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Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity

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Background: Fatigue is a frequent and persistent problem among Hodgkin lymphoma (HL) survivors. We investigated the prevalence of clinically relevant fatigue in HL survivors and the relation between fatigue and anxiety and depression.

Methods: Fatigue was measured through the generic European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and Fatigue Assessment Scale (FAS). Anxiety and depression were measured with the Hospital Anxiety and Depression Scale. Questionnaires were mailed to 267 HL survivors. Results were compared with a Dutch age-matched normative population.

Results: Response rate was 68% (median age 46 years, mean time since diagnosis 4.6 years). Prevalence of fatigue was significantly higher among HL survivors than in the norm population (FAS 41% *vs* 23%, QLQ-C30 43% *vs* 28%), as were fatigue levels. There was a significant association between fatigue, anxiety and depression. Of the HL survivors with high symptom levels of depression, 97% also reported fatigue. In multivariate analysis, depression was strongly associated with high levels of fatigue and, to a lesser extent, anxiety and comorbidity.

Conclusions: Prevalence rates of fatigue are significantly higher in HL survivors than in the general population and differences are clinically relevant. Depression and anxiety were strongly associated with high levels of fatigue. Reducing fatigue levels by treatment of depression and anxiety should be further explored.

Over the past decades, survival of Hodgkin lymphoma (HL) patients has improved dramatically with 5-year overall survival rates ranging from 90 to 95% (Engert *et al*, 2010, 2012). This has mainly been due to the introduction of multi-agent chemotherapy and improved radiotherapy techniques. However, with improved life expectancy, patients often face long-term effects caused by their treatment, such as treatment-induced secondary tumours or cardiovascular disease (van Leeuwen *et al*, 2000; Aleman *et al*, 2003; De Bruin *et al*, 2009; van den Belt-Dusebout *et al*, 2009).

Apart from these adverse physical effects, many HL survivors also report suffering from long-term psychosomatic and psychosocial problems (Loge *et al*, 1997, 2000; Hjermstad *et al*, 2005; Mols *et al*, 2006). A number of studies have focused on these psychosocial issues in HL survivors, mainly addressing overall health-related quality of life (HRQoL). A recent review of HRQoL in HL survivors showed persistent problems in physical, role physical, social and cognitive functioning (Oerlemans *et al*, 2011). These problems were most prevalent in HL patients treated with combined modality treatment, in women and in patients of older age. Furthermore, a number of studies have focused specifically on fatigue, because this is one of the most frequently reported and most persisting symptoms in HL survivors, and has consistently been reported to have significant impact on HR-QoL (Fobair *et al*, 1986; Joly *et al*, 1996; Flechtner *et al*, 1998; Loge *et al*, 1999;

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Ruffer *et al*, 2003; Hjermstad *et al*, 2005). The mechanism that causes fatigue is largely unknown. Associations between fatigue and clinical or patient characteristics have been made, mainly focusing on the influence of treatment, time since diagnosis and age. However, such studies have provided conflicting results (Loge *et al*, 1999; Ruffer *et al*, 2003; Hjermstad *et al*, 2005; Ng *et al*, 2005; Heutte *et al*, 2009). The impact of comorbid conditions, whether or not caused by cancer treatment, on perceived fatigue has been studied less frequently. All conducted studies reported increased fatigue in HL survivors with comorbidities (Knobel *et al*, 2001; Ng *et al*, 2005; Miltenyi *et al*, 2010). Of these studies, only Ng *et al* (2005) compared their results with a norm population consisting of a group of siblings. Fatigue in the HL survivors was more frequent and was associated with the presence of cardiac disease.

Fatigue is reported to be a frequent symptom of depression. Few studies have explored the relationship between fatigue and depression in HL survivors. Loge *et al* (2000) reported increased levels of psychological distress in nearly 50% of fatigued HL survivors; however, no comparison with a norm population was made. Ng *et al* (2005) found that having a psychiatric condition was a significant variable for increased fatigue. Because of high prevalence rates of fatigue in the general population, results on fatigue surveys of cancer survivors should be interpreted with caution and be compared with an age- and sex-matched norm population.

The purpose of this study was to investigate the prevalence of clinically relevant fatigue in HL survivors in The Netherlands compared with an age- and sex-matched Dutch population, and to determine the relationship between fatigue and depression, and other comorbid conditions.

