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Labour market participation for patients diagnosed with haematological malignancies

- Observational and longitudinal studies on disability pension, return to work and long-term sickness absence

PhD dissertation

Trine Allerslev Horsbøl

Health
Aarhus University
2014

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Preface

This PhD thesis is based on four studies carried out during my employment at the Department of Haematology, Aarhus University, and in close collaboration with Marselisborgcentret, Public Health and Quality Improvement, Central Denmark Region, Denmark.

I would like to express my sincere gratitude to those who made this work possible.

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Trine Allerslev Horsbøl

Abbreviations

AML/ALL	Acute myeloid leukaemia/acute lymphoid leukaemia
CAR	The Danish Cancer Registry
CCI	Charlson Comorbidity Index
CLL	Chronic lymphoid leukaemia
CML	Chronic myeloid leukaemia
CRS	The Danish Civil Registration System
DLBCL	Diffuse large B-cell lymphoma
DNPR	The Danish National Prescription Registry
DP	Disability pension
DREAM	The Danish Register for Evaluation of Marginalisation
FL	Follicular lymphoma
HADS	Hospital Anxiety and Depression Scale
HL	Hodgkin lymphoma
HR	Hazard ratio
LTSA	Long-term sickness absence
MFI-20	Multiple Fatigue Inventory
MM	Multiple myeloma
NPR	The Danish National Patient Register
OR	Odds ratio
RTW	Return to work
RR	Relative risk
SD	Standard deviation
95% CI	95% confidence interval

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This PhD thesis is based on the following papers:

1. **Factors associated with work outcome for survivors from haematological malignancies a systematic literature review**

   Horsboel TA, de Thurah A, Nielsen B, Nielsen CV
   Eur J Cancer Care (Engl). 2012;21(4):424-35.

2. **Risk of disability pension for patients diagnosed with haematological malignancies: a register-based cohort study**

   Horsboel TA, Nielsen CV, Andersen NT, Nielsen B, de Thurah A
   Acta Oncol. 2014 Jan 23.

3. **Type of hematological malignancy is crucial for the return to work prognosis: a register-based cohort study**

   Horsboel TA, Nielsen CV, Nielsen B, Jensen C, Andersen NT, de Thurah A
   J Cancer Surviv. 2013;7(4):614-623.

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

   Horsboel TA, Bültmann U, Nielsen CV, Nielsen B, Andersen NT, de Thurah A
   Submitted to Psycho-Oncology, April 2014

INTRODUCTION

The treatment of haematological malignancies has improved markedly during recent years, and more people therefore survive from these diseases (1). More than one third of the patients are of working age (20-64 years), and they are therefore at risk of facing impaired working ability due to their disease and its treatment (2). Qualitative studies consistently indicate that work forms a central basis for self-identity and self-esteem for patients diagnosed with cancer. It provides financial security, forms and maintains social relationships, and represents the individual's abilities, talents and health. In order for the patients to sustain or regain these benefits, maintaining labour market participation is of utmost importance (3, 4).

Previous studies report that patients diagnosed 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 populations (5-7) and patients with other cancer types (8-10). However, none of these studies have studied patients diagnosed with haematological malignancies as a group in its own right. Haematological malignancies only comprised one to four minor subgroups of the total study population, and malignancies with different treatments and prognoses were mixed.

Recent years have seen a number of reviews evaluating factors associated with labour market participation for cancer patients. However, in these reviews, patients with haematological malignancies are either not represented, or the reviews have included only one or two studies on this patient group (11-15).

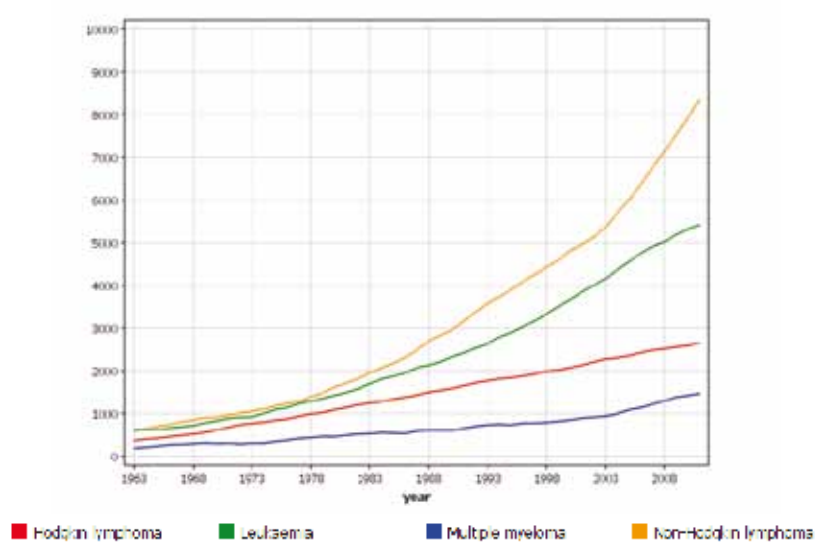
Treatment of haematological malignancies differs from that of other malignancies in several aspects. It rarely involves surgery, but more often chemotherapy for extended time periods. In some cases, initial therapy is not indicated, and in many cases the diseases have a chronically progressive character with intermittent needs for treatment. It is therefore necessary to study patients with haematological malignancies as a separate group to obtain specific knowledge about factors associated with their labour market participation.

A better understanding of the role such factors play is needed to design and initiate early rehabilitation interventions that may support the patients in maintaining or facilitating their labour market participation. Thus, the focus of this PhD thesis is on the labour market participation of patients with haematological malignancies and factors associated with this group's labour market participation.

Haematological malignancies

The incidence of haematological malignancies was 76.1 new cases per 100 000 person years in Denmark in 2011. In all, 2 118 persons were diagnosed with haematological malignancies in Denmark in 2011. Among these, 37% were of working age (20-64 years). The treatment of haematological malignancies is continuously being improved, and its prevalence is therefore rising (Figure 1). At the end of 2011, the prevalence was 0.3% of the entire Danish population; and 17 836 persons who had previously been diagnosed with haematological malignancies, were alive (2).

Figure 1 Historical prevalence of patients diagnosed with haematological malignancies



NORDCAN © Association of the Nordic Cancer Registries (15.12.2013)

The various subtypes of haematological malignancies differ markedly in terms of their presentation, treatment, progression and outcome. The simplest categorisation is leukaemias, lymphomas and multiple myeloma. However, these diagnoses also comprise several subgroups of which some run a highly acute course, whereas others are chronic conditions (16-21). The diagnoses have been categorised in various ways. Many studies group acute myeloid/lymphoid leukaemia and chronic myeloid/lymphoid leukaemia as one single group under the name of "leukaemias" in spite of large differences in their treatment and clinical course. Likewise, the very heterogeneous group of non-Hodgkin lymphomas is often grouped together. In this present thesis, we have chosen to group the diagnoses into the following eight subtypes of haematological malignancies:

* Hodgkin lymphoma (HL)
* Diffuse large B-cell lymphoma (DLBCL)
* Follicular lymphoma (FL)
* Multiple myeloma (MM)
* Acute myeloid/lymphoid leukaemia (AML/ALL)
* Chronic myeloid leukaemia (CML)
* Chronic lymphoid leukaemia (CLL)
* Others

This categorisation reflects a clinical perspective on prognosis and treatment and its intention is to group diagnoses according to similarity of treatment and disease.

★ HL occurs in two peaks; the first peak is seen in young adulthood (age 15–35) and the second in persons who are more than 55 years old. At the time of diagnosis, most patients only have few symptoms which include enlarged lymph nodes and B-symptoms (fever, night sweats and weight loss). The disease is most often curable, and its prognosis is good even though it depends on the stage of disease. Treatment consists of chemotherapy and radiotherapy and is usually completed within three to six months. The five-year survival rate for this subtype of haematological malignancies is 85% (18).

- ★ Non-Hodgkin lymphoma is a term covering several different types of lymphomas with different symptoms, treatments and courses. The two most common types are DLBCL and FL. These diseases are most common among adults older than 60 years, but they also occur among younger people. DLBCL accounts for 40% of the cases of non-Hodgkin lymphoma. Presenting symptoms at diagnosis are enlarged lymph nodes and B-symptoms. The disease is aggressive, but potentially curable. Again, the prognosis depends on the stage of disease. Treatment consists of chemotherapy, immunotherapy and radiotherapy and is usually completed within three to six months. The five-year survival rate for this subtype of haematological malignancies is 60% (19).
- ★ FL accounts for 20% of cases of non-Hodgkin lymphoma. The disease is more indolent than DLBCL, and some patients have no symptoms at the time of diagnosis except from enlarged lymph nodes. Most cases of this disease are incurable, and the disease characteristically runs an indolent, progressive course. A "wait and watch" strategy is often adopted if the patients do not have symptoms at the time of diagnosis. However, an average of three years after diagnosis, treatment with immunotherapy and/or chemotherapy will often be necessary. The median survival for patients diagnosed with this malignancy is 10-12 years (20).
- ★ MM is cancer in the bone marrow. The debut symptoms vary, but they often comprise fatigue (because of anaemia) and pain in the back and extremities (because the disease affects the bones). Most patients are over 60 years old at diagnosis, but the disease also occurs among younger individuals. The disease is incurable, but treatment with chemotherapy and, for younger and middle-aged patients, autologous haematopoietic stem cell transplantation (age limit approximately 65 years) can prolong survival and alleviate symptoms. Initial treatment is usually completed within six months. The overall five-year survival rate for patients with MM is 40%, depending of disease stage, age, etc. (21). Among patients younger than 65 years, the five-year survival rate is 59% (22).
- ★ AML/ALL occurs in all age groups; however, the incidence of AML rises with increasing age, whereas ALL is the most common leukaemia in childhood. Both diseases are curable, but treatment needs to be initiated immediately after

diagnosis due to quick and aggressive progression. At the time of diagnosis, patients are often acutely ill with symptoms of anaemia, bleeding tendencies, infection and high fever. Treatment consists of chemotherapy and sometimes allogeneic haematopoietic stem cell transplantation. Initial treatment (except for those treated with allogeneic transplantation) is usually completed within six months. These first six months are often characterised by frequent hospital admissions due to infections, anaemia and risk of bleeding. The five-year survival rate for all patients with AML is 19%, and the prognosis depends much on the patient's age. Thus, the five-year survival for AML patient below 60 years treated in Denmark is 43%. The five-year survival rate for ALL is 40% for adults (16, 17, 23).

★ CML usually occurs after the age of 40 years. The patients often have no symptoms when they are diagnosed. In most cases, the disease is incurable. Allogeneic stem cell transplantation is the only curable treatment, and it is only offered to young patients. Instead, the patients are often treated with biological therapy (a tyrosine kinase inhibitor) administered as oral tablets. Such treatment has very few side-effects and prolongs survival considerably. The five-year survival rate for this subtype of haematological malignancies is 90% (24).

★ CLL usually occurs after the age of 40 years, and only 15% of patients are younger than 60 years at diagnosis. The disease is twice as common among men as among women. The patients often do not have symptoms when they are diagnosed. In most cases, this disease is incurable, and it characteristically runs an indolent, progressive course. Only 20-25% of the patients need treatment at the time of diagnosis. Treatment consists of immunotherapy and/or chemotherapy, and sometimes allogeneic stem cell transplantation (25). The three-year survival rate for this subtype of haematological malignancies is 82% (26)

★ Others include a mixed group of the remaining haematological malignancies. Most of them are rare subtypes of non-Hodgkin lymphomas with very different clinical features and therapies.

Symptom burden

Previous studies have found that patients diagnosed with haematological malignancies experience many symptoms following diagnosis and treatment. Frequently reported symptoms include fatigue, psychological distress, sleeping difficulties, lack of concentration, dyspnoea, pain, dry mucous membranes, gastrointestinal problems and sexual problems, among others (27-29). An Australian cross-sectional study recently measured the symptom burden among 180 patients diagnosed with haematological malignancies. It reported an overall mean number of cancer- and treatment-related symptoms of 8.8, which is comparable to the number of symptoms seen in patients with metastatic non-haematological malignancies (30). A similar Danish cross-sectional study found a mean of 4.3 symptoms experienced by patients with haematological malignancies. The Danish study, however, used a symptom scale with fewer possible symptoms than the Australian study. In the Danish study the number of experienced symptoms ranged from 2.3 among patients with acute myeloid leukaemia to 5.6 among patients with multiple myeloma (31).

Fatigue is reported to be the most frequently reported symptom among patients diagnosed with haematological malignancies. Thus, the proportion of patients experiencing fatigue varied from 55% to 72% in recently published studies (27, 31, 32). Furthermore, in an Australian qualitative study, patients with haematological malignancies reported that fatigue was the symptom that most frequently prevented them from returning to work (33). The aetiology of fatigue in cancer patients is not completely established. It is considered to be multifactorial, involving both physical and psychological factors. Causes found to be associated with the presence of cancer-related fatigue include tumour burden, malnutrition, infection, psychological distress, pain, sleep disturbance, depression, anxiety, inactivity, late medical effects, inflammation and anaemia (29, 34-36). Some patients experience fatigue as a side-effect of cancer treatment that resolves once they begin to recover from therapy. However, fatigue may persist for years after completed treatment and remission in some patients (29).

Psychological symptoms are also reported to be frequent among patients with haematological malignancies. A Danish cross-sectional study found that 65% of

patients with leukaemia and 57% of patients with lymphoma experienced symptoms of anxiety and, furthermore, that 60% of patients with leukaemia and 72% of patients with lymphoma felt depressed (37). Another cross-sectional study from Australia found that patients with haematological malignancies had higher levels of psychological distress than patients with metastatic non-haematological malignancies, and more than 70% of the patients were occasionally or frequently feeling sad, nervous or worried (30). Furthermore, a recently published Danish report concludes that symptoms related to psychological problems need more attention in cancer patients' treatment and rehabilitation. The results of this report are based on questionnaire data from a cross-sectional study among 2 568 patients diagnosed with mixed types of cancer conducted in 2012 (32).

Symptom burden has been found to be associated with quality of life and with physical, social, emotional and cognitive function among patients with cancer (38). However, to date, only few studies have investigated the impact of these symptoms on future labour market participation among patients diagnosed with haematological malignancies (39).

Labour market participation

This thesis explores the labour market participation of patients diagnosed with haematological malignancies; specifically, how these diagnoses affect the patients' future work life. Hence, the main focus of the thesis is *(i)* the risk of long-term sickness absence or permanently reduced work capacity (disability pension) and *(ii)* the rate of return to work following long-term sickness absence. In the following section, these aspects of labour market participation are described in the context of the Danish social security system.

The Danish system is organised into three political and administrative levels: The state, five regions and 98 municipalities. The municipalities administrate most of the public transfer payments (sickness absence benefits, disability pension, etc.). Denmark has a high level of social security, and most welfare services are tax-financed. Social security covers the entire population, and the social security system is obligated to support a person financially through public transfer payments if the person is unable to work due to physical or mental disability.

All employed, self-employed and unemployed persons in Denmark are included in the public sickness absence benefit program, which covers both work-related and non-work related reasons for sickness absence. If a person has been employed for at least 8 weeks (working at least 74 hours), the employer is obliged to defray the sickness absence benefits for the first 30 days of a period of sickness absence. The length of this period has ranged from 14 to 30 days from 2000 to 2012. After this period, sickness absence benefits are administrated and covered by the municipalities. During a long-term sickness absence period, the sickness-absent person is required to attend follow-up meetings at the municipality. However, persons with life-threatening conditions, like for example cancer, are excused from participating in these follow-up meetings. Sickness absence benefits are temporary and available for a period of maximum 52 weeks within a period of 18 month. When a sickness absence period approaches this limit, the municipality has to evaluate if the sickness-absent person is able to return to work or if the person is permanently work-disabled. Special circumstances may result in an extension of the sickness absence period. Such circumstances include critical illness and being under treatment (40, 41). Not all patients diagnosed with haematological malignancies do automatically become long-term sickness-absent following diagnosis. This may for example include patients with chronic conditions with mild debut symptoms like patients with CLL or FL. However, due to the character of both these diseases and their treatment, some of these patients will probably be sickness-absent later on in the course.

If a person is permanently work-disabled, wage-subsidised employment or disability pension is granted by the authorities. An individual who has a wage-subsidised job works reduced working hours and has special job tasks. To be granted wage-subsidised employment, the person's work capacity must be permanently reduced to a level that prevents him or her from having an ordinary job. Disability pension is granted if the work capacity is permanently reduced to an extent that makes return to work unlikely. All options available for improving labour-market participation through rehabilitation, treatment or wage-subsidised employment must have been exhausted before disability pension is granted (42-44).

The present PhD project was conducted from 2000 to 2012. During this period, persons were eligible for old-age pension from the age of 67 years. On 1 July 2004, the age limit was reduced to 65 years. During the entire period, there was an anticipatory retirement scheme from the age of 60 years (44, 45)

A systematic review of the literature (Study I)

Up to now, only few systematic reviews about labour market participation for patients diagnosed with cancer have been published (11-15). In these reviews, patients diagnosed with haematological malignancies were either not or only very sparsely represented. Moreover, the results of reviews of non-haematological malignancies are not directly applicable to haematological malignancies which often require other kinds of treatment and run a different course.

Hence, a systematic review was performed (39) in order to *(i)* identify previous studies of factors associated with labour market participation for patients diagnosed with haematological malignancies and *(ii)* discuss important aspects of study designs suitable for such studies. A summary of the methods and the main findings of the systematic review is given in this section of the thesis. Further descriptions may be found in Paper I.

Systematic searches were carried out in Pubmed, Embase, Cochrane Library and Cinahl using the following search terms: Haematological neoplasms, haematological malignancies, lymphoma, leukaemia, and multiple myeloma combined with employment, unemployment, work, work ability, pensions, retirement, supported employment, absenteeism, sick leave, sickness absence, and return to work.

Studies were included if the study population consisted of working-age adult survivors from haematological malignancies and if they focused on factors potentially associated with labour market participation. Only studies in English, Norwegian, Swedish and Danish were considered. Studies including adult survivors from childhood cancers were excluded as were studies applying qualitative methods. The inclusion criteria did not include publication year, study design and methodological quality. The inclusion of studies is illustrated in Figure 2.

Eight studies published between 1986 and 2011 were included in the systematic review (Tables 1 and 2). Three of the studies were prospective cohort studies (8, 46, 47). The last five studies had a cross-sectional design (48-52). None of the studies included a control group.

Figure 2 Flowchart of inclusion of studies

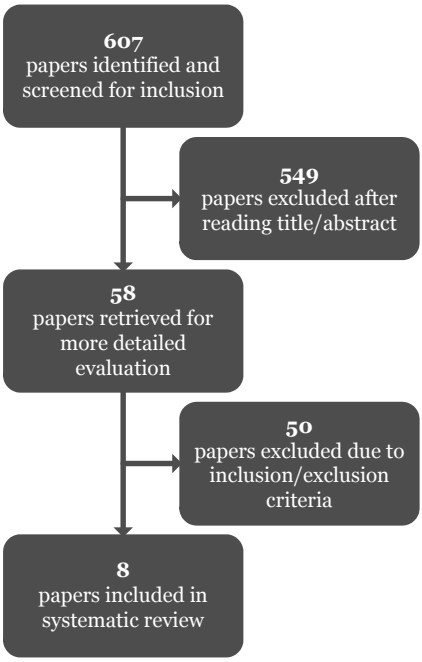


Table 1 Presentation of included cohort studies

Study	Data source	Study population				Outcome	Factors evaluated		Methodological quality
		Diagnosis	Sample	Age	Follow-up		Negatively associated	Non-associated	
(47) USA	Questionnaire and medical records No control group	Leukaemia and lymphoma Autologous or allogeneic haematopoietic cell transplantation	**N = 281**	Mean age at transplant: **36** (18-62)	Pre-transplant, 90 days, 1, 3 and 5 years post-transplant	**Time to return to work**	**Gender (female)** HR 0.52 (95% CI 0.33- 0.82)	**Diagnosis** **Stem cell donor** (autologous vs. allogeneic) **Total body irradiation** **Radiation therapy or chemotherapy pre-transplant** **Age** **Education** **Income** **Marital status** **Pre-transplant levels of physical limits, depression and treatment distress** **GVHD**	**Risk of information bias:** Patients provided date of return to work 3 and 5 years after diagnosis **Risk of selection bias:** 317 did not consent to participate Non-participants had higher survival rates and differed from participant in terms of cancer type and ethnicity. The group of non-responders (n=18) was not compared with responders
(46) USA	Questionnaire No control group	Haematological malignancies Autologous or allogeneic haematopoietic cell transplantation	**N = 106**	**<35** (N=33) **35-49** (N=69) **>50** (N=28) (For the 130 patients working full-time before transplantation)	Pre-transplant, 6 months, 1, 2, 3 and 5 years post-transplant	**Time to return to work**	**Physical dysfunction** (SF36) HR 2.38 (95% CI 1.26-4.49) **Gender** (female) HR 0.54 (95% CI 0.29- 0.99)	**Mental health** (SF36) HR 1.22 (95% CI 0.58,-2.54) **Age** <35 years: HR 1.00 35-49 years: HR 0.82 (95% CI 0.42-1.58) >50 years: HR 0.60 (95% CI 0.25-1.40) **Education** HR 0.85 (95% CI 0.46- 1.59) **Marital status** HR 1.08 (95% CI 0.56- 2.07) **Income**	Low precision due to small sample size **Risk of selection bias:** 37 declined to participate and 118 were not invited There were differences between participants and non-participants in terms of gender, donor type, transplant type and cancer type
(8) The Netherlands	Registers No control group	Leukaemia and lymphoma	**N = 297**	Mean age at diagnosis: **42.3** (18-60)	At diagnosis and 2 years after diagnosis	**Time to return to work**	**Gender** (female) HR 0.60 (95% CI 0.50-0.90)	**Age** <35 years: HR 1.00 35–44 years: 1.00 (95% CI 0.70–1.50) 45–54 years: 0.80 (95% CI 0.50–1.20) >55 years: 1.00 (95% CI 0.70–1.50)	Only age and gender were included in analyses as exposures and confounders

Table 2 Presentation of included cross-sectional studies

Study	Data source	Study population				Outcome	Factors evaluated		Methodological quality
		Diagnosis	Sample	Age	Time since treatment		Negatively associated	Non-associated	
(48) USA	Questionnaire and interview No control group	Hodgkin lymphoma	**N = 403**	Mean age at diagnosis: **36.3** (15-78)	Median (range): **9 years** (1-21) (Since end of treatment)	**Number of weekly working hours**	**Female gender** **Depression** (CES-D) **High age** **Low energy-level** **Disease status** (relapsers)	**Stage of disease** **Treatment type**	Neither estimates nor confidence intervals presented Some participant were beyond working age **Risk of selection bias**: It is not clear if there was a group of patients that did not turn up for regular follow-up and therefore were not invited to participate There is no information about the non-responders.
(52) Belgium	Questionnaire-structured interview and medical records No control group	Non-Hodgkin and Hodgkin lymphoma	**N = 41**	Mean age at diagnosis: **41.3** (19-61)	Mean (range): **52,7 months** (1-204) (Since end of treatment)	**Rate of return to work**	**Anxiety/depression** (HADS) **High treatment toxicity** **Time since treatment** (short)	**Stage of disease** **Age** **Gender** **Fatigue** (POMS)	Low precision due to small sample size Neither estimates nor confidence intervals presented **Risk of selection bias**: No descriptions if all eligible patients were approached for inclusion **Risk of information bias:** Outcome (return to work) not defined
(51) Norway	Questionnaire No control group	Hodgkin lymphoma	**N = 459**	Mean age at diagnosis: **44** (19-74)	Range: **3 - 23 years** (Since start of first-line treatment)	**Disability more than 12 month after first line treatment**	**Age** (> 40 years at diagnosis) **Full-time employment at diagnosis** **Chemotherapy/radiotherapy** **Depression** (HADS) **Anxiety** (HADS) **Fatigue** (FQ) **Stage III and IV disease**		Neither nor confidence intervals presented Only univariate analysis were performed (no confounder control) Some participant were beyond working age **Risk of information bias:** Disability>12 month not defined **Risk of selection bias**: No descriptions if all eligible patients were approached for inclusion. There is no information about the non-responders.
						Permanent disability	**Age** (> 40 years at diagnosis) **Full-time employment at diagnosis** **Chemotherapy/radiotherapy** **Depression** (HADS) **Anxiety** (HADS) **Fatigue** (FQ) **Low educational status**		

Table 2 Presentation of included cross-sectional studies (continued)

Study	Data source	Study population				Outcome	Factors evaluated		Methodological quality
		Diagnosis	Sample	Age	Time since treatment		Negatively associated	Non-associated	
(49) Finland	Questionnaire No control group	Leukaemia, Hodgkin lymphoma, multiple myeloma Allogeneic haematopoietic cell trans-plantation	**N = 109**	Mean age at trans-plantation: **42** (21-59)	Mean (range): **55 months** (4-171) (Post-transplant)	**Rate of return to work**	**Job type** (Manual work)		Neither estimates nor confidence intervals presented **Risk of information bias:** It is not clear how exposure (job type) and outcome (return to work) were defined **Risk of selection bias:** Low response rate, and there were significant differences between responders and non-responders in terms of age and time since treatment
(50) Germany	Questionnaire No control group	Hodgkin and Non-Hodgkin lymphoma, Multiple myeloma, acute leukaemia and solid tumours (26%) Autologous haematopoietic cell trans-plantation	**N = 238**	Median age at trans-plantation: **49** (17-67)	Median: **36 month** (Post-transplant)	**Rate of return to work**	**Low education** **High age** **Physical function** (EORTC QLQ-C30) **Cognitive function** (EORTC QLQ-C30) **Social function** (EORTC QLQ-C30)	**Gender** **Participation in rehabilitation programmes**	Neither estimates nor confidence intervals presented **Risk of information bias:** Participants had to remember their employment status before treatment **Risk of selection bias:** There is no information about the non-responders

Results of the systematic review

A total of 21 different factors and their association with labour market participation were investigated in the included studies. The main finding of the systematic review was that knowledge in this area did not rest on firm evidence as the results were disparate. The prevailing inconsistency allowed us to draw no conclusions on the association of any single factor with labour market participation. Regarding most of the factors evaluated, the results were directly diverging between the studies. However, marital status and income did not seem to be related to labour market participation, whereas some relation was indicated between psychological symptoms (such as depression and anxiety) and labour market participation (Figure 3). Still, the included studies were heterogeneous in terms of study characteristics and methodology, and a comparison of the results was consequently complicated. Also, there were methodological weaknesses in some of the included studies, which may have blurred the results.

