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Are fatigue, depression and anxiety associated with labour market participation among patients diagnosed with haematological malignancies? A prospective study

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Abstract

***Objectives*: The objectives of this study are to examine levels of fatigue, depression and anxiety following diagnosis of a haematological malignancy, to determine the incidence of return to work (RTW) and long-term sickness absence (LTSA) during 1-year follow-up and to examine whether fatigue, depression and anxiety are associated with RTW and LTSA in this group of cancer patients.**

***Methods*: Questionnaire-based data on fatigue, depression and anxiety were obtained at baseline. In all, 196 patients returned the questionnaire. Of these, 106 patients were on sick leave and 90 patients were working. They were all followed prospectively for 1 year using register-based data on labour market participation.**

***Results*: At baseline, high levels of fatigue, depression and anxiety were more prevalent among sickness absent patients than in those working. Half of the sickness absent patients returned to work during follow-up, and only 10 (11%) working patients experienced LTSA. Sickness absent patients with highest scores of physical fatigue were less likely to RTW than those with lowest scores (RR_{adj} 0.43, 95% CI 0.23–0.78). Similar, we found an association between symptoms of anxiety and RTW ($p = 0.048$). This association was though non-significant in multivariable analyses ($p = 0.068$). No significant association was found between depression and RTW.**

***Conclusion*: Half of sickness absent patients returned to work, and only a few of working patients experienced LTSA during follow-up. Patients reporting high levels of physical fatigue were less likely to RTW. There was a similar tendency for anxiety, whereas we found no association between depression and RTW. Larger prospective studies are needed.**

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Background

Patients with haematological malignancies are at increased risk of work disability, high sick leave rates, unemployment, reduced work ability and not returning to work compared with cancer-free control groups [1–3] and patients with other cancer types [4–6]. Two recent register-based cohort studies showed that only two-thirds of patients on long-term sick leave diagnosed with haematological malignancies returned to work [7]. Moreover, according to haematological cancer subtype, these patients had a twofold to 12-fold higher risk of being granted disability pension compared with a reference cohort without a history of haematological malignancies [8].

Fatigue, depression and anxiety are some of the most frequently reported symptoms in patients diagnosed with haematological malignancies [9–11]. Yet, little is known about prospective associations between these symptoms and labour market participation for this patient group [12]. In a recent Australian qualitative study, patients with haematological malignancies reported fatigue as the most frequent late-effect interfering in return to work (RTW) [13]. Furthermore, two Danish register-based cohort studies including 3616 and 1741 patients diagnosed with haematological malignancies, respectively, showed that the need of treatment with antidepressants or anxiolytics was associated with both lower RTW rates and higher risk of being granted disability pension compared with patients who did not use these types of medication [7,8]. More knowledge of the role of fatigue, depression and anxiety is needed to target early rehabilitation interventions and to support patients diagnosed with haematological malignancies in

maintaining labour market participation or returning to work. Therefore, the aims of this study were to (a) examine levels of fatigue, depression and anxiety among sickness absent patients and patients working 6 to 9 months following diagnosis of a haematological malignancy, (b) determine the cumulative incidence of RTW during 1-year follow-up among the sickness absent patients, and examine if fatigue, depression and anxiety are associated with RTW and (c) determine the cumulative incidence of long-term sickness absence (LTSA) during 1-year follow-up among the working patients, and examine if fatigue, depression and anxiety are associated with LTSA.

Materials and methods

We conducted a prospective study with 1-year follow-up. Data were obtained from questionnaires and Danish population-based registers.

Administrative context

The welfare system in Denmark is tax-financed, and if a citizen is not able to work because of physical or mental disability, financial support is provided through public transfer payments (sickness absence benefits, disability pension etc.). Sickness absence benefits are temporary and available for a maximum of 52 weeks within a period of 18 month. The financial support depends on the working hours per week and the salary but is limited to a maximum of approximately €530 per week.

