SUMMARY
In chapter 1 (the general introduction) the subject of Medically Unexplained Physical Symptoms (MUPS) was introduced. We provided an overview of commonly used MUPS related definitions and summarized the available literature about classification, course, prediction and treatment of MUPS. Furthermore, we presented the rationale and outline of this thesis, in which we aimed to answer the following research questions:

1. 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?
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, medical, psychological, behavioural or biological) factors, which predict the 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?

In chapter 2 we described the study design of the PROSPECTS study, a prospective, multicenter longitudinal cohort study, assessing the course and prognosis of MUPS, in terms of symptom severity and physical and mental functioning. We described that we aimed to select 450 MUPS patients (aged 18-70) in primary care and in specialized MUPS programs in secondary/tertiary care. We planned to assess the course of symptoms and functioning, as well potential predictors of this course, using 1 baseline and 4 follow-up measurements during a 3 year period. Potential predictors were based on empirical literature and theoretical literature describing the course and perpetuation of MUPS and they included demographic, medical, psychological and behavioural characteristics.

In chapter 3 we used baseline data of the PROSPECTS study to assess the clinical value of DSM IV and DSM 5 criteria for diagnosing the most prevalent somatoform disorders in patients with MUPS. Ultimately, 325 patients were included in the PROSPECTS study. Within this population we used baseline questionnaires about symptom severity (PHQ-15), physical and mental functioning (RAND 36 subscales), anxiety (BAI), depression (QIDS-SR), health anxiety (WI) and illness perceptions (IPQ-K) as proxy measures for operationalization of DSM IV and DSM 5 diagnostic criteria. We found that 92.9% of participants fulfilled criteria of a DSM IV somatoform disorder, while 45.5% fulfilled criteria of DSM 5 Somatic Symptom Disorder (SSD). Participants fulfilling criteria of DSM 5 SSD suffered from more severe symptoms than those only fulfilling criteria of a DSM IV somatoform disorder. Furthermore their level of physical functioning was significantly lower. We therefore concluded that in this MUPS population DSM5 criteria for a ‘Somatic Symptom Disorder’ (SSD) are more restrictive than DSM IV criteria for ‘somatoform disorders’ (SD). 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 to improve utility in research and practice.
In chapter 4 we used longitudinal data of the PROSPECTS study to assess the 2-year course of MUPS in terms of symptom severity (PHQ-15), physical functioning (RAND 36 PCS) and mental functioning (RAND 36 MCS). We used outcome measurements collected at baseline and 6, 12 and 24 months afterwards. In order to identify different course types, we applied Latent Class Growth Modeling (LCGM), but as clinical usability of the results was limited, we also analysed change scores and directions of change. LCGM identified three course trajectories for all outcomes: a “stable severe”, a “stable moderate” and an “improvement” trajectory. The greater majority of participants was assigned to the stable trajectories. However, levels of within-trajectory heterogeneity were high. Based on total change scores (using only two measurement moments), physical symptoms of 27% of the participants deteriorated, while 63% improved. 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. Based on these results we concluded that frequency distributions of course types are highly dependent on the chosen classification method. Although the majority of patients showed a fluctuating course of MUPS, these fluctuations were not detected by LCGM, due to high levels of interpersonal heterogeneity. Improvements and deterioration rates based on change scores are in line with literature. However, based on the highly prevalent fluctuations, we conclude that temporal stability of these outcomes is limited.

In chapter 5 we used baseline data of the PROSPECTS study to assess 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. We chose the Cortisol Awakening Response (CAR) as a cortisol parameter, using saliva samples. In order to assess symptom type we used confirmatory factor analysis for the identification of 4 specific symptom clusters: (1) gastro-intestinal symptoms; (2) pain; (3) cardio-pulmonary symptoms; and (4) fatigue. For this factor analysis we used the PSQ questionnaire, which assesses the occurrence and frequency of 51 physical symptoms. Symptom severity was measured with the PHQ-15. Duration of symptoms was based on self-reported duration of top 3 symptoms. We performed multiple linear regression to assess relations between CAR and individual factor scores on symptom clusters, symptom severity and duration of symptoms. Our results suggested that within a heterogeneous MUPS population there is no relation between cortisol levels and any of the described symptom characteristics.