Figure 3 Associations evaluated in studies included in the systematic review. Green references represent prospective studies and red references represent cross-sectional studies

Evaluated factors	Associated with labour market participation	Not associated with labour market participation
Cancer survivor characteristics		
Gender	(46), (47), (8), (48)*	(50)*, (52)*
Age	(51)*, (48)*, (50)*	(46), (52)*, (8), (47)
Marital status		(46), (47)
Educational level	(51)*, (50)*	(46), (47)
Income		(46), (47)
Work demands		
Employment status at diagnosis	(51)*	
Manual work	(49)*	
Cancer and treatment		
Stage of disease	(51)*	(48)*, (52)*
Disease status	(48)*	
Treatment type	(51)*	(48)*, (47)
Time since end of treatment	(52)*	
Diagnosis		(47)
Symptoms after cancer and treatment		
Depression	(51)*, (48)*, (52)*	(47)
Anxiety	(51)*, (52)*	
Mental health		(46)
Treatment distress		(47)
Fatigue	(51)*	(52)*
Treatment toxicity	(52)*	
Function after cancer and treatment		
Physical function	(50)*, (46)	(47)
Cognitive function	(50)*	
Social function	(50)*	

*For these factors, neither estimates, nor confidence intervals appeared in the papers.

Thus, due to the inconsistency of the reported results, no conclusions could be drawn about the association between any single factor and labour market participation for patients diagnosed with haematological malignancies. This emphasised the need for more well-designed studies in this area. The systematic review made it clear that the design of future studies should be prospective and that future studies should include a control group of age-paired individuals without a history of haematological malignancies. Possible factors related to labour market participation should be evaluated at an early time point after diagnosis to allow for establishing cause-effect relations. The role of comorbidity and the differences between haematological cancer subtypes ought to be established, and outcomes should be well-defined and recorded with valid methods. This will be further discussed in the following section in the context of the planning of the studies for this thesis.

Considerations for planning our studies

The design of the studies in this thesis rests on a discussion of the strengths and limitations in the studies in the above-mentioned systematic review.

Study design

The designs of the systematically reviewed studies were either cross-sectional or prospective and in general, their results differed accordingly. The three prospective studies largely found the same results. They all found no association between age, marital status, educational level, and income and labour market participation; and they all found that female gender was associated with low return-to-work rates (8, 46, 47). By contrast, there was no clear-cut agreement between the individual cross-sectional studies or between them and the prospective studies (48-52) (Table 3).

The focus in the present PhD thesis is on the labour market participation of patients diagnosed with haematological malignancies and factors associated with their labour market participation. For such purposes, the prospective design seems to yield the most reliable results, since information on exposure and outcome then are obtained at different time-points, and therefore the design allows for interpretation of causal associations. On the contrary, the cross-sectional study design provides information

about associations only, because exposures and outcome are measured at the same time point (53, 54).

It is obvious that time since diagnosis is of much importance in studies exploring labour market participation. In the cross-sectional studies included in the systematic review, time since diagnosis differed widely between the patients, up to 20 years between individuals in the same study. It seems, however, unlikely that the association between e.g. fatigue and labour market participation would lead to the same result at one year and at 20 years after diagnosis. From a clinical point of view, it would seem most advantageous to measure factors possibly associated with labour market participation within a short timeframe after diagnosis, notably if the results are meant to be applicable to clinical practice and to serve the purpose of identifying the patients at risk of work-related problems.

Based on above mentioned perspectives, the studies in this present thesis are prospective. Furthermore, we have included a reference cohort when relevant in order to be able to determine if any associations found between factors and labour market participation are patient-specific or applied to the general population as well.

Choice of outcome

The systematic review also focused our attention on how labour market participation was measured. In the included studies, measures included return to work (8, 46, 47, 49, 50, 52), weekly work hours (48) and disability pension (51). Some of the studies did not define return to work, or this measure was flawed by recall problems which could lead to misclassification (53, 54)

In this thesis, the overall outcome is labour market participation. The outcomes measures in the studies are risk of long-term sickness absence, risk of permanently reduced work capacity (disability pension) and rate of return to work following long-term sickness absence. In an attempt to avoid misclassification of the outcomes, we use well-defined outcome measures. Hence, permanently reduced work capacity is defined as being granted disability pension; return to work is defined as the first period of four consecutive weeks without receiving sickness absence benefits or other public transfer payments (55); and long-term sickness absence is defined as at least five consecutive weeks of sickness absence. Furthermore, all data on labour market

participation are obtained from a nationwide, population-based register containing information on public transfer payments at the level of the individual recipient.

Choice of exposures

Many of the factors that might play an important role for labour market participation among patients diagnosed with haematological malignancies (for example depression and fatigue) were measured and defined in ways that differed between the systematically reviewed studies. This, again, blurred the results and complicated comparison between the studies.

Previous studies on other cancer groups' labour market participation have suggested that the presence of comorbidity is negatively associated with labour market participation (5, 56). Unfortunately, none of the included studies had examined this association for patients diagnosed with haematological malignancies.

In the studies forming the backbone of the present thesis, we include exposures like demographic and socio-economic factors which previous studies have found may have an impact on the future labour market participation of patients with haematological malignancies. The role of comorbidity and haematological malignancy subtype for future labour market participation is also analysed. Among cancer-related symptoms, we choose to focus on fatigue, depression and anxiety as symptoms that could affect the patients' labour market participation. This choice is informed by previous studies which have found that these symptoms were particularly prominent among patients diagnosed with haematological malignancies (27, 30-33, 37). Furthermore, the results of the systematic review showed that these symptoms tended to be associated with labour market participation. In the studies in this present thesis we evaluate symptoms of fatigue, depression and anxiety with the use of validated, self-reported scales in questionnaires, and we use register-based data where such data were available. The symptoms are assessed at an early time point after diagnosis to make it possible to examine longitudinal associations.

Study population

None of the studies in the systematic review evaluated the association between different subtypes of haematological malignancies and the patients' labour market participation; and malignancies with different treatments and prognoses were mixed in most of the studies. Three studies included a mix of haematological malignancies (46, 49, 50). Only survivors from lymphoma were included in yet another three studies (48, 51, 52); and, finally, both survivors from lymphoma and leukaemia were included in two studies (8, 47). Furthermore, treatment with haematopoietic cell transplantation was an inclusion criterion in half of the studies, and patients treated in this way only form a small subgroup of patients treated for haematological malignancies. As is the case with other cancer types (5, 6, 56), labour market participation could be affected by the varying degrees of severity of the different haematological malignancies and by differences in their nature and treatment. Studies must therefore be conducted in which labour market participation is compared across subtypes of haematological malignancies.

The study populations in the present thesis consist of all patients diagnosed with haematological malignancies in Denmark during well-defined time periods. This approach ensures a high degree of external validity. We divide the population into the previously described eight clinically relevant subgroups of haematological malignancies whenever possible in order to avoid the problems that arise from mixing patients with different courses and treatment regimens, as seen in previous studies, and in order to be able to examine whether subtypes of haematological malignancies are associated with labour market participation.

AIMS OF THE THESIS

The overall aim of the thesis was to investigate future labour market participation among patients diagnosed with haematological malignancies and to evaluate the impact of fatigue, depression, anxiety, comorbidity and socio-economic and demographic factors on labour market participation in this patient group. The specific aims of the studies were to:

Study II

a. Compare the risk of disability pension (DP) among patients diagnosed with eight clinically relevant subtypes of haematological malignancies to an age- and gender-matched reference cohort without a history of these malignancies, and to determine if relative risks differ between these subtypes.

b. Evaluate the influence of socio-economic factors, demographic factors, comorbidity, and post-diagnosis use of anxiolytics and antidepressants on the risk of DP.

c. Investigate if these associations differ between the reference cohort and the patient cohort.

Study III

a. Determine the proportions of return to work (RTW) among patients diagnosed with eight clinical relevant subtypes of haematological malignancies between 2000 and 2007, who were on long-term sick leave following diagnosis.

b. Evaluate the influence of type of haematological malignancy, comorbidity, use of anxiolytics and antidepressants, socio-economic and demographic factors on RTW.

c. Investigate if these associations differ between genders.

Study IV

a. Examine levels of fatigue, depression and anxiety among sickness absent patients and patients working six to nine months following diagnosis of a haematological malignancy.

b. Determine the cumulative incidence of return to work (RTW) during one year follow-up among the sick absent patients, and to examine if fatigue, depression and anxiety are associated with RTW

c. Determine the cumulative incidence of long-term sickness absence (LTSA) during one year follow-up among the working patients, and examine if fatigue, depression and anxiety are associated with LTSA.

MATERIAL AND METHODS

This section gives a summary of material and methods in Studies II-IV. Additional information and more detailed presentations are available in the appended papers.

Design

Studies II and III are nationwide, register-based cohort studies. Study IV is a nationwide, prospective study based on data from registers and questionnaires.

Data sources

Data from registers and questionnaire-based data were used in this thesis. Table 4 gives an overview of the data sources used in Studies II-IV.

Table 4 Data sources and data used in Studies II-IV

Data source	Data	Study
The Danish Civil Registration System	• Sampling of reference cohort • Date of death or emigration • Ethnicity	Study II Study II, III & IV Study II & III
The Danish Cancer Registry	• Sampling of patient cohort • Haematological malignancy subtype	Study II & III Study II, III & IV
The Danish National Patient Register	• Sampling of patient cohort • Comorbidity	Study IV Study II, III & IV
The Danish National Prescription Registry	• Use of antidepressants and anxiolytics	Study II & III
Statistics Denmark	• Educational level • Income • Cohabitation status • Children living at home • Housing tenure	Study II & III
DREAM database	• Disability pension • Return to work • Long-term sickness absence	Study II Study III & IV Study II, III & IV
Questionnaire	• Fatigue (MFI-20) • Anxiety & depression (HADS)	Study IV

The Danish Civil Registration System (CRS)

Since 1968, all residents of Denmark have been registered in the Civil Registration System and assigned a unique personal identification number (CPR number) that contains their date of birth and sex and a unique, individual number. Individual information is kept under this identification number in all Danish national registries, which enables unambiguous linkage of information between the registries at the level of the individual. Among other things, the register contains information about name, address, citizenship and date of death of all residents of Denmark (57, 58).

The Danish Cancer Registry (CAR)

The Danish Cancer Registry is a population-based, nationwide register, which contains data on all incident cancer cases in the Danish population since 1943. Reporting to the register by medical doctors has been mandatory since 1987. High completeness and validity is ensured through quality control routines applied on a daily basis, complete annual publication of the register's data, and also by the use of multiple notifications from different data sources (The Danish National Patient Register, the Danish Pathology Register, and the Danish Register of Causes of Death). Important variables recorded in the register include diagnosis (according to the International Classification of Diseases, 10th edition (ICD-10)), topography, morphology, extent of tumour at time of diagnosis (stage), and date of diagnosis (58, 59).

The Danish National Patient Register (NPR)

The Danish National Patient Register includes information on all hospital admissions in Denmark since 1977, and all contacts to emergency rooms or outpatient clinics since 1995. Diagnostic information has been coded by physicians according to the ICD-10 at each contact since 1994 (58, 60, 61). A positive predictive value greater than 90% has been found for almost all ICD-10 diagnostic codes used to ascertain the Charlson comorbidity conditions (which is measured in this thesis, and will be further described in the section regarding exposures) in the register (62). Variables in the register include, among others, information on hospital and department admissions, dates of admission and discharge, diagnoses and surgical procedures (58, 60, 61).

The Danish National Prescription Registry (DNPR)

The Danish National Prescription Registry contains individual-level information on all prescription drugs sold in Danish pharmacies since 1994. Only a few studies have investigated the quality of the data in the register. It is assumed that the Register enjoys high completeness and validity because record keeping is reimbursement-driven, and data are entered through an automated bar-code based system. Individual data in the register include the type and amount of drug prescribed according to the Anatomical Therapeutical Chemical Classification System (ATC) and the date of drug redemption (63).

Registers administered by Statistics Denmark

Statistics Denmark is a central authority compiling and publishing statistics from several registries on the Danish society, especially on social and economic factors. In our studies, Statistic Denmark provided data from The Registry for Education of the Population, The Building and Housing Registry and The Registry of Income Statistics.

The Danish Register for Evaluation of Marginalisation (DREAM)

The Danish Register for Evaluation of Marginalisation (DREAM) contains information on all public transfer payments administered by Danish ministries and municipalities for Danish residents on a weekly basis since 1991 (64). The register is based on data from the Danish Ministry of Employment, the Danish Ministry of Education, the CRS and SKAT (the Danish tax authority). The type of transfer payment is recorded for each week if the person has received the benefit for one day or more. At present, the DREAM database includes 105 different codes for social transfer payments. If no transfer income is registered for a specific week, the person is supposed to be self-supported. DREAM is increasingly applied in research, and its validity has been compared to other sources of information (65-67).

Self-administered questionnaire

A self-administered questionnaire was used to obtain information about self-reported symptoms of anxiety and depression. Together with an invitation letter, it was distributed to all eligible patients six to nine months after they had been diagnosed with a haematological malignancy. If the questionnaire was not returned within two weeks, a reminder was sent. Patients not responding to the reminder were contacted by telephone if possible.

Study populations

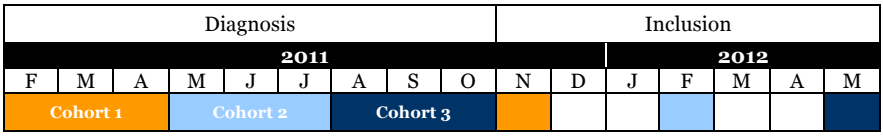
In Studies II and III, eligible persons included all patients diagnosed with a haematological malignancy at the age of 19 to 55 years in Denmark during the period from 1 January 2000 to 31 December 2007.

In Study II, we excluded permanently work-disabled patients (disability pensioners and patients in wage-subsidised employment) and patients who had emigrated at the time of diagnosis. Furthermore, a random reference cohort was included in Study II. Each patient was individually matched on gender and date of birth to ten persons without a history of haematological malignancies. The individuals in the reference cohort were assigned the same date of diagnosis as the patient to whom they were matched. Reference individuals who were permanently work-disabled or had emigrated at the time of diagnosis were excluded. Furthermore, reference individuals who were matched to patients who had been excluded because of the above-mentioned criteria were also excluded.

In Study III, we included employed patients who had been on sick leave for more than two weeks within twelve weeks after having been diagnosed.

In Study IV, all patients who had been diagnosed with a haematological malignancy six to nine months before the date of inclusion at the age of 19-59 years were considered eligible. Furthermore, they should be employed at the date of inclusion. Patients were included at three time-points: 1 November 2011 (patients diagnosed between 1 February and 30 April 2011), 1 February 2012 (patients diagnosed between 1 May and 31 July 2011) and 1 May 2012 (patients diagnosed between 1 August and 31 October 2011) (Figure 4).

Figure 4 Inclusion process in Study IV



Exposures and outcomes

Table 5 gives an overview of the variables and outcomes included in the three studies. A more detailed description is given below.

Table 5 Study population, exposure and outcome in Studies II-IV

Study	Study population	Exposures	Outcome
II	All patients diagnosed with a haematological malignancy in Denmark from 1 Jan 2000 to 31 Dec 2007 at the age of 19-55 years who were not permanently work-disabled	Haematological malignancy subtype, socio-economic factors, demographic factors, comorbidity and post-diagnosis use of anxiolytics and antidepressants	Disability pension
III	All patients diagnosed with a haematological malignancy in Denmark from 1 Jan 2000 to 31 Dec 2007 at the age of 19-55 years who were employed and on long-term sick leave following diagnosis	Haematological malignancy subtype, socio-economic factors, demographic factors, comorbidity and post-diagnosis use of anxiolytics and antidepressants	Return to work
IV	All patients diagnosed with a haematological malignancy in Denmark from 1 Feb 2011 to 31 Oct 2011 at the age of 19-59 years who were employed six to nine months following diagnosis	Self-reported fatigue, depression and anxiety (age, gender, time since diagnosis)	Return to work/ long-term sickness absence

Outcomes

Data on labour market participation were obtained from DREAM in all three studies.

In Study II, the outcome was being granted DP, and individuals in the patient cohort and the matched reference cohort were followed from the date of diagnosis until DP, emigration, anticipatory pension or old age pension, death or 26 February 2012, whichever came first.

In Study III, the outcome was RTW defined as the first period of four consecutive weeks without receiving sickness absence benefits or other public transfer payments (66, 67). Patients who received unemployment benefits for at least four weeks were

also considered to have returned to work under the assumption that these individuals were capable of working. Patients were followed until RTW, emigration, permanent withdrawal from the labour market, death or 26 February 2012, whichever came first.

In Study IV, the outcomes were RTW and LTSA. RTW was defined as in Study II (66, 67). LTSA was defined as at least five consecutive weeks of sickness absence. Patients who were on sick leave at baseline were followed until RTW, death, emigration, permanent exit from the labour market or one year after baseline, whichever came first; patients who were working at baseline were followed until LTSA, death, emigration, old age pension, permanent exit from the labour market or one year after baseline, whichever came first.

Exposures

Haematological cancer subtype

In Studies II-IV, haematological malignancies was categorised according to morphology into the following subgroups: Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), multiple myeloma (MM), acute myeloid/lymphoid leukaemia (AML/ALL), chronic myeloid leukaemia (CML), chronic lymphoid leukaemia (CLL) and others (Table 6).

Table 6 Categorisation of haematological malignancies

Diagnosis	Morphology codes	ICD-10
Hodgkin lymphoma	96503, 96513, 96523, 96533, 96593, 96633, 96643, 99903	C81
Diffuse large B-cell lymphoma	96803, 96843, 96843	C83.3
Follicular lymphoma	96893, 96903, 96913, 96953, 96983	C82
Multiple myeloma	97313, 97323, 97333, 97343	C90
Acute leukaemia	98713, 98353, 98373, 98403, 98603, 98613, 98663, 98673, 98723, 98733, 98743, 98913, 98953	C91-94, except from C91.1, C92.1 and 93.1
Chronic myeloid leukaemia	98633, 98753, 98763	C92.1
Chronic lymphoid leukaemia	96703, 98013, 98233	C91.1
Others	98343, 80003, 95903, 95913, 96713, 96733, 96753, 96793, 96873, 96993, 97003, 97013, 97023, 97053, 97083 , 97093, 97143, 97163, 97173, 97183, 97193, 97283, 97293, 97413, 97503, 97583, 97613, 98003, 98323, 98333, 99103, 98733, 99203, 99303, 99313, 99403, 99453, 99993	All other diseases classified as C91-96

Fatigue

In Study IV, fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20), which has been validated in populations of patients with cancer (68-70). The MFI-20 encompasses five dimensions of fatigue: General Fatigue includes overall feelings of being tired; Physical Fatigue refers to the physical sensations related to fatigue; Mental Fatigue includes deficits in cognitive functioning; Reduced Motivation and Reduced Activity refer to reduction in activities and lack of motivation to start activities. Each dimension contains four items which are scored on a five-point scale. A summary score is calculated for each dimension, varying from 4 to 20. Higher scores indicate more fatigue. No cut-off points have been suggested for this scale; hence, it is usually reported as a continuous score. We choose to use quartiles of the score as cut-off points because we wanted to investigate if RTW rates differed across different levels of fatigue (71).

Depression and anxiety

In Study IV, symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), which has been developed to identify the presence of anxiety disorders and depression among patients in non-psychiatric hospital clinics (72). The scale has been validated in several populations of cancer patients (73, 74). Seven items in the scale concern depression (HAD-D), and seven items assess anxiety (HAD-A). The total score of each scale ranges from 0 to 21. The developers of the scale suggest thresholds of > 8 (possible cases of having a depression or anxiety disorder) and >11 (subclinical cases of having a depression or anxiety disorder) (75). However, suggestions for optimal cut-off points vary widely across other validation studies (74). In the present study, we used the original cut-off points (76). Validation studies have demonstrated sensitivity and specificity of approximately 0.80 of the HADS scales compared with results from diagnostic interviews (73).

Use of antidepressants or anxiolytics

In Studies II and III, the use of anxiolytics or antidepressants served as an indicator of mental health status following diagnosis. The ATC codes of interest were antidepressants (N06A) and anxiolytics (N05B). It was registered if the patients were

prescribed these types of medication during the first three years following diagnosis. This information was included as a time-dependent variable and categorised as yes/no.

Comorbidity

In Study II-IV, we computed a Charlson Comorbidity Index (CCI) score on the basis of the diagnoses recorded in the NPR for each patient during a five-year period before they were diagnosed with the haematological malignancy. In the CCI, a weight is assigned to define categories of comorbid diseases, and the index is the sum of these weights (from 0 to 6). A higher CCI score indicates an increased severity of comorbid condition (77). Since we only had few patients with high levels of comorbidity prior to diagnosis, we classified the score into three groups: 0, 1-2, and >=3.

Socio-economic factors

In Studies II and III, we obtained information on the highest educational level attained (primary school or high school, higher education and vocational education) from 1 October the year before diagnosis. Data on cohabiting status (cohabiting, living alone), children living at home (yes, no), housing tenure (owner-occupied, rental) and household income adjusted for number of persons in the household (quartiles) were assessed from 1 January in the year of diagnosis.

Demographic factors

Data on age and gender were obtained in Studies II-IV, and age was calculated as age at the time of diagnosis. In Studies II and III, information on ethnicity (Danish citizens, immigrants or descendants from Western countries, immigrants or descendants from non-Western countries) was also obtained.

Statistical analysis

Time-to-event analyses were applied in all three studies.

Study II

Cumulative incidence curves were computed to illustrate the incidence of DP according to the type of haematological malignancy.
Generalised linear regression models for pseudo observations (78) were used to estimate age- and gender-adjusted cumulative relative risks (RR) of DP and associated 95% confidence intervals (CIs) two, four and six years after diagnosis for the eight subgroups of haematological malignancies compared with the reference cohort (Model 1).
The associations between comorbidity, socio-economic and demographic factors and the risk of DP four years after diagnosis were studied separately for the patient cohort and the reference cohort (Model 2). Wald tests were used to test for overall interaction between the two cohorts and to test for interaction between each factor and the two cohorts.
In Model 3, the use of antidepressants or anxiolytics after diagnosis was the main independent variable, and we used the same strategies as in Model 2.
In all three models, 2-sided Wald tests were used to test the overall association between each independent variable and the risk of DP. Death, anticipatory pension, and old age pension were considered competing events in all the analyses.

Study III

Cumulative incidence curves were computed to illustrate the course of RTW according to the type of haematological malignancy.
The associations between haematological malignancy subtype, comorbidity, socio-economic and demographic factors and RTW were studied with and without gender stratification (Model 1 and 2). In the last model, tests for gender-interaction were conducted. Cox proportional hazards regression was used to estimate crude and adjusted hazard ratios (HR) and associated 95% CIs.
Analysis following the same steps was performed with the use of antidepressants or anxiolytics after diagnosis as the main independent variable (Model 3).

In all models, 2-sided Wald tests were used to test the overall association between each independent variable and the rate of RTW. Death and permanent withdrawal from the labour market were considered competing events to RTW in all the analyses.

Study IV

Baseline data of sickness-absent and working patients were compared using parametric and non-parametric tests.
Cumulative incidence curves were computed to illustrate the course of RTW according to level of fatigue scores.
Generalised linear regression models for pseudo observations (78) were used to estimate cumulative relative risks (RR) of RTW and LTSA including 95% CIs one year after baseline for the levels of fatigue and depression and anxiety case classification. Tests for linear trends in the association between fatigue, depression and anxiety scores and RTW or LTSA were conducted. Death and permanent exit from the labour market were considered competing events.

RESULTS

This section of the thesis gives a summary of the main findings of Studies II-IV. Additional results and more detailed presentation are available in the appended papers.