Subjects

All patients between 19 and 59 years of age in Denmark diagnosed with a haematological malignancy 6 to 9 months prior to inclusion date and who were employed at inclusion were eligible for study. Patients were included at three time points: 31 October 2011 (patients diagnosed between 1 February and 30 April 2011), 31 January 2012 (patients diagnosed between 1 May and 31 July 2011) and 30 April 2012 (patients diagnosed between 1 August and 31 October 2011).

Patients were identified through the Danish National Patient Register (NPR), which holds information on all hospital admissions and contacts to emergency or outpatient care, including diagnostic information according to the ICD-10 [14]. The diagnoses were validated using data from the Danish Cancer Register [15].

Fatigue, depression and anxiety

Data on self-reported fatigue, depression and anxiety were gathered by a questionnaire, which was distributed to the patients at the inclusion date. If the questionnaire was not returned within 2 weeks, a reminder was sent. Patients not responding to the reminder were contacted by telephone if possible.

The questionnaire included the *Multidimensional Fatigue Inventory* (MFI-20) [16], which encompasses five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. A summary score varying between 4 and 20 was calculated for each dimension, higher scores indicating increased fatigue. Summary scores were divided into quartiles for analytic purposes [17].

The 14-item self-reported *Hospital Anxiety and Depression Scale* (HADS) [18] was also included in the questionnaire. The HADS includes seven items on depression (HAD-D) and seven items on anxiety (HAD-A). The total score of each scale ranges from 0 to 21. Patients scoring 8 or higher on the scales were defined as being possible cases of having a depression or anxiety disorder; if they scored 11 or higher, they were considered subclinical cases of having a depression or anxiety disorder [19].

Covariates

Age and gender were retrieved from the Civil Registration System [20], and comorbidity was measured using data from the NPR. A Charlson comorbidity index score was computed on the basis of the diagnoses recorded in NPR for the 5-year period before the patients were diagnosed with a haematological malignancy [21]. In the Charlson index, a weight is assigned to defined categories of comorbid diseases; the index is the sum of these weights (from 0 to 6). We dichotomized the index score: 0 (no comorbidity) and ≥1 (comorbidity). Time since diagnosis was calculated as the time between date of diagnosis and date of completing the questionnaire.

Incidence of return to work and long-term sickness absence

Information on RTW and LTSA was obtained from the Danish Register for Evaluation of Marginalisation (DREAM). DREAM includes data on all Danish residents who have received any social transfer payments since 1991. Each person is registered once a week with a code representing the type of social transfer payment received in that particular week [22].

Incidence of RTW was defined as the first period of four consecutive weeks without receiving sickness absence benefits or other social transfer payments [23,24]. Incidence of LTSA was defined as at least five consecutive weeks of sickness absence (because sickness absence was only registered in DREAM after 30 days of sick leave from January 2012).

Statistical analyses

Baseline data on age, gender, comorbidity, diagnosis, time since diagnosis, and levels of fatigue, depression and anxiety

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were compared between sickness absent and working patients using Mann–Whitney *U*-test for comparison of continuous variables and chi-squared tests or Fisher's exact test for comparison of categorical variables.

To determine the cumulative incidence of RTW during 1-year follow-up, sickness absent patients were followed until RTW, death, emigration, permanent exit from the labour market or 1 year after baseline, whichever came first. To determine the cumulative incidence of LTSA, working patients were followed until LTSA, death, emigration, permanent exit from labour market or 1 year after baseline, whichever came first.

Using generalised linear regression models for pseudo observations [25], cumulative relative risks (RR) of RTW and LTSA including 95% confidence intervals (CIs) 1 year after baseline were estimated for the levels of fatigue (quartiles) and depression and anxiety case classification (no case, possible case and subclinical case). All analyses were performed in three steps. In model 1, crude analyses were conducted. In model 2, we adjusted for time since diagnosis (continuous variable), and in model 3, we further adjusted for age (continuous variable) and gender. As depression has been found to be a confounder in the association between fatigue and future labour market participation [26], a fourth step was applied in the analysis of fatigue including further adjustment for depression (continuous score). In all models, we performed a test for linear trend. Death and permanent exit from the labour market were considered competing events.

