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This thesis is focused on fatigue as a main symptom presented in primary care. In chapter 1, the subject of fatigue in primary care is briefly introduced, followed by the background and aims of our study. We performed a prospective cohort study among adult patients visiting their GP with symptoms of fatigue, to answer questions on the course of fatigue and associated problems, prognostic factors and diagnoses within one year after presentation.

In chapter 2, the results of our question on diagnoses are presented. While many studies have focused on 'unexplained' fatigue, little is known about the distribution of diagnoses that account for fatigue presented in primary care. We aimed to describe the diagnoses established within one year after the consultation that are likely to explain fatigue presented as a main symptom in primary care. Diagnoses were evaluated on the possibility of an association with presented fatigue, in a Delphi procedure and by GP expert opinion. After initial content-based evaluation, diagnoses were also evaluated by taking into account the time period between onset of fatigue and establishment of diagnosis. For 571 patients, data on diagnoses were available. One-fourth of these patients received a diagnosis that provided a plausible explanation for their fatigue; these diagnoses included both psychological problems (16%) and somatic diseases (8%). About one fifth of patients received symptom diagnoses, most often musculoskeletal problems, that could possibly explain the fatigue but for which there was no consensus regarding a plausible explanation of the presented fatigue. Except for infections, considering the time period between onset of fatigue and establishment of diagnoses in the assessment of a plausible explanation proved to be difficult because of insufficient clinical information. The results do show that a minority of patients were diagnosed with serious pathology, and most patients did not receive a diagnosis that clearly explained their fatigue. However, considering the results of self-reported psychosocial problems, including sleep, the recording of such diagnoses by GPs seems to be an underestimation. The wide range of the conditions and symptoms that may explain or co-occur with fatigue indicate that it is a multidimensional problem that deserves attention not only as a symptom of underlying specific disease.

To summarize the available evidence on the course and prognostic factors of fatigue, we conducted a systematic review in both primary care patients and in the community. The results are presented in chapter 3. Two reviewers independently screened identified citations, discussed eligible studies, and assessed the methodological quality of selected studies. Data concerning study population, duration of follow-up, measurement of fatigue, outcome, and prognostic factors were extracted. Studies with populations selected by a specific disease or postpartum condition were excluded. We selected 21 articles reporting on 11 (partly) primary care cohorts and six community cohorts. Follow-up was up to 1 year in primary care and up to 4 years in the community,
and in most studies that presented duration of fatigue, participants were chronically fatigued. Because of the wide heterogeneity of studies, a qualitative analysis was performed. Recovery of fatigue varied widely, but no differences were found between settings. Sufficient evidence for an association with recovery was found for lower severity of fatigue, and limited evidence was found for good self-reported health, mental health, and psychological attributions. A major shortcoming in methodological quality of most studies was a potential bias due to a lack of information on response or loss to follow-up. Most studies on fatigue included patients with long symptom duration at baseline, which renders studying prognosis early in the course of fatigue impossible. We therefore conclude that prognostic studies should use an optimal design including selection of an inception cohort with limited duration of fatigue at baseline, a sufficient sample size, and information on rates and selectivity of response and loss to follow-up.

In chapter 4, we describe the results of our cohort study on the course of fatigue, functioning and associated symptoms. We performed an observational cohort study in 147 primary care practices. Patients consulting their general practitioner for a new episode of fatigue were sent questionnaires at 1, 4, 8, and 12 months after baseline. We collected measures of fatigue, perceived health and functioning, absenteeism, psychological symptoms, and sleep using the Checklist Individual Strength, the 36-Item Short Form Health Survey, the Four-Dimensional Symptoms Questionnaire, and the Pittsburgh Sleep Questionnaire Inventory. Of 856 recruited patients, 642 were enrolled in the study (response rate 75%). Completion rates during follow-up ranged between 82% and 88%. Patients were classified into 4 subgroups based on fatigue severity scores over time. We assessed patterns in the course of all outcomes in these subgroups and in the total population, and tested changes over time and differences between subgroups. For 75% of enrolled patients, four distinct groups could be discerned: 26% of patients had continuously high scores for fatigue, 17% had a fast recovery, 25% had a slow recovery, and 32% initially improved but then had a recurrence of fatigue. Patterns for the secondary outcomes of symptoms and functioning were all similar to the pattern for fatigue within each of the subgroups. The findings of this study suggest a longitudinal relationship between the severity of fatigue, impaired functioning, psychological symptoms, and poor sleep. Based on our results, we recommend physicians to be aware that a substantial proportion of patients seeking care for fatigue have these additional health and psychosocial problems.

In chapter 5, we show the results of a prediction analysis of prognostic factors of the course of fatigue in our cohort. Our aim was to determine which combination of factors was most strongly associated with a favourable or unfavourable outcome when patients presented with fatigue as a main symptom in primary care. The prognostic value of potential predictors was assessed by applying multivariable logistic regression analysis.
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The outcome was severity of fatigue, defined as a combination of dichotomised scores on several repeated measurements with the Checklist Individual Strength. Two separate models were used to predict either a favourable or an unfavourable course of fatigue. Baseline severity of fatigue and patient expectations of chronicity consistently predicted a poor outcome. Additional factors predicting a chronic course were baseline pain intensity and less social support. Baseline characteristics predicting a fast recovery were: male sex, not providing care for others (for example, for older people), better perceived health, and fewer (serious) prolonged difficulties. Both models had good reliability and discriminative validity. The identified combination of predictors reflects the biological, psychological and social dimensions of fatigue, with a significant contribution of patient expectations of chronicity in the prediction of a poor prognosis. We conclude that these negative perceptions, which are modifiable, should receive more attention in the initial assessment of patients presenting with fatigue.

In chapter 6 we focus on the temporal relationship between fatigue and pain. So far, most studies on the association between pain and fatigue have used cross-sectional data. Pain was measured using the Short-Form health survey (SF-36) and fatigue using the severity scale of the Checklist Individual Strength (CIS). Longitudinal associations were analysed using generalized estimated equations (GEE). We used three different models assessing possible relationships between the symptoms in time, either in the same intervals or with a time-lag, suggesting either a synchronous association or temporal association. The regression coefficients were strongest in the model assessing synchronous change, indicating that a one-point improvement in pain was associated with a 0.25 improvement in fatigue in the same time interval (adjusted for potential confounding). Baseline duration of fatigue and expectations of its future course significantly modified the association in this model, with stronger associations between changes in pain and fatigue found in patients with a shorter duration of fatigue or more positive expectations. The results indicate that changes in pain and fatigue are directly related in time, rather than showing temporal associations.

In the final discussion chapter, the results of our studies are discussed in relation to each other and the literature. Some methodological issues are considered, and suggestions for future research and practice are made. We conclude that many different factors may play a role in patients presenting with fatigue, including perceptions, pain and psychosocial problems. The identification of patients with a poor prognosis may therefore require more exploration by the GP.