Figure 5 Flowchart of inclusion in Studies II and III

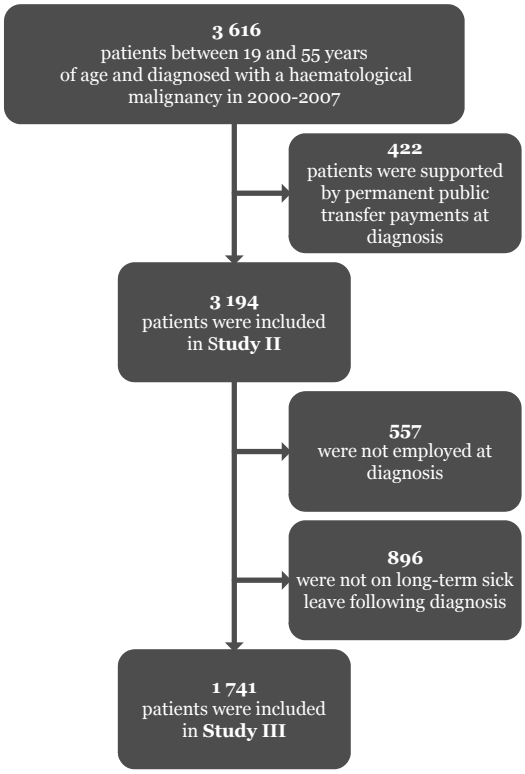
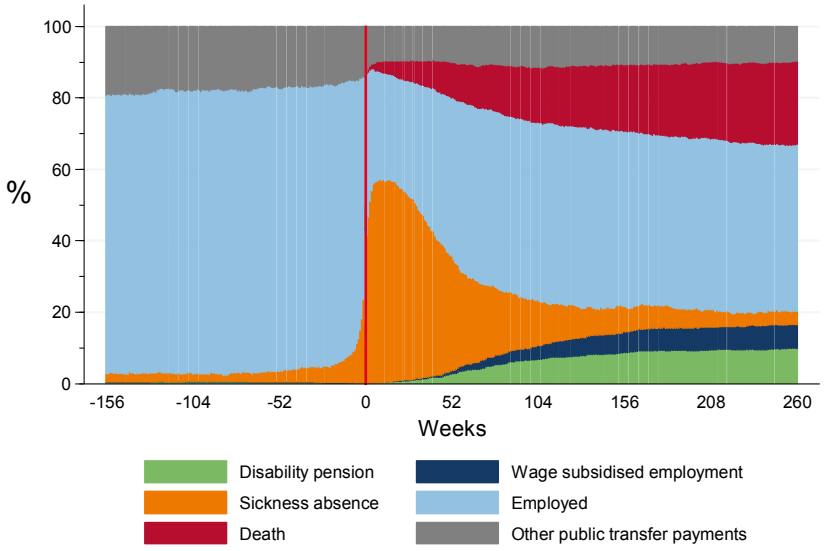


Figure 5 illustrates the inclusion process in Studies II and III.

A week-by-week overview of the proportion of public transfer payments from three years before diagnosis until five years after diagnosis is given in Figure 6. The Figure comprises all 3 194 patients included in Study II. The red line indicates the date of diagnosis. The Figure illustrates how the proportion of patients granted DP increased during the years after diagnosis. This process is further investigated in Study II.

The Figure also shows that sickness absence increased during the period after diagnosis. Similarly, RTW increased during the years after diagnosis. This process is investigated further in Study III, where patients on long-term sick leave are included and followed until RTW.

Figure 6 Overview of the proportion of social transfer payments in the patient cohort (N=3 194)



Study II

A total of 3 616 patients between 19 and 55 years were diagnosed with haematological malignancies for the first time between 1 January 2000 and 31 December 2007; hence the reference cohort initially consisted of 36 160 individuals. Of these, a total of 3 194 (88%) patients and 28 627 (79%) matched reference individuals were potential active members of the labour market, and they were therefore included in the study. In all, 17% of the patients and 5% of the reference individuals were granted DP during the follow up-period.

Subtypes of haematological malignancies

All subgroups of patients with haematological malignancies had higher cumulative incidences of DP than the reference cohort. This result was confirmed in multivariable analyses, which showed that haematological malignancy subtype was significantly associated with the risk of DP both two, four and six years after diagnosis (p<0.001), and RRs differed significantly between the eight subgroups (p<0.001). The RRs were lowest for patients with HL; and this subgroup had a 2.5-fold higher risk of receiving DP than the reference cohort four years after diagnosis (adjusted RR 2.64, 95% CI 1.84-3.78). The highest RRs was found for patients with MM; and their risk of DP was twelve times higher than the reference cohort's risk four years after diagnosis (adjusted RR 12.53, 95% CI 10.57-14.85). At this time point, the other subgroups of haematological malignancies had three- to six-fold higher risks of DP than the reference cohort (Table 7).

Table 7 Cumulative relative risk of disability pension two, four and six years after diagnosis for haematological malignancy subtypes of compared with the reference cohort

Diagnosis	N = 3 194 (%)	RR* 2 years (95% CI)	RR* 4 years (95% CI)	RR* 6 years (95% CI)
Hodgkin lymphoma	591 (18)	2.07 (1.14-3.78)	2.64 (1.84-3.78)	2.20 (1.60-3.03)
Diffuse large B-cell lymphoma	467 (15)	5.13 (3.54-7.45)	4.25 (3.24-5.58)	3.24 (2.52-4.16)
Follicular lymphoma	364 (11)	4.97 (3.36-7.36)	4.18 (3.14-5.57)	3.45 (2.67-4.47)
Multiple myeloma	270 (8)	22.10 (17.98-27.16)	12.53 (10.57-14.85)	8.93 (7.64-10.45)
Acute leukaemia	445 (14)	5.63 (3.83-8.28)	5.15 (3.96-6.71)	4.21 (3.33-5.34)
Chronic myeloid leukaemia	155 (5)	6.97 (3.79-12.81)	6.44 (4.33-9.59)	5.38 (3.81-7.59)
Chronic lymphoid leukaemia	273 (9)	3.49 (2.09-5.83)	3.22 (2.24-4.63)	3.01 (2.22-4.09)
Others	629 (20)	5.34 (3.93-7.26)	4.16 (3.30-5.24)	3.20 (2.58-3.96)

* Adjusted for age and gender.

As a secondary result, we found that haematological malignancy subtype was significantly associated also with the risk of being granted wage-subsidised employment (p<0.001), and RRs differed significantly between the eight subgroups (p<0.001). However, the patterns were different than for the risk of DP since patients with CML had the highest risk of being granted wage-subsidised employment (Table 8).

Table 8 Cumulative relative risk of wage-subsidised employment two, four and six years after diagnosis for haematological malignancy subtypes compared with the reference cohort

Diagnosis	N = 3 194 (%)	RR*$_{2\ years}$ (95% CI)	RR*$_{4\ years}$ (95% CI)	RR*$_{6\ years}$ (95% CI)
Hodgkin lymphoma	591 (18)	3.01 (1.49-6.12)	2.47 (1.46-4.16)	2.51 (1.69-3.87)
Diffuse large B-cell lymphoma	467 (15)	2.15 (1.01-4.57)	2.91 (1.89-4.48)	3.06 (2.21-4.50)
Follicular lymphoma	364 (11)	4.29 (2.31-7.98)	3.40 (2.19-5.28)	3.48 (2.50-5.12)
Multiple myeloma	270 (8)	13.37 (8.59-20.81)	8.48 (6.22-11.56)	6.83 (5.45-9.36)
Acute leukaemia	445 (14)	2.89 (1.42-5.88)	3.69 (2.44-5.57)	3.22 (2.34-4.80)
Chronic myeloid leukaemia	155 (5)	13.79 (7.71-24.68)	10.83 (7.15-16.40)	8.74 (6.03-12.66)
Chronic lymphoid leukaemia	273 (9)	7.69 (4.41-13.40)	5.81 (3.90-8.64)	5.14 (3.62-7.31)
Others	629 (20)	4.39 (2.75-7.00)	3.97 (2.85-5.51)	4.14 (3.17-5.43)

*Adjusted for age and gender.

Influence of clinical, socio-economic and demographic factors

In the patient cohort, we found that female gender, high age, comorbidity, non-Western ethnicity, low educational level, low household income, history of long-term sick leave and need of treatment with anxiolytics or antidepressants after diagnosis (Table 9) were associated with the risk of DP. Most of the these associations were pointing in the same direction in the reference cohort; but they were stronger than in the patient cohort, and most tests for interaction between the individual factors and the two cohorts showed statistically significant interaction. Furthermore, a statistically significant overall interaction between the two cohorts and the clinical, socio-economic and demographic factors was also found (p<0.001). These results indicate that the haematological malignancy modified the associations between most of the exposures and DP.

Table 9 The cumulative relative risk of disability pension four years after diagnosis according to use of antidepressants or anxiolytics after diagnosis stratified on patients/references

	Patients		References		Difference between patients/references
	N=3 194 (%)	RR$_{adj}$* (95% CI)	N=28 627 (%)	RR$_{adj}$* (95% CI)	p**/ p***
Anxiolytics					.006/.10
No	2 895 (91)	1	28 144 (98)	1	
Yes	299 (9)	1.37 (1.10-1.70)	480 (2)	2.40 (1.72-3.35)	
Antidepressants					0.088/.021
No	2 811 (88)	1	26 928 (94)	1	
Yes	383 (12)	1.33 (1.05-1.67)	1 699 (6)	1.77 (1.39-2.24)	

* Adjusted for age, gender, household income, family type, educational level, ethnicity, housing tenure, diagnosis and history of sick leave.
** Wald test for interaction (model with interaction between all factors and patient/reference cohort).
*** Wald test for interaction (models with interaction between one factor at a time and patient/reference cohort).

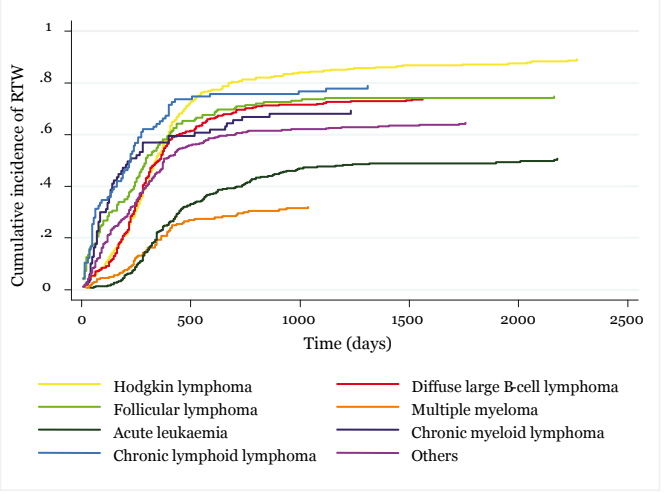
Study III

Of the 3 194 patients, who were potential active members of the labour market an thereby included in Study II, a total of 1 741 individuals were employed and on long-term sick leave following diagnosis. These patients were included din Study III. In all, 65% of these patients returned to work during the follow-up period; 43% returned to work during the first year, 60% during two years and, finally, 64% had returned to work after four years.

Subtypes of haematological malignancies

Figure 7 illustrates that the cumulative incidence of RTW differed by haematological malignancy subtype. The highest incidence of RTW was found among patients diagnosed with HL and the lowest among patients diagnosed with MM and AML/ALL. This result was confirmed in the multivariable analyses, where an association between diagnosis and RTW (p<0.001) was found; and RTW rates for patients with MM and patients with AML/ALL were lower than RTW rates for patients with HL (adjusted HR 0.37, 95% CI 0.27-0.49 and 0.44, 95% CI 0.36-0.54).

Figure 7 Cumulative incidence of RTW by haematological malignancy subtype
(Death and permanent withdrawal from labour market are considered competing events)



Influence of clinical, socio-economic and demographic factors

Female gender, high age and low educational level were associated with low RTW rates. Furthermore, there was a tendency towards a positive, though not statistically significant, association between household income and RTW. Neither ethnicity nor family type or housing tenure was associated with RTW. No association was found between comorbidity and RTW (Table 10).

The need of treatment with antidepressants or anxiolytics after diagnosis was found to be associated with RTW; thus, those who were prescribed antidepressants or anxiolytics within three years after diagnosis of haematological malignancies were less likely to RTW than those who were not prescribed these types of medication (adjusted HR 0.65, 95% CI 0.54-0.78).

The only association that was significantly modified by gender was the association between age and RTW. This association was a tendency only since we found significant interaction only when allowing for interaction between all factors and gender (p=0.03), whereas no association was found when allowing for interaction between only age and gender (p=0.20). Furthermore, no statistically significant overall gender interaction was found (p=0.09), which also indicates that gender did not modify the associations between the independent variables and RTW to any considerable extent.

Table 10 Cox proportional hazard regression analyses of return to work

	N = 1741 (%)	HR_{crude} (95% CI)	HR_{adj}* (95% CI)	*p*
Diagnosis				**<0.001**
Hodgkin lymphoma	289 (17)	1	1	
Diffuse large B-cell lymphoma	293 (17)	0.92 (0.77-1.10)	0.90 (0.74-1.09)	
Follicular lymphoma	163 (9)	0.91 (0.73-1.13)	0.93 (0.73-1.17)	
Multiple myeloma	195 (11)	0.36 (0.27-0.47)	0.37 (0.27-0.49)	
Acute leukaemia	305 (17)	0.48 (0.39-0.59)	0.44 (0.36-0.54)	
Chronic myeloid leukaemia	79 (5)	1.00 (0.75-1.34)	1.04 (0.77-1.41)	
Chronic lymphoid leukaemia	84 (5)	1.20 (0.91-1.58)	1.21 (0.90-1.62)	
Others	333 (19)	0.87 (0.72-1.04)	0.85 (0.70-1.04)	
Comorbidity				0.94
0	1531 (88)	1	1	
0<	210 (12)	0.97 (0.80-1.17)	1.01 (0.83-1.23)	
Gender				**<0.001**
Male	1031 (59)	1	1	
Female	710 (41)	0.78 (0.69-0.88)	0.72 (0.64-0.82)	
Age				**0.02**
19-35 years	345 (20)	1.02 (0.82-1.23)	0.96 (0.78-1.17)	
36-40 years	213 (12)	1.10 (0.89-1.37)	0.95 (0.76-1.19)	
41-45 years	285 (16)	1	1	
46-50 years	360 (21)	1.19 (0.98-1.43)	1.08 (0.89-1.31)	
51-55 years	538 (31)	0.92 (0.76-1.10)	0.79 (0.64-0.97)	
Educational level				**0.007**
Basic school/high school	504 (28)	1.02 (0.88-1.18)	1.09 (0.94-1.26)	
Vocational education	726 (42)	1	1	
Higher education	483 (29)	1.27 (1.11-1.46)	1.27 (1.09-1.47)	
Missing	28 (1)	-	-	
Household income				0.089
Low (1. quartile)	434 (25)	0.96 (0.83-1.10)	0.90 (0.77-1.05)	
Medium (2.-3. quartile)	868 (50)	1	1	
High (4. quartile)	434 (25)	1.09 (0.95-1.25)	1.12 (0.96-1.30)	
Missing	5 (0)	-	-	
Ethnicity				0.43
Danish	1616 (93)	1	1	
Western	67 (4)	1.09 (0.80-1.47)	1.09 (0.80-1.50)	
Non-Western	58 (3)	0.79 (0.57-1.10)	0.81 (0.57-1.16)	
Family type				0.26
Couple with children	795 (46)	1	1	
Couple without children	490 (28)	0.87 (0.76-1.00)	0.97 (0.82-1.14)	
Single with children	85 (5)	0.85 (0.64-1.13)	1.14 (0.84-1.54)	
Single without children	366 (21)	0.84 (0.72-0.97)	0.86 (0.73-1.03)	
Missing	5 (0)	-	-	
Housing tenure				0.61
Owner-occupied	1212 (70)	1	1	
Rental	497 (28)	0.89 (0.78-1.01)	0.96 (0.83-1.12)	
Missing	32 (2)	-	-	

*All variables in the table are mutually adjusted.

Study IV

A total of 451 patients aged 19 to 59 years were diagnosed with haematological malignancies in Denmark in the period from 1 February 2011 through 31 October 2011. Of these, 302 were alive and employed and thereby eligible for inclusion in the study. Forty-two patients had errors in their data files or lived at undisclosed addresses. The remaining 250 patients received the questionnaire (83% of eligible patients). 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. Finally, 196 patients were included in the study (65% of eligible patients). The only variable that differed significantly between responders and non-responders was time since diagnosis which was shorter for non-responders (7.3 months) than for responders (8.1 months).

Among the 196 included patients, 106 (54%) were on sick leave at baseline 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.

Fatigue, depression and anxiety at baseline

At baseline, scores on all fatigue dimensions, except Reduced Motivation, were statistically significant higher for patients on sick leave than for working patients. The same was seen for depression and anxiety scores. In all, 40% of patients on sick leave were categorised as possible cases or subclinical cases of depression, whereas 15% of the patients who worked fulfilled these criteria. As regarding anxiety scores, 61% of patients on sick leave were categorised as possible cases or subclinical cases of anxiety, whereas 47% of the patients who worked were in this group.

Incidence of LTSA

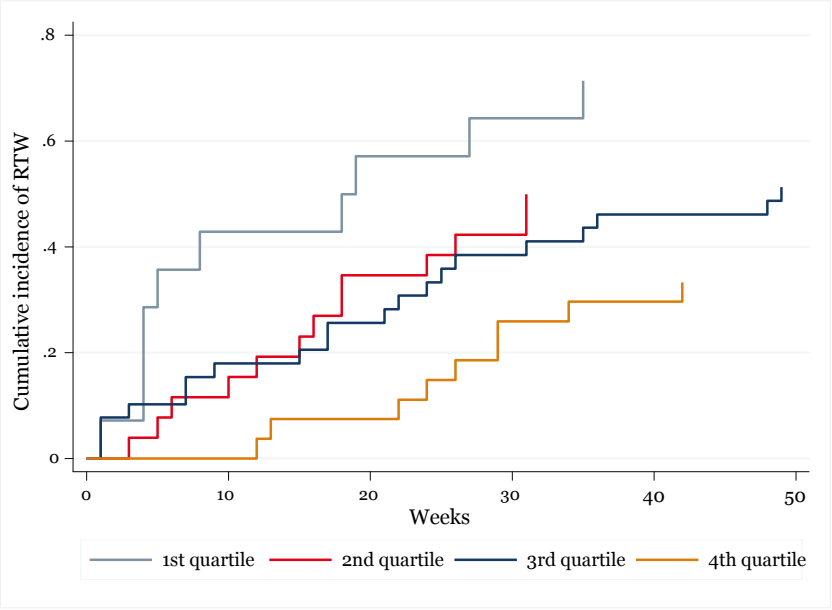
Among the 90 patients who were working at baseline, two (2%) emigrated and ten (11%) experienced a period of LTSA during the following year. The remaining 78 (87%) patients stayed at work during follow-up. Due to the small number of patients who experienced LTSA, we did not have sufficient power to examine the associations between fatigue, depression and anxiety and LTSA.

Associations of fatigue, depression and anxiety with RTW

Among the 106 patients on sick leave at baseline, 52 (49%) patients returned to work during the following year. Furthermore, 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.

The only fatigue dimension that was associated with RTW in all models was Physical Fatigue (Figure 8). 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).

Figure 8 Cumulative incidence of RTW according to level of Physical Fatigue (p=0.03)



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 11).

Table 11 RTW one year after diagnosis according to HAD-D and HAD-A case classification (N=105)

	N (%)	RR* (95% CI)	*p*	RR** (95% CI)	*p*	RR*** (95% CI)	*p*
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 this patient was therefore not included in the analyses.
* Crude analysis.
** Adjusted for time since diagnosis.
*** Adjusted for time since diagnosis, age and gender.

DISCUSSION

Methodological considerations across the studies are given in the first part of this section of the thesis. This will be followed by a discussion of the main results of the studies in the light of the results of other studies in the area.

Weaknesses and strengths of the studies

In general, two types of errors afflict epidemiological studies: Systematic errors and random errors. Since we do not know the true values of the estimates in our studies, we cannot determine the actual nature of errors in the studies; however, we are able to discuss features of design and analyses that may have contributed to or prevented errors. Systematic errors, also called bias, can be divided into three main categories: Selection bias, information bias and confounding (53, 54), which will be discussed below in relation to the studies in this thesis. Further, random errors will shortly be touched upon.

Selection bias

Selection bias is caused by procedures used to sample subjects and by factors that influence study participation. It is a systematic error that occurs when the association between exposure and outcome among those actually included in the analysis differs from the association among those who are eligible for inclusion. Selection bias usually does not arise if the selection is non-differential (not associated with exposure and outcome) or is associated either with exposure or with outcome. Differential selection (associated with both exposure and outcome) may, however, cause biased relative estimates (53, 54).

Study II

In the present study, we obtained data from The Danish Cancer Registry on all patients diagnosed between 1 January 2000 and 31 December 2007. This register has a high degree of completeness and validity (59), and we are therefore confident that the sample represents all incident haematological malignancies from the defined study period. Furthermore, a potential selection would not be related to the outcome

(future risk of DP) as it was not known at the time of inclusion. Furthermore, it is unlikely that registrations in The Danish Cancer Registry should be related to the patients' labour market participation. We do therefore believe that the risk of selection bias at this level is negligible.

We excluded permanently work-disabled patients (disability pensioners and patients in wage-subsidised employment) and patients who had emigrated at the time of diagnosis based on registrations in DREAM. The positive predictive value of DP in DREAM compared with self-reported data has been found to be 95%; and it is 68.4% for wage-subsidised employment. However, most incorrect registrations of wage-subsidised employment were observed among disability pensioners, who should be excluded anyway (65). Hence, we believe that the number of patients who have been erroneously excluded in Study II is modest; and the risk of selection bias at this level is accordingly negligent.

In Study II, the reference cohort was sampled so that individuals could not develop haematological malignancies during the inclusion period. This selection could lead to a so-called "healthy worker bias" because the reference cohort was potentially "more healthy" than the patient cohort. This has possibly led to an overestimation of the effect of being diagnosed with a haematological malignancy on the future risk of DP in our study. Due to the low incidence of haematological malignancies in the general population, we do, however, expect this potential selection bias to have only minor impact on the relative estimates in our study.

In the registers, values were missing on some of the explanatory variables. The analyses were performed as complete-case analyses, and individuals with missing data were therefore not included in these analyses. However, only few data were missed, and we assume that they were missing at random. Therefore, we do not expect that this issue has biased our estimates (79, 80).

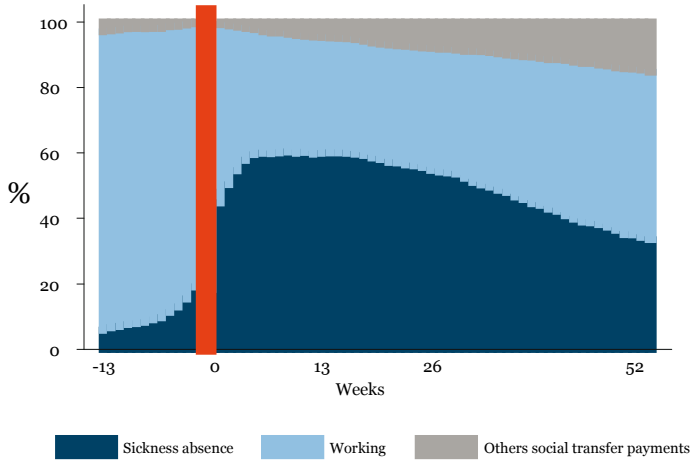
We achieved complete follow-up on all individuals in DREAM. This decreases the risk of self-selection bias due to loss-to-follow up (53, 54).

Study III

In Study III, we included subjects from the same cohort of patients as in Study II. However, the study included only those who were employed and who had been on sick leave for more than two weeks within twelve weeks following their diagnosis. We chose to include only those who had been on sick leave for more than two weeks because shorter periods were not registered in DREAM in the inclusion period. A high level of agreement has been found between DREAM data on sickness benefits and workplace-registered sick leave of at least 15 days (sensitivity 96.7% and specificity close to 100%) (66). Hence, we believe that the number of patients erroneously excluded from Study III is modest, and the risk of selection bias at this level is therefore negligible.

The twelve-week period was chosen because a considerable proportion of the patients went on sick leave within twelve weeks following diagnosis (Figure 9).

Figure 9 Overview of sickness absence following diagnosis among the 2637 patients who were employed at diagnosis



Some of the haematological malignancies give rise to sick leave for some of the patients later than within the first 12 weeks after diagnosis, and these patients were not included in this study. However, we performed sensitivity analyses in which we prolonged the inclusion period to three years; this changed neither the absolute nor the relative estimates considerably.

Considerations regarding missing data are the same as those mentioned in Study III.

Study IV

In Study IV, patients were identified in the NPR instead of CAR, because CAR is only updated once annually. However, the completeness of diagnoses is higher in CAR than in the NPR (81), and we therefore obtained data from CAR when the updated version was ready in order to validate the haematological malignancy diagnoses in our study population. This procedure identified 19 patients who had not been registered in the NPR although they were registered in CAR as having been diagnosed with haematological malignancies in the inclusion period. Together with 23 patients who lived at secret addresses, these patients have not received our questionnaire. We assume that these two types of selection happened at random and that it caused no selection bias (80).

However, 43 patients did not respond to the questionnaire, and this selection could be associated with both exposures and outcome. As far as baseline data were concerned, time since diagnosis was the only factor that differed significantly between responders and non-responders. Unfortunately, we do not know why some of the patients did not respond, but high scores of fatigue, depression and anxiety could explain non-response. If this is the case, non-response is associated with the study exposures; and if non-response was also associated with RTW rates, this selection might have biased the results towards or against the null hypothesis.

Information bias

Systematic errors can arise due to erroneous measurement of exposures or outcome. This can lead to measurement bias. If the variables are measured on a categorical scale, this error is called misclassification if it causes an incorrect categorisation of an individual. Misclassification can be either non-differential or differential. Non-differential misclassification is unrelated to other study variables, whereas differential misclassification differs according to other study variables. This means either that exposure is misclassified differentially according to the outcome, or that the outcome is misclassified differentially according to the exposure. Differential misclassification can lead to over- or underestimation of an effect, whereas non-differential misclassification usually biases the relative estimates towards the no-effect value. However, if the exposure variable has more than two categories, generalisation of a bias towards the null must be made with caution (53, 54).

Study II

The outcome in Study II was DP. As mentioned previously, the positive predictive value of DP in DREAM compared with self-reported data has been found to be 95% (65). We therefore believe that the risk of misclassification of the outcome is negligible in this study. Nor do we suspect considerable misclassification of the exposures since the data on diagnosis, comorbidity, use of antidepressants and anxiolytics, demographic and socio-economic variables are considered to be valid and reliable. However, caution is advised in the interpretation of the information on the use of antidepressants and anxiolytics. Patients treated with these medications do not necessarily suffer from clinical depression or anxiety. A risk of misclassification arises if these variables are considered as an expression of the presence of clinical depression or anxiety. The information on the use of antidepressants and anxiolytics can therefore only be interpreted as an indicator of mental health status, not as an expression of the presence of a clinically diagnosed depression or anxiety.