Results

Baseline characteristics

A total of 451 patients aged 19 to 59 years were diagnosed with haematological malignancies in Denmark in the inclusion period. Of these, 302 were alive and employed at time of inclusion, and thereby eligible for this study. However, 19 patients were not registered in the NPR, and 33 lived at undisclosed addresses. The remaining 250 patients (83% of eligible patients) received the questionnaire. A total of 207 patients returned the questionnaire, of which 11 patients were excluded, because it turned out that they were not employed at inclusion (Figure 1). Finally, 196 patients (65% of eligible patients) were included in the study. Age, gender, type of diagnosis, comorbidity and work status did not differ significantly between responders ($N = 196$) and non-responders ($N = 43$), although time since diagnosis was significantly shorter for non-responders (7.3 months) compared with responders (8.1 months).

At baseline, 106 (54%) patients were on sick leave and 90 (46%) were working. Except for haematological malignancy subtypes, the distribution of age, gender, time since diagnosis and comorbidity did not differ significantly between the two groups (Table 1).

Fatigue, depression and anxiety at baseline

Scores on all MFI-20 fatigue dimensions except reduced motivation were significantly higher for patients on sick leave compared with working patients. The same was observed for depression, and 15% of working patients were categorised as possible cases or subclinical cases of depression, compared with 40% of sickness absent patients ($p < 0.001$). In relation to anxiety, the mean score also differed significantly between working patients and patients on sick leave. In all, 47% of working patients fulfilled the criteria as possible cases or subclinical cases of anxiety compared with 61% among patients on sick leave ($p = 0.13$) (Table 1).

Incidence of return to work

Among the 106 patients on sick leave at baseline, 52 (49%) patients returned to work during the following year. Twelve patients (11%) left the labour market permanently, and 5 (5%) died. The likelihood of RTW decreased with 20% per month following diagnosis (RR_{crude} 0.80, 95% CI (0.68–0.94). Furthermore, fatigue, depression and anxiety scores increased with increasing time since diagnosis.

Associations between fatigue, depression and anxiety and return to work

Patients with highest scores of physical fatigue were more than 50% less likely to RTW compared with patients with scores in the lowest quartile (model 1: RR 0.47, 95% CI 0.25–0.88). This association became stronger and remained statistically significant after adjustment for age, gender, time since diagnosis and depression score (model 4: RR 0.43, 95% CI 0.23–0.78). Patients with a reduced activity score in the highest quartile were also less likely to RTW compared with patients with scores in the lowest quartile (model 1: RR 0.50, 95% CI 0.29–0.85). This association did though attenuate and became non-significant in multivariable analyses (Table 2). Similar, we found an association between symptoms of anxiety and RTW ($p = 0.048$). This association was though non-significant in multivariable analyses (model 2: $p = 0.073$; model 3: $p = 0.068$). No significant association was found between depression and RTW (Table 3).

Incidence of long-term sickness absence

Among the 90 patients working at baseline, 10 (11%) experienced LTSA during the following year and two (2%) emigrated; the remaining 78 patients stayed at work. Because of the small number of patients who experienced LTSA, we did not have sufficient power to examine associations between fatigue, depression and anxiety and LTSA.