MATERIALS AND METHODS

HL survivors. A cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR) among HL survivors. The ECR records data on all newly diagnosed cancers in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and 2 large radiotherapy institutes. The ECR was used to select all patients who were diagnosed with HL between 1 January 1999 and 1 December 2010. Deceased patients were excluded by linking the ECR database with the Central Bureau for Genealogy. Hodgkin lymphoma survivors were contacted by mail through their physicians and were asked to participate in this cross-sectional study by completing and returning a set of questionnaires. In May 2009, patients between 6 months and 10 years after diagnosis received the first questionnaire. In November 2009, patients diagnosed between May 2008 and May 2009 were invited to participate, and in May 2011, patients diagnosed between May 2009 and December 2010 were invited. Ethical approval for this study was obtained from the University of Tilburg-certified Medical Ethics Committee.

Questionnaires. Survivors of HL were asked to complete the validated Dutch version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The QLQ-C30 measures cancer-specific HRQoL and contains five functional scales (physical, cognitive, emotional, social and role functioning), a global health status/QoL scale, six single items assessing additional symptoms and three symptom scales (pain, fatigue and nausea/vomiting). For all items, Likert-type response scales are used, with total scores per item ranging from 4 to 7 points. All subscales and individual item responses are linearly converted to 0–100 scales (Aaronson *et al*, 1993). As a cut-off value for fatigue caseness, we defined a score >23.9 for the EORTC QLQ-C30 (Cocks *et al*, 2011), although the fatigue symptom subscale has not been validated as a stand-alone measure for fatigue. For partially incomplete questionnaires, imputation of the mean was used for scales containing at least 50% of the scores (http://groups.eortc.be/qol/).

Fatigue was also measured with the Fatigue Assessment Scale (FAS), a validated 10-item questionnaire reflecting mental and physical fatigue (Michielsen *et al*, 2003, 2005). Total scores range from 10 to 50, with a higher score reflecting a higher level of fatigue. A score over 21 points indicates probable caseness of fatigue (Michielsen *et al*, 2003).

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983; Snaith and Zigmond, 1986), which measures levels of symptoms of anxiety and depression in two subscales of seven items each. A score >8 on either subscale indicates a possible caseness for an anxiety or depressive disorder; a score >11 indicates a probable caseness. For HADS, a score >8 on either subscale was used as a cut-off value for defining caseness of anxiety or depression, as this score achieves an optimal balance between sensitivity and specificity (Zigmond and Snaith, 1983; Snaith and Zigmond, 1986; Bjelland *et al*, 2002).

Comorbidity was evaluated by the Self-administered Comorbidity Questionnaire (Sangha *et al*, 2003). Education and marital status were also recorded in the questionnaire. Information on tumour and treatment characteristics was available from the ECR.

Norm population. The norm population was selected from a reference cohort of $\sim$2200 individuals from the general Dutch population (CentER panel; van de Poll-Franse *et al*, 2011b). The set of questionnaires completed for this study included the QLQ-C30, FAS and HADS questionnaires, and also data on socio-demographics and comorbid conditions were provided. To compare the results with that of the HL survivor cohort, we made an age- and sex-matched selection from this normative population. This reference cohort is representative for the Dutch-speaking population in the Netherlands (van de Poll-Franse LV *et al*, 2011a, b).

Statistical analysis. All statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Patient, tumour and treatment characteristics between respondents, non-respondents and patients with unverifiable addresses were compared using *t*-test (numerical variables) and χ^2-test (categorical variables). A two-sided P-value <0.05 was considered statistically significant.

Differences between fatigue caseness from the EORTC QLQ-C30 and FAS, and/or caseness of anxiety or depression from the HADS in HL survivors and the norm population, were calculated by χ^2-tests.

Mean fatigue scores from the EORTC QLQ-C30 and FAS were compared between HL survivors and the norm population using independent sample *t*-tests. Clinical relevance of the differences was defined according to guidelines for the interpretation of the EORTC QLQ-C30 (Cocks *et al*, 2011) and according to Norman's rule of thumb for the FAS, indicating a ± 0.5 s.d. difference of the norm in scores as a discriminating change (Norman *et al*, 2003).