Since exposures were measured before outcome, we believe that any potential misclassification of the exposures would be unrelated to being granted DP and should thus be expected to cause underestimation of the associations; at least among those exposures with two categories.

Study III

The outcome in Study III was RTW defined as not receiving public transfer payments for four consecutive weeks. This definition might have caused misclassification of the outcome, since we could have misclassified individuals as having returned to work if they were supported by their partner or parents for at least four weeks following a period of receiving sickness absence benefits. We do consider this to be a rare scenario, and we are aware that a possible misclassification will have caused an overestimation of the number of patients who accomplished RTW in our study. This misclassification could be differential according to several of the exposures since it could be related to age and gender; being provided for by parents to young age and being supported by spouse to female gender. This differential misclassification could have over- or underestimated the relative estimates; however, as mentioned previously, the scenario is considered to be rare, and we therefore believe that the impact on our relative estimates is of minor importance.

The choice of defining RTW as four weeks without receiving public transfer payments was based on a comparison of different register-based measures of RTW. It is, however, important to have in mind that this measure does not necessarily capture sustainable RTW since the measure does not take into account if the patients have to go on sick leave again after the four-week period (67). In order to investigate the impact of the definition of RTW, we repeated our analyses defining RTW as both eight and twelve weeks without receiving public transfer payments. This caused a minor decrease in the proportions of patients who returned to work, but the relative estimates remained almost unchanged.

Considerations regarding the risk of misclassification of the exposures are the same as in Study II.

Study IV

The outcome in Study IV was RTW and LTSA. Since RTW was defined as in Study III, this study is subject to the same considerations regarding risk of information bias as Study III. 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 as from 2 January 2012). As previously mentioned, a high level of agreement has been found between DREAM data on sickness benefit and workplace-registered sick leave of at least 15 days (66). We therefore believe that the risk of misclassification of this outcome is negligible.

Validated scales were used to measure fatigue, depression and anxiety. The HADS was applied to measure symptoms of depression and anxiety (75). We used the original cut-off points, which have been found to have relatively high sensitivity and specificity compared with diagnostic interviews. Fatigue was assessed using the MFI-20 (69). No cut-off points have been suggested for this scale. We chose to use quartiles of the score as cut-off points, because we wanted to investigate if RTW rates differed across levels of fatigue. Seen in this light, it would have been more appropriate to use a scale that was validated to provide categories of levels of fatigue. Based on the above-mentioned aspects, some cases of misclassification of self-reported fatigue, depression and anxiety are likely to have occurred. We do not suspect this misclassification to be differential since the outcome was unknown when the three exposures were measured. However, since we applied more than two

categories of levels of all three exposures, we cannot for sure determine in which direction a potential misclassification may have biased the results.

Confounding

Confounding means that the effect of an exposure is mixed with the effect of another variable, which leads to bias of the estimates. Bias arises if the confounding factor is associated with both the exposure and the outcome under investigation; and the confounding factor must not be an effect of the exposure (53, 54). An important weakness of the observational design is the lack of randomisation. Hence, even though we used multivariate modelling to control for confounding, it is only possible to adjust for well-known confounders (53, 54). Thus, some residual confounding is very probable, and it is obviously difficult to predict in which direction this residual confounding would lead our estimates. We chose to include confounding factors in our multivariable models based on the findings from previous studies within the area (39). All factors were selected a priori, and they were kept in the statistical models regardless of their statistical impact on the results.

Studies II and III

In Studies II and III, we included diagnosis, comorbidity, socio-economic and demographic factors in our multivariable analyses. In Study II, reference individuals were categorised in the same groups of haematological malignancy subtype as the patients with whom they were matched. We expected to find no association between haematological malignancy subtype and DP in the reference cohort since this assignment was pro forma only. However, since the reference individuals were matched to the patients according to age and gender, the distribution of these variables differed between the subgroups according to the age and gender distribution in the subgroups of the patient cohort. This explains why we found an association between haematological malignancy subtype and DP in the reference cohort in the crude analyses. This association attenuated after adjustment of comorbidity and demographic and socioeconomic variables, which shows that a considerable amount of the confounding effect was controlled for (Table 12).

Table 12 Crude and adjusted results of the association between haematological malignancy subtype and DP in the reference cohort

Diagnosis	N=28 627 (%)	RR_{crude} (95% CI)	P	RR_{adj}* (95% CI)	P
HL	5 384 (19)	1		1	
DLBCL	4 176 (15)	1.63 (1.26-2.12)		0.84 (0.59-1.19)	
FL	3 240 (11)	1.46 (1.10-1.95)		0.56 (0.36-0.88)	
MM	2 368 (8)	1.80 (1.34-2.41)	< 0.001	0.88 (0.61-1.29)	0.40
AML/ALL	4 007 (14)	1.07 (0.79-1.43)		0.85 (0.55-1.30)	
CML	1 409 (5)	1.17 (0.78-1.76)		0.73 (0.38-1.41)	
CLL	2 404 (8)	1.88 (1.41-2.51)		0.82 (0.55-1.24)	
Others	5 639 (20)	1.55 (1.21-1.99)		0.89 (0.64-1.25)	

* Adjusted for age, gender, household income, family type, educational level, ethnicity, housing tenure, diagnosis and sick leave in the second year before diagnosis.

We had no access to data on treatment type and disease status (complete or partial remission), which could be assumed to be associated with both exposures like age and haematological malignancy subtype and with future labour market participation. Treatment type and disease status could hence be plausible confounding factors.

Study IV

In Studies II and III, we found that haematological malignancy subtype, socio-economic status and comorbidity were associated with future labour market participation. Unfortunately, however, we were unable to adjust for these factors in Study IV due to a small sample size. The results may therefore be biased due to confounding. However, in Study III, where the outcome was RTW like in Study IV, the relative estimates of the associations between the use of antidepressant and anxiolytics and RTW did not change considerably when adjusted for these factors. Still, the results from Study IV should be interpreted with caution.

Effect measure modification

In Study II, the multivariable analyses were performed under the assumption that except for the patient/reference cohort there would be no interaction between any other variables. Similarly, in Study III, multivariable analyses were performed under the assumption that except for gender there would be no interaction between any other variables. In Study IV, multivariable analysis was conducted under the assumption that no interaction would exist between any variables. Still, these

assumptions may be invalid. However, due to lack of power, we were unable to make further stratifications even though it seemed relevant to stratify on both age groups and diagnoses.

Chance

Throughout this thesis, we have reported 95% CIs to ensure transparency of our results. Furthermore, we have reported the p-values of statistical tests of the overall association between exposures and outcomes. The widths of the CIs express the precision of our estimates, and even though Studies II and III included relatively large populations, some of the intervals were wide (82).

In Study II, most of the factors had a stronger impact on the risk of DP in the reference cohort than in the patient cohort. However, since the reference cohort had a stronger statistical power than the patient cohort, any comparison of the levels of significance for associations in the two cohorts must be made with caution. However, tests showed a statistically significant interaction between most of the factors and the two cohorts, and these tests are independent of power differences between the two cohorts.

An important limitation in Study IV was its small sample size. The study might therefore have been underpowered to detect differences in RTW across categories of fatigue, depression and anxiety.

Summary

Overall, based on the methodological discussion, it is concluded that there is only a small risk of selection bias, information bias and confounding in Studies II and III. The estimates in Study IV may be affected by selection bias, information bias and confounding, and it is not possible to determine in which way these potential errors have biased the estimates. This should be borne in mind when interpreting the results of Study IV.

Discussion in relation to existing literature

As documented in our systematic review (Study I), only a few studies have investigated labour market participation among patients diagnosed with haematological malignancies. There are therefore only few results with which the present results may be compared.

No previous studies have reported on the number of patients with different haematological malignancies being granted DP, and we therefore have no frame of reference for intra-group comparison. A Danish cohort study that followed 2 661 women with breast cancer for a mean of 2.8 years (range 0-7 years) found that 8.7% of the women were granted DP during the follow-up period (83). Study II in this present thesis reported that 17% of the patients with haematological malignancies were granted DP during the follow-up period. Some of the discrepancy between the breast cancer study (83) and our study may be explained by a different length of follow-up since we followed the patients for a much longer period (up to 12 years). However, it is also likely that the risk of DP is higher for patients with haematological malignancies than for women with breast cancer because the former suffer more sequelae from disease and treatment. Two Norwegian studies recently investigated the risk of being granted DP among patients diagnosed with breast cancer and colorectal cancer. A total of 1 548 women diagnosed with breast cancer at the age of 45-54 years and 1 548 cancer-free women were followed for up to 14 years. During that period, 42% of the patients and 26% of the controls obtained DP (84). In the colorectal cancer study, 740 patients between 45-54 years and 740 matched controls were followed for up to 14 years. During that period, 36% of the patients and 29% of the controls became DP holders (85). Both proportions are considerably higher than the proportions reported in Study II in this present thesis. However, there are considerable differences between the social security systems in the Nordic countries. In Norway, DP is granted to individuals with a degree of disability varying between 50 and 100% (84), whereas an individual in Denmark with a disability degree of 50% would probably be granted wage-subsidised employment instead of DP. In the population of patients diagnosed with haematological malignancies in Study II, 25% became work-disabled to a degree that they were granted either DP or wage-subsidised employment. This proportion is more comparable to the proportions of patients reported to have received DP in the Norwegian studies. The remaining

difference could be explained by a higher age of the participants the Norwegian studies than in our studies since the risk of permanently reduced work capacity increases with age.

Previous studies have reported much variation in the proportion of patients with cancer who accomplish RTW. In a systematic review on employment after cancer, a mean of 63.5% of the participants (range 24–94%) managed to RTW. RTW was strongly correlated with the period of time after cancer treatment (12). A Dutch study included 297 patients with leukaemia and lymphoma, and found that 62% of these patients had managed to RTW two years after diagnosis (8). This proportion is similar to the results of Study III in this present thesis, where RTW accomplished within the first two years after diagnosis was seen in 60%. Only 43% returned to work during the first year. This indicates that the RTW process may be long for some of the patients.

Previous studies have documented that patients with haematological malignancies have a higher risk of a poorer prognosis than cancer-free populations (5-7) and patients with other cancer types (8, 9, 86) as far as labour market participation is concerned. To the best of our knowledge, the studies in this present thesis are the first to estimate the rate of RTW and also the risk of DP in clinically relevant subgroups of patients with haematological malignancies compared with a reference cohort. In most previous studies on labour market participation among patients with cancer, haematological malignancies have been pooled into groups that are biologically, but not clinically relevant. For instance, diseases like AML/ALL, CML and CLL have been pooled under the term “leukaemia”, and non-Hodgkin and HL under the term “lymphoma” even though these diseases run very different courses as described in the Introduction section of this thesis. However, Studies II and III showed that both the rate of RTW and the risk of DP differed between these subgroups. Patients with MM had the poorest prognosis for labour market participation, which may be explained by the chronic and progressive nature of this disease. Inversely, the best prognosis was found for patients with HL, which is a curable disease. However, the proportions of patients who died differed widely between the subgroups, and this should be taken into account when interpreting the results. The highest proportion of deaths was found for patients with AML/ALL of whom 44% died during the follow-up period. This illustrates that although this

subgroup did not have the poorest prognosis regarding labour market participation, these diseases have serious consequences for the patients.

As a secondary result, we found that haematological malignancy subtype was associated also with wage-subsidised employment. However, the patterns differed from those of DP and RTW since patients with CML had the highest risk of wage subsidised employment compared with the reference cohort. This is a surprising result since the treatment of this disease has very few side-effects and prolongs survival considerably. To our knowledge, no previous studies have investigated this association, and we have therefore no reference with which to compare the results.

A general tendency in Study II was that except for gender, the haematological malignancy modified the association between the socio-economic, demographic and clinical factors and the risk of DP, and most of the factors had a stronger impact on the risk of DP in the reference cohort than in the patient cohort. We cannot explain the mechanisms behind this result, but the result may indicate that the impact of the haematological malignancy on the risk of DP was so predominant that it diminished the effect of presence of comorbidity, history of long-term sick leave, socio-economic and demographic factors and need for treatment with antidepressants or anxiolytics after diagnosis. Most previous studies have not investigated these associations separately for both cancer patient cohorts and reference cohorts. Conclusions about factors associated with the risk of DP for cancer patients have therefore only been based on results from patient populations. This study adds new knowledge to the area since it shows that even though some factors are associated with the risk of DP among patients diagnosed with haematological malignancies these factors are even stronger in the general population.

In Study II in this present thesis we found that the presence of comorbidity was associated with the risk of DP in both the reference cohort and the patient cohort. A similar association between comorbidity and the risk of DP has been documented in studies on other cancer groups (5, 83, 87, 88). Surprisingly, we found no association between comorbidity and RTW in Study III. To the best of our knowledge, this association has not been investigated in previous studies on patients with haematological malignancies. A recently published American study investigated the probability of RTW 6, 18, 36, and 60 months after diagnosis in a sample of 274 low-income, employed, underinsured/uninsured women treated for stage 0–III breast

cancer. As opposed to us, they found that the presence of comorbidity was associated with a low probability of RTW (odds ratio (OR) 0.25, 95% CI 0.08-0.73) (89). Comorbidity was measured and categorised like in our study. However, the social security differs between USA and Denmark and the patient populations also differed, which might explain the converging results. In future studies, it would though be relevant to investigate if risk factors for not returning to work differ across levels of social status among patients diagnosed with haematological malignancies in Denmark.

In Studies II and III, we also found that patients treated with antidepressants or anxiolytics after having been diagnosed with haematological malignancies, were more likely to be granted DP and had lower RTW rates than those who were not. We are aware that the use of antidepressants or anxiolytics can only be regarded as a surrogate marker of mental health. In order to dig deeper into this issue, we measured self-reported symptoms of depression and anxiety in Study IV. However, in that study we found only a trend for low RTW rates in patients reporting the highest level of symptoms of self-reported anxiety, and we found no association between self-reported symptoms of depression and RTW. As previously mentioned, these results should be interpreted with caution and they should be investigated in larger studies. In Study IV, we also found an association between Physical Fatigue and RTW. To our knowledge, similar associations among patients with haematological malignancies have only previously been investigated in two prospective studies (47, 90) and three cross-sectional studies (91-93). Generally, the results diverge between the two types of studies. The cross-sectional studies found associations between symptoms of fatigue, depression and anxiety and labour market participation; in line with the results of our study, the prospective studies foundnd no association between RTW and depression and mental health. These contradictory results could be explained by differences in the study populations or the study designs. As regarding study populations, the two previous prospective studies included populations of patients treated with hematopoietic cell transplantation, and the three cross-sectional studies, only comprised patients diagnosed with different types of lymphoma. These two patient groups differ and they are both subgroups of the study population in the present study making direct comparisons pointless. As far as the differences in study design are concerned, the prospective design is more suitable for investigating causality than the cross-sectional study design since exposure and outcome are

measured at different time points (94). Another advantage of the prospective design is that time since diagnosis is equal for all patients. In the three mentioned cross-sectional studies, time since diagnosis varied up to 20 years between individuals in the same study. This possibly impacts the results. Thus, in the present study, we found that time since diagnosis was associated with both RTW and with fatigue, depression and anxiety.

In Studies II and III, we found that a number of demographic and socioeconomic factors were associated with future labour market participation among patients with haematological malignancies. Female gender and high age were associated with both the risk of DP and with low RTW rates. Ethnicity was found to be associated with DP, but not with RTW. Educational level was also associated with both DP and RTW; the same was the case for household income which, however, was not statistically significantly associated with RTW. No associations for either of the outcomes were found for family type and housing tenure. The results on the association between socio-economic and demographic factors and labour market participation are diverging between previous studies on patients with haematological malignancies. Still, similar to the studies in this thesis, previous cohort studies have found that female gender is associated with low RTW rates (39). Unlike the studies in this thesis, however, previous cohort studies found no association between either age or educational level and RTW among patients with different types of haematological malignancies. The diverging results are most likely due to differences between the patient populations studied. Hence, two of the cohort studies were limited to mixed populations of patients with haematological malignancies treated with autologous or allogeneic haematopoietic cell transplantation (46, 47); this is a small subgroup of the population in our study, which evidently complicates a comparison. However, prospective studies of socio-economic and demographic factors associated with labour market participation among patients with cancer in general produce results similar to ours, and they document that old age, female gender, low education and low income are negatively associated with labour market participation (95).

MAIN CONCLUSIONS

Based on the results obtained in our studies and the evaluation of potential biases and confounding, the following conclusions may be drawn.

Over time a considerable proportion of patients with haematological malignancies experienced permanently reduced work capacity and became DP holders. Among those patients who were on long-term sick leave following diagnosis, the RTW process was long for some, and one third did not RTW.

Haematological malignancy subtype seemed to have the most considerable impact on the prognosis regarding labour market participation. Patients with HL, DLBCL, FL, MM, AML/ALL, CML, CLL and other haematological malignancies all had a higher risk of DP than individuals without these malignancies. The RRs differed between the subtypes of haematological malignancies, and were highest for patients with MM. Similar results were found for the risk of wage-subsidised employment. However, the risk of this outcome was highest for patients with CML. The RTW rate also differed between the subtypes, and, again, patients with MM had the lowest RTW rate.

High age, female gender, non-Western ethnicity, low educational level, low household income, history of long-term sick leave, comorbidity and the need for treatment with anxiolytics or antidepressants after diagnosis were all associated with the risk of DP. However, the influence of these associations was reduced by the impact of the haematological malignancy, since they were stronger among individuals without these malignancies. Similarly, high age, female gender, low educational level and need of treatment with anxiolytics or antidepressants after diagnosis were found to be associated with RTW.

High levels of fatigue, depression and anxiety were more prevalent among sickness-absent patients than among those who were working six to nine months following diagnosis. Only few of the patients working at that time experienced LTSA during the one-year follow-up. Patients with highest scores of Physical Fatigue were less likely to RTW than those with lowest scores. Similar, a tendency for an association between symptoms of anxiety and RTW was found. No significant association was found between depression and RTW. However, due to small sample size and limited confounder control in Study IV, these results should be interpreted with caution and they should be confirmed in larger studies.

PERSPECTIVES

The results of this thesis show that a considerable proportion of patients diagnosed with haematological malignancies have a poor labour market prognosis. This either indicates that these diseases and their treatment leave the patients with symptoms that reduce their function to a level that makes labour market participation impossible. On the other hand, the results could also imply that there is a need for more support, rehabilitation interventions and workplace adjustments for this patient group in order to help them get back to their everyday life, including their work life.

The results also imply that clinicians should be aware that the risk of permanently reduced work capacity and the rate of RTW differ between patients with different haematological malignancy subtypes; and that age, gender, ethnicity, social status, presence of comorbidity, mental health and fatigue also play a role in the prognosis regarding future labour market participation. This knowledge is important in order to be able to identify vulnerable groups of patients and to inform and initiate early, targeted rehabilitation interventions aimed at preventing permanently reduced work capacity and maintaining appropriate labour market participation, if possible. However, on the other hand, some of these patterns of risk factors are similar to those in the general population, but they are not necessarily as dominant, and attention should therefore also be paid to haematological cancer patients who are not exposed to risk factors that are generally known to be associated with a higher risk of permanently reduced work capacity.

Clearly, there is a need for further studies of labour market participation for patients diagnosed with haematological malignancies. First of all, there is a need for further investigation into the patterns that we have found, for instance into the impact of the symptom burden following diagnosis and treatment of haematological malignancies on future labour market participation. The results of this present thesis showed a tendency towards an association between fatigue, depression and anxiety and labour market participation. However, there is a need for larger studies within this area. Such studies should use both self-reported and register-based data. Moreover, it would be relevant to examine if other frequent reported symptoms among these

patients, such as sleeping difficulties and concentration problems, have an impact of their prognosis for labour market participation.

Second, studies that focus on specific patient groups, such as patients with MM, are relevant to obtain more knowledge of why they have a poor prognosis regarding labour market participation. It would also be relevant to further explore the mechanisms behind the high relative risk of wage-subsidised employment among patients with CML since this result was surprising given the new, improved treatment possibilities for these patients.

Both qualitative and quantitative research within this area may help inform the design and development of specific rehabilitation interventions for patients diagnosed with haematological malignancies aimed at maintaining or regaining labor market participation when possible. The effect of such interventions should be evaluated in clinical studies, so that effective and feasible rehabilitation interventions could be implemented in clinical practice.

SUMMARY

More than one third of patients diagnosed with haematological malignancies are of working age, and previous studies report that these patients have a poorer prognosis for labour market participation than cancer-free populations and patients with other cancer types. However, such studies have paid only scant attention to differences between haematological malignancy subtypes. It is therefore necessary to separately study patients with haematological malignancies in order to acquire specific knowledge of factors associated with their labour market participation.

The overall aim of the thesis was accordingly to investigate future labour market participation among patients diagnosed with haematological malignancies, and to evaluate the impact of fatigue, depression, anxiety, comorbidity and socio-economic and demographic factors on their labour market participation.

First, we conducted a systematic literature review on factors associated with labour market participation among patients with haematological malignancies (Study I). Eight studies were included. Overall, the included studies' methodological limitations and their heterogeneity made it impossible to draw firm conclusions about the associations of any single factors with labour market participation.

This thesis further includes three nationwide, observational and longitudinal studies, which were designed on the basis of a discussion of the strengths and limitations of the studies included in Study I.

In Study II, we used data from national registers to investigate the risk of disability pension (DP) among 3 194 patients diagnosed with haematological malignancies between 2000 and 2007 and 28 627 reference individuals. These individuals were followed from the date of their diagnosis until February 2012, and during that period a total of 550 (17%) patients and 1 511 (5 %) reference individuals were granted DP. All eight subtypes of haematological malignancies (Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, acute myeloid/lymphoid leukaemia, chronic myeloid leukaemia, chronic lymphoid leukaemia and others) were associated with an increased risk of DP compared with the reference cohort. The relative risks differed according to haematological malignancy subtype, and patients with multiple myeloma had the highest risk of DP. Similar results were found for the

risk of wage-subsidised employment. However, the risk of this outcome was highest for patients with chronic myeloid leukaemia. In the patient cohort, we found that female gender, high age, comorbidity, non-Western ethnicity, low educational level, low household income, history of long-term sick leave, and need of treatment with anxiolytics or antidepressants after diagnosis were associated with receiving DP. However, most of these associations were stronger in the reference cohort than in the patient cohort.

In all, 1 741 of the 3 194 patients included in Study II were employed and on long-term sick leave following diagnosis. These patients were included in Study III, where the rate of return to work (RTW) was investigated. Again, the patients were followed until February 2012, and during that period, a total of 1140 (65%) patients returned to work. A strong association was found between type of diagnosis and RTW, and the proportion of patients who accomplished RTW was lowest in the group diagnosed with multiple myeloma. Furthermore female gender, high age, low educational level, and need of treatment with anxiolytics or antidepressants after diagnosis were also associated with RTW. Surprisingly, comorbidity was not associated with RTW.

In Study IV, we obtained questionnaire-based data on fatigue, depression and anxiety on 196 patients diagnosed with haematological malignancies six to nine months earlier. We followed them prospectively for one year using register-based data on labour market participation. At baseline, levels of fatigue, depression and anxiety were highest among patients on sick leave. Half of these patients returned to work during the following year. Physical Fatigue was associated with RTW. A similar tendency was found for anxiety, but no association was seen between depression and RTW.

In conclusion, a considerable proportion of patients diagnosed with haematological malignancies are granted DP, and a substantial proportion does not RTW following long-term sick leave. A number of factors are associated with a poor prognosis regarding labour market participation. The haematological malignancy seems to be the most important factor; but, age, gender, ethnicity, social status, presence of comorbidity, mental health and fatigue also play a role. The haematological malignancy does, however, seem to reduce the influence of most of these factors, since they are stronger among individuals without these malignancies.

DANSK RESUME

Mere end en tredjedel af patienter diagnosticeret med hæmatologisk kræft er i den arbejdsdygtige alder. Tidligere studier tyder på, at patientgruppen har en dårligere prognose i forhold til arbejdsmarkedstilknytning end populationer uden kræftdiagnoser og grupper, der er diagnosticeret med andre kræfttyper. I de fleste af disse studier indgår patienter med hæmatologisk kræft dog som en mindre undergruppe, og der er ikke tidligere udført større, landsdækkende og dybdegående studier af arbejdsmarkedstilknytning og faktorer af betydning herfor for netop denne patientgruppe.

Det overordnede formål med denne afhandling er derfor at undersøge fremtidig arbejdsmarkedstilknytning hos patienter diagnosticeret med hæmatologisk kræft. Et yderligere formål er at afdække i hvilket omfang diagnosetype, komorbiditet, socioøkonomiske og demografiske faktorer samt træthed og mental helbredstilstand efter diagnosen influerer på arbejdsmarkedstilknytningen i denne patientgruppe.

Vi udførte først et systematisk litteraturstudie af hvilke faktorer, der kan have betydning for arbejdsmarkedstilknytningen for patienter diagnosticeret med hæmatologisk kræft (Studie I). Otte studier fandtes egnet til inklusion. Samlet set kunne vi på baggrund af litteraturstudiet ikke drage konklusioner vedrørende sammenhænge mellem specifikke faktorer og arbejdsmarkedstilknytning. Dette skyldtes heterogenitet mellem og metodologiske svagheder i de inkluderede studier.

Udover Studie I indeholder afhandlingen tre landsdækkende, observationelle og prospektive studier, som er designet på baggrund af diskussioner af styrker og svagheder i de studier, som indgik i det systematiske litteraturstudie.

