CHAPTER 10

General discussion.
Rationale

In all health care settings patients present with physical symptoms for which no sufficient somatic explanation can be found after proper medical examination. Such symptoms are called medically unexplained physical symptoms (MUPS). Persistent MUPS can be severe and disabling. MUPS populations are very heterogeneous. Therefore, adequate MUPS classification is challenging. Furthermore, very little is known about the course of MUPS and about predictors of this course, which makes it difficult to recognise patients at risk for an adverse course of MUPS in clinical practice. Finally, knowledge about effective MUPS treatments is scarce, leading to problems in MUPS management.

This thesis describes the PROSPECTS study, a study in which we followed 325 MUPS patients over a period of 2 years. We aimed to enlarge the body of evidence about MUPS classification systems by comparing different classification criteria within our study population. Furthermore, we aimed to describe the course of MUPS and to identify factors predicting this course. We also assessed the cross-sectional relation between cortisol (a stress hormone) and MUPS symptom characteristics. Ultimately, we reviewed literature about MUPS treatments and provided practical advice for future MUPS management.

Main findings

MUPS classification

We found that in our MUPS population DSM5 criteria for a ‘Somatic Symptom Disorder’ (SSD), which include psychological criteria, are more restrictive than DSM IV criteria for ‘somatoform disorders’ (SD), which only include physical criteria. They are also associated with higher symptom severity and lower physical functioning. We considered this to be an improvement, as the DSM IV SD is deemed to be highly overinclusive, but we also stated that further specification of the psychological criteria of DSM5 SSD is necessary.

Course of MUPS

By applying Latent Class Growth Modeling (LCGM), we identified three course trajectories in terms of symptom severity and physical and mental functioning: a “stable severe”, a “stable moderate” and an “improvement” trajectory. However, clinical usability of the results was limited, due to high levels of intraclass heterogeneity. Therefore we also analysed change scores and directions of change. Analyses of directions of change using data of all four measurement moments showed that for all outcomes almost 80% of the participants reported a fluctuating course type. These fluctuating course types were not detected by LCGM. Based on change scores (using only 2 measurement moments), reported improvement and deterioration rates are in line with literature (physical symptoms of 27% of the participants deteriorated, while 63% improved). However, based on the highly prevalent fluctuations, we concluded that temporal stability of these outcomes is limited.
Factors related to MUPS severity and course of MUPS

We assessed the cross-sectional relation between levels of cortisol, a human stress hormone, and the presence of symptoms from specific symptom clusters, symptom severity and duration of symptoms in our population of MUPS patients. Our results suggested that within a heterogeneous MUPS population there is no cross-sectional relation between cortisol levels and any of these symptom characteristics.

In order to assess factors related to the course of MUPS, we firstly performed a qualitative analysis by asking improved patients which factors contributed to their improvement. Acceptance of symptoms and their consequences seemed to be the most important condition for improvement of MUPS. This acceptance was often reached after a moment of personal crisis. After this crisis, patients started taking control of their own well-being by coping differently (e.g. by pacing activities or resting effectively), mostly supported by a therapist. This ultimately led to symptom improvement.

Furthermore, we developed three prediction models for the course of MUPS (one for symptom severity, one for physical functioning and one for mental functioning). A wide range of potential predictors was assessed. Identified predictors of an adverse course of MUPS included physical comorbidity, higher severity and longer duration of MUPS at baseline, anxiety, catastrophizing cognitions, embarrassment and fear avoidance cognitions, avoidance or resting behaviour and neuroticism. Predictors of a favourable course included limited alcohol use, higher education, higher levels of physical and mental functioning at baseline, symptom focusing, damage cognitions and extraversion. Explained interpersonal variance for all three models varied between 70.5 and 76.0%. Performance was comparable for both primary care and secondary/tertiary care patients, and according to the bootstrapping procedure bias of the presented models was low.