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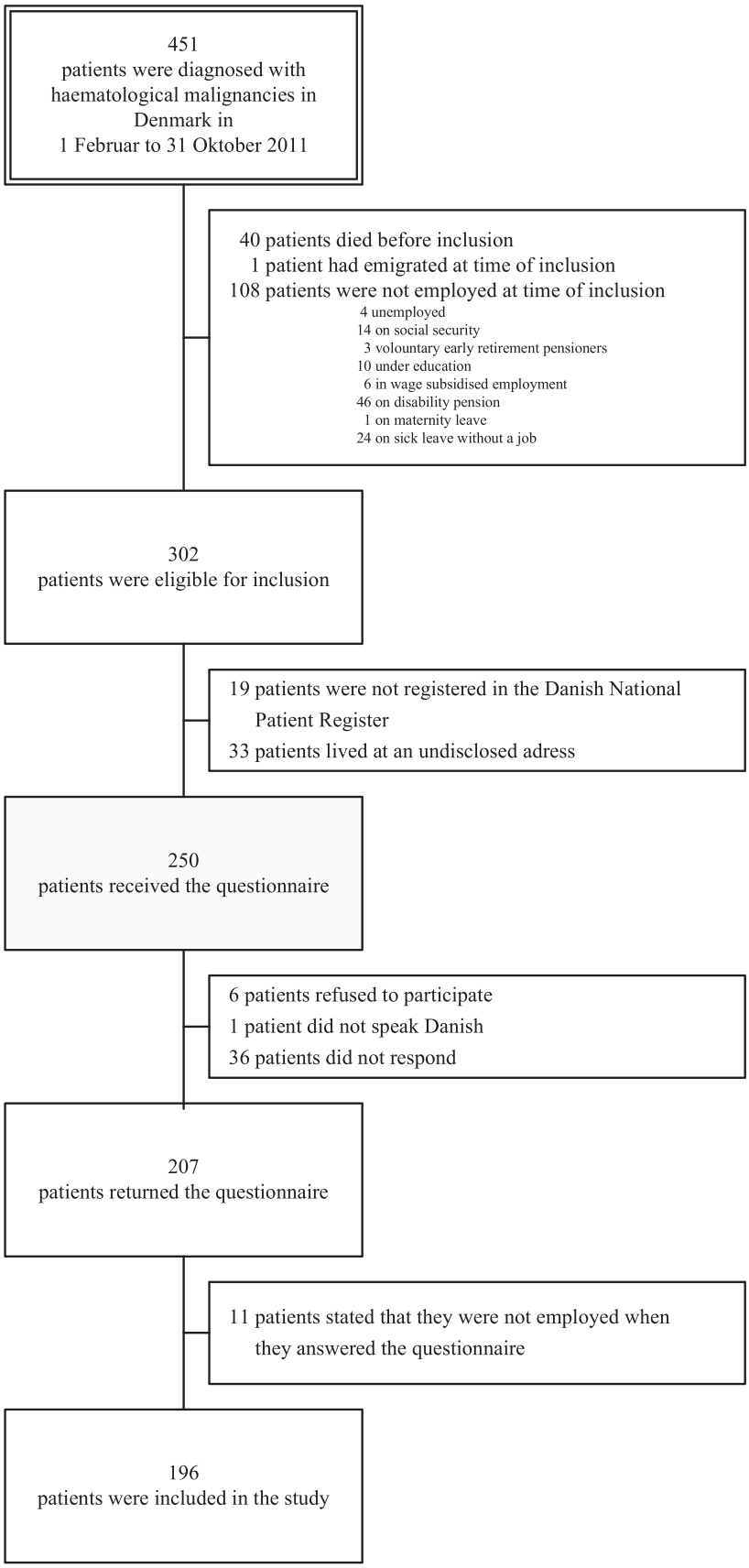

Figure 1. Flowchart of inclusion

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Table 1. Baseline characteristics for patients on sick leave and patients at work six to nine months after a diagnosis of haematological malignancies

