptom will be used in this study. By using this threshold, we aim to select a population which reflects the entire spectrum of MUPS, covering patients with mild symptoms, as well as patients with severe symptoms.

Exclusion criteria

- A sufficient medical explanation for the symptoms, according to the physician
- Incomplete diagnostic evaluation of the symptoms, according to the physician
- Insufficient command of the Dutch language
  - A cognitive or visual impairment that prohibits participating in a questionnaire survey
- Severe psychopathology (e.g. psychotic disorder, bipolar disorder)
- Pregnancy
- Cancer diagnosed in the 5 years prior to inclusion
- Another life threatening condition or a short life expectancy

Inclusion procedure

A flowchart of the inclusion methods, both in primary and in secondary/tertiary care, is given in figure 1.

In primary care, patients at risk for MUPS will be searched, using an electronic database search, based on a list of 23 unexplained physical complaints composed by Robbins et al (Robbins et al., 1997). The symptoms on this list are associated with functional somatic syndromes such as Chronic Fatigue Syndrome or Irritable Bowel Syndrome. Symptoms are likely to be unexplained when they are on the ‘Robbins list’ and a matching diagnosis ICPC code (meaning an ICPC code >70) is lacking. Patients who visited their general practitioner (GP) twice or more in the last 3 months with one or more of these symptoms (without a matching ICPC diagnosis code >70 in the patient’s electronic file) will be selected. We use 2 visits as a cut off, as the presentations of symptoms which are limited to one doctor-patient contact are not the subject of this study. However, as MUPS
patients can suffer from multiple symptoms, symptoms presented in these 2 visits are allowed to be different. Selected patients are checked for exclusion criteria by their own GP. The first 2 exclusion criteria (a sufficient medical explanation for the symptoms and incompleteness of diagnostic evaluation) are based on the criteria for MUPS as described in the introduction. Patients without exclusion criteria receive the PHQ-15 questionnaire by mail. Patients who return the questionnaire and have a score of 2 for at least one symptom are eligible and will be approached for informed consent and inclusion.

**Figure 1: Flowchart inclusion process PROSPECTS study**

In secondary and tertiary care, all newly referred patients with MUPS as the reason for referral are screened for in- and exclusion criteria by the physician performing the intake consultation. The same criteria as in primary care are used. Selected patients receive the PHQ-15 by mail. Patients who return the questionnaire and have score of 2 for at least one symptom are eligible and will be approached for informed consent.
Outcomes

Patient characteristics
We will mail questionnaires at baseline to assess general characteristics (i.e. gender, age, length, weight, country of origin, education level, occupation) and medical characteristics (medical history, chronic medical conditions and lifestyle parameters). Additionally, a more extensive overview of number and severity of physical symptoms will be created using the PSQ questionnaire, an extensive Dutch questionnaire on 51 physical symptoms (van Hemert, 2003).

Primary and secondary outcomes
All questionnaires used to assess the outcomes were selected based on their validity, previous use in this specific population, availability of reference values and questionnaire length. Severity of symptoms and functional impairment at follow-up are the primary outcomes, measured respectively with the Patient Health Questionnaire-15 (Kroenke et al., 2002; van Ravesteijn et al., 2009) and the RAND 36-item Health survey questionnaire (van der Zee and Sanderman, 1993). Secondary outcomes are health care use (Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (Hakkaart-van Roijen, 2002)) and level of depressive symptoms and anxiety (Quick Inventory of Depressive Symptomatology (Rush et al., 2003) and Beck Anxiety Inventory (Beck et al., 1988; Muntingh et al., 2011) questionnaires). These outcomes will be measured at baseline and at all follow-up moments.

Potential predictors
The choice of potential predictors of the course of MUPS is based on a number of theories incorporated in the cognitive behavioural model. Therefore, the theories mentioned in the introduction and most other theories in the meta-model will be reflected.

