

Is Fatigue a Disease-Specific or Generic Symptom in Chronic Medical Conditions?

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Objective: Severe fatigue is highly prevalent in various chronic diseases. Disease-specific fatigue models have been developed, but it is possible that fatigue-related factors in these models are similar across diseases. The purpose of the current study was to determine the amount of variance in fatigue severity explained by: (a) the specific disease, (b) factors associated with fatigue across different chronic diseases (transdiagnostic factors), and (c) the interactions between these factors and specific diseases. **Method:** Data from 15 studies that included 1696 patients with common chronic diseases and disorders that cause long-term disabilities were analyzed. Linear regression analysis with the generalized least-squares technique was used to determine fatigue-related factors associated with fatigue severity, that is, demographic variables, health-related symptoms and psychosocial variables. **Results:** Type of chronic disease explained 11% of the variance noted in fatigue severity. The explained variance increased to 55% when the transdiagnostic factors were added to the model. These factors were female sex, age, motivational and concentration problems, pain, sleep disturbances, physical functioning, reduced activity and lower self-efficacy concerning fatigue. The predicted variance increased to 61% when interaction terms were added. Analysis of the interactions revealed that the relationship between fatigue severity and relevant predictors mainly differed in strength, not in direction. **Conclusions:** Fatigue severity can largely be explained by transdiagnostic factors; the associations vary between chronic diseases in strength and

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This work was supported by the Dutch Diabetes Research Foundation (Diabetes Fonds, Grant 2012.00.1483).

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significance. This suggests that severely fatigued patients with different chronic diseases can probably benefit from a transdiagnostic fatigue-approach which focuses on individual patient needs rather than a specific disease.

Keywords: chronic disease, fatigue, health-related factors, psychosocial factors, transdiagnostic approach

Supplemental materials: <http://dx.doi.org/10.1037/hea0000598.supp>

Severe fatigue is highly prevalent in patients with chronic diseases and medical conditions that cause long-term disabilities, with prevalence rates varying from 40% to 74% (Goedendorp et al., 2014; Kalkman et al., 2005; van der Werf et al., 1998; van der Werf, van den Broek, Anten, & Bleijenberg, 2001; van Hoogmoed, Fransen, Bleijenberg, & van Riel, 2010). Several studies have shown that severely fatigued patients report more limitations in physical, social, and mental functioning than those without severe fatigue as well as describing fatigue as one of the most debilitating symptoms of their disease (Droogleever Fortuyn et al., 2012; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Goedendorp et al., 2014; Kalkman et al., 2005).

It has been suggested that fatigue in chronic disorders is a disease-specific symptom, with disease-specific somatic underlying processes. Hence, terms such as “post-stroke fatigue,” “multiple sclerosis fatigue,” or “rheumatoid arthritis fatigue” have been introduced. However, the relationship between fatigue and somatic processes associated with a specific disease, such as inflammation in rheumatoid arthritis (van Hoogmoed et al., 2010) or glycemic control in diabetes (Menting et al., 2016) is often weak or absent altogether. Studies of fatigue at the individual patient level have been more successful, investigating not only the fatigue’s relationship with somatic abnormalities, but also with patients’ behavior and other symptoms. This has led to several cognitive-behavioral—but still disease-specific—models of fatigue (Hewlett et al., 2011; Ingles, Eskes, & Phillips, 1999; van Kessel et al., 2006). Most models differentiate between factors that trigger fatigue, which is frequently a somatic process that is part of the disease, and factors that maintain or are associated with fatigue. It has been demonstrated that several factors such as demographic variables, health-related symptoms, psychosocial factors and aspects of patients’ daily functioning, are linked with or maintain fatigue. For example, age and sex are correlated with fatigue in patients with Type 1 diabetes and neuromuscular diseases (Goedendorp et al., 2014; Kalkman et al., 2005); depressive symptoms, sleep disturbances, and pain have been found to be related to fatigue in patients with narcolepsy and rheumatoid arthritis (Droogleever Fortuyn et al., 2012; van Hoogmoed et al., 2010); social and physical functioning are associated with fatigue in patients with Ehlers-Danlos syndrome (Voermans et al., 2010); and concentration problems, reduced motivation and activity along with a low self-efficacy concerning fatigue are related to fatigue in patients with rheumatoid arthritis, narcolepsy and neuromuscular disorders (Droogleever Fortuyn et al., 2012; Kalkman et al., 2005; van Hoogmoed et al., 2010; Voermans et al., 2010).

To date, studies have investigated fatigue and the factors associated with it in different chronic diseases, mostly treating both fatigue and such factors as disease-specific. However, it is

potentially likely that factors linked with fatigue are generic and thus similar across diseases. Perhaps the prevalence of these factors varies between diseases, like depression, but the relationship with fatigue is most likely not dependent on the specific disease. If this is true, there are implications for both assessment and management of this highly prevalent and burdensome symptom. Thus far, most research has focused on the development of disease-specific fatigue treatments, such as cognitive-behavioral therapy for patients with multiple sclerosis (van Kessel et al., 2008) or aerobic exercise therapy for those with neuromuscular disorders (Voet et al., 2014). However, if fatigue-related factors are the same across chronic diseases, it might be possible to generalize findings from one chronic disease to another. Consequently, a transdiagnostic treatment for fatigue could be developed, defined as an approach where processes and factors are common across disorders (Harvey, 2004), and hence interventions targeting these factors are similar across diseases. It would also imply that the pathophysiology of fatigue is not disease-specific, but that the (neuro)biological mechanisms underlying the perception of fatigue are a generic response to illness in a substantial subgroup of patients.

To our knowledge, it has not been empirically tested to what extent fatigue severity in chronic diseases and disorders that cause long-term disabilities can be explained by transdiagnostic factors that are the same across various chronic diseases or whether fatigue is a unique or disease-specific symptom. As studies evaluating fatigue in chronic diseases so far have found a number of overlapping fatigue-related factors, we hypothesize that more variance in fatigue severity will be accounted for by transdiagnostic, non-disease-specific factors, such as sleep disturbances or self-efficacy concerning fatigue. The purpose of the present, explorative study was to reanalyze data of patients suffering from 15 common chronic diseases and disorders that cause long-term disabilities. We sought to demonstrate the extent to which variance in fatigue severity can be explained by (a) the specific chronic disease, (b) non-disease-specific factors related to fatigue, irrespective of the specific chronic disease, and (c) interactions between non-disease-specific factors and type of illness. A significant interaction would indicate a variable strength and/or direction of the relationship between non-disease-specific factors and fatigue severity for one or more chronic diseases. A different direction of the effect in particular would suggest a disease-specific effect of the factor and therefore indicate that the studied factor does not have a transdiagnostic association with fatigue. The non-disease-specific factors studied were demographic variables, current health-related symptoms, aspects of daily functioning and cognitive-behavioral factors.