MUPS treatment

We evaluated 21 randomized controlled trials assessing the effectiveness of some form of psychological therapy, compared to another therapy. We could not find any study assessing the effectiveness of physical therapies. We concluded that all psychological therapies combined were superior to usual care in terms of reduction of symptoms. However, effect sizes were small. As a single treatment, only Cognitive Behavioural Therapy (CBT) has been adequately studied. Compared with usual care or waiting list conditions, CBT reduced symptoms, with a small effect.

Interpretation of main findings

MUPS classification - steps in the right direction

As pointed out in chapter 1, many concepts have been proposed to distinguish the group of patients with problematic MUPS from the greater majority with self-limiting symptoms. Most of these concepts were based on somatic symptom counts only, providing a rather unidimensional concept of MUPS (Voigt et al., 2010). In the past few years however, a tendency has emerged to
include psychological and behavioural characteristics in MUPS related classifications (American Psychiatric Association, 2013; Voigt et al., 2010). Very recently, it was even suggested to use psychological and behavioural characteristics with predictive value to classify patients based on their prognostic profile instead of their type and number of symptoms (Rosendal et al., 2017). The addition of psychological and behavioural features to classification criteria is assumed to increase their clinical utility, as these features are directly relevant for the choice of treatment (Rief et al., 2010; Rosendal et al., 2017). In the light of this classification shift, we believe that this thesis provides relevant new information about (potentially) relevant psychological and behavioural features, which can be of value for new classification criteria.

In chapter 3 we describe our findings that the addition of two psychological criteria (excessive health related anxiety and negative illness thoughts) to the DSM 5 Somatic Symptom Disorder (SSD) improved clinical value of the diagnosis in a MUPS population, as compared to the DSM IV Somatoform Disorders (which only included physical criteria), the DSM 5 SSD includes patients with higher symptom severity and lower physical and mental functioning, indicating that the chosen psychological criteria are actually related to the severity of MUPS. The addition of psychological criteria therefore ‘solves’ the problem of relative overinclusiveness of the DSM IV criteria.

Moreover, chapter 7 provides additional information about potential classification features, as the development of a prediction model for the course of MUPS led to the identification of additionally prognostically relevant psychological and behavioural factors. Although external validation of the predictive value of these factors is still needed, it is conceivable that results are generalizable to other populations, as almost all identified predictors have been described before in literature and as the model performed well in all included health care settings.

**MUPS classification - remaining issues and personal considerations**

Although the addition of psychological and behavioural characteristics to the classification criteria is a clear step in the right direction, there are still some issues to overcome. Below I share my personal considerations about these issues.

First, consensus is needed about the role of the unexplained nature of symptoms as a classification criterion. Alongside the introduction of psychological criteria for the SSD, the DSM 5 handbook developers left out the unexplained nature of symptoms as a criterion (American Psychiatric Association, 2013). As a consequence, patients with explained physical symptoms can now also meet the criteria of a somatoform disorder, as long as they have excessive thoughts or worries about their symptoms. In the field of MUPS this choice has both been complimented and criticized (Barsky, 2016; Frances and Chapman, 2013; Mayou, 2014; Rief and Martin, 2014). From a diagnostic perspective, the omission of physical symptoms being unexplained as a criterion is understandable, as it remains aberrant to only use physical criteria for the establishment of a psychiatric disorder (Mayou et al., 2005; Rief and Isaac, 2007). It should be emphasized that psychological and beha-
vioural factors can play a great role in patients with explained symptoms as well. However, from a patient's perspective, the unexplained nature of symptoms forms a very relevant aspect of MUPS. Our interviews with MUPS patients (chapter 6) revealed that the acceptance of the unexplained nature of the symptoms may be the most difficult but at the same time the most crucial step on the way to recovery. Previous literature also showed that unexplained symptoms are far more difficult to deal with than explained symptoms (de Waal et al., 2004). Finally, although psychological and behavioural factors also play a role in explained symptoms, in MUPS they are the only available starting point for treatment. In other words: the unexplained nature of symptoms influences symptom perception as well as choice of treatment. I therefore believe that its place in MUPS related classification criteria remains justified.