	At work (*N* = 90)					On sick leave (*N* = 106)					Test of difference between patients at work and patients on sick leave
	n	%	Mean	SD	Range	*n*	%	Mean	SD	Range	*P*
Gender											
Female	31	(34)				48	(45)				0.12
Age (in years)			48	10	(22–59)			49	7	(26–59)	0.88
Months since diagnosis			8.0	1.0	(4–12)			8.2	1.2	(5–10)	0.34
Comorbidity											
Yes (≥1)	13	(14)				10	(9)				0.28
Diagnosis											
Hodgkin lymphoma	13	(14)				13	(12)				0.003
Diffuse large B-cell lymphoma	14	(16)				19	(18)				
Follicular lymphoma	15	(17)				10	(9)				
Multiple myeloma	5	(6)				19	(18)				
Acute leukaemia	3	(3)				15	(14)				
Chronic myeloid leukaemia	5	(6)				2	(2)				
Chronic lymphoid leukaemia	14	(16)				6	(6)				
Others	21	(23)				22	(21)				
Fatigue (MFI-20)											
General fatigue			9.8	4.1	(4–19)			13.2	4.3	(4–20)	<0.001
Physical fatigue			10.1	4.4	(4–19)			13.5	4.3	(4–20)	<0.001
Mental fatigue			8.7	3.5	(4–16)			11.2	4.2	(4–20)	<0.001
Reduced activity			9.0	4.2	(4–18)			12.7	4.7	(4–20)	<0.001
Reduced motivation			8.1	3.4	(4–19)			8.8	3.3	(4–18)	0.07
Depression (HAD-D) score			3.7	3.3	(0–11)			6.5	4.6	(0–18)	<0.001
Depression (HAD-D) case classification											
No case	76	(85)				63	(60)				<0.001
Possible case (≥8)	12	(14)				20	(19)				
Subclinical case (≥11)	1	(1)				22	(21)				
Anxiety (HAD-A) score			7.2	4.6	(0–17)			8.7	4.3	(0–21)	0.02
Anxiety (HAD-A) case classification											
No case	48	(53)				39	(39)				0.13
Possible case (≥8)	18	(20)				25	(24)				
Subclinical case (≥11)	24	(27)				39	(37)				

Discussion

This is one of the first prospective studies on possible associations between self-reported fatigue, depression and anxiety and RTW among patients diagnosed with haematological malignancies. Patients with highest scores of physical fatigue were less likely to RTW than those with lowest scores. Similar, we found tendency for an association between symptoms of anxiety and RTW. No significant association was found between depression and RTW.

To the best of our knowledge, similar associations among patients diagnosed with haematological malignancies have only previously been investigated in two prospective studies [27,28] and three cross-sectional studies [29–31]. The results of these studies are diverging. All three cross-sectional studies found an association between self-reported symptoms of depression and labour market participation [29–31], whereas one prospective study found no such association [28]. The second prospective study found no association between mental health and RTW [27]. Two of the cross-sectional studies found an association between symptoms of anxiety and labour market participation [30,31]. Further, one of the cross-sectional studies found an association between fatigue and labour market participation [31], whereas another cross-sectional study found no association [30].

Recently, we have published two register-based cohort studies showing that the need of treatment with antidepressants or anxiolytics following diagnosis of a haematological malignancy is associated with lower RTW rates and higher risk of being granted disability pension [7,8]. Even though use of antidepressants or anxiolytics can only be regarded as surrogate markers of mental health symptoms, these findings indicate that mental health is negatively associated with labour market participation among patients diagnosed with haematological malignancies. Surprisingly, the results of our present study do not completely corroborate these previous findings. One explanation could be differences in sample size as our sample was significantly smaller in the present study than in our former register-based studies. Thus, in the present study, the precision of some of the relative estimates is rather low with wide CIs, and hence, we

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Table 2. Return to work 1 year after diagnosis according to level of fatigue scores ($N = 106$)