Method

Study Design, Participants, and Selection of Studies

Data from 15 cross-sectional studies involving patients with the following chronic diseases or medical disorders causing long-term disabilities were reanalyzed: (a) neuralgic amyotrophy (NA; van Alfen, van der Werf, & van Engelen, 2009); (b) cerebrovascular accident (CVA; van der Werf et al., 2001); (c) Ehlers-Danlos syndrome (EDS; Voermans et al., 2010); (d) immunoglobulin deficiency (ID; Strik-Albers, Nikolaus, van Deuren, Knoop, & Simon, 2018); (e) narcolepsy Type I (NC; Droogleeve Fortuyn et al., 2012); (f) chronic kidney disease (CKD); (g) renal transplantation (RT; Goedendorp, Hoitsma, Bloot, Bleijenberg, & Knoop, 2013); (h) chronic pancreatitis (CP); (i) primary Sjögren's syndrome (pSS); (j) facioscapulohumeral muscular dystrophy (FSHD; Kalkman et al., 2005); (k) adult-onset myotonic dystrophy (MD; Kalkman et al., 2005); (l) hereditary motor and sensory neuropathy Type I (HMSN-I; Kalkman et al., 2005); (m) multiple sclerosis (MS; van der Werf et al., 1998; Vercoulen et al., 1996); (n) rheumatoid arthritis (RA; van Hoogmoed et al., 2010); and (o) Type 1 diabetes mellitus (T1DM; Goedendorp et al., 2014).

In selecting the individual studies, we contacted as many authors as possible of which we knew had studied fatigue in chronic diseases with the Checklist Individual Strength (CIS) questionnaire. We chose only studies that assessed fatigue severity with the CIS and evaluated at least the following potential determinants: sex, age, concentration problems, reduced motivation and reduced activity.

Of the 15 study cohorts, data from 11 studies were published. The data on CKD, CP, and pSS were collected, but were not previously published. The data on ID are also not yet published. A total of 1696 patients were included for the statistical analysis. The number of patients per study is listed in Table 1. For each study, patients were recruited from different universities and general hospitals in the Netherlands between 1999 and 2015.

The medical ethical committee gave approval for each of the published studies or decided that the study did not fall under the remit of the Medical Research Involving Human Subjects policy. The same was true for the four unpublished studies—the study of Strik-Albers and colleagues (ID) was approved by the medical ethical committee; the studies of Goedendorp and colleagues (CKD) along with Bleijenberg and coworkers (CP and pSS) were remitted of judgment. The medical ethical committee also reviewed the present study and decided that no further judgment was necessary according to Dutch law, specifically the Medical Research Involving Human Subjects Act.

Instruments

Demographic variables. Demographic variables were sex and age assessed by patient self-reporting.

Fatigue severity. Fatigue severity was measured using the CIS questionnaire, in particular the fatigue severity subscale (Worm-Smeitink et al., 2017). The subscale consists of eight items, for example, “I am feeling tired”. Each item is scored on a 7-point Likert scale ranging from 1 (*Yes, that is true*) to 7 (*No, that is not true*). Scores on the questionnaire range from eight to 56, with higher scores indicating more fatigue severity. A score of 35 is

used as a cut-off for severe fatigue. The CIS has been demonstrated to be a valid and reliable instrument (Worm-Smeitink et al., 2017).

Concentration problems. Concentration problems were evaluated with the concentration subscale of the CIS (Worm-Smeitink et al., 2017). The scale comprises five items, for example, “It takes a lot of effort to concentrate on things”; each item is scored on a Likert scale ranging from 1 (*Yes, that is true*) to 7 (*No, that is not true*). Higher scores on this subscale indicate more concentration problems. The psychometric properties of the CIS subscale are robust (Worm-Smeitink et al., 2017).

Reduced motivation. Reduced motivation was assessed using the motivation subscale of the CIS (Worm-Smeitink et al., 2017), which consists of four items (e.g., “I do not feel like doing anything”) scored on a 7-point Likert scale ranging from 1 (*Yes, that is true*) to 7 (*No, that is not true*). The validity and reliability of the CIS subscale are regarded as strong (Worm-Smeitink et al., 2017).

Reduced activity. Reduced activity was determined using the activity subscale of the CIS (Worm-Smeitink et al., 2017). This subscale features of three items (e.g., “I think I do very little in a day”); each item is scored on a 7-point Likert scale ranging from 1 (*Yes, that is true*) to 7 (*No, that is not true*). Once again, the CIS is considered a valid and reliable instrument (Worm-Smeitink et al., 2017).

Depressive symptoms. Depressive symptoms were established with the Beck Depression Inventory for Primary Care (BDI-PC; Beck, Guth, Steer, & Ball, 1997) in 14 studies, and one study employed the Symptom Checklist (SCL-90), depression subscale (Arrindell & Ettema, 1986/2003). The BDI-PC is a widely used self-reporting questionnaire with robust psychometric properties (Beck et al., 1997). The questionnaire is comprised of seven items; each item is scored on a 4-point Likert scale ranging from 0 to 3. The seven items deal with the symptoms of sadness, loss of pleasure, pessimism, past failure, self-dislike, self-criticalness, and suicidal thoughts and wishes. Scores range from zero to 21, with scores of four and higher indicating clinically relevant depressive symptoms (Beck et al., 1997). Meanwhile, the SCL-90 is a multidimensional symptom checklist measuring psychological and physical symptoms. The depression subscale of the SCL-90 consists of 16 items (e.g., the symptom, “lack of motivation”), which are scored on a 5-point scale from zero (*Not at all*) to 4 (*Extremely*) to reflect the extent to which the symptoms have been manifested. The scores range from 16 to 80. Higher scores suggest more severe depressive symptoms. A cut-off score of 29—the mean score plus one standard deviation from the normal population (Arrindell & Ettema, 1986/2003)—was utilized to indicate clinically relevant depressive symptoms. The SCL-90 has strong psychometric properties (Arrindell & Ettema, 1986/2003). To determine whether depressive symptoms predicted severe fatigue, the score of the BDI-PC and the depression subscale of the SCL-90 were transformed into a dichotomous variable to indicate the presence of depressive symptoms using the aforementioned cut-off scores (0 = no, 1 = yes).