I Studie II anvendte vi data fra nationale registre og undersøgte risikoen for førtidspensionering blandt 3 194 patienter diagnosticeret med hæmatologisk kræft i 2000-2007 samt en referencekohorte. Alle individer blev fulgt indtil februar 2012, og i den periode blev 550 (17%) af patienterne og 1 511 (5%) af referencepersonerne tilkendt førtidspension. Patienter med alle undertyper af hæmatologisk kræft (Hodgkin lymfom, diffust storcellet B-lymfom, follikulært lymfom, myelomatose, akut myeloid/lymfoid leukæmi, kronisk myeloid leukæmi, kronisk lymfoid leukæmi og andre undertyper) havde forhøjet risiko for førtidspensionering sammenlignet med referencekohorten. Risikoen varierede mellem diagnosetyperne og var højst

blandt patienter med myelomatose. Vi fandt lignende resultater for risikoen for at få tilkendt fleksjob. Her var risikoen dog højest for patienter med kronisk myeloid leukæmi. I patientkohorten var det at være kvinde, høj alder, komorbiditet, ikke-vestlig etnicitet, lavt uddannelsesniveau, lav indkomst samt behov for behandling med antidepressiva og anxiolytika forbundet med risikoen for førtidspensionering. Flere af disse sammenhænge var dog stærkere i referencekohorten end i patientkohorten.

I alt var 1 741 af de 3 194 patienter, som blev inkluderet i Studie II, langtidssygemeldte fra deres arbejdsplads efter diagnosen. I Studie III anvendte vi data fra nationale registre og undersøgte om disse patienter kom tilbage til arbejdet. Igen blev alle individer fulgt indtil februar 2012, og i den periode kom 1 140 (65%) af de langtidssygemeldte patienter tilbage til arbejde. Vi fandt en stærk association mellem diagnosetype og chancen for at vende tilbage til arbejdet, og færrest patienter med myelomatose kom tilbage til arbejdet. Herudover var det at være kvinde, høj alder, lavt uddannelsesniveau, og behov for behandling med antidepressiva og anxiolytika også associeret med chancen for tilbagevenden til arbejdet, hvilket komorbiditet ikke var.

I Studie IV indsamlede vi spørgeskemadata vedrørende fatigue, depression og angst blandt 196 patienter diagnosticeret med hæmatologisk kræft seks til ni måneder tidligere, og vi fulgte dem prospektivt i et år ved hjælp af registerbaserede data vedrørende arbejdsmarkedtilknytning. Ved studiestart var niveauerne af fatigue, depression og angst højst blandt sygemeldte patienter. Halvdelen af disse patienter kom tilbage til arbejdet i løbet af det følgende år. Fysisk fatigue var associeret med tilbagevenden til arbejdet. Vi fandt en lignende tendens for angst, mens vi ikke fandt nogen association mellem depression og tilbagevenden til arbejdet.

Vi kan konkludere, at en væsentlig del af patienter med hæmatologisk kræft får tilkendt førtidspension, og at en betydelig del ikke kommer tilbage efter arbejdet efter langtidssygemelding. Flere faktorer er associeret til dårlig prognose i forhold til arbejdsmarkedstilknytning for denne gruppe. Diagnosetypen synes at være den vigtigste. Køn, alder, komorbiditet, etnicitet, social status, psykiske symptomer samt fatigue spiller dog også en rolle. Den hæmatologiske kræftdiagnose synes dog at reducere betydningen af mange af disse faktorer, som spiller en større rolle for arbejdsmarkedstilknytning hos individer uden disse sygdomme.

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APPENDICES

Paper I-IV representing Studies I-IV:

I. Factors associated with work outcome for survivors from haematological malignancies a systematic literature review

Horsboel TA, de Thurah A, Nielsen B, Nielsen CV
Eur J Cancer Care (Engl). 2012;21(4):424-35.

II. Risk of disability pension for patients diagnosed with haematological malignancies: a register-based cohort study

Horsboel TA, Nielsen CV, Andersen NT, Nielsen B, de Thurah A
Acta Oncol. 2014 Jan 23.

III. Type of hematological malignancy is crucial for the return to work prognosis: a register-based cohort study

Horsboel TA, Nielsen CV, Nielsen B, Jensen C, Andersen NT, de Thurah A
J Cancer Surviv. 2013;7(4):614-623.

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

Horsboel TA, Bültmann U, Nielsen CV, Nielsen B, Andersen NT, de Thurah A
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Paper I

European Journal of Cancer Care

Feature and review paper

Factors associated with work outcome for survivors from haematological malignancies – a systematic literature review

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HORSBOEL T.A., DE THURAH A., NIELSEN B. & NIELSEN C.V. (2012) *European Journal of Cancer Care* **21**, 424–435

Factors associated with work outcome for survivors from haematological malignancies – a systematic literature review

Recent years have seen a growing number of survivors from haematological malignancies. As biology and treatment for these malignancies differ from other malignancies, we performed a systematic literature review of factors associated with work outcome for these survivors. A systematic literature search was conducted. Eight studies with different methodology and characteristics met the inclusion criteria. Three prospective studies agreed, to a high extent, on their findings, whereas results of five cross-sectional studies collectively were inconclusive. Overall, this review – like reviews on other cancer survivors – found no certain association of single factors with work outcome. However, based on possible explanations of the converging findings, this review pinpointed a number of issues that may inform future studies. The design should preferably be prospective, including comparison with age-paired cancer-free individuals. The role of co-morbidity and of differences between haematological diagnoses ought to be established, and work outcomes must be well defined and recorded with valid methods. To establish cause–effect relations, factors possibly associated to work outcome should be evaluated at an early time point after diagnosis. Such studies would assist identification of individuals at increased risk of encountering work-related problems and would hence help establish knowledge on which rehabilitation measures could rest.

Keywords: social, Hodgkin lymphoma, leukaemia, non-Hodgkin lymphoma, psychological, symptoms.

INTRODUCTION

Recent years have seen a marked improvement in the treatment of haematological malignancies (leukaemia, lymphoma and multiple myeloma) which has been accompanied by a rise in the number of survivors from these diseases (Engholm *et al*. 2011). Approximately half of all patients diagnosed with haematological malignancies are younger than 65 years of age and therefore at risk of facing impaired working ability due to their disease and its treatment (National Board of Health 2009). For the individuals, this may lead to loss of identity and affect their self-esteem and it may also give rise to financial concerns (Kennedy *et al*. 2007; Amir *et al*. 2008; Rasmussen & Elverdam 2008; Feuerstein 2009).

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For the society the increase in costs of social welfare benefits is of growing concern, and governments across the whole Europe are increasingly looking to make savings from the social welfare budgets. Unfortunately, this inexpediently affects the group of cancer survivors that are having prolonged impaired working ability due to disease and treatment (Glasdam 2011; O'Connor 2012). Further studies in the causes of impaired working ability after cancer conducted by economically impartial health researchers are needed to guide establishment and initiation of appropriate occupational rehabilitation programmes for this group.

Previous studies report that among cancer survivors those who survive from haematological malignancies are among those at the greatest risk of delayed return to work, unemployment, reduced working ability and early retirement (Short *et al*. 2005; Carlsen *et al*. 2008; De Boer *et al*. 2008; Park *et al*. 2008; Syse *et al*. 2008). Still, no systematic reviews have solely focused on factors associated with work outcome after haematological malignancies. Recent years have seen few reviews evaluating factors associated with work outcome in cancer survival; however, in those reviews, survivors of haematological malignancies are either not represented, or only one to two studies on this group of survivors have been included (Spelten *et al*. 2002; Steiner *et al*. 2004; Taskila & Lindbohm 2007; Feuerstein *et al*. 2010; Mehnert 2011). Treatment of haematological malignancies differs from that of other malignancies as it rarely involves surgery, but often the use of regimes such as whole-body radiation and/or chemotherapy for extended time periods. Therefore, it is relevant to look at patients with haematological cancer alone, in order to provide specific knowledge of factors associated with work outcome for survivors in this group.

The identification of factors associated with adverse work outcomes for patients recovering from haematological malignancy is crucial to early intervention and rehabilitation of this group (Taskila & Lindbohm 2007). Thus, we conducted this systematic review to identify such risk factors, and also to discuss important aspects of study designs suitable for research in this area.

METHODS

Systematic searches in PubMed, Embase, Cochrane Library and Cinahl were conducted. References were cross-checked to identify all studies relevant for inclusion. Two sets of terms were combined in the searches: (1) haematological neoplasms, haematological malignancies, lymphoma, leukaemia and multiple myeloma; and (2) employment, unemployment, work, work ability, pensions, retirement, supported employment, absenteeism, sick leave, sickness absence and return to work.

There were no restrictions applied to publication year. Inclusion and exclusion criteria were: (1) study population had to consist of adult survivors from haematological malignancies (lymphoma, leukaemia or multiple myeloma) in working age (>18 years); (2) focus should include factors potentially associated with work outcome; (3) only studies in English, Norwegian, Swedish and Danish were considered; and (4) studies including adult survivors from childhood cancers were excluded as were studies applying qualitative methods. There were no inclusion criteria regarding study design and methodological quality since a part of the purpose was to discuss important aspects of study designs suitable for research in this area. In order to perform such a discussion, the methodological quality of the included studies was evaluated and the risks of bias and confounding were discussed. This was done on the basis of Evidence-Based Practice Workbook which contains a description of how to critically appraise scientific papers (Glasziou *et al*. 2007).

One of the authors (T. A. H.) performed the literature search and was responsible for selection and initial review of the studies. Whenever there were doubts regarding inclusion, it was discussed by all authors until agreement was reached. The critical appraisal and interpretation of results were discussed between all authors.

The searches produced a total of 608 hits. All titles were screened and abstracts of potentially relevant studies were reviewed. Thus, 58 studies were retrieved in full text. In this process 50 studies were excluded, primary because the study population was not adult survivors of haematological malignancy, or they were survivors of childhood cancer. Also, a great deal of the excluded studies focussed solely on work outcome not on factors associated with work outcome.

RESULTS

Study characteristics and methodological quality of included studies

Eight studies published between 1986 and 2011 were included in the present review (Tables 1 and 2) (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002; Syrjala *et al*. 2004; Kirchhoff *et al*. 2010; Roelen *et al*. 2010).

Study design

Three of the studies were prospective cohort studies (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010; Roelen *et al*.

Table 1. Presentation of included cohort studies

		Study population					Factors evaluated		
Study	Data source	Diagnosis	Selection	Age	Follow up	Work outcome	Negatively associated	Non-associated	Methodological quality
(Syrjala *et al.* 2004) USA	Questionnaire and medical records No control group	Leukaemia and lymphoma Autologous or allogeneic hematopoietic cell transplantation	***n* = 281** 636 received hematopoietic cell transplantation 335 were invited and 319 completed pre-transplant assessment 281 patients were working or in school before transplantation and survived past 1 year without recurrent malignancy 18 of these did not report return to work information and were excluded from analyses	Mean age at transplant: **36** (18–62) (For the 319 patients completing pre-transplant assessment)	Pre-transplant, 90 days, 1, 3 and 5 years post-transplant	**Time to return to work** (Either full-time work outside the home, full-time school, or part-time school coupled with part-time work) All participants were working full-time pre-transplantation	■ **Gender** (female) HR 0.52 (0.33, 0.82)	■ **Diagnosis** ■ **Stem cell donor** (autologous vs. allogeneic) ■ **Total body irradiation** ■ **Radiation therapy or chemotherapy pre-transplant** ■ **Age** ■ **Education** ■ **Income** ■ **Marital status** ■ **Pre-transplant levels of physical limits, depression, and treatment distress** ■ **GVHD**	**Risk of information bias:** Patients provided date of return to work 3 and 5 years after diagnosis **Risk of selection bias:** 317 did not consent to participate Non-participants had higher survival rates and differed from participant in cancer type and ethnicity The group of non-responders (*n* = 18) were not compared to responders
(Kirchhoff *et al.* 2010) USA	Questionnaire No control group	Haematological malignancies Autologous or allogeneic hematopoietic cell transplantation	***n* = 106** 540 adults received hematopoietic cell transplantation 199 consented to participate of whom 130 worked full-time pre-transplantation 106 of these were alive and had not return to work 6 months post-transplantation	**<35** (*n* = 33) **35–49** (*n* = 69) **>50** (*n* = 28) (For the 130 patients working full-time before transplantation)	Pre-transplant, 6 months, 1, 2, 3 and 5 years post-transplant	**Time to return to work** (Full-time work) All participants were working full-time pre-transplantation	■ **Physical dysfunction** (SF-36) HR 2.38 (1.26, 4.49) ■ **Gender** (female) HR 0.54 (0.29, 0.99)	■ **Mental health** (SF-36) HR 1.22 (0.58, 2.54) ■ **Age** 35–49 years HR 0.82 (0.42, 1.58) >50 years HR 0.60 (0.25, 1.40) ■ **Education** HR 0.85 (0.46, 1.59) ■ **Marital status** HR 1.08 (0.56, 2.07) ■ **Income**	Low precision due to small sample size **Risk of selection bias:** 37 declined to participate and 118 were not invited There were differences between participants and non-participants in gender, donor type, transplant type, cancer type
(Roelen *et al.* 2010) the Netherlands	Registers No control group	Leukaemia and lymphoma	***n* = 297** All Dutch patients diagnosed with leukaemia or lymphoma in 2004–2006 were included if they met following eligibility criteria: ● Sickness absent due to cancer ● Aged 18–60 years ● In permanent paid employment at the time of diagnosis	Mean age at diagnosis: **42.3** (18–60)	At diagnosis and continuously until 2 years after diagnosis	**Time to return to work** (Equal earnings as before sickness absence) All participants were in permanent paid employment at diagnosis	■ **Gender** (female) HR 0.60 (0.5–0.9)	■ **Age** HR <35 years: 1 35–44 years: 1.0 (0.7–1.5) 45–54 years: 0.8 (0.5–1.2) >55 years: 1.0 (0.7–1.5)	Only age and gender were included in analyses as exposures and confounders

GVHD, Graft-Versus-Host Disease; SF-36, Short Form 36 Health Survey.

Table 2. Presentation of included cross-sectional studies

		Study population					Factors evaluated		
Study	Data source	Diagnosis	Selection	Age	Time since treatment	Work outcome	Negatively associated	Non-associated	Methodological quality
(Fobair *et al.* 1986) USA	Questionnaire and interview No control group	Hodgkin lymphoma	***n* = 403** All patients returning for regular follow up were invited to participate Response rate 95%	Mean age at diagnosis: **36.3** (15–78)	Median: **9 years** (1–21) (Since end of treatment)	**Number of weekly working hours**	■ **Gender** (female) ($P = 0.000001$) ■ **Depression** (CES-D) ($P = 0.0003$) ■ **Age** (high) ($P = 0.009$) ■ **Energy-level** (low) ($P = 0.01$) ■ **Disease status** (relapsers) ($P = 0.04$)	■ **Stage of disease** ■ **Treatment type**	No estimates nor confidence intervals presented Some participant were beyond working age **Risk of selection bias:** It is not clear, if there was a group of patients that did not turn up to regular follow up and therefore were not invited to participate There is no information about the non-responders.
(Razavi *et al.* 1993) Belgium	Questionnaire structured interview and medical records No control group	Non-Hodgkin and Hodgkin lymphoma	***n* = 41** 127 patients attending an outpatient clinic were approached in 1989–1990 41 were finished with treatment and likely to return to work Response rate 100%	Mean age at diagnosis: **41.3** (19–61)	Mean: **52.7 months** (1–204) (Since end of treatment)	**Rate of return to work**	■ **Anxiety/depression** (HADS, high) ($P = 0.05$) ■ **Treatment toxicity** (high) ($P < 0.01$) ■ **Time since end treatment** (short) ($P = 0.04$)	■ **Stage of disease** ■ **Age** ■ **Gender** ■ **Fatigue** (POMS)	Low precision due to small sample size No estimates nor confidence intervals presented **Risk of selection bias:** No descriptions if the 127 patients consist of all eligible patient **Risk of information bias:** Outcome (return to work) not defined
(Abrahamsen *et al.* 1998) Norway	Questionnaire No control group	Hodgkin lymphoma	***n* = 459** 557 consecutive patients aged 15–61 years when diagnosed in 1971–1991 and still alive in complete remission at the age of 74 years or younger by the end of 1993 were invited Response rate 82%	Mean age at diagnosis: **44** (19–74)	Range: **3–23 years** (Since start of first-line treatment)	**Disability more than 12 months after first-line treatment** **Permanent disability** (Receiving disability pension)	■ **Age** (>40 years at diagnosis) ($P = 0.40$) ■ **Full-time employment at diagnosis** ($P < 0.001$) ■ **Chemotherapy/ radiotherapy** ($P < 0.001$) ■ **Depression** (HADS, high) ($P < 0.001$) ■ **Anxiety** (HADS, high) ($P = 0.05$) ■ **Fatigue** (FQ, high) ($P = 0.05$) ■ **Stage III and IV disease** ($P = 0.007$) ■ **Age** (>40 years at diagnosis) ($P < 0.001$) ■ **Full-time employment at diagnosis** ($P = 0.002$) ■ **Chemotherapy/ radiotherapy** ($P = 0.005$) ■ **Depression** (HADS, high) ($P < 0.001$) ■ **Anxiety** (HADS, high) ($P < 0.001$) ■ **Fatigue** (FQ, high) ($P < 0.001$) ■ **Educational status** (low) ($P < 0.001$)		No estimates nor confidence intervals presented Only univariate analysis were performed (no confounder control) Some participant were beyond working age **Risk of information bias:** Disability >12 month not defined **Risk of selection bias:** No descriptions if the 557 patients consist of all eligible patients. There is no information about the non-responders.

Table 2. *Continued*

		Study population					Factors evaluated		
Study	Data source	Diagnosis	Selection	Age	Time since treatment	Work outcome	Negatively associated	Non-associated	Methodological quality
(Heinonen *et al.* 2001) Finland	Questionnaire No control group	Leukaemia, Hodgkin lymphoma, multiple myeloma Allogeneic hematopoietic cell transplantation	***n* = 109** 162 patients who had received an allogeneic hematopoietic cell transplantation in 1988–1997 were invited 132 patients agreed to participate Response rate 68%	Mean age at transplantation: **42** (21–59)	Mean: **55 months** (4–171) (Post-transplant)	**Rate of return to work**	■ **Job type** (manual work) ($P < 0.01$)		No estimates nor confidence intervals presented **Risk of information bias:** It is not clear how exposure (job type) and outcome were defined **Risk of selection bias:** Low response rate, and there were significant differences between responders and non-responders in age and time since treatment
(Hensel *et al.* 2002) Germany	Questionnaire No control group	Hodgkin and Non-Hodgkin lymphoma, multiple myeloma, acute leukaemia and solid tumours (26%) Autologous hematopoietic cell transplantation	***n* = 238** In 1987–1999 799 patients underwent hematopoietic cell transplantation in a unit Questionnaires were mailed to all patients still alive in 1999 ($n = 391$) 304 responded 238 were working before transplantation Response rate 78%	Median age at transplantation: **49** (17–67)	Median: **36 months** (Post-transplant)	**Rate of return to work** (Defined as return full-time or part-time to previous occupation)	■ **Education** (low) ($P = 0.007$) ■ **Age** (high) ($P < 0.0001$) ■ **Physical function** (EORTC QLQ-C30) ($P = 0.002$) ■ **Cognitive function** (EORTC QLQ-C30) ($P = 0.04$) ■ **Social function** (EORTC QLQ-C30) ($P = 0.008$)	■ **Gender** ($P = 0.72$) ■ **Participation in rehabilitation programmes** ($P = 0.54$)	No estimates nor confidence intervals presented **Risk of information bias:** Participants had to remember their employment status before treatment **Risk of selection bias:** There is no information about the non-responders

CES-D, Center for Epidemiologic Studies Depression Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FQ, Fatigue Questionnaire; HADS, Hospital Anxiety and Depression Scale; POMS, Profile of Mood States.

2010). The last five studies had a cross-sectional design (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002), which is a weaker design than a longitudinal design, when investigating associations (Glasziou *et al*. 2007). None of the studies included a healthy control group.

In four studies, a standardised questionnaire was administered (Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002; Kirchhoff *et al*. 2010). In one study, data were obtained from official registers (Roelen *et al*. 2010). Another study combined data acquired from questionnaires and medical records (Syrjala *et al*. 2004), whereas data were obtained through questionnaires and structured interviews in one study (Fobair *et al*. 1986), and, finally, one study applied both questionnaires, medical records and structured interview (Razavi *et al*. 1993).

Study population

In some of the studies it remained unclear how and from which study population the samples were recruited and what characterised those who did not consent to participate (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002; Syrjala *et al*. 2004; Kirchhoff *et al*. 2010), which of course might complicate generalisation of the results and in worst case, if the selection was differential, have caused selection bias (Glasziou *et al*. 2007).

Mean time since diagnosis was 3–5 years in most of the cross-sectional studies; however, it ranged from 1 month to 23 years for the individuals in the studies (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002). In contrast, survivors were followed continuously for 2–5 years after treatment or diagnosis in the cohort studies (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010; Roelen *et al*. 2010).

In most of the cross-sectional studies, it was unclear from which population the study sample had been recruited (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001). Response rates varied from 68% to 100% (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002). In the register-based cohort study, all patients diagnosed with leukaemia or lymphoma in the period from 1 January 2004 to 31 December 2006 were included (Roelen *et al*. 2010). Finally, participants in the remaining two cohort studies were recruited consecutively during undefined study periods. However, exclusion and inclusion procedures as well as patient dropout during the follow-up periods were well described (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010).

Diagnoses and treatments varied between the studies. Three studies included a mix of haematological malignancies (Heinonen *et al*. 2001; Hensel *et al*. 2002; Kirchhoff *et al*. 2010). Only survivors from lymphoma were included in yet another three studies (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998); and, finally, both survivors from lymphoma and leukaemia were included in two studies (Syrjala *et al*. 2004; Roelen *et al*. 2010). Treatment with hematopoietic cell transplantation was an inclusion criterion in four studies (Heinonen *et al*. 2001; Hensel *et al*. 2002; Syrjala *et al*. 2004; Kirchhoff *et al*. 2010). Patients received autologous hematopoietic cell transplantation in one study (Hensel *et al*. 2002), allogeneic hematopoietic cell transplantation in another (Heinonen *et al*. 2001), and either allogeneic or autologous hematopoietic cell transplantation in the last two studies (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010).

Sample size and precision

In total, 2062 survivors from haematological malignancies participated in the studies on which this review is based. The samples size varied from 41 to 459 survivors and was modest in some of the studies (Razavi *et al*. 1993; Kirchhoff *et al*. 2010), which might have affected their power to detect significant findings.

However, several of the studies only presented their results with *P*-values, which made it difficult to evaluate the size of the sample. A more transparent presentation of the concrete estimates with appertaining confidence intervals would have made the statistical variability more visible (Glasziou *et al*. 2007).

Outcome measures

Work outcomes differed between studies: rate of return to work (Razavi *et al*. 1993; Heinonen *et al*. 2001; Hensel *et al*. 2002), time to return to work (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010; Roelen *et al*. 2010), weekly work hours (Fobair *et al*. 1986) and disability pension (Abrahamsen *et al*. 1998). Furthermore, the definition of return to work varied. Return to both part-time and full-time job were defined as return to work in one study (Hensel *et al*. 2002), whereas the term comprised full-time work outside the home as well as full-time school or part-time school coupled with part-time work in another (Syrjala *et al*. 2004). At the other end of the scale, only return to full-time job was accepted (Kirchhoff *et al*. 2010), while return to work was defined as the same earnings as before sickness absence in another study (Roelen *et al*. 2010). Finally, some of the studies did not define work outcome (Razavi

et al. 1993; Abrahamsen *et al.* 1998; Heinonen *et al.* 2001), or patients had to remember date of return to work potentially years earlier (Syrjala *et al.* 2004). This could lead to misclassification of the outcome, being differential or non-differential, and potentially cause information bias (Glasziou *et al.* 2007).

Exposures

A total of 21 different exposures, which will be referred to as 'factors' in this study, and their association with work outcome were investigated in the included studies. Data on these factors were collected from registers, medical records and through questionnaires. Fatigue, psychological symptoms, treatment toxicity and functional ability were measured using validated scales (Fobair *et al.* 1986; Razavi *et al.* 1993; Abrahamsen *et al.* 1998; Hensel *et al.* 2002; Syrjala *et al.* 2004; Kirchhoff *et al.* 2010).

In the present review, the factors are presented under the following headings: cancer survivor characteristics, work demands, cancer and treatment, symptoms after cancer and treatment, and function after cancer and treatment (Table 3). These headings are inspired by a model related to work and cancer developed by Feuerstein *et al.* (Feuerstein *et al.* 2010).

Table 3. Associations evaluated in included studies

Factors evaluated	Associated with work outcome	Not associated with work outcome
Cancer survivor characteristics		
■ Gender	[1], [2], [3], [4]	[6], [7]*
■ Age	[4], [5], [6]	[1], [2], [3], [7]*
■ Marital status		[1], [2]*
■ Educational status	[5], [6]	[1], [2]*
■ Income		[1], [2]*
Work demands		
■ Employment status	[5]	
■ Manual work	[8]	
Cancer and treatment		
■ Stage of disease	[5]	[4]*, [7]*
■ Disease status	[4]	
■ Treatment type	[5]	[2]*, [4]*
■ Time since end of treatment	[7]	
■ Diagnosis		[2]*
Symptoms after cancer and treatment		
■ Depression	[4], [5], [7]	[2]*
■ Anxiety	[5], [7]	
■ Mental health		[1]
■ Treatment distress		[2]*
■ Fatigue	[5]	[7]*
■ Treatment toxicity	[7]	
Function after cancer and treatment		
■ Physical function	[1], [6]	[2]*
■ Cognitive function	[6]	
■ Social function	[6]	

1 = Kirchhoff *et al.* 2010, 2 = Syrjala *et al.* 2004, 3 = Roelen *et al.* 2010, 4 = Fobair *et al.* 1986, 5 = Abrahamsen *et al.* 1998, 6 = Hensel *et al.* 2002, 7 = Razavi *et al.* 1993, 8 = Heinonen *et al.* 2001.