A second issue that has to be overcome concerns the fact that general MUPS populations are always very heterogeneous populations, including patients with all sorts of symptoms, backgrounds, comorbidity, coping strategies, and symptom course types over time. To make it even more complicated: studies showed that on top of this interpersonal heterogeneity there are also high levels of intrapersonal heterogeneity in MUPS patients, as patients themselves seem to have multiple explanatory models for their own condition, covering the whole spectrum from physical to psychological, social and existential explanations, neither of them being necessarily dominant (Risør, 2009). Consequently, I can only emphasize that the typical MUPS patient does not exist, and I therefore believe that it may be impossible to develop one unidimensional classification instrument that fits all MUPS patients and that is also clinically useful.

Several researchers expressed comparable doubts and some of them stated that the heterogeneity of the MUPS population, as well as the diversity in influencing mechanisms on a personal level, necessitates a change of paradigm from unidimensional to multidimensional diagnostics and classification (Eriksen et al., 2013; Janssens et al., 2017; Musalek and Scheibenbogen, 2008), in which symptom characteristics as well as the role of a variety of prognostic psychological and behavioural factors can be mapped for each patient, resulting in personal MUPS profiles (Janssens et al., 2017). The presence and number of prognostically adverse characteristics in such a profile could be used for classification of the severity level and necessity of treatment for the individual patient. I believe that a multidimensional classification system as described above would have the potential to provide health care workers with useful MUPS classification tools and MUPS patients with a more personalized approach. However, as multidimensional systems in MUPS have not been studied yet, they are currently only a distant prospect for clinical practice.

The course of MUPS

To our knowledge, our study on the course of MUPS, described in chapter 4, was one of the first studies detecting the high levels of fluctuations in the course of MUPS. This puts previous literature about the course of MUPS (mostly using only two measurement moments) in a different perspective, as the reported improvement or deterioration may not be as stable as previously assumed.
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(Olde Hartman et al., 2009). It is important to take this relative instability of outcomes into account in future studies, as well as in clinical practice.

Our results also indicated that the fluctuations showed so much inter-individual heterogeneity, that they could not be adequately detected using Latent Class Growth Analysis (which only showed stable course trajectories). We therefore argued that in prediction research, it would be best to use more than two measurement moments and to take potential course fluctuations into account by performing other longitudinal data analysis techniques such as mixed model analysis (using outcome scores at all measurement moments) (Twisk, 2014). In chapter 7 we actually used mixed model analyses for the development of our prediction models for the course of MUPS. By applying this method as one of the first in the field of MUPS, we used a high quantity of data (including many moments of improvement or deterioration) which strengthened the robustness of our findings.

**MUPS treatment**

The systematic review in chapter 8 and the literature overview in chapter 9 showed that well-studied MUPS treatments that have shown to be effective are scarce, and that effect sizes are small. It is thinkable that this may partly be caused by the fact that in all studies included in the review interventions were equal for all participants, not taking into account personal symptom characteristics or psychological of behavioural factors. This may be problematic, as these aspects may differ from person to person. Currently used treatments (such as cognitive behavioural therapy) may focus on factor A (e.g. negative illness thoughts), while in an individual patient factor B (e.g. coping with life events) may play a much bigger role (Janssens et al., 2017). MUPS treatments might therefore become more effective, when (1) they are only offered to those patients who actually need treatment based on their prognostic profile and when (2) therapeutic targets are tailored to factors that play an actual role in individual patients situations.

For a better identification of treatment target populations (1), an overview of relevant prognostic factors of MUPS is essential. The predictors for the course of MUPS, as identified in chapter 7, contribute to this overview and can be useful in quantifying the heterogeneity of treatment benefits. When applied in MUPS classification models, they could contribute to the identification of patients who would benefit most (or least) from treatment.