Sleep disturbances and disrupted sleep-wake pattern. Sleep disturbances and disrupted sleep-wake patterns were gauged using the Sickness Impact Profile-8 (SIP-8), specifically the sleep and rest subscale (Bergner, Bobbitt, Carter, & Gilson, 1981). The SIP-8 measures limitations in daily functioning across eight

Table 1
Overview of the 15 Included Cohorts ($n = 1696$)

Author	Chronic disease	Study population & setting	Objective of the study	Potential associated factors	Female sex (%)	Mean age (SD)	Mean CIS fatigue severity (SD)	Percentage of severely fatigued patients (95% CI)
Van Alfen et al. (2009)	Neuralgic amyotrophy (NA)	87 patients with the diagnosis of NA were included. Patients were recruited from the outpatient clinic of one university medical center.	The objective of this study was to investigate the prevalence of fatigue and pain, and to describe the severity of psychological symptoms, the functional status and quality of life in patients with NA.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (yes/no) • Pain • Social functioning • Physical functioning	33(38%)	44.7 (13.8)	29.6 (14.2)	40 (30 to 51)
Van der Werf et al. (2001)	Cerebrovascular accident (CVA)	74 patients with the diagnosis of a CVA one year before the start of the study were included. The patients were recruited from a stroke database of one teaching hospital.	The purpose of this study was to investigate the prevalence of severe fatigue after a CVA had occurred. In addition, the relationship between fatigue and levels of physical impairment and depression was studied.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Sleep disturbances	20 (27%)	61.5 (8.8)	35.2 (14.7)	58 (47 to 70)
Voermans et al. (2010)	Ehlers-Danlos syndrome (EDS)	273 patients with EDS were included. Patients were recruited from a Dutch EDS patient organization and the outpatient clinic from one university medical center.	The objective of this study was to investigate the prevalence of fatigue in EDS, as well as its clinical relevance and association with potential variables.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances • Self-efficacy concerning fatigue	244 (89%), 2 missing	40.7 (12.7)	41.7 (11.3)	77 (73 to 82)
Strik-Albers et al. (2018)	Immunoglobulin deficiency (ID)	43 patients with ID were included. Patients were recruited from the Expert Center for Immunodeficiency and Autoinflammation from one university medical center.	The objective of this study was to investigate the prevalence and associated factors of fatigue in patients with ID.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances • Self-efficacy concerning fatigue	18 (42%)	45.1 (15.3)	32.3 (12.0)	51 (38 to 70), 2 missing

(table continues)

Table 1 (continued)

Author	Chronic disease	Study population & setting	Objective of the study	Potential associated factors	Female sex (%)	Mean age (SD)	Mean CIS fatigue severity (SD)	Percentage of severely fatigued patients (95% CI)
Droogleever Fortuyn et al. (2012)	Narcolepsy type 1 (NC)	80 patients under active treatment for NC were included. The patients were recruited from one university medical center.	The objective of this study was to determine the prevalence of severe fatigue in patients with NC, as well as to study its association with excessive daytime sleepiness, psychological distress, functional impairment and quality of life.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances • Self-efficacy concerning fatigue	46 (58%)	48.3 (14.7)	38.9 (11.6)	63 (52 to 73)
Goedendorp, M. M. (2012) ^a	Chronic kidney disease (CKD)	137 patients with the diagnosis CKD were included. The patients were recruited from one university medical center.	The purpose of this study was to investigate the prevalence of severe fatigue in patients with CKD, as well as the impact of severe fatigue on daily functioning. In addition, potential associations of severe fatigue were studied.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances	57 (42%)	54.3 (11.6)	37.4 (13.4)	61 (53 to 70), 2 missing
Goedendorp, M. M. (2012)	Renal transplantation (RT)	180 patients who underwent a renal transplantation were included. The patients were recruited from one university medical center.	The objective of this study was to determine the prevalence, impact and associated factors of severe fatigue in patients with a RT. The latter were specific transplantation-related factors and nonspecific somatic, behavioral and psychosocial factors.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances	61 (34%)	54.1 (12.4)	28.8 (14.8)	39 (32 to 46), 1 missing
Bleijenberg, G. (1999) ^a	Chronic pancreatitis (CP)	61 patients with CP were included. The patients were recruited from a Dutch CP patient organization.	The objective of this study was to investigate the prevalence and potential associated factors of severe fatigue in CP.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning	29 (48%)	51.5 (11.0)	40.3 (12.6)	72 (62 to 85), 1 missing

Table 1 (continued)

Author	Chronic disease	Study population & setting	Objective of the study	Potential associated factors	Female sex (%)	Mean age (SD)	Mean CIS fatigue severity (SD)	Percentage of severely fatigued patients (95% CI)
Bleijenberg et al. (2007) ^a	Primary Sjögren's syndrome (pSS)	31 patients with the diagnosis pSS were included. The patients were recruited from one university medical center.	The objective of this study was to gain more knowledge about the characteristics of severely fatigued patients with pSS. In addition, potential psychosocial factors associated with fatigue were studied.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Self-efficacy concerning fatigue	28 (90%)	50.5 (15.8)	38.1 (12.8)	68 (50 to 85)
Kalkman et al. (2005)	Facioscapulohumeral muscular dystrophy (FSHD)	65 patients with the diagnosis of FSHD were included. The patients were recruited from the Neuromuscular Center of one university medical center. In addition, patients were recruited from a Dutch Neuromuscular Diseases Association.	The objective of this study was to investigate the prevalence of fatigue and its impact on functional impairment in daily life in patients with relatively common types of neuromuscular disorders.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances • Self-efficacy concerning fatigue	27 (42%)	43.1 (10.3)	36.1 (11.9)	62 (49 to 74)
Kalkman et al. (2005)	Adult-onset myotonic dystrophy (MD)	79 patients with the diagnosis of MD were included. The patients were recruited from the Neuromuscular Center of one university medical center. In addition, patients were recruited from a Dutch Neuromuscular Diseases Association.	The objective of this study was to investigate the prevalence of fatigue and its impact on functional impairment in daily life in patients with relatively common types of neuromuscular disorders.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances • Self-efficacy concerning fatigue	35 (44%)	41.0 (9.9)	38.7 (11.2)	66 (55 to 77)
Kalkman et al. (2005)	Hereditary motor and sensory neuropathy type 1 (HMSN-I)	73 patients with the diagnosis of HMSN-I were included. The patients were recruited from the Neuromuscular Center of one university medical center. In addition, patients were recruited from a Dutch Neuromuscular Diseases Association.	The objective of this study was to investigate the prevalence of fatigue and its impact on functional impairment in daily life in patients with relatively common types of neuromuscular disorders.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Sleep disturbances • Self-efficacy concerning fatigue	43 (59%)	42.4 (9.8)	38.1 (11.9)	66 (55 to 77)