			Model 1			Model 2			Model 3			Model 4		
	N	(%)	RR[a]	(95% CI)	*P*	RR[b]	(95% CI)	*P*	RR[c]	(95% CI)	*P*	RR[d]	(95% CI)	*P*[e]
General fatigue														
First quartile	16	(15)	1	—	0.62	1	—	0.82	1	—	0.62	1	—	0.63
Second quartile	28	(26)	0.57	(0.32–1.01)		0.64	(0.37–1.12)		0.63	(0.37–1.05)		0.62	(0.36–1.06)	
Third quartile	25	(24)	0.64	(0.37–1.11)		0.67	(0.40–1.15)		0.62	(0.39–1.00)		0.60	(0.31–1.16)	
Fourth quartile	37	(35)	0.75	(0.47–1.18)		0.85	(0.55–1.31)		0.78	(0.51–1.18)		0.74	(0.40–1.36)	
Physical fatigue														
First quartile	14	(13)	1	—	0.023	1	—	0.02	1	—	0.01	1	—	0.004
Second quartile	26	(25)	0.70	(0.42–1.17)		0.71	(0.45–1.13)		0.69	(0.44–1.06)		0.69	(0.44–1.06)	
Third quartile	39	(38)	0.72	(0.46–1.13)		0.76	(0.51–1.14)		0.73	(0.51–1.04)		0.72	(0.50–1.04)	
Fourth quartile	27	(25)	0.47	(0.25–0.88)		0.48	(0.26–0.86)		0.47	(0.26–0.84)		0.43	(0.23–0.78)	
Mental fatigue														
First quartile	24	(23)	1	—	0.27	1	—	0.74	1	—	0.60	1	—	0.69
Second quartile	19	(18)	0.59	(0.30–1.15)		0.73	(0.36–1.48)		0.71	(0.38–1.35)		0.72	(0.36–1.44)	
Third quartile	32	(30)	0.85	(0.54–1.34)		1.05	(0.62–1.77)		1.00	(0.60–1.69)		1.01	(0.52–1.96)	
Fourth quartile	31	(29)	0.67	(0.40–1.13)		0.81	(0.45–1.47)		0.78	(0.44–1.37)		0.80	(0.41–1.58)	
Reduced activity														
First quartile	17	(16)	1	—	0.07	1	—	0.19	1	—	0.21	1	—	0.19
Second quartile	26	(25)	0.54	(0.31–0.97)		0.62	(0.34–1.14)		0.62	(0.32–1.20)		0.62	(0.31–1.25)	
Third quartile	26	(25)	0.93	(0.61–1.41)		1.05	(0.70–1.57)		1.01	(0.66–1.54)		1.03	(0.61–1.75)	
Fourth quartile	37	(35)	0.50	(0.29–0.85)		0.57	(0.33–1.01)		0.54	(0.29–1.02)		0.52	(0.26–1.04)	
Reduced motivation														
First quartile	28	(26)	1	—	0.73	1	—	0.89	1	—	0.85	1	—	0.90
Second quartile	20	(19)	1.20	(0.72–2.01)		1.45	(0.91–2.32)		1.30	(0.79–2.15)		1.31	(0.80–2.15)	
Third quartile	35	(33)	0.80	(0.46–1.39)		0.94	(0.56–1.60)		0.85	(0.47–1.54)		0.87	(0.47–1.60)	
Fourth quartile	23	(22)	1.04	(0.61–1.79)		1.18	(0.71–1.97)		1.10	(0.67–1.82)		1.11	(0.61–2.01)	

[a]Crude estimates.
[b]Adjusted for time since diagnosis.
[c]Adjusted for time since diagnosis, age and gender.
[d]Adjusted for time since diagnosis, age, gender and depression score.
[e]Test for trend.

Table 3. Return to work 1 year after diagnosis according to HAD-D and HAD-A case classification ($N = 105$)

			Model 1			Model 2			Model 3		
	N	(%)	RR[a]	(95% CI)	*P*	RR[b]	(95% CI)	*P*	RR[c]	(95% CI)	*P*[d]
Depression (HAD-D)											
No case	63	(60)	1	—	0.63	1	—	0.95	1	—	0.90
Possible case	20	(19)	0.67	(0.35–1.27)		0.74	(0.41–1.33)		0.75	(0.44–1.29)	
Subclinical case	22	(21)	0.95	(0.59–1.55)		1.07	(0.66–1.75)		1.05	(0.66–1.69)	
Anxiety (HAD-A)											
No case	41	(39)	1	—	0.048	1	—	0.073	1	—	0.068
Possible case	25	(24)	0.79	(0.49–1.27)		0.77	(0.47–1.25)		0.73	(0.44–1.21)	
Subclinical case	39	(37)	0.63	(0.39–1.01)		0.67	(0.43–1.06)		0.68	(0.44–1.06)	