*For these factors nether estimates, *P*-values nor confidence intervals appeared in the articles.

Cancer survivor characteristics

Cancer survivor characteristics comprise demographic and socioeconomic data at the time of diagnosis, including marital status, income, educational level, age and gender.

The association between marital status and work outcome was evaluated in two prospective cohort studies of 106 and 281 survivors of leukaemia and lymphoma treated with allogeneic or autologous hematopoietic cell transplantation. In both studies, marital status was registered pre-transplantation and return to work was recorded during a 5-year period after transplantation. Both studies found that marital status did not predict time to return to work (Kirchhoff *et al.* 2010).

Income and educational level before diagnosis did not seem to be predictors of return to work since the same two cohort studies found no association between none of these two factors and time to return to work after hematopoietic cell transplantation during a 5-year follow-up period (Syrjala *et al.* 2004; Kirchhoff *et al.* 2010). However, two cross-sectional studies found low educational level at diagnosis to be associated with decreased rates of return to work at a mean of 3 years after treatment (Hensel *et al.* 2002) and with permanent disability 3–23 years after treatment (Abrahamsen *et al.* 1998).

With regard to the possible relationship between age and work outcome, the findings were also contradictory. The same two cohort studies mentioned above found no association between age and time to return to work (Syrjala *et al.* 2004; Kirchhoff *et al.* 2010). Age groups were divided into <35, 35–49 and >50 years in one of the studies (Kirchhoff *et al.* 2010). In the other one, the age groups were not described (Syrjala *et al.* 2004). Similarly, a third cohort study of survivors from lymphoma and leukaemia studied during a 2-year follow-up period found no difference in time to return to work between survivors in the age groups <35, 35–44, 45–54 >55 years (Roelen *et al.* 2010). Again the opposite result was found in three cross-sectional studies (Fobair *et al.* 1986; Abrahamsen *et al.* 1998; Hensel *et al.* 2002). In these studies, however, individual follow up after treatment spanned a wide range, survivors were divided into two age groups only, and outcome measures were not time to return to work, but disability pension (Abrahamsen *et al.* 1998), number of

weekly working hours (Fobair *et al*. 1986) and rate of return to work (Hensel *et al*. 2002).

Diverging results have also been reported regarding the association between gender and work outcome. However, the three prospective cohort studies showed that female gender was associated with a delayed time to return to work (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010; Roelen *et al*. 2010). The discrepancy between the different study designs must again be taken into account since cross-sectional studies again revealed contradictory results. Thus, no association between gender and rate of return to work was observed in two cross-sectional studies at a mean of approximately 3 years after treatment (Razavi *et al*. 1993; Hensel *et al*. 2002). However, individual follow up after treatment spanned a wide range in both studies and return to work was either not defined (Razavi *et al*. 1993) or defined as return to full-time or part-time work (Hensel *et al*. 2002), whereas the before-mentioned cohort studies defined return to work as return to full-time work only and individual follow up since treatment varied.

Work demands

The association between the individual's occupational situation before cancer diagnosis and work outcome after cancer and treatment was only evaluated in two cross-sectional studies.

In a study of 459 survivors from Hodgkin lymphoma, survivors with full-time employment at diagnosis were more likely to receive disability pension at follow up (3–23 years after first-line treatment) compared with those who were working part-time or were unemployed before diagnosis (Abrahamsen *et al*. 1998). Another work-related aspect was evaluated in a study of 109 survivors from leukaemia. Within a range of 4–171 months after allogeneic hematopoietic cell transplantation, having manual work was associated with lower rates of return to work compared with having sedentary work (Heinonen *et al*. 2001).

Cancer and treatment

Results regarding cancer diagnosis and treatment are also conflicting. In a cohort study of 281 survivors from leukaemia and lymphoma treated with allogeneic or autologous hematopoietic cell transplantation, neither diagnosis nor treatment type predicted time to return to work during a 5-year follow-up period (Syrjala *et al*. 2004). Similarly, treatment type was not associated with the number of weekly working hours within a range of 1–21 years after treatment in a cross-sectional study among 403 survivors from Hodgkin lymphoma (Fobair *et al*. 1986). Conversely, another cross-sectional study of 459 survivors from Hodgkin lymphoma found that survivors treated with a combination of chemotherapy and radiotherapy were more likely to be permanently disabled than survivors treated with just one of these treatment types (Abrahamsen *et al*. 1998).

Unsurprisingly, time since treatment was found to be positively associated with rate of return to work within a range of 1–204 month after treatment in a small study among 41 survivors from Hodgkin and non-Hodgkin lymphoma (Razavi *et al*. 1993). The same study concluded that stage of disease was not associated with return to work (Razavi *et al*. 1993). Similarly, another cross-sectional study found that at a median of 9 years after treatment, there was no association between stage of lymphoma and number of weekly working hours among 403 survivors from Hodgkin lymphoma (Fobair *et al*. 1986). Conversely, the results of a study among 459 survivors from Hodgkin lymphoma showed that survivors from Stage III and IV disease were more likely to be absent from work more than 12 months after first-line treatment than survivors from Stage I and II disease (Abrahamsen *et al*. 1998). Also, relapse of disease has been reported to be associated with work outcome. Hence, in a study among 403 survivors from Hodgkin lymphoma, relapsers were working less hours weekly than non-relapsers within a range of 1–21 years after treatment (Fobair *et al*. 1986).

Symptoms after cancer and treatment

Factors related to symptoms after cancer and treatment included psychological symptoms, fatigue and treatment toxicity. These symptoms are all potentially caused by the cancer and its treatment (Johnsen *et al*. 2009; Mitchell *et al*. 2011) and they have all been measured at varied times after diagnosis and treatment.

Again, the inconsistency of the findings can be related to study design and follow-up time since cross-sectional studies and cohort studies found contradictory results. Two prospective cohort studies found that psychological symptoms were not a predictor of time to return to work. One of them included 106 survivors from haematological malignancies treated with hematopoietic cell transplantation. The mental component score, which is one of eight dimensions in the validated generic instrument Short Form 36 Health Survey (Ware & Sherbourne 1992; McHorney *et al*. 1993, 1994), was applied 6 months post-transplantation to measure mental health and return to work was recorded in a 5-year period after transplantation

(Kirchhoff *et al.* 2010). The other study included 281 survivors from leukaemia and lymphoma who had also been treated with hematopoietic cell transplantation. Yet, in the latter study, mental conditions were measured before transplantation. Depression and distress were measured pre-transplantation by validated scales, the Depression Inventory (Beck 1979) and the Cancer Treatment Distress Scale (Syrjala & Chapko 1995); and return to work was recorded in a 5-year period after transplantation (Syrjala *et al.* 2004). The association between psychological symptoms and work outcome among survivors from haematological malignancies not treated with hematopoietic cell transplantation has only been evaluated in cross-sectional studies (Fobair *et al.* 1986; Razavi *et al.* 1993; Abrahamsen *et al.* 1998). Various work outcomes were measured at different times after diagnosis. Unlike the above mentioned cohort studies (Syrjala *et al.* 2004; Kirchhoff *et al.* 2010), these studies found an association between psychological symptoms and work outcome. Two studies among 41 and of 459 survivors from lymphoma measured symptoms of anxiety and depression by means of the validated Hospital Anxiety and Depression Scale (Zigmond & Snaith 1983). One of the studies found that these symptoms were negatively associated with the rate of return to work within a range of 1–204 months after diagnosis (Razavi *et al.* 1993). The other study came to similar results. Thus, within a range of 3–23 years after treatment, symptoms of anxiety and depression were associated with receiving permanent disability pension (Abrahamsen *et al.* 1998). Similarly, a study among 403 survivors from Hodgkin lymphoma found that within a range of 1–21 years after diagnosis, those survivors who reported symptoms of depression were working fewer hours than those who were not reporting these symptoms (Fobair *et al.* 1986). The validated 20-item Center for Epidemiologic Studies Depression Scale (Radloff 1977) was applied to measure symptoms of depression.

An association between high scores of fatigue and permanent disability pension was established in a cross-sectional study that included 459 survivors from Hodgkin lymphoma 3–23 years after diagnosis (Abrahamsen *et al.* 1998), whereas another cross-sectional study of 41 survivors from Hodgkin and non-Hodgkin lymphoma did not find fatigue to be associated with return to work within a range of 1–204 months after treatment (Razavi *et al.* 1993).These studies did not measure fatigue by the same scale, but the scales they used were validated (Pollock *et al.* 1979; Chalder *et al.* 1993).

The association between treatment toxicity and rate of return to work within a range 1–204 months after treatment was evaluated in a small cross-sectional study among 41 survivors from Hodgkin and non-Hodgkin lymphoma. Treatment toxicity was assessed with the WHO grading system for acute and sub-acute toxicity which involves an evaluation of a number of physical conditions that can be affected by cancer treatment, including both results of different urine and blood samples and an evaluation of symptoms like pain and constipation (World Health Organization 1979). The results showed that high levels of treatment toxicity were associated with decreased rates of return to work (Razavi *et al.* 1993).

Function after cancer and treatment

The association between functional disability and work outcome was only evaluated among survivors from haematological malignancies treated with allogeneic or autologous hematopoietic cell transplantation and the results are conflicting.

In a cohort study of 281 survivors from leukaemia and lymphoma, physical limitations were measured pre-transplantation by means of a validated scale, the Sickness Impact Profile. Return to work was measured in a 5-year follow-up period after transplantation and physical limitations pre-transplantation did not affect time to return to work (Syrjala *et al.* 2004). Conversely, another cohort study found that physical dysfunction had an impact on return to work in a 5-year follow up of 106 survivors from haematological malignancies (Kirchhoff *et al.* 2010). In this study, though, physical function was measured 6 months after transplantation by means of the psychical component score, which is one of eight dimensions in the validated generic Short Form 36 Health Survey instrument (Ware & Sherbourne 1992; McHorney *et al.* 1993, 1994). The same findings were seen in a cross-sectional study among 238 survivors from haematological malignancies. In this study, the association between work outcome and physical, cognitive and social functions was evaluated at a mean of 3 years after treatment. These factors were measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EORTC QLQ-C30 (Aaronson *et al.* 1993). The results showed that unemployed survivors reported significantly lower scores than their employed counterparts in physical, cognitive and social functions (Hensel *et al.* 2002).

DISCUSSION

To the best of our knowledge, the present systematic review is the first to report on factors associated with work outcome for survivors from haematological malignancies.

The main finding is that knowledge in the area does not rest on firm evidence as results are disparate and often widely diverging. The prevailing inconsistency hardly allows us to draw conclusions on the association of any single factor with work outcome. Regarding most of the factors evaluated, for example, age, gender, fatigue etc., results were directly diverging between studies. It could seem like some socioeconomic and demographic factors like marital status and income, were not related to work outcome, whereas psychological symptoms and physical function seemed to be associated to work outcome. However, the included studies were heterogeneous in terms of both study characteristics, methodology, outcome measures and factors investigated, and consequently a comparison of the results were complicated. Also, as mentioned earlier there were a number of methodological weaknesses in some of the included studies, which may have blurred the results.

First of all, the disparity between the results of cross-sectional studies and cohort studies stands out as a notable finding. Thus, prospective studies agreed, to a high extent, on their findings with regard to the possible association or non-association with marital status, low educational level, high age and female gender (Syrjala *et al*. 2004; Kirchhoff *et al*. 2010; Roelen *et al*. 2010), whereas there where no clear cut agreement between the single cross-sectional studies or between them and the cohort studies (Fobair *et al*. 1986; Razavi *et al*. 1993; Abrahamsen *et al*. 1998; Heinonen *et al*. 2001; Hensel *et al*. 2002). For the purpose of the present review, the cohort studies seem to yield the most reliable results. First, a cross-sectional design provides information about associations only; it does not allow causal inference (Glasziou *et al*. 2007). In the cohort studies, all survivors were continuously followed for 2–5 years from diagnosis or hematopoietic cell transplantation and factors possibly associated with work outcome were measured before outcome. As opposed to this, in the cross-sectional studies, it was, for example, not clear if work outcome was caused by symptoms of depression, or if symptoms of depression were caused by the work situation, because the possibly associated factors and work outcome were measured at the same time. Thus, the cohort study is naturally a more appropriate design for investigating relations between selected factors and work outcome.

Another disadvantage of using the cross-sectional design in this area is that it does not allow time since treatment to be equal for all the study subjects. As a result, time since treatment varied up to 20 years between individuals in the same study. It seems, however, unlikely that the association between, for example, fatigue and work outcome would lead to the same result 1 year and 20 years after treatment. Furthermore, from a clinical point of view, it must be preferable to measure factors possibly associated with work outcome within a short timeframe after diagnosis, notably if the results are meant to be applicable to clinical practice and to serve the purpose of identifying the survivors at risk of work-related problems.

Another explanation of the diverging findings across the included studies was that the definition of work outcome differed among studies. This misclassification of the outcome, being differential or non-differential, could seriously weaken the possibility of making causal inferences, as, for example, factors that were not associated with return to part-time work might, for instance, be associated with full-time work or with permanent disability.

Also, many of the factors that might potentially play an important role for the haematological patients return to labour market on completion of treatment (e.g. depression and fatigue) were measured and defined in different ways among the included studies. Yet, again this blurs the results and complicates comparison between studies.

Previous studies on work outcome in other cancer groups have suggested that the presence of co-morbidity is negatively associated with work outcome (Taskila *et al*. 2007; Carlsen *et al*. 2008). Unfortunately, none of the included studies have examined this association. In connection to this, none of the studies evaluated the association between work outcome and different specific haematological diagnosis or treatment strategies. As is the case with other cancer survivors (Taskila *et al*. 2007; Carlsen *et al*. 2008; Syse *et al*. 2008), the varying degrees of severity among both the different haematological diseases and their treatment could potentially influence work outcome and thus desirably both co-morbidity and a stratification of different haematological diagnosis and treatments should be included in future studies.

The inconsistent results of this systematic review are in agreement with earlier systematic reviews on factors associated with work outcome for cancer survivors (Spelten *et al*. 2002; Steiner *et al*. 2004; Taskila & Lindbohm 2007; Feuerstein *et al*. 2010; Mehnert 2011). In these reviews, though, survivors from haematological malignancies were either not or only very sparsely represented. Moreover, the treatment and the course of haematological malignancies often differ from that of other malignancies, which may complicate direct transferability of the results to this survivor group. These reviews do, however, conclude that work outcome appears to be associated with cancer survivor characteristics, cancer and treatment, work demands, symptoms after cancer and treatment, and function after cancer and treatment. Even so, they, as in this present

systematic review, report diverging results and identify several weaknesses in design of the included studies (Spelten *et al.* 2002; Steiner *et al.* 2004; Taskila & Lindbohm 2007; Feuerstein *et al.* 2010; Mehnert 2011).

In conclusion, due to inconsistency of the reported results, we cannot at the moment draw any conclusions about the association of any single factors with work outcome for haematological malignancies. This emphasises the need for more well-designed research in this area of factors associated with work outcome for survivors of haematological malignancies.

Based on possible explanations of the converging findings in this systematic review, we recommend that the design of future studies should be prospective and should include a control group of age-paired cancer-free individuals. Possible factors related to work outcome should be evaluated at an early time point after diagnosis to allow for establishing cause-effect relations, the role of co-morbidity and of differences between haematological diagnoses ought to be established, and work outcomes must be well defined and recorded with valid methods.

Knowledge based on such studies will enable identification of individuals at increased risk of work-related problems and hence, allow early rehabilitation interventions, aimed at obtaining affiliation to labour market and to return to working life, to be initiated.

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ORIGINAL ARTICLE

Risk of disability pension for patients diagnosed with haematological malignancies: A register-based cohort study

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ABSTRACT

Patients with haematological malignancies are at increased risk of experiencing work-related problems. The aims of this study were to compare the risk of disability pension (DP) among patients diagnosed with eight subtypes of haematological malignancies to a reference cohort, and to determine if relative risks differ between these subtypes; to evaluate the influence of socioeconomic factors, demographic factors, and clinical factors on the risk of DP; and to investigate if these associations differ between the reference cohort and the patient cohort.

Material and methods. We combined data from national registers on Danish patients diagnosed with haematological malignancies between 2000 and 2007 and a reference cohort without a history of these diseases. A total of 3194 patients and 28 627 reference individuals were followed until DP, emigration, old age pension or anticipatory pension, death or 26 February 2012, whichever came first.

Results. A total of 550 (17%) patients and 1511 (5%) reference individuals were granted DP. Age- and gender-adjusted relative risks differed significantly between the subgroups of haematological malignancies and ranged from 2.64 (95% CI 1.84–3.78) for patients with Hodgkin lymphoma to 12.53 (95% CI 10.57–14.85) for patients with multiple myeloma. In the patient cohort we found that gender, age, comorbidity, ethnicity, educational level, household income, history of long-term sick leave, and need of treatment with anxiolytics or antidepressants after diagnosis were associated with receiving DP. However, most of these associations were stronger in the reference cohort.

Conclusion. All eight subtypes of haematological malignancies were associated with an increased risk of DP compared to the reference cohort. The relative risks differed according to subtype, and patients with multiple myeloma had the highest risk of DP. Furthermore, most socioeconomic, demographic and clinical factors had a stronger impact on the risk of DP in the reference cohort than in the patient cohort.

More than one third of patients diagnosed with haematological malignancies are between 20 and 64 years of age. Previous studies have documented that these patients are at increased risk of experiencing work-related problems compared to cancer-free control groups [1–3] and patients with other cancer types [4–7].

Denmark has a widespread tax-financed welfare system and it is thus possible for persons with permanently reduced work capacity to retire due to their disability and be financially compensated. A Danish cohort study showed that patients with leukaemia had a three-fold risk and patients with non-Hodgkin lymphoma a two-fold risk of disability pension compared to cancer-free controls [1]. However, in this study haematological malignancies with very different treatment regimens and prognoses were pooled, and a recent study on return to work after long-term sick leave for patients diagnosed with haematological malignancies found that return to work was highly dependent on the type of haematological malignancy [8]. To the best of our knowledge, no studies have

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investigated the risk of permanently reduced work capacity in patients with haematological malignancies divided into clinically relevant subtypes in comparison to a reference cohort without these types of malignancies.

It is well known, that, for example high age, low socioeconomic status and comorbidity are risk factors for receiving disability pension in the general population [9], however, documentation on factors possibly associated with increased risk of permanently reduced work capacity among patients with haematological malignancies is scarce [10].

Therefore the present study aimed to: 1) Compare the risk of disability pension (DP) among patients diagnosed with eight clinically relevant subtypes of haematological malignancies to an age- and gender-matched reference cohort without a history of these malignancies, and to determine if relative risks differ between these subtypes; 2) Evaluate the influence of socioeconomic factors, demographic factors, comorbidity, and post-diagnosis use of anxiolytics and antidepressants on the risk of DP; 3) Investigate if these associations differ between the reference cohort and the patient cohort.

Material and methods

Source population

The study period proceeded from 1 January 2000 to 26 February 2012 within the entire Danish population of approximately 5.6 million inhabitants.

In Denmark, the entire population has free access to tax-financed health care, and a considerable amount of health-related information is recorded in national population-based registers. Accurate and unambiguous linkage of register data at the individual level is possible by means of a unique civil registration number assigned to all Danish citizens [11].

During the entire study period it was possible to retire due to age at 65 years in Denmark and there was an anticipatory retirement scheme from the age of 60 years.

Patient cohort

Patients diagnosed with haematological malignancies during a period from 1 January 2000 to 31 December 2007 were identified in the Danish Cancer Register, which contains data on the incidence of cancer in the Danish population since 1943 [12]. Patients with haematological malignancies were identified according to the International Classification of Disease (ICD-10) and time of diagnosis. Information regarding morphology was also obtained. Haematological malignancies were categorised according to morphology into the subgroups: Hodgkin lymphoma (C81), diffuse large B-cell lymphoma (C83.3), follicular lymphoma (C82), multiple myeloma (C90), acute myeloid/lymphoid leukaemia (C91.0, C91–94, except from C92.1 and 93.1), chronic myeloid leukaemia (C92.1), chronic lymphoid leukaemia (C91.1) and others (all other diseases classified as C91–96).

We included patients between 19 and 55 years of age, because they had to be of working age at time of diagnosis and at least five years following diagnosis. We excluded permanently work disabled patients or patients emigrated at time of diagnosis.

Reference cohort

A random reference cohort was sampled among the Danish population using the Danish Civil Registration System (CRS) containing personal data on all permanent residents in Denmark. Each cancer patient was individually matched on gender and date of birth to 10 persons without a history of haematological malignancies. Each individual in the reference cohort was assigned the same date of diagnosis, as the patient they were matched to. Included reference individuals could not develop haematological malignancies during the inclusion period (2000 to 2007).

We excluded reference individuals who were permanently work disabled or emigrated at time of diagnosis. Furthermore, reference individuals who were matched to patients that were excluded because of the above mentioned criteria, were also excluded.

Outcome

In Denmark DP is granted by the authorities if a person's work capacity is reduced in permanence to such an extent that return to work is unlikely.

Information on granted DP was obtained from the Danish Register for Evaluation of Marginalisation (DREAM), which is based on data from the Danish Ministry of Employment, the Danish Ministry of Education, CRS and SKAT (the Danish tax system). DREAM includes data on all Danish citizens who have received welfare benefits since 1991. Each person is registered once a week with a code indicating the type of welfare benefit received. DREAM has a 100% coverage of those granted DP in Denmark from 2000 and until now [13].

Socioeconomic factors

Information on cohabiting status, children living at home, household income, educational level, and housing tenure was obtained from registers administered by Statistics Denmark, which is a central authority compiling and publishing statistics on the

Danish society, especially on social and economic factors.

We obtained information on educational level from 1 October the year before diagnosis. Cohabiting status, children living at home, household income and housing tenure were assessed from 1 January the year of diagnosis.

Demographic factors

Data on age and gender were retrieved from the CRS [11], and age was calculated at the time of diagnosis. Information on ethnicity was obtained from DREAM.

Comorbidity

Data on comorbidity was obtained from the Danish National Patient Register (NPR), which includes information on all hospital admissions in Denmark since 1977, as well as contacts to emergency rooms or outpatient clinics since 1995. Diagnostic information has been coded by physicians according to the ICD-10 system since 1994 at each contact [14].

We computed a Charlson Comorbidity Index (CCI) score on the basis of the diagnoses recorded in the NPR for each patient during a five-year period before they were diagnosed with the haematological malignancy. In CCI, a weight is assigned to define categories of comorbid diseases, and the index is the sum of these weights (from 0 to 6). A higher CCI score indicates an increased severity of conditions. Conditions with a weight of one includes: Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes. Conditions with a weight of two includes: Haemiplegia, moderate or severe renal disease, diabetes with end organ damage and any malignancy. Moderate or severe liver disease is given a weight of 3 and metastatic solid tumour or HIV receives a weight of 6 [15]. A positive-predictive value greater than 90% have been found for almost all ICD-10 diagnostic codes used to ascertain the Charlson comorbidity conditions in the NRP [16].

Since we only had few patients with high levels of comorbidity prior to diagnosis, we classified the score into three groups: 0, 1–2, and ≥ 3.

Use of anxiolytics or antidepressants

Use of anxiolytics or antidepressants was used as an indicator of mental health status following diagnosis. To investigate whether patients who needed treatment with either anxiolytics or antidepressants after diagnosis had a higher risk of receiving DP, data on the prescription-based use of these drugs was obtained from the Danish National Prescription Register, which contains information on all dispensed prescriptions since 1994. These data include the type and amount of drug prescribed according to the Anatomical Therapeutical Chemical Classification System (ATC), and the date of drug redemption [17].

The ATC codes of interest were antidepressants (N06A) and anxiolytics (N05B), and it was registered if the patients were prescribed these types of medication during the first three years following diagnosis.

Statistics

Individuals in the patient cohort and the matched reference cohort were followed from date of diagnosis until DP, emigration, old age pension or anticipatory pension, death or 26 February 2012, whichever came first.

Cumulative incidence curves were computed to illustrate the incidence of DP according to type of haematological malignancy.

Using generalised linear regression models for pseudo observations [18], age- and gender-adjusted relative cumulative risks (RR) of DP and associated 95% confidence intervals (CI) two, four and six years after diagnosis were estimated for the eight subgroups of haematological malignancies (Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, acute myeloid/lymphoid leukaemia, chronic myeloid leukaemia, chronic lymphoid leukaemia and others) compared to the reference cohort (Model 1). Wald tests were used to test if the RRs differed between subgroups.

The associations between comorbidity, socioeconomic and demographic factors and the risk of DP four years after diagnosis were studied separately for the patient cohort and the reference cohort (Model 2). Covariates in the model included: Diagnosis (Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, acute myeloid/lymphoid leukaemia, chronic myeloid leukaemia, chronic lymphoid leukaemia and others); gender (male, female); comorbidity (0, 0<); age (19–35, 36–40, 41–45, 46–50, 51–55 years); ethnicity (Danish citizens, immigrants or descendants from western countries, immigrants or descendants from non-western countries); cohabiting status (cohabiting, living alone); children living at home (yes, no); housing tenure (owner-occupied, rental); highest attained educational level (primary school or high school, higher education, vocational education); history of sick leave 12–24 months before diagnosis; (3–7 weeks, 8–13 weeks, 14–25 weeks and >26 weeks); household

income (low income (first quartile), middle income (second and third quartiles), and high income (fourth quartile)). The household income was reported after taxation and adjusted for number of persons in the household in the following way: household income/(no. of persons in household$^{0.6}$). Wald test was used to test for overall interaction between the two cohorts and all the independent variables. In order to test for interaction for each factor and the two cohorts two tests were conducted. In the first test an interaction term was included between the two cohorts and all the independent variables at the same time. This model thereby enabled interaction between all factors and the two cohorts. In the second test, an interaction term was included between the two cohorts and each of the independent variables one at a time (without including other interactions). This model did thereby not enable interaction between any of the other factors and the two cohorts.