(table continues)

Table 1 (continued)

Author	Chronic disease	Study population & setting	Objective of the study	Potential associated factors	Female sex (%)	Mean age (SD)	Mean CIS fatigue severity (SD)	Percentage of severely fatigued patients (95% CI)
Van der Werf et al. (1998) & Vercoulen et al. (1996)	Multiple sclerosis (MS)	71 patients with the diagnosis MS were included. For the present study, data from two studies were combined that both studied fatigue in MS. The patients were recruited from one university medical center.	• The objective of the study of Van der Werf and colleagues was to investigate the potential cerebral abnormalities in fatigued patients with MS. • The objective of the study of Vercoulen and colleagues was to investigate the multidimensional character of fatigue in patients with MS.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Sleep disturbances	48 (68%)	36.7 (8.7)	40.8 (12.2)	73 (63 to 84)
Van Hoogmoed et al. (2010)	Rheumatoid arthritis (RA)	228 patients with the diagnosis of RA were included. The patients were recruited from the outpatient rheumatology clinic of one university medical center.	The objective of this study was to determine the prevalence of severe fatigue in patients with RA. In addition, the patients' perception of fatigue and potential associated factors of fatigue were determined.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Social functioning • Physical functioning • Self-efficacy concerning fatigue	144 (63%)	55.9 (10.8)	31.5 (12.8)	42 (36 to 49)
Goedendorp et al. (2014)	Type 1 diabetes (T1DM)	214 patients with the diagnosis of type 1 diabetes were included. The patients were recruited from a diabetes clinic of one university medical center.	The objective of this study was to investigate the prevalence and impact of severe fatigue in patients with type 1 diabetes. In addition, potential determinants of fatigue were studied.	• Sex • Age • Concentration problems • Reduced motivation • Reduced activity • Depressive symptoms (continuous variable) • Pain • Sleep disturbances • Self-efficacy concerning fatigue	114 (53%)	48.0 (13.0)	30.9 (14.4)	44 (38 to 51)

Note. SD = standard deviation.
^a Not published.

domains: sleep and rest, homemaking, mobility, social interactions, ambulation, leisure activities, alertness behavior, and work limitations. The sleep and rest subscale consists of seven items (e.g., "I sleep or nap during the day"). The subject is asked to check only those items that are applicable to their health. The checked items are added to a score ranging from zero to 499; a higher score indicates more sleep disturbances. As with the other scoring procedures in this study, the SIP-8 has high reliability and validity (Bergner et al., 1981).

Pain. Pain and pain symptoms were evaluated by the Health Survey Short Form-36 (SF-36) questionnaire, in particular the bodily pain subscale (Aaronson et al., 1998). The SF-36 measures the health status across eight domains: vitality, physical functioning, bodily pain, general health perceptions, role limitations based on physical health problems, role limitations owing to emotional problems, social functioning, and general mental health. The raw scale scores of the bodily pain subscale are transformed into one score ranging from zero to 100; a higher score indicates better functioning and accordingly less pain. The psychometric properties of the SF-36 are highly reliable (Aaronson et al., 1998).

Social functioning. Social functioning was assessed with the SF-36 questionnaire, specifically the social functioning subscale (Aaronson et al., 1998). The SF-36 evaluates the health status across eight domains, including social functioning. Scores on the social functioning subscale range from zero to 100; a greater score on this subscale is demonstrative of better social functioning. The social functioning subscale of the SF-36 has documented validity and reliability (Aaronson et al., 1998).

Physical functioning. Physical functioning was measured via the SF-36 questionnaire, physical functioning subscale (Aaronson et al., 1998). Scores from the physical functioning subscale range from zero to 100 with higher scores suggestive of a better physical functioning. As per the other subscales employed herein, the physical functioning subscale of the SF-36 has high validity and reliability (Aaronson et al., 1998).

Self-efficacy concerning fatigue. Self-efficacy concerning fatigue relates to the patients' confidence in coping with fatigue and was evaluated with the Self-Efficacy Scale (SES) for fatigue (Prins et al., 2001). The SES for fatigue is a seven-item questionnaire (e.g., "Do you think you can influence your fatigue?"); each item is scored on a four-point scale ranging from one (*No, I do not think so*) to four (*Yes, I do think so*). Scores ranged from seven to 28 with higher scores indicating more self-efficacy concerning fatigue.

Assessment of Risk of Bias in the Included Studies

We rated the risk of bias for three biases that we thought to be the most important and common in cross-sectional studies: the selection of participants, the accuracy of the medical diagnosis and the sample size. Each potential bias was classified into a low risk, an unclear risk and a high risk of bias. The potential risks were systematically gauged by two raters (JM, HK); agreement was reached through discussion.

Selection of participants. In cross-sectional studies, potential selection biases can arise based on the procedure of selecting participants. We defined the risks of this bias as follows:

- Low risk: participants were selected by picking a random sample from a pool of eligible participants; all forms of systematically selecting participants;
- Unclear risk: insufficient information about the sample selection; and
- High risk: the sample for the study was picked by convenience.

Accuracy of medical diagnosis. The present paper included studies with patients that suffered from a medical condition. It may be possible that potential bias could have been present because of how the patients were included in these studies.

- Low risk: a medical practitioner selected the participants; participants were chosen from an outpatient pool of a hospital; the medical diagnosis was tested by a medical practitioner;
- Unclear risk: insufficient information on how the patients were selected; and
- High risk: self-report scale; patients were selected from a patient organization.

Sample size. A small sample size could be cause of a potential bias. We defined the risk of this bias as follows:

- Low risk: >100 participants;
- Unclear risk: 50–99 participants; and
- High risk: <50 Participants.