However, when it comes to the identification of relevant therapeutic targets (2), results of predictive studies such as ours should be interpreted with caution, as factors that predict the course of MUPS do not necessarily have a causal relation with outcomes (Moons et al., 2009). Future studies are needed to assess whether changes in the identified psychological and behavioural factors actually lead to changes in symptom severity or functional outcome.

The implementation of personalized treatment for MUPS in regular health care would be in line with the multidimensional classification of MUPS. Although personalized treatment has been
proposed in literature (Janssens et al., 2017), in chapter 8 we showed that actual intervention studies in general MUPS populations are currently lacking. However, research on the effects of personalized treatment has been done in other fields of research and has for example been found promising for several psychiatric disorders (Ozomaro et al., 2013), and in more specific MUPS subpopulations such as populations with chronic fatigue syndrome (Brown, 2014).

**Methodological considerations**

In all chapters we described methodological strengths and limitation of the specific study. However, as data of the PROSPECTS study were used for most chapters, this is the appropriate place to discuss some general methodological considerations concerning this cohort of MUPS patients.

**Number of included participants**

First of all, as described in chapter 2, we aimed to include 450 patients. Unfortunately, this number was not reached: out of 2000 invited patients, only 325 (15%) decided to participate. The phenomenon that the recruitment of patients for a study takes much more time and effort than investigators have estimated is not new and has been coined “Lasagna’s law”, after the American clinical pharmacologist Louis Lasagna who was the first to give a name to this problem. Dutch researchers found that “Lasagna’s law” also holds in Dutch primary care research, and they provided several recommendations to prevent problems as much as possible (van der Wouden et al., 2007). We implemented most of these recommendations in our study design (e.g. by minimizing the effort for practitioners in the recruitment process, by adapting study procedures to practitioners’ wishes and by performing a pilot study). However, we did not succeed to include the aimed number of participants. This has two important consequences. Firstly, according to our original power analyses, the included number of patients was too low to develop prediction models for the course of MUPS for primary and secondary/tertiary care separately. Secondly, the low response rate may raise questions regarding the representativeness of our study population: does our population adequately reflect the ‘real’ MUPS population in clinical practice? We will discuss both consequences below.

Regarding the first consequence, we decided to develop prediction models for our total study population only. This choice was supported by the finding that many patients who were selected in primary care also reported visits to specialized MUPS settings in secondary care. In other words: although we aimed to include a primary care group and a secondary/tertiary care group, in reality there was much overlap between both groups. To evaluate the consequences of our choice, we decided to perform a sensitivity analyses by assessing the performance of the final prediction models (developed in the total group) in both subgroups. As these analyses showed that performance of the model was comparable in primary care and secondary/tertiary care subpopulations, we concluded that the identified predictors proved their relevance in both subpopulations.

The second consequence, concerning the representativeness of our findings, was more difficult to handle. We performed a non-response analysis among eligible patients, which showed that
between participants and non-participants there were no statistical differences in age and symptom severity. However, 12% of the non-responders reported that they did not want to participate due to too much suffering because of the symptoms. We therefore believe that a subgroup of patients with relatively high levels of functional impairment may not have been included in our study population, which may have influenced our study results.

**Primary outcome measure**

In addition to the number of included patients, a second consideration of the PROSPECTS study concerns the use of the Patient Health Questionnaire 15 (PHQ-15) as the outcome measure to assess symptom severity (Kroenke et al., 2002). Although this questionnaire is commonly used in MUPS research and although it is considered a valid instrument, it is only a somatic symptom count, consisting of 15 symptoms. By using this questionnaire, the (un)explained nature of reported symptoms was not evaluated, neither were symptoms which are not on the list. In order to enlarge the information about MUPS characteristics and severity we additionally used the (more extended) Physical Symptoms Questionnaire (van Hemert, 2003), self-reported symptom top three's and a questionnaire about newly established diagnoses at several time points. However, as these measures were only developed for descriptive purposes, they have not been validated as an outcome measure in research. As the PHQ-15 was the only validated outcome measure, it is important to realize that the reported symptom severity levels and course types in this thesis (which were based on the PHQ-15 score only) are a simplified representation of real MUPS severity levels and course types in clinical practice.