In Model 3 use of antidepressants or anxiolytics after diagnosis (entered as a time dependent variable and categorised as yes/no) was the main independent variable, and we adjusted for all covariates included in Model 2. The same analysis was also performed with the two drug groups separately. Again, we estimated the RRs four years after diagnosis, the analyses were performed separately in the two cohorts, and we tested for interaction between the two cohorts and the main independent variables using the same strategies as in Model 2.

In all three models two-sided Wald tests were used to test the overall association between each independent variable and the risk of DP. Death, anticipatory pension, and old age pension were considered competing events in all the analyses.

Results

A total of 3616 patients between 19 and 55 years of age were diagnosed with haematological malignancies for the first time between 2000 and 2007; and hence initially the reference cohort consisted of 36 160 individuals.

A total of 29 (1%) patients were excluded as they were emigrated and 393 (11%) because they were already permanently work disabled at time of diagnosis. Furthermore, 37 (0.1%) individuals were excluded from the reference cohort as they had a history of a haematological malignancy, 716 (2%) were excluded due to emigration and 2560 (7%) because they were permanently work disabled at diagnosis. Thus, a total of 3194 (88%) patients and 28 627 (79%) reference individuals were included in the study (Figure 1).

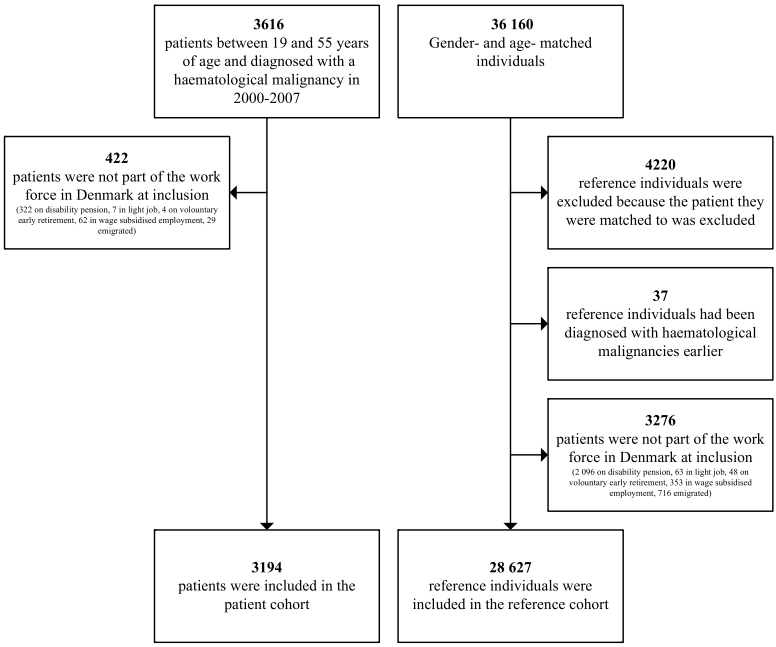

Figure 1. Flowchart of inclusion.

In the end, at least four reference individual were matched to each patient. The median age was 45 years ranging from 19 to 55 years and 41% were women.

Subtypes of haematological malignancies

The 3194 patients were followed for a median of six years [interquartile range (IQR): 2–8], and a total of 550 (17%) were granted DP during the follow-up period. The highest proportion was found for patients with multiple myeloma (44%), and the lowest for patients with Hodgkin lymphoma (9%). The reference cohort was followed for a median of seven years (IQR: 6–10), and in all, a total of 1511 (5%) were granted DP during the follow-up period (Table I).

The cumulative incidence of DP by type of haematological malignancy is illustrated in Figure 2. All sub-groups had higher incidences of DP than the reference cohort. The highest incidence was found for patients with multiple myeloma, and especially the first three years after diagnosis there was a notable increase in the incidence of DP for this subgroup of patients.

Table II presents the results of the multivariable analyses of the risk of DP according to subtype of haematological malignancy compared to the reference cohort (Model 1). Both two, four and six years after diagnosis, haematological malignancy subgroup was significantly associated with the risk of DP ($p < 0.001$), and RRs differed significantly between the eight subgroups ($p < 0.001$). These associations were strongest two years after diagnosis and became slightly weaker year by year, as the risk of DP increased in the reference cohort with increasing age. The relative risks were lowest for patients with Hodgkin lymphoma and four years after diagnosis this subgroup had a 2.5-fold higher risk of receiving DP than the reference cohort (adjusted RR 2.64, 95% CI 1.84–3.78). The highest relative risk was found for patients with multiple myeloma, and four years after diagnosis, the risk of DP was 12-fold higher for this patient group compared to the reference cohort (adjusted RR 12.53, 95% CI 10.57–14.85). At this time-point, the other sub-groups of haematological malignancies had three- to six-fold higher risks of DP compared to the reference cohort.

Influence of clinical, socioeconomic and demographic factors

The influence of clinical, socioeconomic and demographic factors on the risk of DP in the patient cohort and the reference cohort was investigated in Models 2 and 3, and the results of those analyses are presented in Tables III and IV.

Most of the associations were pointing in the same direction for the two cohorts but were stronger in the reference cohort compared to the patient cohort. An overall interaction between the two cohorts and the clinical, socioeconomic and demographic factors was found ($p < 0.001$). This indicates that the haematological malignancy modified the associations between the independent variables and DP. P-values from tests of interaction for each factor are presented in the last column in Tables III and IV.

*Socioeconomic and demographic factor*s. The socioeconomic and demographic factors seemed to be equally distributed in the two cohorts. In both cohorts gender was found to be associated with the risk of DP, as the risk was higher for women than men (adjusted RR 1.31, 95% 1.10–1.57 and 1.33, 95% 1.09–1.62). A negative association was found between both income and educational level and the risk of DP in the two cohorts. A positive association was found between both age and the extent of sick leave before diagnosis and receiving DP in the two cohorts (Table III).

Table I. Reference and patient cohort outcome stratified by subtype of haematological malignancy.

	$N_{patients}/N_{references}$	No events[a] b/c	Emigrated b/c	Old-age or anticipatory pension b/c	Dead b/c	Disability pension b/c
Hodgkin lymphoma	591/5384	80%/90%	2%/3%	2%/2%	7%/1%	9%/4%
Diffuse large B-cell lymphoma	467/4176	56%/78%	1%/2%	8%/12%	20%/2%	15%/6%
Follicular lymphoma	364/3240	59%/78%	1%/1%	11%/13%	12%/2%	17%/6%
Multiple myeloma	270/2368	21%/69%	0%/1%	6%/21%	29%/2%	44%/7%
Acute myeloid/lymphoid leukaemia	445/4007	36%/83%	1%/3%	2%/8%	44%/1%	17%/5%
Chronic myeloid leukaemia	155/1409	65%/86%	1%/2%	1%/6%	16%/1%	17%/5%
Chronic lymphoid leukaemia	273/2404	53%/68%	1%/1%	13%/22%	16%/2%	17%/7%
Others	629/5639	54%/81%	1%/2%	8%/11%	22%/1%	15%/5%
In all	3194/28 627	55%/80%	1%/2%	6%/11%	21%/2%	17%/5%

[a]Followed until end of follow-up period (February 26, 2012) without experiencing any of the events (death, old-age pension, anticipatory pension, emigration, disability pension).
[b]Proportion of patient cohort.
[c]Proportion of reference cohort (references are in the same subgroup of haematological malignancy as the patients they are matched to).

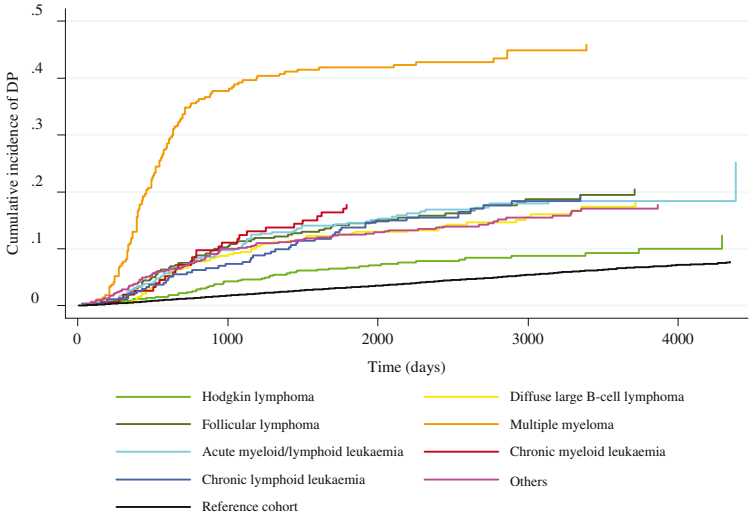

Figure 2. Cumulative incidence of DP according to type of haematological malignancy (death, old age pension and anticipatory pension were considered as competing events).

*Clinical factor*s. The proportion of individuals with a presence of comorbidity according to the Charlson Comorbidity Index was higher in the patient cohort (11%) than the reference cohort (6%). Furthermore, there was a positive association between level of comorbidity and the risk of DP in both cohorts. Individuals with a CCI score ≥ 3 had a 1.5-fold higher risk of DP in the patient cohort (adjusted RR 1.58, 95% CI 1.16–2.14), and a three-fold higher risk in the reference cohort (adjusted RR 2.98, 95% CI 1.52–5.83) compared to those with a CCI score of 0 (Table III).

In the patient cohort, 18% were prescribed anxiolytics and/or antidepressants after diagnosis, compared to 7% in the reference cohort (Table IV). Moreover, we found an association between use of antidepressants and/or anxiolytics and the risk of DP, as patients who were prescribed these types of medication after the diagnosis of haematological malignancies were more likely to be granted DP compared to those who were not (adjusted RR 1.29, 95% CI 1.07–1.55). This association was also found when analysing the two drug groups separately and could also be observed in the reference cohort (adjusted HR 1.77, 95% CI 1.43–2.20).

Discussion

In this nationwide register-based cohort study we found that patients with eight subtypes of haematological malignancies (Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, acute myeloid/lymphoid leukaemia,

Table II. Age- and gender-adjusted relative cumulative risk of disability pension two, four and six years after diagnosis for subtypes of haematological cancer compared to the reference cohort.

Diagnosis	N = 3194 (%)	$RR^a_{2\ years}$ (95% CI)	$RR^a_{4\ years}$ (95% CI)	$RR^a_{6\ years}$ (95% CI)
Hodgkin lymphoma	591 (18)	2.07 (1.14–3.78)	2.64 (1.84–3.78)	2.20 (1.60–3.03)
Diffuse large B-cell lymphoma	467 (15)	5.13 (3.54–7.45)	4.25 (3.24–5.58)	3.24 (2.52–4.16)
Follicular lymphoma	364 (11)	4.97 (3.36–7.36)	4.18 (3.14–5.57)	3.45 (2.67–4.47)
Multiple myeloma	270 (8)	22.10 (17.98–27.16)	12.53 (10.57–14.85)	8.93 (7.64–10.45)
Acute myeloid/lymphoid leukaemia	445 (14)	5.63 (3.83–8.28)	5.15 (3.96–6.71)	4.21 (3.33–5.34)
Chronic myeloid leukaemia	155 (5)	6.97 (3.79–12.81)	6.44 (4.33–9.59)	5.38 (3.81–7.59)
Chronic lymphoid leukaemia	273 (9)	3.49 (2.09–5.83)	3.22 (2.24–4.63)	3.01 (2.22–4.09)
Others	629 (20)	5.34 (3.93–7.26)	4.16 (3.30–5.24)	3.20 (2.58–3.96)

[a]Adjusted for age and gender. Wald test of equal RRs: $p < 0.001$ for all three years. Wald test of overall association between subgroups and risk of DP: $p < 0.001$ for all three years.

Table III. The relative cumulative risk of disability pension four years after diagnosis according to clinical, demographic, socioeconomic factors and stratified by patients/references.

Clinical, demographic, socioeconomic factors	Patients				References				Difference between patients and references
	N = 3194 (%)	RR_{crude} (95% CI)	RR_{adj}[a] (95% CI)	p	N = 28 627 (%)	RR_{crude} (95% CI)	RR_{adj}[a] (95% CI)	p	p^b/p^c
Diagnosis				<0.001				0.40	<0.001/<0.001
Hodgkin lymphoma	591 (18)	1	1		5384 (19)	1	1		
Diffuse large B-cell lymphoma	467 (15)	1.91 (1.27–2.87)	1.59 (0.99–2.56)		4176 (15)	1.63 (1.26–2.12)	0.84 (0.59–1.19)		
Follicular lymphoma	364 (11)	2.13 (1.40–3.24)	1.57 (0.97–2.55)		3240 (11)	1.46 (1.10–1.95)	0.56 (0.36–0.88)		
Multiple myeloma	270 (8)	6.91 (4.87–9.82)	4.38 (2.84–6.75)		2368 (8)	1.80 (1.34–2.41)	0.88 (0.61–1.29)		
Acute myeloid/ lymphoid leukaemia	445 (14)	2.23 (1.50–3.33)	1.67 (1.03–2.68)		4007 (14)	1.07 (0.79–1.43)	0.85 (0.55–1.30)		
Chronic myeloid leukaemia	155 (5)	2.39 (1.45–3.96)	1.82 (0.89–3.69)		1409 (5)	1.17 (0.78–1.76)	0.73 (0.38–1.41)		
Chronic lymphoid leukaemia	273 (9)	1.85 (1.16–2.95)	1.34 (0.81–2.23)		2404 (8)	1.88 (1.41–2.51)	0.82 (0.55–1.24)		
Others	629 (20)	1.92 (1.31–2.84)	1.55 (1.01–2.39)		5639 (20)	1.55 (1.21–1.99)	0.89 (0.64–1.25)		
Gender				0.003				0.006	0.94/0.78
Male	1884 (59)	1	1		16 998 (59)	1	1		
Female	1310 (41)	1.40 (1.17–1.67)	1.31 (1.10–1.57)		11 629 (41)	1.13 (0.98–1.31)	1.33 (1.09–1.62)		
Age				<0.001				<0.001	0.006/0.25
19–35 years	741 (23)	0.50 (0.35–0.73)	0.46 (0.30–0.70)		6757 (24)	0.45 (0.33–0.62)	0.30 (0.17–0.53)		
36–40 years	362 (11)	0.91 (0.62–1.33)	0.90 (0.60–1.34)		3378 (12)	0.85 (0.61–1.18)	0.74 (0.43–1.29)		
41–45 years	480 (15)	1	1		4400 (15)	1	1		
46–50 years	638 (20)	1.21 (0.89–1.65)	1.30 (0.96–1.75)		5671 (20)	1.55 (1.21–2.00)	1.96 (1.23–3.12)		
51–55 years	973 (31)	1.70 (1.29–2.23)	1.57 (1.20–2.06)		8421 (29)	2.02 (1.60–2.54)	2.65 (1.65–4.28)		
Etnicity				0.012				<0.001	0.007/0.005
Danish	2846 (89)	1	1		25 362 (89)	1	1		
Western	119 (4)	0.57 (0.30–1.07)	0.62 (0.28–1.37)		959 (3)	0.97 (0.65–1.47)	0.92 (0.47–1.79)		
Non-western	169 (5)	1.73 (1.29–2.31)	1.42 (1.11–1.80)		1437 (5)	4.02 (3.36–4.81)	2.52 (1.90–3.324		
Missing	60 (2)	–	–		869 (3)	–	–		
Education level				0.029				<0.001	0.15/0.011
Basic school/high school	1049 (33)	1.21 (1.00–1.47)	1.13 (0.93–1.37)		8833 (31)	1.97 (1.67–2.32)	1.53 (1.20–1.96)		
Vocational education	1202 (38)	1	1		10 853 (38)	1	1		
Longer education	827 (26)	0.50 (0.38–0.66)	0.77 (0.58–1.02)		7683 (27)	0.62 (0.49–0.79)	0.86 (0.59–1.27)		
Missing	116 (3)	–	–		1258 (4)	–	–		
Household income				<0.001				<0.001	0.16/<0.001
Low (1 quartile)	807 (25)	1.47 (1.22–1.77)	1.64 (1.31–2.05)		6948 (24)	2.60 (2.23–3.02)	2.04 (1.63–2.57)		
Medium (2–3 quartile)	1587 (50)	1	1		13 921 (49)	1	1		
High (4 quartile)	742 (23)	0.64 (0.49–0.84)	0.62 (0.47–0.83)		7012 (24)	0.51 (0.40–0.66)	0.48 (0.32–0.72)		
Missing	58 (2)	–	–		746 (3)	–	–		
Cohabitation status				0.087				0.84	0.20/<0.001
Living alone	859 (27)	1	1		6861 (24)	1	1		
Cohabiting	2277 (71)	0.86 (0.71–1.05)	1.21 (0.97–1.51)		21 020 (73)	0.48 (0.42–0.56)	0.97 (0.76–1.26)		
Missing	58 (2)	–	–		746 (3)	–	–		
Children living at home				0.25				0.02	0.28/0.032
No	1643 (51)	1	1		13 905 (48)	1	1		
Yes	1493 (47)	0.81 (0.67–0.96)	0.88 (0.71–1.09)		13 976 (49)	0.60 (0.52–0.70)	0.73 (0.56–0.95)		
Missing	58 (2)	–	–		746 (3)	–	–		
Housing tenure				0.31				0.003	0.12/<0.001
Owner-occupied	2052 (64)	1	1		18 789 (66)	1	1		
Rental	1025 (32)	0.75 (0.62–0.89)	0.90 (0.73–1.11)		8569 (30)	0.37 (0.32–0.42)	0.69 (0.55–0.88)		
Missing	117 (4)	–	–		1269 (4)	–	–		

(*Continued*)

Table III. (*Continued*)

Clinical, demographic, socioeconomic factors	Patients N = 3194 (%)	Patients RR_{crude} (95% CI)	Patients RR_{adj}[a] (95% CI)	Patients p	References N = 28 627 (%)	References RR_{crude} (95% CI)	References RR_{adj}[a] (95% CI)	References p	Difference between patients and references p^b/p^c
Sick leave second year before diagnosis				<0.001				<0.001	0.21/0.001
None	2720 (85)	1	1		28 780 (87)	1	1		
3–7 weeks	305 (10)	1.02 (0.75–1.40)	0.88 (0.62–1.25)		2604 (9)	1.38 (1.08–1.75)	0.96 (0.67–1.38)		
8–13 weeks	77 (2)	1.67 (1.07–2.61)	1.62 (1.18–2.22)		479 (2)	3.09 (2.16–4.41)	1.48 (0.74–2.95)		
14–25 weeks	44 (1)	2.91 (1.95–4.36)	2.18 (1.50–3.16)		407 (1)	5.43 (4.07–7.25)	2.52 (1.73–3.68)		
>26 weeks	48 (2)	3.00 (2.06–4.39)	1.96 (1.17–3.30)		357 (1)	12.12 (9.91–14.82)	4.02 (2.88–5.61)		
Comorbidity				0.009				<0.001	0.065/<0.001
0	2831 (89)	1	1		27 147 (94)	1	1		
1–2	294 (9)	1.62 (1.26–2.08)	1.16 (0.89–1.51)		1389 (5)	4.24 (3.53–5.09)	1.69 (1.27–2.26)		
>=3	69 (2)	2.22 (1.50–3.30)	1.58 (1.16–2.14)		91 (1)	10.59 (7.21–15.54)	2.98 (1.52–5.83)		

[a]All variables in the table are mutually adjusted and missing values are not included in the analyses.
[b] Wald test for interaction (model with interaction between all factors and patient/reference cohort).
[c]Wald test for interaction (models with interaction between one factor at a time and patient/reference cohort).

chronic myeloid leukaemia, chronic lymphoid leukaemia and others) had a higher risk of DP compared to a reference cohort; However, the relative risks differed considerably between the subtypes. The highest relative risks were found for patients with multiple myeloma, which might be explained by the chronic and progressive nature of this disease. The lowest relative risks were found for patients with Hodgkin lymphoma, which in contrary, is a curable disease. However, the proportion of death differed widely between the subgroups, and this should be taking into account when interpreting the results. The highest proportion of death was found for patients with acute myeloid/lymphoid leukaemia where 44% patients died during the follow-up period. This illustrates that although this subgroup did not have the highest relative risks of DP, these diseases have serious consequences for the patients. To the best of our knowledge, this is the first major study where the risk of DP has been estimated in clinically relevant subgroups of patients with haematological malignancies compared to a reference cohort. In most previous studies on the risk of DP among patients with cancer, haematological malignancies have been pooled in groups relevant in term of biology, but not by clinical relevance. Diseases such as acute myeloid/lymphoid leukaemia, chronic myeloid leukaemia, and chronic lymphoid leukaemia have, for instance been pooled under the term "leukaemia", even though the relative survival five years after

Table IV. The relative cumulative risk of disability pension four years after diagnosis according to use of antidepressants and/or anxiolytics after diagnosis stratified on patients/references.

Use of antidepressants and/or anxiolytics	Patients N = 3194 (%)	Patients RR_{crude} (95% CI)	Patients RR_{adj}[a] (95% CI)	Patients p	References N = 28 627 (%)	References RR_{crude} (95% CI)	References RR_{adj}[a] (95% CI)	References p	Difference between patients/references p^b/p^c
Anxiolytics				0.005				<0.001	0.006/0.10
No	2895 (91)	1	1		28 144 (98)	1	1		
Yes	299 (9)	1.62 (1.29–2.05)	1.37 (1.10–1.70)		480 (2)	3.46 (2.58–4.65)	2.40 (1.72–3.35)		
Antidepressants				0.016				<0.001	0.088/0.021
No	2811 (88)	1	1		26 928 (94)	1	1		
Yes	383 (12)	1.60 (1.29–1.97)	1.33 (1.05–1.67)		1699 (6)	3.53 (2.99–4.17)	1.77 (1.39–2.24)		
Antidepressants and/or anxiolytics				0.009				<0.001	0.029/0.007
No	2612 (82)	1	1		26 584 (93)	1	1		
Yes	582 (18)	1.54 (1.28–1.85)	1.29 (1.07–1.55)		2043 (7)	3.47 (2.97–4.05)	1.77 (1.43–2.20)		

[a]Adjusted for age, gender, household income, family type, educational level, ethnicity, housing tenure, diagnosis and sick leave second year before diagnosis.
[b]Wald test for interaction (model with interaction between all factors and patient/reference cohort).
[c]Wald test for interaction (models with interaction between one factor at a time and patient/reference cohort).

diagnosis in these groups range from 19% to 71% [19]. This present study, however, showed that the risk of DP differed between many of the subgroups. A recent study on return to work for patients diagnosed with haematological malignancies on long-term sick leave showed similar results [8], and together these two studies confirm a clear need of distinguishing between different types of haematological malignancies when considering future labour market participation.

A general pattern in this present study was that except for gender there was a tendency that the haematological malignancy modified the association between the socioeconomic, demographic and clinical factors and the risk of DP, and most of the factors had a stronger impact on the risk of DP in the reference cohort compared to the patient cohort. Since the reference cohort had stronger statistical power than the patient cohort, comparisons of level of significance for associations in the two cohorts must be made with caution. However, the tests of interaction also showed significant interaction between most of the factors and the two cohorts. We do not know the mechanisms behind this result, but it could maybe indicate that the impact of the haematological malignancy on the risk of DP was so predominant that it diminished the effect of both presence of comorbidity, history of long-term sick leave, socioeconomic and demographic factors and needing treatment with antidepressants or anxiolytics after diagnosis. Most previous studies have not investigated these associations separately for both cancer patient cohorts and reference cohorts, and therefore conclusions about factors associated with the risk of DP for cancer patients have only been based on results from patient populations. This study adds new knowledge since it shows that even though some factors are associated with the risk of DP among patients diagnosed with haematological malignancies these are even stronger in the general population. Furthermore, the results indicate that inclusion of reference cohorts in general should be considered when performing studies on labour market participation in patient cohorts.

We found that the proportion of patients with comorbidity was higher in the patient cohort compared with the reference cohort. The reason for this is unclear, though a few cases may relate to the increased risk of lymphomas in patients with diseases of the immune system, and of leukaemias and lymphomas in patients treated with chemotherapy [20]. We also found the presence of comorbidity to be positively associated with the risk of DP in both the reference cohort and the patient cohort. Similar to our study, an association between comorbidity and risk of DP has been documented in studies on other cancer groups [21–23].

We also found that patients treated with antidepressants or anxiolytics after the diagnosis of haematological malignancies were more likely to be granted DP compared to those who were not. To our knowledge, the association between mental health status following a haematological malignancy and the risk of DP has only been investigated in a Norwegian cross-sectional study from 1994. The study comprised 459 patients diagnosed with Hodgkin lymphoma 3–23 years before the study was conducted. Symptoms of depression and anxiety were measured using a validated self-reporting scale, and similar to the results of our study, both high scores of anxiety and depression were found to be associated with higher risk of being granted DP [24]. We are aware that use of antidepressants or anxiolytics can only be regarded as a surrogate marker of mental health. We had no clinical observations except the haematological diagnosis, hence caution is necessary when comparing the findings to results based on self-reporting or to studies where anxiety and/or depression has been evaluated by other methods, i.e. evaluation by health professionals, audit of patient records, or central databases such as the NPR.

Strengths and limitations

One of the strengths of our study is the use of population-based registries with complete follow-up. This enabled us to describe the risk of DP among patients with haematological malignancies in a relatively large unselected population. The design was prospective allowing us to evaluate temporal associations, and all patients between 19 and 55 years of age diagnosed between 2000 and 2007 were eligible for inclusion. The fact that information on all variables was obtained through registers reduced the risk for recall and selection bias, and finally the risk of measurement bias due to misclassification of the outcome is modest, since we assume that DREAM has a 100% coverage of granted DPs in Denmark [25].