Statistical Analysis

Statistical analysis was performed using IBM's Statistical Package for the Social Sciences (SPSS) Version 22.0 (IBM Corp., 2013). Descriptive statistics with means and their standard deviations or frequencies and percentages were reported. Linear regression analysis with the generalized least-squares (GLS) technique with fatigue severity as the dependent variable was employed to test which factors were significantly related to fatigue severity. As fixed effects, the following independent variables were entered: chronic disease (1 = NA, 2 = CVA, 3 = EDS, 4 = ID, 5 = NC, 6 = CKD, 7 = RT, 8 = CP, 9 = pSS, 10 = FSHD, 11 = MD, 12 = HMSN-I, 13 = MS, 14 = RA, 15 = T1DM), age, sex, concentration problems, reduced motivation, reduced activity, depressive symptoms, pain, sleep disturbances, social functioning, physical functioning and self-efficacy concerning fatigue, and the interactions between these variables and each chronic disease. Missing values were not replaced. A stepwise procedure was used to analyze the explained variance (R^2) of fatigue severity explained by (a) the main effect of chronic disease, (b) the main effects of the chronic disease and other independent variables, and (c) the main effects plus the interaction effects between the chronic disease and the independent variables. Significant main effects indicated an overall effect of the independent variables on fatigue severity across all chronic diseases. Significant interaction effects suggested that the relationship between fatigue severity and the independent variables differed between chronic diseases. To interpret significant interactions, the size and direction of the estimates and their 95% confidence intervals (CI) for each chronic disease were calculated and plotted. Plots were visually inspected to aid interpretation.

As not all studies assessed all potential fatigue-related factors, the stepwise procedure was executed for five different

fatigue models: model one (15 chronic diseases and seven independent variables), model two (13 chronic diseases and eight independent variables), model three (11 chronic diseases and eight independent variables), model four (11 chronic diseases and 10 independent variables), and model five (nine chronic diseases and nine independent variables). A detailed overview of the fatigue-related factors assessed in each study is provided in Table 1. *p* values were considered to be significant at $p < .05$. As this study had an explorative character, correcting the *p*-level for multiple testing was purposely refrained from.

Results

Demographic Characteristics and Prevalence of Severe Fatigue

The mean age of the sample was 48.3 years ($SD = 13.7$) and 947 patients (56%) were female. More than half of the patients (57%) reported fatigue scores above the cut-off for severe fatigue. Prevalence rates of severe fatigue varied between chronic diseases from 39% to 77%. Table 1 presents an overview of the age, sex, mean fatigue severity score, and the number of severely fatigued patients for each chronic disease.

Effect of Chronic Disease and Potential Fatigue-Related Factors on Fatigue Severity

In the first step of the fatigue model with the largest number of cases, chronic disease [$F(14, 126.82) = 15.61, p < .001$] was found as a significant predictor of fatigue severity (see Table 2). The effect of chronic disease in the other fatigue models was similar and can be reviewed in Tables 1.1 to 1.4 in the online

supplemental material. Chronic disease accounted for 11% of the variance in fatigue in Model 1 (range between the other models was 11% to 12%). When adding the other potential fatigue-related factors in a second step to the model, the explained variance rose to 55% in Model 1 (range between the other models was 60% to 62%). Chronic disease still significantly predicted fatigue severity [$F(14, 154.39) = 13.68, p < .001$], however the impact of chronic disease was less strong compared with step 1 as can be inferred from Figure 1. In Figure 1, the mean value of fatigue severity and its 95% CIs for each chronic disease is displayed for step 1 and step 2. In step 2, the value is adjusted for chronic disease and the other fatigue-related factors. It is apparent that the mean values of fatigue severity are more similar for the chronic diseases and their 95% CIs are decreased in the second step. This suggests that the effect of chronic disease becomes smaller when adding transdiagnostic factors to the model.

We report the potential transdiagnostic factors that are significantly related to fatigue severity and thus are similar across all chronic diseases. When the effects were significant in multiple fatigue-models, the effect of the model with the highest number of cases is reported. The effects of fatigue model one can be found in Table 2 and the effects of models two to five are located in Tables 1.1 to 1.4 in the Appendix. Concentration problems [$F(1, 1542.01) = 105.63, p < .001$; Model 1], motivational problems [$F(1, 1509.38) = 180.25, p < .001$; Model 1] and reduced activity [$F(1, 1554.97) = 269.19, p < .001$; Model 1] were observed as significant predictors of fatigue severity. Both pain [$F(1, 1385.90) = 182.76, p < .001$; Model 2] and sleep disturbances [$F(1, 1074.85) = 77.32, p < .001$; Model 3] predicted fatigue severity. For each of these factors, a more problematic score was associated with more fatigue severity. Also social functioning [$F(1,$

Table 2
Fixed Effects of the Main and Interaction Effects Presented for Model 1 ($n = 1628$)

Effect	Step 1		Step 2		Step 3	
	<i>F(df)</i>	<i>p</i>	<i>F(df)</i>	<i>p</i>	<i>F(df)</i>	<i>p</i>
Main effects						
Disease	15.61 (14)	<.001	13.68 (14)	<.001	5.83 (14)	<.001
Age			23.40 (1)	<.001	13.35 (1)	<.001
Sex			17.27 (1)	<.001	17.60 (1)	<.001
Concentration problems			105.63 (1)	<.001	57.93 (1)	<.001
Reduced motivation			180.25 (1)	<.001	116.44 (1)	<.001
Reduced activity			269.19 (1)	<.001	113.50 (1)	<.001
Depressive symptoms (yes/no)			7.14 (1)	.008	5.01 (1)	.026
Interaction effects						
Disease × Age					2.32 (14)	.006
Disease × Sex					1.97 (14)	.024
Disease × Concentration Problems					2.12 (14)	.015
Disease × Reduced Motivation					1.27 (14)	.235
Disease × Reduced Activity					4.68 (14)	<.001
Disease × Depressive Symptoms (yes/no)					1.60 (14)	.085
Predicted variance R^2	.11		.55		.61	

Note. Model 1: $n = 1628$, seven potential independent variables, 15 chronic diseases (NA, CVA, EDS, ID, NC, CKD, RT, CP, pSS, FSHD, MD, HMSN-I, MS, RA, T1DM); NA = neuralgic amyotrophy; CVA = cerebrovascular accident; EDS = Ehlers-Danlos syndrome; ID = immunoglobulin deficiency; NC = narcolepsy type 1; CKD = chronic kidney disease; RT = renal transplantation; CP = chronic pancreatitis; pSS = primary Sjögren's syndrome; FSHD = facioscapulohumeral muscular dystrophy; MD = adult-onset myotonic dystrophy; HMSN = hereditary motor and sensory neuropathy type 1; MS = multiple sclerosis; RA = rheumatoid arthritis; T1DM = type 1 diabetes mellitus.