**Timing of patient selection**

A third consideration concerns the timing of patient selection. The reported duration of symptoms at baseline varied widely, indicating that participants were selected at different moments in their personal course of MUPS. Ideally, one would select all patients at the start of their symptoms, especially in a study like ours, where the aim is to identify course types. However, we believe that this is not feasible in MUPS research, due to variety in duration of symptoms before the first presentation to a doctor and variety in time intervals between first presentation of symptoms and the conclusion that they remain unexplained. Furthermore, as the result of our analyses of the course of MUPS (chapter 4) show that in MUPS patients, symptom severity can considerably fluctuate over time, it may be very difficult to identify one specific moment at which symptoms started (as symptoms may continuously come and go).

**Potential predictors of the course of MUPS**

A final consideration regards the choice of potential predictors, used to develop the prediction models for the course of MUPS (chapter 7). We mainly assessed the potential predictive role of intrapersonal factors, such as personality aspects, illness thoughts or illness behaviours. The role of more external factors, such as the relation with health care providers, job requirements or living environment was not assessed. Consequently, no conclusion can be drawn about the role of these factors.
Taking into account all described considerations, we believe that the principal strengths of the PROSPECTS study lie in its multi-center prospective design, the use of widely validated measures and the long duration of follow-up using multiple measurement moments. Furthermore, the focus on physical and mental functioning provided a new perspective on the course of MUPS, adding new information to the body of evidence.

Implications for practice
It is reassuring that the Dutch MUPS guidelines (which currently lack a strong scientific basis) are in line with our findings. In essence, the guidelines provide the advice to evaluate and manage somatic, cognitive, emotional, behavioural and social aspects in cases of MUPS (Landelijke Stuur-groep, 2011; Dutch College of GPs, 2013). Our results provide a scientific underpinning for this advice. We can therefore conclude that in the Netherlands we already are on the right track when it comes to MUPS management. However, we also believe that our results add some new specifications to these (quite general) guidelines, which can be very useful in clinical practice. Therefore, and in line with chapter 9, we provide the following advices to clinicians for consultations with patients whose symptoms are determined to be MUPS after thorough and adequate examination:

- Take the patient seriously. By acknowledging the symptoms and by being truly interested and empathic a relation of trust can be built (chapter 6).
- Once the relation of trust has been established: be honest. Patients appreciate it if clinicians are being transparent, reflective and strict if necessary. However, without trust, these actions could lead to emotional blocking, ultimately resulting in a damaged therapist-patient relationship (chapter 6).
- Explore all symptom dimensions (somatic, cognitive, emotional, behavioural, and social) and pay extra attention to the exploration of the psychological and behavioural factors which showed to have a predictive value for the course of MUPS (i.e. anxiety, catastrophizing cognitions, embarrassment and fear avoidance cognitions, avoidance or resting behaviour, neuroticism and extraversion) (chapter 7).
- Share your findings with the patient and explain that no underlying medical condition has been identified or is likely to be identified in the near future (chapter 9).
- Assess to which extent the patient is ready to accept the unexplained nature of symptoms. If the patient is not yet ready for acceptance: explore what is needed to come to acceptance and support the patient on this path (chapter 6).
- Provide prognostic information about MUPS (including information about the risk of a fluctuating course type) (chapter 4).
- Where possible, provide personal explanations for the persistence of symptoms, based on the identified predictive factors (chapter 7).