Multivariate logistic regression analyses using the dichotomous FAS score were performed to analyse the association of socio-demographic, tumour, treatment and comorbidity variables and fatigue. Variables were included into the model in separate steps. Demographic variables were added first, then clinical variables and, third, psychological distress. A two-sided P-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the respondents and non-respondents. In total, 180 (68%) of the 267 HL survivors completed and returned

the questionnaires. Missing items on the completed questionnaires were <3% ($n=17$). Responders were more often male and older than non-responders and those with unverifiable addresses (Table 1). Mean time since diagnosis was 4.6 years, mean age at the time of survey among HL responders was 46 years and 55% had received combined modality treatment. Only 3% had been treated with radiotherapy alone. There were no statistically significant differences between HL responders and the norm population concerning marital status or education (Table 2). With regards to comorbidities, HL responders less often reported hypertension (9% *vs* 20%) but more often thyroid disease (9% *vs* 5%) and depression (11% *vs* 3%) than the norm population.

Fatigue prevalence and symptoms of anxiety and depression. There were significantly more persons with fatigue among the HL survivors compared with the norm population (Figure 1 and Table 3). The QLQ-C30 fatigue subscale identified a 43% prevalence of fatigue among the HL survivors *vs* 28% in the norm population ($P=0.002$). The FAS questionnaire showed fatigue prevalence rates of 41% and of 23%, respectively ($P<0.001$). Identification of fatigue cases was consistent between the QLQ-C30 and the FAS questionnaire in 83% of the HL survivors and in 81% of the norm population. Among the HL patients, 23% had high symptom levels of anxiety and 18% of depression, compared with 13% and 12% in the norm population, respectively.

Of all responding HL survivors, 20% were identified both as a fatigue case and an anxiety case; 17% were both fatigued and had symptoms of depression. These numbers were significantly lower in the norm population (8%, $P<0.001$, and 9%, $P=0.004$, respectively; Figure 1). The prevalence of fatigue among HL survivors with a high symptom level of depression was 97% compared with 76% in the norm population.

Similar relationships were found for cognitive functioning (impairment of concentration and memory) and fatigue, with significantly lower social functioning and especially lower cognitive functioning among HL survivors compared with the norm population (Table 3). There was a clear association between fatigue and cognitive impairment. The mean scores of cognitive function were lower among fatigued HL survivors and fatigued participants of the norm population (74.5 and 86.4 points, respectively) than in the non-fatigued participants (HL survivors 95.7 and norm population 98 points). Differences are clinically relevant in both groups, and reflect a large difference in the HL survivors group and a medium difference in the norm population.

Clinical relevance of fatigue scores. Fatigue scores were significantly higher among HL survivors than in the norm population, and these differences were clinically relevant (Table 3). Mean QLQ-C30 fatigue scores differed 9.8 points (28.7 *vs* 18.9), reflecting a small but clinically relevant difference. The FAS total fatigue scores were 21.4 *vs* 18.4 points (>0.5 s.d.), which also reflects a clinically relevant (albeit small) difference.

Association of fatigue with patient and treatment factors and comorbid conditions. Multivariate regression analysis using the FAS scores showed that a lower level of education was associated with a higher risk of fatigue (Table 4). After adding clinical variables to the regression analysis, the significance of level of education disappeared, and having one to two comorbid conditions (OR 4.7) or >2 comorbid conditions (OR 17.5) were significantly associated with fatigue.

After adding psychological distress symptoms, however, the influence of comorbidities lacked statistical significance. Symptoms of depression (OR 1.8) and anxiety (OR 1.2) were the only factors significantly associated with high levels of fatigue.

Table 1. Patient and treatment characteristics of the HL survivor cohort

	HL responders		Non-responders		Unverifiable address		
	N	**%**	***N***	**%**	***N***	**%**	***P*-value**
Total	180		35		52		
Mean age at time of survey in years (s.d.)	46 (15.6)		40 (13.6)		40 (13.9)		0.01
Range	19–84		21–79		20–83		
<40	75	41	18	51	34	65	0.02
40–60	70	39	14	40	14	27	
>60	35	19	3	9	4	8	
Mean time since diagnosis in years (s.d.)	4.6 (2.9)		5.9 (3.2)		4.6 (3.0)		0.07
<5	102	57	14	40	29	56	0.11
5–10	76	42	19	54	23	44	
>10	2	1	2	6	0		
Sex							0.06
Male	99	55	23	66	37	72	
Female	81	45	12	34	14	28	
Stage at diagnosis							0.60
I	31	17	7	20	9	17	
II	94	52	14	40	19	37	
III	26	15	6	17	12	23	
IV	18	10	4	12	6	12	
Treatment							0.50
RT	6	3	0		1	2	
CT	74	41	18	51	25	48	
RT + CT	99	55	16	46	23	44	

Abbreviations: CT = chemotherapy only; HL = Hodgkin lymphoma; RT = radiotherapy only; RT + CT = radiotherapy and chemotherapy.