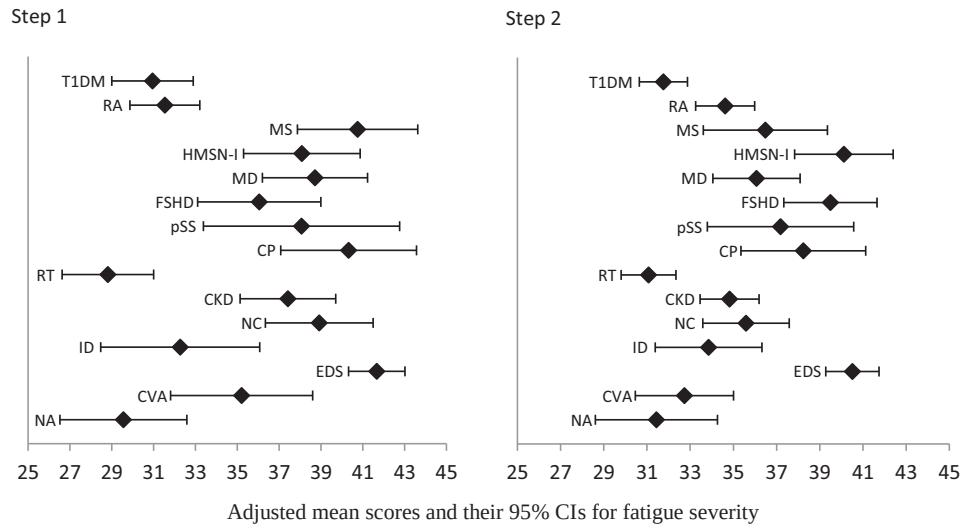


Figure 1. Adjusted mean scores and their 95% CIs for fatigue severity for each chronic disease in step one and step two of the fatigue model. Step one: only chronic disease as independent variable; step two: chronic disease and transdiagnostic factors as independent variables. NA = neuralgic amyotrophy; CVA = cerebrovascular accident; EDS = Ehlers-Danlos syndrome; ID = immunoglobulin deficiency; NC = narcolepsy Type I; CKD = chronic kidney disease; RT = renal transplantation; CP = chronic pancreatitis; pSS = primary Sjögren's syndrome; FSHD = facioscapulohumeral muscular dystrophy; MD = adult-onset myotonic dystrophy; HMSN-I = hereditary motor and sensory neuropathy Type I; MS = multiple sclerosis; RA = rheumatoid arthritis; T1DM = Type 1 diabetes mellitus.

1101.74) = 7.52, $p = .006$; Model 4], physical functioning [$F(1, 1153.72) = 51.05$, $p < .001$; Model 4] and self-efficacy concerning fatigue [$F(1, 911.63) = 90.34$, $p < .001$; Model 5] predicted fatigue severity. Here, lower social functioning, physical functioning, and self-efficacy concerning fatigue were related to a higher fatigue severity. Being younger [$F(1, 1371.46) = 23.40$, $p < .001$; Model 1] was associated with higher fatigue severity, and in most models, female sex [$F(1, 1384.02) = 17.27$, $p < .001$; Model 1] was associated with being more severely fatigued. Depressive symptoms evaluated with the dichotomous variable ("yes/no") predicted fatigue severity in model one [$F(1, 1402.69) = 7.14$, $p = .008$], but not in model two. Depressive symptoms assessed via the BDI-PC questionnaire predicted fatigue severity in model five [$F(1, 191.06) = 5.00$, $p = .027$], but not in models three or four.

Effect of Significant Interaction Effects Between Chronic Diseases and Fatigue-Related Factors on Fatigue Severity

By adding the interaction effects between chronic diseases and fatigue-related factors in the third step of the model, the explained variance increased slightly to 61% in Model 1 (range between the other models was 66% to 69%). In eight of the 12 potential fatigue-related factors, an interaction effect was found, which indicated differences in the predictive value of these variables on fatigue severity between chronic diseases. Figure 2 depicts the estimates and their 95% CIs of the significant interaction effects. It is clear that associations of sex and age with fatigue severity were significant for fewer than half of the chronic diseases. Sex was related to fatigue severity in patients with FSHD, T1DM, and pSS. With these three diseases, being female was associated with

being more fatigued. In five of 15 diseases, being younger was associated with greater severity of fatigue. These associations were determined in patients with RT, T1DM, RA, CP, and ID. In the majority of diseases, pain was significantly related to fatigue severity. There was a clear trend indicating that more pain was associated with more severe fatigue. The same was true for concentration problems with the majority of diseases. In half of the chronic diseases, lower levels of physical functioning as well as reduced physical activity were associated with fatigue severity. In all of these chronic diseases, reduced activity was associated with being more fatigued. In approximately half of the diseases, both sleep disturbances and self-efficacy concerning fatigue were related to fatigue severity. More sleep disturbances were associated with being more severely fatigued in patients with MS, HMSN-I, EDS, T1DM, RT and CKD. Lower self-efficacy concerning fatigue was connected with more severe fatigue in patients with EDS, RA, T1DM and HMSN-I.

Risk of Bias in Included Studies

Table 2 in the online supplemental materials outlines the risk of the three biases for each individual study.

Selection of Participants

Two studies were rated to be of low risk; they systematically selected a random pool of potential participants for their study. Twelve studies determined to have an unclear bias risk as it was not apparent whether the selection of participants was random or not. One study established to have a high bias risk. In this study, a select group of participants of a Dutch patient organization was chosen.