One patient had more than one missing item in the HAD-D and HAD-A scale and was therefore not included in the analyses.
[a]Crude estimates.
[b]Adjusted for time since diagnosis.
[c]Adjusted for time since diagnosis, age and gender.
[d]Test for trend.

cannot entirely rule out the risk of type 2 errors. Further, it is well known that antidepressants and anxiolytics are sometimes prescribed by physicians without carefully assessing the mental health status of a patient. Thus, these surrogate markers probably have low specificity and sensitivity regarding clinical depression and anxiety. It is therefore likely that the self-ported data on anxiety and depression do not correspond to the use of antidepressants and anxiolytics.

We found that the proportion of chronic lymphoid leukaemia or follicular lymphoma was higher among patient working at baseline than those on sick leave. This is in agreement with our previous findings showing that sick leave patterns differ between haematological malignancy subtypes [7,8]. Chronic lymphoid leukaemia or follicular lymphoma might not result in sick leave in the following years after diagnosis. However, because of the nature of disease and treatment,

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some of these patients will probably be sickness absent at a later time point. This difference in diagnosis subtype between the two groups may explain why a large percentage of working patients stayed at work the following year.

Strengths and limitations

The strength of our study is the use of self-reported data on fatigue, depression and anxiety obtained with validated scales in combination with the use of complete follow-up data on labour market participation from a highly valid and reliable population-based register. Furthermore, the prospective design allowed us to evaluate associations between fatigue, depression and anxiety and future labour market participation. Finally, all patients diagnosed with haematological malignancies in Denmark during the inclusion period were eligible for the study leading to a high degree of external validity.

The small sample size is a limitation as the study might have been underpowered and thus less likely to detect differences in RTW across categories of fatigue, depression and anxiety. Consequently, we were not able to make adjustments for haematological malignancy subtype, socio-economic status and comorbidity, all of which have been associated with future labour market participation in previous studies [7,8]. Furthermore, we had no access to data on work-related factors, disease status and treatment type, which also could have had an impact on labour market participation. Therefore, we cannot entirely rule out residual confounding.

Forty-three patients did not respond to the questionnaire, and this selection could be associated with both exposures and outcome. Unfortunately, we do not know the reason for this non-response, but it could potentially have been caused by high scores of fatigue, depression and anxiety. In this case, non-response is highly associated with study exposures. If non-response is associated with RTW rates, the selection might have biassed the results towards or against the null hypothesis [32].

Finally, time since diagnosis was found to be an important confounder in this study. Ideally, baseline scores of self-reported symptoms should therefore have been measured at the same time point following diagnosis for all patients in order to avoid that time since diagnosis confounded the relative estimates.

Conclusion

In conclusion, high levels of fatigue, depression and anxiety were more prevalent among patients on sick leave than among those working at baseline. The majority of working patients stayed at work, whereas half of those on sick leave returned to work during 1-year follow-up. The haematological malignancy subtypes differed significantly between patients working at baseline and those on sick leave, which could have impacted these results.

Patients with highest scores of physical fatigue were less likely to RTW than those with lowest scores. Similar, we found tendency for an association between symptoms of anxiety and RTW. No significant association was found between depression and RTW. The results implicate that clinicians should focus on fatigue in rehabilitation of patients with haematological malignancies. However, taking the weaknesses of this study into account, further research is needed, before more comprehensive practical implications can be provided. To establish the causal relationships between fatigue, depression and anxiety and labour market participation, future studies must be conducted in larger populations of patients with haematological malignancies and should include clinical and work-related factors as covariates. Time since diagnosis plays an important role in the association between fatigue, depression and anxiety and labour market participation, and therefore, baseline scores of these symptoms should be measured at the same time point following diagnosis for all patients.

Ethics

The study was conducted in line with the Declaration of Helsinki, it was approved by the Danish Data Protection Agency (journal number 2013-41-1921) and reported to the Danish Ethical Committee (reference number 75/2011).

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Conflict of interest

The authors have declared no conflicts of interest.

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