Table 2. Characteristics of the study participants

	HL responders		Norm population		
	N	**%**	***N***	**%**	***P*-value**
Total	180		327		
Mean age at survey in years (s.d.)	46.1 (15.6)		48.8 (15.7)		0.90
Range	19–84		20–85		
<40	75	42	117	36	0.28
40–60	70	39	129	39	
>60	35	19	81	25	
Sex					0.43
Male	99	55	168	51	
Female	81	45	159	49	
Self-reported comorbidity					
Cardiac	17	9.4	21	6.4	0.07
Stroke	2	1.1	1	0.3	0.16
Hypertension	16	8.9	65	19.9	0.01
COPD	19	10.6	41	12.5	0.92
Diabetes mellitus	8	4.4	25	7.6	0.39
Anaemia	4	2.2	14	4.3	0.44
Thyroid disease	17	9.4	16	4.9	0.008
Depression	19	10.6	11	3.4	<0.001
Comorbidity conditions					0.37
No comorbidity	87	48	149	46	
⩽2 Comorbidities	63	35	134	41	
>2 Comorbidities	21	12	44	13	
Marital status					0.62
Partner	133	74	252	77	
No partner	44	24	75	23	
Education level					0.10
Low	14	8	13	4	
Medium	107	59	191	58	
High	56	31	122	37	

Abbreviations: COPD = chronic obstructive pulmonary disease; HL = Hodgkin lymphoma.

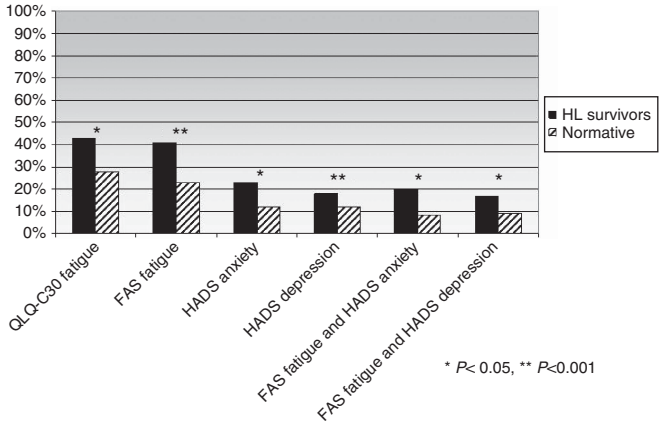

Figure 1. Prevalence of caseness of fatigue. Prevalence of caseness of fatigue according to fatigue subscale of the EORTC QlQ-C30 and FAS, and caseness of anxiety or depression according to the HADS scale for both HL survivors and the age-matched Dutch population. The two last columns describe the prevalence of combined fatigue and anxiety or depression among all HL survivors and of the norm population. *$P<0.05$; **$P<0.001$.

Logistic regression analysis of the QLQ-C30 fatigue data did not differ from the FAS data (data not shown). Using the QLQ-C30 having one to two comorbidities (OR, 3.0; 95% CI, 1.3–7.3; $P=0.02$) and symptoms of depression (OR, 1.2; 95% CI, 1.1–1.4; $P=0.04$) were the only variables associated with fatigue.

DISCUSSION

In this cross-sectional study, we found a higher prevalence rate of fatigue in HL survivors compared with an age- and sex-matched Dutch normative population of 15% and 18% using two different validated fatigue measures (QLQ-C30 fatigue and FAS, respectively). We also observed a significant association between fatigue caseness and high levels of depression and anxiety, especially in the HL cohort. Mean fatigue levels were significantly increased in the HL survivors compared with the norm population, and differences were also found to be clinically relevant. Symptoms of depression, and (to a lesser extent) anxiety and comorbidities, were found to be the only variables associated with long-lasting fatigue.