The sensitivity theory will be covered by the incorporation of questionnaires about personality (NEO Personality questionnaire - Five Factor Inventory (Costa and McCrae, 1992; Hoekstra et al., 1996)), perfectionism (Multi-dimensional Perfectionism Scale (Flos et al., 2000; Frost et al., 1990)), psychiatric co-morbidity (medical chart, Quick Inventory of Depressive Symptomatology (Rush et al., 2003), Beck Anxiety Inventory (Beck et al., 1988; Muntingh et al., 2011) and Whitely Index for hypochondria (Pilowsky, 1967; Speckens et al., 1996a)), positive affect (subscale of Positive And Negative Affect Schedule (Watson et al., 1988)), life events (Life Events Questionnaire (Garnefski and Kraaij, 2001)), social support (Social Support scale (Feij et al., 1992)) and physical activity (International Physical Activity Questionnaire (Ainsworth et al., 2000; Vandelanotte et al., 2005)).

Based on the somatosensory amplification theory the concepts of hypervigilance (SomatoSensory Amplification Scale (Barsky and Wyshak, 1990; Speckens et al., 1996a)), illness cognitions, causal attributions and coping (Cognitive and Behavioural Responses to symptoms Questionnaire (Skerrett and Moss-Morris, 2006)) and illness perception (Illness Perception Questionnaire (Broadbent et al., 2006; de Raaij et al., 2012)) were selected.
An overview of all questionnaires and moments of administration is given in table 1. Follow-up measurements will take place after 6, 12, 24 and 36 months. At baseline and follow-up all relevant questionnaires will be presented to participants as one instrument (one booklet), for ease of use. The baseline measurement consists of questionnaires regarding a comprehensive set of possible predictors. Only the questionnaires measuring perfectionism and personality will be postponed until the first follow-up measurement (T1), in order to reduce participant burden at baseline. In adults these factors are considered to be relatively stable over time (McCrae et al., 2000).

<table>
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<tr>
<th>Instrument</th>
<th>T0 baseline</th>
<th>T1 6 months</th>
<th>T2 12 months</th>
<th>T3 24 months</th>
<th>T4 36 months</th>
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<td>History and chronic medical conditions</td>
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<td>Received diagnostics / treatments for MUPS</td>
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<td>Potential predictors</td>
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<td>Cognitions and coping</td>
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<td>Positive affect</td>
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<td>Hypervigilance</td>
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<td>Illness Perception</td>
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<td>Causal attributions</td>
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<td>Depression</td>
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<td>Physical activity</td>
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Table 1: Used questionnaires and time points for administration.
**Potential predictors - physiological assessments**

The theory of endocrine dysregulation (see introduction) will be tested by measurement of free salivary cortisol levels. Salivary cortisol levels correspond well with cortisol levels in plasma (Kirschbaum and Hellhammer, 1994). As solitary cortisol measurements have low intra-individual stability, in this study cortisol levels in response to a stressor will be investigated. As a measure of a natural stress response of the HPA axis, the morning Cortisol Awakening Response (CAR) will be assessed at baseline and after 12 months of follow-up. All patients will collect saliva samples at awakening time (T0), and 30 (T1) and 60 minutes (T2) afterwards, as it is known that cortisol levels rise during the first 30 minutes after awakening and remain elevated for at least 60 minutes (Fekedulegn et al., 2007). They collect saliva at home using Salivettes® (Sarstedt, Etten-Leur, the Netherlands), according to the guideline of the manufacturer. Samples will be stored in home refrigerators and returned by mail as quick as possible. Returned swabs will be centrifuged and analyzed. The area under the curve with respect to the ground (AUCg) and the area under the curve with respect to the increase (AUCi) will be calculated using the formulas described by Pruessner et al. in 2003 (Pruessner et al., 2003). The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, whereas the AUCi is a measure of its time-dependent change.

**Treatments**

In this study the natural course of MUPS is investigated, therefore no specific treatment is offered to participants. However, during follow-up patients might be treated by their GP or specialist. As treatment may influence the course of MUPS, we will ask about received treatments at follow-up. Specific questions will be asked about treatments performed by for example the GP, physiotherapists, psychologists, secondary care somatic specialists or alternative caregivers. Received treatments will be considered as a covariate in the statistical analysis.