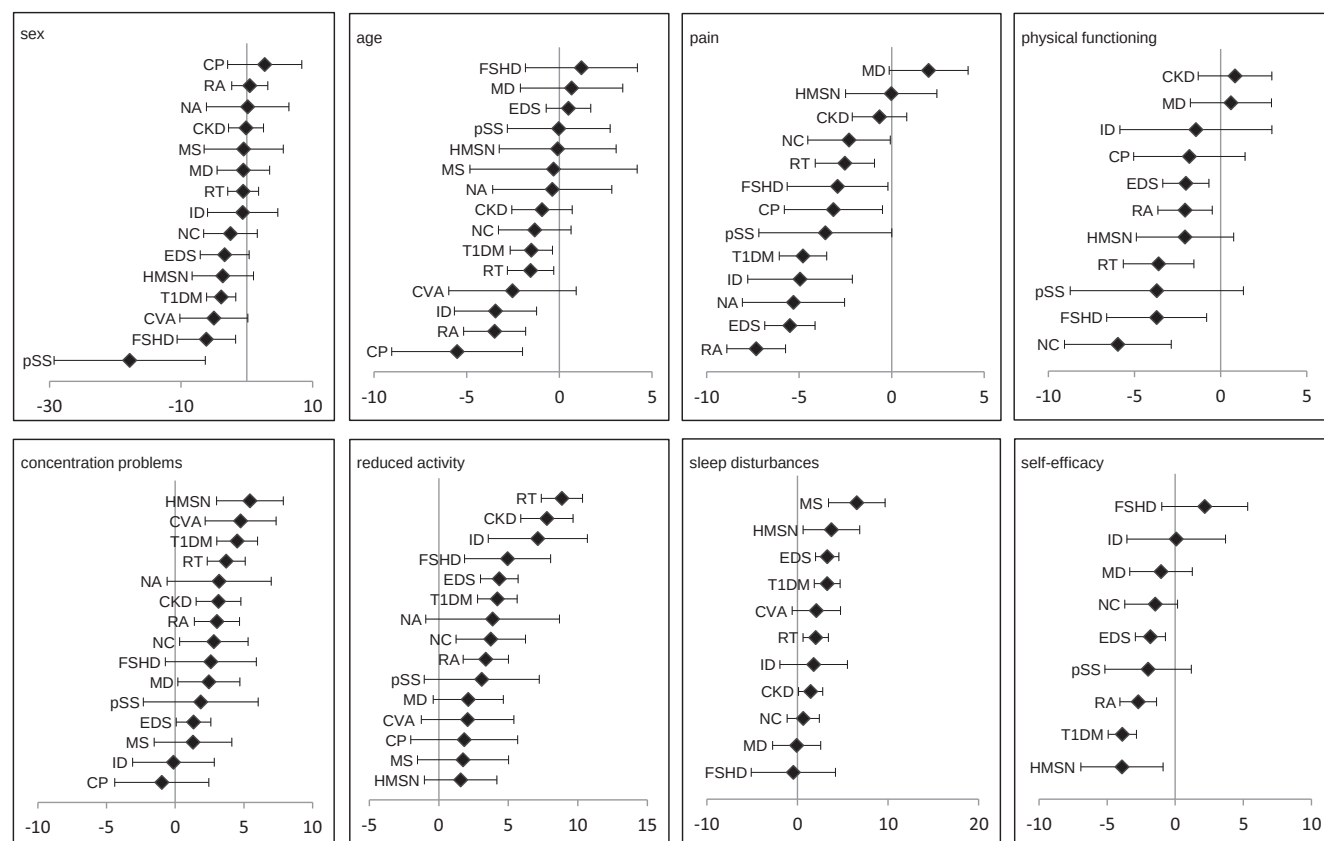


Figure 2. Standardized estimates and 95% CIs of the significant interaction effects for each predictor. NA = neuralgia amyotrophy; CVA = cerebrovascular accident; EDS = Ehlers-Danlos syndrome; ID = immunoglobulin deficiency; NC = narcolepsy Type I; CKD = chronic kidney disease; RT = renal transplantation; CP = chronic pancreatitis; pSS = primary Sjögren's syndrome; FSHD = facioscapulohumeral muscular dystrophy; MD = adult-onset myotonic dystrophy; HMSN = hereditary motor and sensory neuropathy Type I; MS = multiple sclerosis; RA = rheumatoid arthritis; T1DM = Type 1 diabetes mellitus.

Accuracy of Medical Diagnosis

Ten studies were rated to be of low risk as they featured patients from an outpatient clinic datapool and/or medical practitioners had screened patients based on medical diagnosis. Three studies were rated to be of unclear bias risk and two studies were rated to be of high risk. The latter included patients from a patient organization that had not verified the medical diagnoses.

Sample Size

Five studies included more than 100 patients and were rated as having a low risk of bias. Eight studies were rated to feature an unclear risk of bias as they included between 55 and 99 participants. Two studies were rated to have a high risk of bias; they included 43 and 31 patients.

Discussion

To our knowledge, the present study of 15 common chronic diseases and disorders that cause long-term disabilities is one of the first to determine to what extent the variance in terms of fatigue severity can be explained by a chronic disease, transdiagnostic

factors across different diseases and interactions between the chronic disease and those factors. We determined that the type of chronic disease accounted for only 11% (range between 11% and 12%) of the variance with respect to fatigue severity, although this variance increased to 55% (range between 60% to 62%) when accounting for transdiagnostic factors, such as reduced motivation, pain, limitations in physical functioning, concentration problems, lower levels of activity, sleep disturbances, and self-efficacy concerning fatigue. Analysis of the interaction effects between transdiagnostic factors and the particular chronic disease revealed that the explained variance increased slightly (6% in Model 1, range of other models was 5% to 7%), and the direction of the relationship between these factors and fatigue severity was the same for nearly all chronic diseases. The fact that in certain chronic diseases, these relationships failed to reach significance, is probably at least partly attributable to the limited sample size of certain studies. However, the significant interaction effects reflect that future studies should also investigate disease-specific and patient-specific factors concerning fatigue.

Our findings might have implications for both the understanding and management of fatigue. It is possible that the study of fatigue in chronic diseases does not require disease-specific approaches,

such as those suggested in the recent literature (Hewlett et al., 2011; Ingles et al., 1999; van Kessel & Moss-Morris, 2006), but rather a transdiagnostic approach focusing on the identification of relevant fatigue-related factors. The identification of these transdiagnostic fatigue-related factors could assist in the development of interventions for severe fatigue. The work we have presented here has identified several of these factors, though future studies are necessary to discern more factors and generalize findings to other chronic diseases.

Pain severity was found to be positively associated with fatigue severity in all but three chronic diseases. The studies in our analysis were cross-sectional, which does not allow us to draw any firm conclusions about the causal relationship between pain and fatigue. However, recent literature has found pain to be a perpetuating factor of fatigue in chronic diseases (Kalkman, Schillings, Zwarts, van Engelen, & Bleijenberg, 2007; Power, Perruccio, & Badley, 2005), and a randomized controlled trial for patients with RA was effective in reducing pain and fatigue (Evers, Kraaimaat, van Riel, & de Jong, 2002). This suggests that the management of pain as a perpetuating factor of fatigue could have positive impacts on the reduction of fatigue severity. More concentration problems along with reduced activity and physical functioning were significantly positively associated with fatigue severity in more than half of the chronic diseases of this study. With this, previous work has demonstrated the pertinence of these factors to the management of fatigue. For example, lower levels of physical activity have been observed as a perpetuating factor of fatigue severity in neuromuscular disorders (Kalkman et al., 2007). The present study also showed that sleep disturbances and self-efficacy concerning fatigue were correlated to fatigue severity in about half of the chronic diseases reviewed. A more disturbed sleep was linked with more severe fatigue with remarkably large effects in patients with MS. This is in accordance with findings of MS-fatigue models that have uncovered sleep disturbances as the largest contributor to fatigue severity in MS (Strober et al., 2005). The significant relationship between self-efficacy and fatigue severity was negative with lower self-efficacy scores related to higher fatigue severity scores. The role of a low self-efficacy, or “the sense of control over symptoms,” as a predictor of fatigue has been found in previous prospective studies in patients with chronic fatigue syndrome and MS (Ray, Jefferies, & Weir, 1997; Vercoulen et al., 1998; Wiborg, Knoop, Frank, & Bleijenberg, 2012), which suggests that patients can benefit from fatigue interventions that address self-efficacy concerning fatigue.