One of the strengths of our study is that we measured fatigue through both a generic (QLQ-C30) and a fatigue-specific (FAS) questionnaire. Both questionnaires independently measured a significantly higher prevalence of fatigue in the HL survivors. We showed that the identification of fatigue cases between both questionnaires was consistent in 83% of the HL survivors and 81% of the norm population. Our data are robust, as missing items were <3%.

Our study not only shows that HL survivors more often suffer from chronic fatigue but also clearly shows an association between fatigue and depression or anxiety. We showed that a combination of both fatigue and anxiety occurred in 20% of all HL survivors and of fatigue and depression in 17%, compared with 8% and 9%, respectively, in the norm population. This significant association between fatigue and anxiety and depression has also been described by Loge *et al* (2000). They reported high HADS scores (anxiety and depression combined) in 52% of 109 fatigued HL survivors. Their results, however, were not compared with a control group or with a norm population. Our study further showed that almost all (97%) HL survivors with symptoms of depression were also fatigued. As both studies were cross-sectional by design, it is difficult to evaluate whether fatigue and anxiety or depression are two separate entities both occurring more often in HL survivors, or whether fatigue is a consequence of these psychological conditions. The lower level of cognitive functioning that we observed among the HL survivors, reflected in symptoms such as loss of concentration, might be explained as a manifestation of the impact of fatigue and/or psychological distress. In our multivariate analysis, we showed that depression and, to a lesser extent, anxiety were significantly associated with fatigue. However, due to the design of our study, a causal relation between fatigue, anxiety and depression cannot be established.

In daily practice, fatigue in HL survivors has proven to be a prominent problem. Many survivors report to suffer from chronic fatigue, with often significant impact on daily activities, which has proven extremely difficult to treat. Studies evaluating interventions aimed at improvement of fatigue in cancer survivors have often shown improvement in physical endurance, but limited improvement in the subjective feeling of fatigue and lack of energy (De Backer *et al*, 2008). Two recent meta-analyses concluded that exercise interventions in fatigued cancer patients had a near-moderate effect size in reducing fatigue at best (Kangas *et al*, 2008; Cramp and Byron-Daniel, 2012). Increased awareness of fatigue and of depression and anxiety among treating physicians is

Table 3. QLQ-C30, FAS and HADS mean scores for HL survivors *vs* norm population

	HL		Norm			
	Mean	**s.d.**	**Mean**	**s.d.**	***P*-value**	**Clinical relevance (Norman *et al*, 2003; Cocks *et al*, 2011)**
QLQ-C30						
Functional scales						
Role functioning	83.8	24.4	89.6	20.0	0.05	Trivial
Physical functioning	87.1	15.7	90.9	14.8	0.08	Trivial
Cognitive functioning	82.5	22.0	92.5	15.7	<0.001	Medium
Emotional functioning	82.4	22.9	87.9	17.8	0.03	Small
Social functioning	86.4	22.2	92.8	17.6	<0.001	Small
Symptom scales						
Fatigue	28.7	26.4	18.9	20.4	<0.001	Small
Pain	13.0	22.4	14.2	20.9	=0.54	Trivial
Nausea/vomiting	3.3	9.2	2.6	9.9	=0.45	Trivial
Global Health Status	76.8	18.5	77.7	16.9	=0.57	Trivial
FAS						
Total fatigue score	21.4	7.6	18.4	5.8	<0.001	Yes
HADS						
Anxiety mean scores	4.7	4.2	3.8	4.3	<0.001	No
Anxiety mean score in fatigue cases	7.6	4.5	6.5	4.0	0.31	No
Depression mean scores	3.7	3.8	3.4	3.2	0.02	No
Depression mean score in fatigue cases	6.6	4.1	6.4	4.0	0.83	No

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; FAS = Fatigue Assessment Scale; HADS = Hospital Anxiety and Depression Scale; HL = Hodgkin's lymphoma.