**Power calculation**

Our sample size calculation is based on the prediction model for the course of MUPS that we aim to develop. A rule of thumb states that the number of ‘events’ should be ≥ 10 for every variable in a multivariate prediction model (Altman, 1991). We plan to develop a model with approximately 6 variables. Hence at least 6×10= 60 events will be needed. Possible ‘events’ according to the course of MUPS are recovery, chronicity and recurrence (i.e. after a period of absence of symptoms). Of these, chronicity is the most restrictive. According to a Dutch review deterioration of physical symptoms (and thus chronicity) occurs in 10-30% of MUPS patients (Olde Hartman et al., 2009). As this percentage does not include chronic MUPS patients with a stable level of physical symptoms, we estimate the incidence of chronicity to be at least 30%. Therefore we need 200 evaluable patients to expect 60 events (chronicity) in both primary and secondary care study groups.

Taking into account an expected loss to follow up of 10%, we aim at a study sample of 450 patients, divided over the 2 study groups (225 patients per group). For the other study aims, this number of participants is more than sufficient.
Statistical analysis
Descriptive statistics (e.g. frequencies and percentages or mean ±SD) will be used to summarize the demographic characteristics and primary outcomes of the study population in all settings and at all follow-up moments. Cross-sectional relations between severity of MUPS and functional impairment or health care use at baseline will be analysed, corrected for age, gender and co-morbidity.

Latent Class Growth Mixture Modeling
One of the aims of our study is to identify distinct course types of severity of symptoms, functional outcome and health care use. These outcome measures are registered at baseline and 4 times during a 3 year follow-up, leading to 4 estimates of changes in outcomes. As a result, longitudinal patterns (trajectories) of these outcomes can be evaluated over time. It is expected that these trajectories vary across participants. Therefore, Latent Class Growth Mixture Modeling (LCGMM) will be used to form a smaller amount of distinct clusters (latent trajectory classes), based on the outcome measures (Jung and Wickrama, 2008). We will use LCGMM instead of Latent Class Growth Analysis (another modeling method to statistically derive distinct subgroups) as it allows a certain level of variation intercept and slope in one or more classes, leading to larger within class heterogeneity. The optimal number of clusters will be determined using statistical parameters, including Bayesian Information Criterion (Schwarz, 1978) and the bootstrapped likelihood ratio test (McLachlan and Peel, 2000). Additionally, clinical interpretation of the clusters will guide the final classification, in order to avoid clinically uninterpretable clusters. Patients will be assigned to specific clusters based on the posterior probabilities to fit in the cluster, using Bayesian statistics (Quinn and Keough, 2002).

We will use LCGMM, as it allows us to create subgroups based on registered characteristics (and change of characteristics). As a result, identified subgroups will form a closer approximation of the complex reality, compared to subgroups based on predefined (subjective) questionnaire cut offs.

Multivariate prediction model
As a second step, logistic regression will be used to identify the combinations of risk factors which are associated with the identified course types. Depending on the number of subgroups resulting from the latent class analysis, binary logistic regression or ordinal regression will be used. In this analysis all baseline characteristics will be taken into account as potential predictors. Results will be presented as odds ratios with 95% confidence intervals. The aim is to create one or more multifactor prediction models, consisting of approximately 6 determinants predicting the identified course types of MUPS. Predictors with a p≤0.157 will remain in the final prediction model(s) (Altman, 1991). Reliability of the prediction model will be tested through a calibration plot, in which the observed frequency of all course types is plotted against the predicted chance of this course. The discriminating value will be investigated by calculating the area under the ROC-curve (AUC). Internal validity of the model will be investigated through a bootstrapping procedure. Data analysis will be performed with software packages of SPSS and Mplus. Model assumptions will be checked prior to the analysis.
Bias handling

Selection bias
Hypothetically, the prevalence of severe MUPS may be higher among non-responders, as patients with severe complaints may not have the energy to participate. Other groups that may show a lower response (for the same reason) are the elderly and patients with psychiatric co-morbidity. To minimize this effect, we will stimulate all eligible patients to participate, also when they have more severe symptoms. Additionally, we will ask non-responders a few questions about the reason for not participating. A non-response analysis will be performed.