There were also factors that were not or inconsistently associated with fatigue severity. Depressive symptoms were significantly related to fatigue in only half of the tested fatigue models. This is surprising, because most previous research in chronic diseases has established a positive association between fatigue and depressive symptoms, for example in patients with T1DM (Goedendorp et al., 2014) or RA (van Hoogmoed et al., 2010). A potential explanation for these inconsistent findings in our study could be that, in the context of other variables that were added to the models, depressive symptoms did not remain significant in the fatigue models. Additionally, the mean prevalence of patients with clinically relevant levels of depression is relatively low in our group with 15% (ranging 14% to 17%), which could have made it difficult to determine significant connections with fatigue severity.

Female sex was associated with fatigue severity in only three chronic diseases: T1DM, FSHD, and pSS. Although in the case of pSS this could be explained by the high number of female patients in the study (90%), this is not true for T1DM and FSHD, where there is no clear explanation for this relationship. As most chronic diseases are progressive and with the number of comorbidities or complications tending to rise with age (Bauer, Briss, Goodman, & Bowman, 2014), one might expect older age to be associated with fatigue severity, but, in fact, we found the opposite. Younger age was correlated with fatigue severity in four chronic diseases. One reason could be that younger people face more challenges in daily life with regards to careers or families (Westerlund et al., 2010). More research investigating the relationship between age and fatigue is required.

Except for demographic factors, the aforementioned factors associated with fatigue severity can be addressed in behavioral interventions. Several studies have explored the effectiveness of such interventions in specific chronic diseases (Evers et al., 2002; Menting et al., 2017; van den Akker et al., 2017; van Kessel et al., 2008; Voet et al., 2014), observing that cognitive-behavioral therapy or exercise therapy that addressed factors such as sleep disturbances, physical inactivity, or self-efficacy were effective in reducing fatigue. As our findings intimate, a large amount of fatigue severity can be understood through similar fatigue-related factors, and interventions aimed at reducing fatigue might be transdiagnostic. This could encourage the formulation of a generic fatigue model as a starting point for the development of fatigue interventions across various chronic diseases. It would also imply that results of fatigue research in one chronic disease could be transferred or generalized to other chronic diseases more easily.

The factors established in our study differed in terms of the significance and strength of their relationship with fatigue. Therefore, interventions would probably benefit when tailoring them to patients' needs, and it might be the case that tailored interventions are indeed effective. Recent studies with tailored interventions in patients with T1DM (Menting et al., 2017) and cancer survivors (Abrahams et al., 2017; Gielissen, Verhagen, Witjes, & Bleijenberg, 2006) proven them to be efficacious. In line with the findings of the present study, it seems that fatigue models and, consequently, treatments should focus on the transdiagnostic factors of fatigue, but also on the individual needs of patients; additional future research is needed to confirm this.

The overall risk of bias of the included studies, especially with respect to the selection of participants bias, was rated as an unclear risk. The possibility of bias in the included studies should be recognized when interpreting our results. It should also be noted that we did not perform a systematic selection of the studies, but chose studies because we knew of authors that investigated fatigue in chronic diseases with the same fatigue questionnaire, the CIS. In addition, we only included studies that addressed at least five potential transdiagnostic factors to perform a meaningful data analysis. In conclusion, the risk of convenience sampling might be present and should be taken into account in the interpretation of the findings we have presented herein.

As a consequence of the exploratory character of the present study, it was only possible to include variables and instruments that were overlapping between the 15 cross-sectional studies. As such, the present study focused on a limited number of fatigue-related factors; other potentially relevant factors, for example, fear

of disease progression (Beckerman et al., 2013) or illness acceptance (van Engelen, 2015) were not included. In future work, it would be interesting to look at the role of other potential covariates, like, for example demographic variables like the marital status or ethnicity, or the level of disabilities, as well as to conduct more specific analyses to unravel the potentially mediating associations between those factors and fatigue. The limited number of overlapping measures was also the reason why we decided to create a dichotomous measure of depression using the cut-off scores of two measures—the BDI-PC and SCL-90. This procedure has been followed previous (Worm-Smeitink et al., 2016), but should be interpreted with caution as no validity or reliability measures are available. In a future study, it would be important to demonstrate the psychometric properties of this technique when measuring depression. The small sample size of certain included studies—the sample sizes varied from 31 to 273 patients—introduced a risk of bias and is another limitation of our study as it could have influenced the range and interpretability of the estimates and their CIs. Therefore, we cannot rule out that factors were not significantly different in a number of chronic diseases based on the lack of power. To exclude this possibility, it would be beneficial to replicate the present analysis with larger sample sizes. Based on the heterogeneity of the dataset, one should be careful in generalizing the findings from our work; however, the wide range of chronic diseases included in the present analysis strengthens our conclusion that fatigue seems to be a symptom with congruous characteristics as the transdiagnostic factors exhibited large overlap between chronic diseases. Another important issue to consider is the use of the CIS questionnaire in assessing three fatigue-related factors: concentration problems, reduced motivation, and reduced activity. It could be that the subscales of the CIS are correlated with each other and fatigue severity, which may have affected the significance of other tested fatigue-related factors. Based on the use of the fatigue severity subscale of the CIS as a dependent variable, we were unable to study the potential differences between chronic diseases with respect to other dimensions of fatigue, for example, postexertional or mental fatigue. It seems critical that future studies take into account these different fatigue aspects regarding differences between chronic diseases.

Although the present study has limitations, it is one of the first studies to combine fatigue data from a large number of common chronic diseases to evaluate whether there are variables that are related to fatigue severity across diseases. The results showed that fatigue severity can largely be explained by transdiagnostic factors. Our findings suggest that future studies investigating fatigue models and management approaches should focus on transdiagnostic fatigue-related factors, but also involve individual characteristics and patient needs.

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Received May 23, 2017

Revision received November 13, 2017

Accepted November 19, 2017 ■