When it comes to treatment of MUPS, participants of the qualitative study stated that the ideal therapist should have a coaching role and is expected to be supportive and to provide coping tools
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(chapter 6). Offered treatments should match the patients’ personal situation, as this contributes to compliance. The latter is quite challenging as we found that currently effective treatments are scarce, and therefore treatment choices are limited (chapter 8). We believe that in most MUPS patients (who are suffering from mild MUPS) the steps as described above will provide a solid basis for personalized patient education and coaching, as adverse prognostic factors can be identified and addressed. In cases of more severe MUPS cognitive behavioural therapy is worth offering.

Implications for research

In this thesis, we tried to augment the body of evidence about the classification, course and treatment of MUPS. However, more research is highly needed. There are a few recommendations for future research that can be made based on our results.

We pointed out that generally accepted MUPS criteria are currently lacking. Therefore, more research is needed in the field of MUPS classification. The development and evaluation of multidimensional MUPS classification systems, including psychological and behavioural prognostic factors, may be particularly interesting.

Our qualitative study pointed out that acceptance of the unexplained nature of symptoms is the most difficult, but also the most important condition for improvement of MUPS. However, it is still unknown if and how therapists can influence the level of acceptance. It would be interesting to perform additional qualitative studies to unravel the process of acceptance in MUPS patients and to assess whether this process can be externally influenced.

Our prediction models for the course of MUPS (chapter 7) led to the identification of a subset of psychological and behavioural factors related to the course of MUPS. In order to externally validate our findings (as well as those of other predictive studies in the field of MUPS) predictive value of identified factors needs to be re-evaluated in other MUPS populations (Moons et al., 2015). Causal relations between identified predictors and outcomes also need to be assessed, as this may lead to the identification of new therapeutic targets. Therefore, longitudinal mechanistic studies are needed, evaluating the temporal interplay between psychological and behavioural factors on one hand and MUPS severity and functional impairment on the other.

When it comes to the treatment of MUPS, studies assessing other treatment modalities than CBT are highly needed, especially studies concerning physical therapies (such as walking, running or yoga therapy). Furthermore, once psychological and behavioural factors that influence the course of MUPS are identified, it would be worthwhile to develop and assess personalized treatment modalities.

Apart from these recommendations concerning the focus of research, there are also some methodological recommendations. We pointed out before that numerous definitions and criteria are
being used in MUPS research. In addition, there is a great variety in used outcome measures. Consequently, study results are often difficult to compare. In order to enlarge comparability of MUPS studies about prognosis and treatment of MUPS, it is recommendable for future MUPS researchers to clearly define levels of severity (duration and number of symptoms) at baseline and to use MUPS criteria and outcome measures which have already been used in MUPS research. Recently a consensus guideline about relevant outcome domains and measures has been published, which can support the choice of relevant and frequently used outcome measures (Rief et al., 2017). Furthermore, as our study results showed that the course of MUPS is often fluctuating (chapter 4), in future prognostic and intervention studies it would be preferable to use a long duration of follow-up and more than 2 measurement moments in order to detect these course fluctuations.

**To end with**

Having studied MUPS for a few years, I found that it is a challenging subject to approach scientifically. Clear-cut diagnostic criteria, classification systems and outcome parameters are core aspects of evidence-based medicine. As pointed out in this thesis: for MUPS none of these aspects are free of discussion. For this reason it has even been argued that MUPS show the limitations of evidence-based medicine in its current form (Deary, 2005; Soler and Okkes, 2012; Ulvestad, 2008). On the other hand, in the past decade MUPS research has resulted in a solid body of evidence, which can be built upon. The ongoing research on MUPS classification, influencing factors and (personalized) treatments may not lead to one uniform step-by-step MUPS management plan for all MUPS patients, but it will hopefully provide more and more additional clues for treating individual patients dealing with MUPS in daily life. Because as a scientist, who sometimes got frustrated by the intangibility of the subject without even experiencing one unexplained symptom, I can only imagine how important it is for MUPS patients to get a grip on the unexplained.