Table 4. Logistic model of factors associated with fatigue using the FAS TOTAL score

	Model: block 1			Model: block 1 + 2			Model: block 1 + 2 + 3		
Variables	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Block 1: Demographic variables									
Age	0.99	0.97–1.02	0.64	0.97	0.95–1.01	0.09	0.97	0.94–1.02	0.19
Male *vs* female	1.42	0.74–2.73	0.29	1.33	0.64–2.76	0.43	2.1	0.79–5.70	0.13
Education: low *vs* mid	**0.22**	**0.05–0.92**	**0.038**	0.27	0.05–1.37	0.11	0.78	0.06–8.93	0.84
Low *vs* high	**0.14**	**0.03–0.65**	**0.12**	0.29	0.05–1.65	0.16	1.38	0.10–18.72	0.80
Partner	0.51	0.24–1.08	0.08	0.54	0.24–1.25	0.15	0.41	0.13–1.24	0.12
Block 2: Clinical variables									
Time since diagnosis				0.97	0.86–1.11	0.73	0.96	0.81–1.15	0.70
No comorbidity *vs* 1–2				**4.73**	**2.10–10.64**	**<0.001**	2.76	0.93–8.12	0.06
No comorbidity *vs* >2				**17.49**	**4.27–71.51**	**<0.001**	4.25	0.68–26.39	0.12
Treatment: CT *vs* RT				0.69	0.77–6.09	0.73	1.22	0.09–16.03	0.88
Treatment: CT *vs* CMT				0.85	0.41–1.77	0.68	1.09	0.41–2.93	0.86
Block 3: Psychological variables									
HADS anxiety							**1.19**	**1.00–1.41**	**0.46**
HADS depression							**1.80**	**1.37–2.37**	**<0.001**

Abbreviations: CI = confidence interval; CMT = combined modality treatment; CT = chemotherapy; FAS = Fatigue Assessment Scale; HADS = Hospital Anxiety and Depression Scale; OR = odds ratio; RT = radiotherapy. Bold entries are the values from regression analysis reflecting statistically significant values.

essential. However, fatigue is more common and need not be a symptom of depression or anxiety. Differentiating between these symptoms can be challenging in the clinical setting. A possible aid in defining depression could be to shift the focus from fatigue to other dimensions of depression. Symptoms of depression and anxiety could be amenable to treatment. Psychosocial therapies such as cognitive behavioural therapy or educational counselling have proven to be beneficial in reducing symptoms of anxiety and depression (Kangas *et al*, 2008).

It might be beneficial for both patients suffering from fatigue and for patients with depression or anxiety to receive treatment by professionals, although through different methods of focused psychosocial support or specific coping strategies, which might result in a clinically meaningful reduction of fatigue. This approach, however, should be explored in future studies. Ideally, HL survivors suffering from chronic fatigue should be invited for a diagnostic interview to distinguish between fatigue and depression, and then randomly assigned to specific psychosocial therapies. As HL survivors are at risk for a variety of comorbid conditions due to late treatment sequelae, such as cardiovascular diseases (Aleman *et al*, 2003; van den Belt-Dusebout *et al*, 2007), which could predispose for higher levels of fatigue, we examined the possible association of fatigue and comorbid conditions. Hodgkin lymphoma survivors self-reported depression more frequently than the norm population. Our multivariate analysis showed a trend for the association between self-reported comorbidities and fatigue. However, mean time since diagnosis and treatment in this survey was still relatively short (mean 4.6 years, range 6–122 months), which means that the majority of the cohort is not yet at risk for late treatment sequelae. Moreover, with a mean age of 46 years, a large part of both the cohort and the norm population would not yet suffer from serious comorbidities.

Rates of fatigue in HL survivors in this study (43% by using QLQ-C30 and 41% by using FAS) are slightly higher than the rates reported by others (Loge *et al*, 1999; Knobel *et al*, 2001; Hjermstad *et al*, 2005). These three studies reported fatigue rates of 26–30% in HL survivors, but all used the same HL cohort. More recent data on cancer-related fatigue in patients with other types of cancer using the EORTC QLQ-C30 and Multidimensional Fatigue Inventory showed prevalence rates of 36–48%, which are comparable to our results (Cella *et al*, 2001; Kuhnt *et al*, 2009; Schultz *et al*, 2011; Berger *et al*, 2012).

In conclusion, our results show a clinically relevant higher prevalence rate of fatigue in HL survivors when compared with an age- and sex-matched population. We also found a significant association between fatigue and anxiety or depression. The only factors significantly associated with high levels of fatigue were symptoms of depression and anxiety. This might have implications for the diagnosis and treatment of fatigue in the clinical setting, as psychosocial therapies have proven to be effective in reducing anxiety and depression, and could therefore be beneficial in reducing levels of fatigue as well. This should be further examined in future trials.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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