In chapter 6 we presented a qualitative analysis, assessing patients’ perspectives on improvement of MUPS. We conducted semi-structured interviews with nine patients who had at least moderate MUPS at baseline and a substantial decrease of symptoms after 6 or 12 months (according to their PHQ-15 scores). They were asked which factors contributed to their improvement. Interviews were recorded and recordings were transcribed verbatim and analysed in ATLAS.ti. 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 and relaxing effectively), mostly supported by a therapist. This ultimately led to symptom improvement. Participants deemed it important that general practitioners and therapists take MUPS seriously and take on the role of a supportive coach. A wish for multidimensional treatments in regular health care was identified.

In Chapter 7 we used longitudinal data of the PROSPECTS study to develop prediction models for the course of MUPS in terms of symptom severity (PHQ-15), physical functioning (RAND 36 PCS) and mental functioning (RAND 36 MCS) during a 2-year follow-up period. Mixed model analyses were used to develop prediction models for all outcomes, using all follow-up measurements. Potential predictors were based on empirical and theoretical literature and measured at baseline. The final prediction models for all 3 outcomes showed some overlap. Combining all three models, identified adverse predictors for the 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. Favourable predictors 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 of the models was comparable in primary and secondary/tertiary care. The 2 contra-intuitive predictors for a favourable course of MUPS (symptom focusing and damage cognitions) showed an opposite effect in univariate analyses. This turnaround may have been a consequence of multicollinearity. We concluded that the presented prediction models identified several relevant demographic, medical, psychological and behaviourial predictors for the adverse and favourable course of MUPS. External validation of the presented models is needed prior to clinical implementation.

In chapter 8 we presented the results of a systematic review on non-pharmacological interventions for somatoform disorders and MUPS in adults. We performed searches in various literature and trial databases and selected randomised controlled trials and cluster randomised controlled trials involving adults primarily diagnosed with a somatoform disorder or an alternative diagnostic concept of MUPS. Four review authors, working in pairs, conducted data extraction and assessment of risk of bias. We included 21 randomised controlled trials, with 2658 randomised participants, assessing the effectiveness of some form of psychological therapy, compared to usual care, waiting list controls, placebo, enhanced care, or another therapy. No studies concerning physical therapies were identified. We found that all psychological therapies combined were superior to usual care or waiting list in terms of reduction of symptom severity (Standardized Mean Difference -0.34; 95% confidence interval (CI) -0.53 to -0.16; 10 studies, 1081 analysed participants). However, effect sizes were small. As a single treatment, only Cognitive Behavioural Therapy (CBT) has been adequately studied to allow tentative conclusions. Results for the subgroup of studies comparing CBT with usual care were similar to those in the whole group. We concluded that the number of studies investigating various treatment modalities (other than CBT) needs to be increased; this is especially relevant for studies concerning physical therapies.
In chapter 9 we evaluated the evidence for effect of all available MUPS interventions (both non-pharmacological as pharmacological) from a clinical perspective. We evaluated four Cochrane systematic reviews examining efficacy of drugs, psychological interventions, enhanced care and specialist consultation letters for somatoform disorders or persistent unexplained physical symptoms. Studies restricted to specific functional syndromes (such as irritable bowel syndrome) were excluded. Based on the evidence, we provided practical advice about the management of MUPS. In cases of MUPS, we advised physicians to explore all symptom dimensions (somatic, cognitive, emotional, behavioural, and social) and to share all findings with the patient. Based on this exploration, it may be possible to provide a tangible explanation for the persistence of symptoms. Regarding the treatment of MUPS, we considered cognitive behavioural therapy worth offering to patients but we did not advise pharmacological therapy (other than acute pain management). Ultimately, we advised to ask the patient to report changing or worsening of symptoms, or new symptoms which may require reassessment, as not being able to identify an underlying condition does not completely exclude there being one.

In the final chapter (the general discussion) I interpreted our findings in the light of current evidence, reflected on the most important methodological considerations and provided recommendations for clinical practice and future research.