Attrition bias
It is conceivable that patients with severe complaints or co-morbidities may prematurely end study participation, as participation costs energy, but has no apparent personal advantages. To stimulate continuation of participation, small incentives (e.g. gift coupons) will be provided during follow up. In case of discontinuation, patients will be stimulated to resume participation. All reasons for discontinuation will be collected, analyzed and reported. In addition, baseline characteristics, including severity of symptoms, will be compared between participants and drop-outs. In case of missing follow-up data imputation techniques will be considered.

Discussion
Health care workers in primary care and secondary care are confronted with patients with MUPS on a daily basis. MUPS patients, especially those with persistent MUPS face various insecurities, as their symptoms are not (fully) medically explained. Current knowledge about prognosis is limited and treatment options are scarce. This study will add to earlier studies, as it will have a long follow-up period. Additionally, we will register possible treatments, have an additional focus on functional impairment and identify predictors of the course of MUPS.

When designing the study, the greatest challenge concerned the inclusion procedure, especially in primary care. In various previous studies, selection of MUPS patients was based on searches in GPs’ electronic databases. Unfortunately, a specific ICPC code for MUPS is lacking. Therefore, criteria such as the Robbins criteria have often been used as a proxy to identify possible MUPS cases (Smits et al., 2009; Verhaak et al., 2006). As Robbins’ list symptoms are not always unexplained, a disadvantage of this method can be the selection of patients with symptoms that do not fit the criteria for MUPS (false positives). Furthermore, as selection results depend on proper registration by GPs, possible MUPS cases might be missed in case of suboptimal registration of consultations (false negatives). In other studies questionnaires such as the PHQ-15 have been used as a screening instrument for possible MUPS patients (Steinbrecher and Hiller, 2011). The PHQ-15 is a validated and widely used instrument for this aim, evaluating 15 symptoms that account for more than 90% of all reported physical symptoms. The PHQ-15 reflects the symptoms reported by the patient. However, the scale only includes a somatic symptom count. Therefore, an additional evaluation of the nature of the symptoms by a physician is needed to confirm the existence of MUPS.
In this study, we will combine both methods. A digital search strategy based on the Robbins list will be used as a first step. Afterwards, the selected patients will be screened for in- and exclusion criteria by the GP. As a third step, selected patients will be asked to fill in the PHQ-15 questionnaire, to objectify the current existence of symptoms. This combination will lead to a final selection of ‘true’ MUPS patients. This method has the disadvantage that MUPS patients may be missed, for example due to incorrect registration by GPs or a coincidentally low number of doctor visits in the last 3 months. Although we do believe that in this study it is not essential to select all MUPS patients in our population (as we do not study the prevalence of MUPS), we will try to overcome this disadvantage as much as possible, as a representative sample is essential. We will do this by selecting GPs with ICPC coding experience, using relatively low-threshold selection criteria and by the inclusion of patients in different health care settings.

In secondary care, we will recruit patients in specialized MUPS care settings. Therefore, it is a limitation to this study that the results in this study group are not generalizable to the complete population as seen by somatic specialists in secondary care. Despite the fact that we do not include patients in these settings, we do believe that the described group will not be completely missed. At some point patients with MUPS who are seen by somatic specialists will be referred back to their GP (as no diagnosis can be established) or to specialized MUPS care. As a result, an unknown percentage of these patients will be included via the included study groups.

The aim of this study is restricted to patient related factors influencing the course of MUPS. As a result, other potential influencing factors, such as the doctor-patient relationship or communication will not be taken into account in this study.

We believe that study results will provide extensive information about course and prognosis. This information can be used directly in clinical practice, for example in patient education. Additionally, identification of predictors of the course of MUPS may lead to better recognition of patients at risk for persistent symptoms, who may benefit from treatment. It may also lead to identification of relevant treatment targets. Taking together all these practical implications, we do believe that this study has great relevance for clinical practice. We aim to complete the study in 2016.