

SUMMARY

In **Chapter 1** I introduced the subject of medically unexplained physical symptoms (MUPS) and how they put a burden on the patient, the GP, the GP-patient relationship and on the society. Also in this chapter I presented the rationale and outline of this thesis. I focused on the identification of MUPS, structuring management of MUPS and societal aspects of MUPS.

In **Chapter 2** we performed a validation study in which we explored the test characteristics of a screening method in primary care electronic medical records (EMRs) to identify patients with MUPS. This EMR method consisted of three steps: 1) including adult patients (≥ 18) who had at least five general practitioner (GP) contacts in the past 12 months; 2) patients with known chronic (somatic) diseases were excluded; 3) patients were included who had a MUPS syndrome (irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia) or who had at least three physical symptoms suggestive for MUPS. We compared the identified patients with MUPS from the screening method and those identified without MUPS with their scores on the patient health questionnaire-15. We found a high specificity but a low sensitivity, indicating that many potential MUPS patients will be missed. Therefore, before using this method as a screening method for selecting patients with MUPS, it needs to be improved.

In **Chapter 3** we developed two risk assessment models to identify patients at risk for persistent MUPS with two statistical methods in a large primary care EMR database. We operationalized MUPS as an International Classification of Primary Care (ICPC) code for irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome and low back pain without radiation. The methods we used were a more classic logistic regression analysis and a more innovative decision tree analysis. We found that both models performed moderate to good with areas under the curve of 0.70 and 0.81, respectively. The validation showed acceptable stability (0.78 and 0.70, respectively). While these models require further external validation and fine-tuning, they can

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provide a starting point from which GPs could start evolving MUPS management in a proactive, structured manner together with their patients.

In **Chapter 4** we conducted a focus group study with 29 Dutch GPs. We explored how GPs recognize patients with MUPS during their consultations and whether they could recognize subgroups of patients with MUPS. Two researchers independently analysed the data with the constant comparative analysis method. We found that GPs take various characteristics into account when recognizing patients with MUPS. More objective characteristics were multiple physical symptoms, frequent and long consultations and many referrals among other things. Subjective characteristics were negative feelings towards the patient and the feeling that they cannot make sense of the patient's story. Based on the perceptions of the GPs and the predominance of certain characteristics, five subgroups of patients with MUPS were distinguished: the anxious MUPS patient, the unhappy MUPS patient, the passive MUPS patient, the distressed MUPS patient and the puzzling MUPS patient. While these subgroups need further validation, targeting them might improve personalized treatment. For example, an anxious MUPS patient could benefit from extra attention for reassurance and a passive MUPS patient could benefit from an activated treatment.

In **Chapter 5** we assessed the effects of non-pharmacological interventions for somatoform disorders and chronic MUPS in adults in comparison with treatment as usual, waiting list controls, attention placebo, psychological placebo, enhanced care and other psychological or physical therapies within a Cochrane review. We searched different databases such as the Cochrane Depression, Anxiety and Neurosis Review Group's Specialise Register. We also performed several additional searches and we selected both randomized controlled trials (RCTs) and cluster RCTs. Four researchers conducted data extraction and risk of bias assessment. We pooled data from studies addressing the same comparison using standardised mean differences (SMDs) or risk ratios (RRs). The primary outcomes were severity of somatic symptoms and acceptability of the treatment. In total, we included 21 studies (n=2658 patients). All studies assessed the effectiveness of a psychological therapy. Most of them evaluated a form of cognitive behaviour therapy (CBT). We found that when all psychological therapies

were combined they were superior to usual care or waiting list controls in terms of reduction of symptom severity. However, effect sizes were small. Only CBT has been adequately studied which therefore allows a tentative conclusion that it has a small beneficial effect compared to usual care or waiting list controls. CBT was not more effective than enhanced care. The overall quality of evidence was rated low to moderate. Future studies should include various treatment modalities other than CBT, participants from different age groups and with different severity grades and long follow-up assessments. Also researchers should make efforts to blind outcome assessors.

In **Chapter 6** we wrote about how to manage adult patients with persistent MUPS in the light of the existing uncertainties. First we summarized the content of the four Cochrane reviews that were published about MUPS until now, including the one we wrote regarding non-pharmacological interventions: one examining the effect of different types of pharmacological treatments, one examining the effect of enhanced care and one examining the effect of consultation letters. After examining the current state of evidence, we gave recommendations for future research and clinical practice. Regarding future research we recommended large, high quality RCTs with adult MUPS patients, whom have different levels of severity of MUPS. Both pharmacological and non-pharmacological interventions in different settings should be assessed and attention should be paid to the treatment characteristics such as the treatment duration, intensity, and dosage. Outcomes should include severity of symptoms and functional impairments among other things but also longer follow-up durations (minimum 6-12 months) are needed. Regarding clinical practice we advised different steps for GPs to undertake to manage patients with MUPS in a structured manner. Exploring all symptom dimensions, explaining MUPS in a constructive and empathic way and discussion of possible treatments personalized to the patients' needs should be central.

In **Chapter 7** we examined the dialogue between 39 patients with moderate MUPS and five GPs related to symptom explanations and we explored the patients' responses. With the constant comparative analysis method, we analysed 112 audio-recorded

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consultations from two studies of the Symptoms Clinic Intervention, a moderate intensity consultation intervention for patients with MUPS in primary care. From the consultations we extracted 115 explanation sequences. We identified four dialogue types (i.e. lecture, storytelling, contest, deliberation), which differed in the extent to which the GP and/or patient controlled the dialogue. We identified eight patients' responses, ranging from acceptance to rejection of the explanation by the patient. From the results we developed a classification of dialogue types and patients' responses. While it requires validation in future studies, it provides a framework of dialogue types and outcomes. This framework can be used for teaching, evaluation of practice and research.

In **Chapter 8** we examined the association between MUPS and healthcare use (HCU), operationalized as the number of used medical services and number of health care contacts, over two years. Also we assessed the influence of depressive and anxiety disorders and personality traits on this association. We used data from the Netherlands Study of Depression and Anxiety (NESDA), a multisite cohort study and we included participants with current depressive and/or anxiety disorders, patients with subthreshold symptoms and healthy controls from different settings (n=2981). Measurements were taken at baseline and at one and two year follow-up. We analysed the data with generalized estimating equations to take into account the dependency of observations within participants with repeated measurements. We found that MUPS were positively associated with HCU over two years. Neuroticism and depressive disorders had the strongest influence on this association, but the association between MUPS and HCU remained significant. This suggests that good MUPS management is important. Also attention should be paid to comorbid depressive disorders and to personality traits. In future research, the adequacy of HCU should be addressed, the initial reason for HCU and a calculation of associated costs should be made that comes with increased HCU.

In **Chapter 9** we examined the association between MUPS and work functioning, operationalized as disability at work and absenteeism from work, over two years. Again we used data from the NESDA. This this time we only included working participants

(n=1887). We used mixed model analyses to correct for the dependency of observations within participants. We found that MUPS were positively associated with disability and absenteeism over two years. After adjusting for depressive and anxiety disorders, the associations between MUPS and work functioning weakened, but remained significant. Again this suggests that good MUPS management is important. Attention should be paid to comorbid mental health disorders when patients present themselves with MUPS. More insight is needed in favourable and unfavourable job characteristics to develop prevention and treatment interventions for MUPS.

In **Chapter 10** I presented an overall summary of our findings, interpreted the findings in the light of current evidence, discussed the most important methodological considerations and I gave recommendations for future research and clinical practice.