However, the study also has some limitations. First, the multivariable analyses were performed under the assumption that except for the patient/reference cohort there was no interaction between any other variables. It would have been relevant to perform analyses stratified on age groups and on diagnosis in order to investigate if the associations differed according to these variables. However, due to the limited number of individuals in each age group and diagnosis sub-group, we were not able to make this stratification.

Second, for some of the explanatory variables there were missing values. The multivariable analyses were performed as complete-case analyses, and therefore cases with missing data were not included

in the analyses. However, the amount of missing data was modest, and we assume that they were missing at random. Therefore we do not expect that this issue has biased our estimates.

Third, the reference cohort was sampled, so that individuals could not develop haematological malignancies during the inclusion period. The reference cohort was therefore potentially "more healthy" than the patient cohort. Due to the low incidence of haematological malignancies in the general population, we do, however, expect this potential selection bias to have little impact on our study.

Finally, we had no access to data on disease status (complete or partial remission), which could also have had an impact on labour market participation. Unfortunately, this was also the case for type of treatment, and even though treatment clearly is related to the diagnosis, important associations may be overlooked.

Similarly, we had no information on self-reported symptoms of late effects like physical impairments, fatigue, anxiety and depression, which in several studies have been shown to be endemic among patients with haematological malignancies [26]. Future studies might combine register-based data sources with data from questionnaires in order to explore the association between these factors and labour market participation.

Conclusion

In conclusion, patients with all eight subtypes of haematological malignancies had a higher risk of DP compared to the reference cohort. The risk differed between the subtypes of haematological malignancies and the relative risk of DP was highest for patients with multiple myeloma.

In the patient cohort we found that gender, age, ethnicity, educational level, household income, history of long-term sick leave, comorbidity and need of treatment with anxiolytics or antidepressants after diagnosis were associated with risk of DP. However, the haematological malignancy seemed to reduce the influence of most of these factors, since they were stronger in the reference cohort.

The results of this study imply that clinicians should be aware that the risk of permanently reduced work capacity differs between subtypes of haematological cancer. This knowledge is important in order to initiate early targeted rehabilitation interventions aimed at preventing permanently reduced work capacity and maintaining appropriate labour market participation if possible. Furthermore, the results indicate that clinicians should acknowledge that even though the patterns of risk factors for DP in patients with haematological cancer are similar to those in the general population they are not necessarily as dominant, and therefore attention should also be paid to haematological cancer patients who are not exposed to risk factors that are generally known to be associated with a higher risk of DP.

Future studies should focus on which rehabilitations interventions that are feasible and effective for different cancer types and treatments taking age, gender, comorbidity and socioeconomic factors into account.

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Paper III

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Type of hematological malignancy is crucial for the return to work prognosis: a register-based cohort study

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Abstract
Purpose The aims of this study were to determine the proportion of return to work (RTW) among sick-listed patients diagnosed with one of eight subtypes of hematological malignancies; to evaluate the influence of type of hematological malignancy, comorbidity, use of anxiolytics and antidepressants, socioeconomic and demographic factors on RTW; and to investigate if these associations differ between genders.
Methods We combined data from national registers on all Danish patients diagnosed with hematological malignancies between 2000 and 2007. A total of 1,741 patients on long-term sick leave were followed until RTW, emigration, permanent withdrawal from the labor market, death, or February 2012, whichever came first.
Results A total of 1,140 (65 %) patients returned to work. A strong association was found between type of diagnosis and RTW ($p<0.001$), and the proportion of RTW was lowest for patients with multiple myeloma or acute leukemia compared to patients with Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, chronic myeloid leukemia, and chronic lymphoid leukemia. Use of antidepressants or anxiolytics after diagnosis, gender, age, and educational level were also associated with RTW. Surprisingly, comorbidity was not associated with RTW ($p=0.94$); gender only modified the association between age and RTW.
Conclusion Two thirds of patients with hematological malignancies on sick leave RTW. A number of factors seem to lead to a poor prognosis, the hematological diagnosis being the most important, and these should be taken into account when performing studies on work outcome for patients with hematological malignancies.
Implications for Cancer Survivors Knowledge in this area should assist in identification of hematological cancer patients at risk of not returning to work so that early targeted rehabilitation interventions can be initiated.

Keywords Cancer epidemiology · Register-based · Cohort study · Hematological malignancies · Return to work

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Introduction

In recent years, treatment of hematological malignancies (leukemia, lymphoma, and multiple myeloma) has improved markedly resulting in an increased number of survivors [1]. More than one third of patients diagnosed with hematological malignancies are between 20 and 64 years of age [2]. Some will have difficulties returning to work life, affecting

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the income of survivors and their families as well as potentially impacting on psychological and social well-being [3].

Studies have reported that patients with hematological malignancies are at increased risk of having work-related problems. Two Norwegian studies compared work outcome for survivors of different cancer types with cancer-free control groups. They found that 5 years after diagnosis, survivors from lymphoma had more sick leave compared with the control group [4], and that the probability of being employed after diagnosis was lower for survivors of leukemia and non-Hodgkin lymphoma compared to a control group [5]. Similarly, a Danish study found that patients with leukemia had a threefold increased risk and patients with non-Hodgkin lymphoma a twofold increased risk of disability pension compared to cancer-free controls [6]. Finally, previous studies have found that patients with hematological malignancies are among those at greatest risk of higher sickness absence, unemployment, and work-related disability in comparison to patients with solid tumors [7–9].

However, studies on work outcome for patients with hematological malignancies are sparse [10] and in all the above-mentioned studies, patients with these malignancies only comprised one to three minor subgroups of the total study population and diseases with different prognosis and treatment was grouped according to older classifications into "leukemias" and "non-Hodgkin-lymphomas".

Previous studies suggest that socioeconomic and demographic factors, work demands, diagnosis, and treatment as well as symptoms and functional level after cancer and treatment are potentially associated with work outcome for patients with hematological malignancies. The few existing studies have different conclusions and most of them have important methodological limitations [11]. If cancer patients at risk of not returning to work could be identified, early targeted interventions could be initiated in those patients at highest risk of work-related problems.

This register-based cohort study aimed to:

- Determine the proportions of return to work (RTW) among patients diagnosed with eight clinical relevant subtypes of hematological malignancies between 2000 and 2007 who were on long-term sick leave following diagnosis
- Evaluate the influence of type of hematological malignancy, comorbidity, use of anxiolytics and antidepressants, and socioeconomic and demographic factors on RTW
- Investigate if these associations differ between genders

Material and methods

Source population

In Denmark, the entire population has access to tax-financed health care. A considerable amount of health-related information is recorded in national population-based registers. Accurate and unambiguous linkage of register data at the individual level is possible by means of a unique civil registration number assigned to all Danish citizens [12, 13]. The study period proceeded from 1 January 2000 to 26 February 2012 within the entire Danish population of approximately 5.6 million inhabitants.

Identification of the study population

During a period from 1 January 2000 to 31 December 2007, we identified patients diagnosed with hematological malignancies in the Danish Cancer Registry. The registry contains data on the incidence of cancer in the Danish population since 1943; registration is carried out by multiple notifications from different data sources, which secures a high degree of completeness [12, 14]. Cases with hematological malignancies were identified according to the International Classification of Disease (ICD-10) and time of diagnosis. Information regarding morphology was also obtained. We categorized hematological malignancies into Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), multiple myeloma (MM), acute leukemia (acute lymphoid leukemia (ALL)/acute myeloid leukemia (AML)), chronic myeloid leukemia (CML), chronic lymphoid leukemia (CLL), and others.

We only included patients at the age of 19–55 years, who had a job, and were on sick leave for more than 2 weeks within 12 weeks after diagnosis. Patients were followed until RTW, emigration, permanent withdrawal from labor market, death, or 26 February 2012, whichever came first.

Outcome

Denmark has a high level of social security and the main part of the welfare system is tax-financed. Social security covers the entire Danish population; if a citizen is not able to work due to physical or mental disability, the state is obligated to support the person financially through welfare benefits (sick leave benefits, disability pension, etc.).

In this study, information on welfare benefits was obtained from the Danish Register for Evaluation of Marginalisation (DREAM), which contains weekly information on welfare benefits at an individual level [15].

As regarding sick leave benefits, the threshold to enter DREAM between 2000 and 2007 was sick leave for more than two consecutive weeks, because the employer paid the first two consecutive weeks of sick leave. From the third consecutive week of sick leave, the employee was supported by tax-paid sick leave benefits registered in DREAM.

In this study, RTW was defined as the first period of four consecutive weeks without receiving sick leave benefits or other welfare benefits [16]. Patients who received unemployment benefits for at least 4 weeks were also considered to

have returned to work under the assumption that these individuals were capable of working. Information on death and emigration was also obtained from DREAM.

Demographic factors

Age at the time of diagnosis and gender were coded using the civil registration number and information on ethnicity was obtained from DREAM.

Socioeconomic factors

Information on family type, household income, educational level, and housing tenure was obtained from Statistics Denmark [17–19]. These data are updated once annually. We obtained information on educational level from 1 October the year before diagnosis; family type, household income, and housing tenure were assessed on 1 January at the year of diagnosis.

Use of anxiolytics or antidepressants

Use of anxiolytics or antidepressants was used as an indicator of mental health status following diagnosis. In order to investigate whether patients who were exposed to either anxiolytics or antidepressants after diagnosis developed a different RTW course than non-exposed patients, we obtained data on the prescription-based use of these drugs. Data was obtained from the Danish National Prescription Registry, which contains information on all dispensed prescriptions since 1994. These data include the type and amount of drug prescribed according to the Anatomical Therapeutical Chemical Classification System (ATC) and the date of drug redemption. Data are transferred from the pharmacies to the register, which thus includes all reimbursed drugs at the level of the individual user [20].

The ATC codes of interest for this study were antidepressants (N06A) and anxiolytics (N05B); it was registered if the patients were prescribed these types of medication during the first 3 years following diagnosis. Since we were only interested in the impact of exposure following hematological diagnosis, individuals to whom antidepressants or anxiolytics were prescribed the year before diagnosis, were considered non-users.

Comorbidity

Data on comorbidity was obtained from the Danish National Patient Register, which includes information on all hospital admissions in Denmark since 1977, as well as contacts to emergency rooms or outpatient clinics since 1995. Diagnostic information has been coded by physicians according to the ICD-10 codes since 1994 at each contact [12, 21, 22].

We computed a Charlson index score on the basis of the diagnoses recorded in the Danish National Patient Register for each patient in a 5-year period before diagnosis [23]. This index is considered to be a valid and reliable method to measure comorbidity [24]. A weight is assigned to define categories of co-morbid diseases and the index is the sum of these weights (from 0 to 6). Since we only had few patients with high levels of comorbidity prior to diagnosis, we classified comorbidity into only two groups according to the Charlson index score: 0 (no comorbidity) and >0 (comorbidity).

Statistics

The association between socioeconomic, demographic and clinical factors, and RTW was studied. Cumulative incidence curves were computed to illustrate the course of RTW according to type of hematological malignancy. By use of Cox proportional hazards regression, crude and adjusted hazard ratios (HR), and associated 95 % confidence intervals (CI) were estimated. The proportional hazards assumption was evaluated by assessing log-minus–log survivor curves. We used Wald tests to test the overall association between each independent variable and RTW.

In the first model, independent variables included diagnosis (HL, DLBCL, FL, MM, AML/ALL, CML, CLL, and others), comorbidity (0, 0<), gender (male or female), age (19–35, 36–40, 41–45, 46–50, or 51–55 years), highest attained educational level (basic school/high school, vocational education, or higher education), household income (low income, first quartile; middle income, second and third quartiles; and high income, fourth quartile), ethnicity (Danish citizens, immigrants or descendants from western countries, or immigrants or descendants from nonwestern countries), family type (single or couple, with and without children), and housing tenure (owner occupied, rental). The household income was given after taxation and adjusted for number of persons in the household with the following formula: household income/(no. of persons in household$^{0.6}$) [25].

In a second model, the same variables were included, but the analysis was stratified on gender. In order to test if gender modified the associations between independent variables and RTW, we incorporated gender interaction terms on all the other independent variables in the model. Wald test was then used to test for overall interaction between the genders and all the other independent variables. We also performed tests for interaction between gender and each of the other independent variables separately. Furthermore, we tested for gender interaction by using the first model and including an interaction term between gender and each of the other independent variables one at a time (without including other interactions).

The same steps were conducted with use of antidepressants or anxiolytics after diagnosis (entered as a time-

dependent variables and categorized as yes/no) as the main independent variable and adjusted for all covariates included in the first model. Death and permanent withdrawal from the labor market were considered as competing events to RTW in all the analyses.

Some of the hematological diagnoses (i.e., CLL or FL) might not result in sick leave immediately after diagnosis. However, due to the character of both disease and treatment, some of these patients will probably be sickness absent later on in the course. In recognition of this, we repeated the analyses extending the inclusion period to 3 years instead of 12 weeks in order to investigate if this had any impact on the results. Further, we examined if the results changed when we prolonged the 2 weeks sick leave inclusion criterion to 4 weeks. A last sensitivity analysis was performed in order to investigate the impact of the definition of RTW by repeating the analysis defining RTW as both 8 and 12 weeks without receiving welfare benefits.

Results

A total of 3,616 patients between 19 and 55 years (median age, 46 years; 42 % women and 58 % men) were diagnosed with hematological malignancies during the inclusion period. We excluded 979 patients as they were not active on the labor market at the time of diagnosis and another 896 patients were excluded as they were not on long-term sick leave following the diagnosis. Thus, a total of 1,741 patients on long-term sick leave were included in the study. The median age were 46 years ranging from 19 to 55 years; 41 % women and 59 % men.

RTW

Among the 1,741 patients who were on long-term sick leave, 1,140 patients (65 %) returned to work during the study period (Table 1). In all, 43 % returned to work during the first year, 60 % during the 2 years, and finally 64 % had returned to work after 4 years. Among those that did not RTW, 270 (16 %) died, 323 (19 %) left the labor market permanently, 1 (0.1 %) emigrated from Denmark, and 7 (0.4 %) were censured at the end of follow-up the period. For those that returned to work, the median time to RTW was 37 weeks (interquartile range, 21–57).

When excluding those who died, 77 % of the survivors returned to work (Table 1); 48 % during the first year after diagnosis, 70 % during 2 years, and finally 76 % had returned to work after 4 years.

Type of hematological malignancy

Figure 1 illustrates that the cumulative incidence of RTW differed by type of hematological malignancy. The highest incidence of RTW was found for patients with HL and the lowest for patients with MM and AML/ALL.

This was confirmed by the Cox regression analyses, where we found an association between diagnosis and RTW ($p<0.001$); RTW rates for patients with MM and patients with AML/ALL were lower than RTW rates for patients with HL (adjusted HR, 0.37; 95 % CI, 0.27–0.49 and adjusted HR, 0.44; 95 % CI, 0.36–0.54) (Table 2). The type of hematological malignancy was found to be associated with RTW for both men and women (Table 3).

Comorbidity and use of anxiolytics and antidepressants

No association was found between comorbidity and RTW ($p=0.94$; Table 2) and this was the case for both men and women (Table 3). The use of antidepressants or anxiolytics after diagnosis was found to be associated with RTW ($p<0.001$); thus, those who were prescribed antidepressants or anxiolytics within 3 years after diagnosis of hematological

Table 1 Patient outcome stratified by type of hematological malignancy

Diagnosis	*n* (%)	Emigrated *n* (%)	Permanent withdrawal *n* (%)	Dead *n* (%)	Followed until the end of study *n* (%)	RTW *n* (%[a]/%[b])
HL	289 (100)	0	19 (7)	13 (4)	1 (0.4)	256 (89/93)
DLBCL	293 (100)	0	35 (12)	42 (14)	1 (0.3)	215 (74/86)
FL	163 (100)	0	36 (22)	8 (5)	1 (0.6)	118 (72/76)
MM	195 (100)	0	98 (50)	35 (18)	0	62 (32/39)
AML/ALL	305 (100)	1 (0.3)	44 (14)	102 (34)	2 (0.7)	156 (51/77)
CML	79 (100)	0	20 (25)	4 (5)	1 (1)	54 (69/72)
CLL	84 (100)	0	15 (18)	5 (6)	0	64 (76/81)
Others	333 (100)	0	56 (17)	61 (18)	1 (0.3)	215 (65/79)
In all	1,741 (100)	1 (0.1)	323 (19)	270 (16)	7 (0.4)	1,140 (65/77)

[a] Proportion of RTW among the 1,741 included patients (death are considered as not returned to work)

[b] Proportion of RTW among survivors (those who died before they returned to work were excluded)

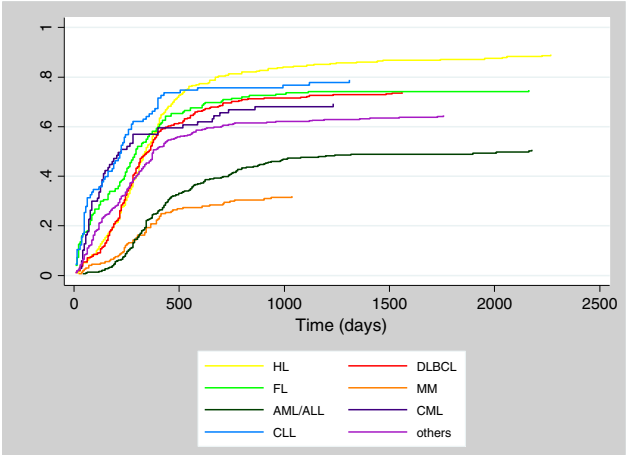

Fig. 1 Cumulative incidence of RTW by type of hematological malignancy (death and permanent withdrawal from labor market are considered as competing events)

malignancies were less likely to RTW compared to those who were not prescribed these types of medication (adjusted HR, 0.65; 95 % CI, 0.54–0.78). The same relationship was found when looking at the use of antidepressants (adjusted HR, 0.63; 95 % CI, 0.48–0.81) and anxiolytics (adjusted HR, 0.74; 95 % CI, 0.59–0.91) separately. Gender was not found to modify this association (data not shown).

Socioeconomic and demographic factors

Gender was found to be associated with RTW ($p<0.001$) as women had lower RTW rates than men (adjusted HR, 0.72; 95 % CI, 0.64–0.82; Table 2). There was a tendency that gender significantly modified the association between age and RTW ($p=0.03/0.20$). However, age was associated with RTW for both men ($p=0.02$) and women ($p=0.04$; Table 3).

Educational level also influenced the RTW rate ($p=0.007$) and patients with higher education had higher RTW rates than patients with vocational education (adjusted HR, 1.27; 95 % CI, 1.09–1.47; Table 2).

There was a tendency towards a positive association between household income and RTW, though not significant ($p=0.089$). Neither ethnicity nor family type or housing tenure was associated with RTW (Table 2).

Gender differences

The only association that was significantly modified by gender was the association between age and RTW, and this was just a tendency since we only found significant interaction when allowing for interaction between all factors and gender ($p=0.03$), whereas no association was found when allowing for interaction between only age and gender ($p=0.20$; Table 3). Furthermore, no overall gender interaction was found ($p=0.09$), which also indicates that gender did not modify the associations between the independent variables and RTW in a considerable matter.

Sensitivity analyses

An additional 283 patients were included in the analyses when changing the inclusion period from 12 weeks to 3 years, and the proportion of RTW changed from 72 to 66 % for patients with FL and from 32 to 37 % for patients with MM. Other estimates remained unchanged (data not shown).

In the sensitivity analysis with 4 weeks of sick leave as inclusion criterion instead of 2 weeks, 1,629 patients were included. However, by and large, both absolute and relative estimates remained unchanged (data not shown).

When defining RTW as 8 and 12 weeks without receiving welfare benefits, the proportions of RTW decreased slightly; 65 % returned to work during the follow-up period when RTW was defined as 4 weeks without receiving welfare benefits. When prolonging the period to 8 and 12 weeks, the proportion of RTW was 64 and 62 %, respectively. Relative estimates remained almost unchanged (data not shown).

Discussion

In this nationwide register-based cohort study on RTW among 1,741 patients with hematological malignancies on long-term sick leave, we found that 65 % of the patients returned to work during the follow-up period. The type of diagnosis, use of antidepressants or anxiolytics after diagnosis,

Table 2 Cox proportional hazard regression analyses of RTW for the entire patient cohort

	N=1,741 (%)	HR_{crude} (95 % CI)	HR_{adj}[a] (95 % CI)	*p*
Diagnosis				
HL	289 (17)	1	1	<0.001
DLBCL	293 (17)	0.92 (0.77–1.10)	0.90 (0.74–1.09)	
FL	163 (9)	0.91 (0.73–1.13)	0.93 (0.73–1.17)	
MM	195 (11)	0.36 (0.27–0.47)	0.37 (0.27–0.49)	
AML/ALL	305 (17)	0.48 (0.39–0.59)	0.44 (0.36–0.54)	
CML	79 (5)	1.00 (0.75–1.34)	1.04 (0.77–1.41)	
CLL	84 (5)	1.20 (0.91–1.58)	1.21 (0.90–1.62)	
Others	333 (19)	0.87 (0.72–1.04)	0.85 (0.70–1.04)	
Comorbidity				
0	1,531 (88)	1	1	0.94
0<	210 (12)	0.97 (0.80–1.17)	1.01 (0.83–1.23)	
Gender				
Male	1,031 (59)	1	1	<0.001
Female	710 (41)	0.78 (0.69–0.88)	0.72 (0.64–0.82)	
Age				
19–35 Years	345 (20)	1.02 (0.82–1.23)	0.96 (0.78–1.17)	0.02
36–40 Years	213 (12)	1.10 (0.89–1.37)	0.95 (0.76–1.19)	
41–45 Years	285 (16)	1	1	
46–50 Years	360 (21)	1.19 (0.98–1.43)	1.08 (0.89–1.31)	
51–55 Years	538 (31)	0.92 (0.76–1.10)	0.79 (0.64–0.97)	
Educational level				
Basic school/high school	504 (28)	1.02 (0.88–1.18)	1.09 (0.94–1.26)	0.007
Vocational education	726 (42)	1	1	
Higher education	483 (29)	1.27 (1.11–1.46)	1.27 (1.09–1.47)	
Missing	28 (1)	–	–	
Household income				
Low (first quartile)	434 (25)	0.96 (0.83–1.10)	0.90 (0.77–1.05)	0.089
Medium (two to third quartiles)	868 (50)	1	1	
High (fourth quartiles)	434 (25)	1.09 (0.95–1.25)	1.12 (0.96–1.30)	
Missing	5 (0)	–	–	
Etnicity				
Danish	1,616 (93)	1	1	0.43
Western	67 (4)	1.09 (0.80–1.47)	1.09 (0.80–1.50)	
Nonwestern	58 (3)	0.79 (0.57–1.10)	0.81 (0.57–1.16)	
Family type				
Couple with children	795 (46)	1	1	0.26
Couple without children	490 (28)	0.87 (0.76–1.00)	0.97 (0.82–1.14)	
Single with children	85 (5)	0.85 (0.64–1.13)	1.14 (0.84–1.54)	
Single without children	366 (21)	0.84 (0.72–0.97)	0.86 (0.73–1.03)	
Missing	5 (0)	–	–	
Housing tenure				
Owner occupied	1,212 (70)	1	1	0.61
Rental	497 (28)	0.89 (0.78–1.01)	0.96 (0.83–1.12)	
Missing	32 (2)	–	–	

[a] All variables in the table are mutually adjusted

gender, age, and educational level were associated with RTW rates, and gender only modified the association between age and RTW significantly.

In previous studies, a wide range of proportions of RTW after cancer have been reported. In a systematic review on employment after cancer, a mean of 63.5 % of the participants (range, 24–94 %) managed to RTW depending on the period of time after cancer treatment [26]. Similarly, a Dutch study by Roelen et al. including 297 patients with leukemia and lymphoma found that 62 % of the patients had returned

Table 3 Cox proportional hazard regression analyses of RTW for the patient cohort stratified by gender

	Male				Female				Difference between male and female
	N=1,031 (%)	HR_{crude} (95 % CI)	HR_{adj}[a] (95 % CI)	*p*	*N*=710 (%)	HR_{crude} (95 % CI)	HR_{adj}[a] (95 % CI)	*p*	p^b/p^c
Diagnosis									
HL	163 (16)	1	1	<0.001	125 (18)	1	1	<0.001	0.20/0.51
DLBCL	193 (19)	0.97 (0.77–1.23)	1.05 (0.82–1.35)		101 (14)	0.80 (0.59–1.08)	0.73 (0.53–1.00)		
FL	86 (8)	1.08 (0.81–1.45)	1.15 (0.84–1.57)		77 (11)	0.77 (0.55–1.07)	0.67 (0.47–0.97)		
MM	108 (10)	0.42 (0.29–0.60)	0.46 (0.32–0.67)		87 (12)	0.28 (0.18–0.45)	0.24 (0.15–0.39)		
AML/ALL	181 (18)	0.51 (0.40–0.66)	0.48 (0.37–0.63)		124 (17)	0.42 (0.31–0.58)	0.38 (0.27–0.52)		
CML	42 (4)	1.37 (0.94–2.01)	1.44 (0.98–2.13)		37 (5)	0.70 (0.44–1.12)	0.70 (0.43–1.13)		
CLL	52 (5)	1.17 (0.82–1.67)	1.36 (0.92–1.99)		32 (4)	1.19 (0.78–1.83)	1.03 (0.65–1.63)		
Others	206 (20)	0.91 (0.72–1.15)	0.96 (0.75–1.24)		127 (18)	0.77 (0.58–1.04)	0.72 (0.52–0.98)		
Comorbidity									
0	897 (87)	1	1	0.55	634 (89)	1	1	0.70	0.50/0.21
0<	134 (13)	0.87 (0.68–1.10)	0.93 (0.72–1.19)		76 (11)	1.14 (0.84–1.55)	1.07 (0.77–1.48)		
Age									
19–35 Years	211 (20)	1.03 (0.80–1.31)	1.05 (0.80–1.37)	0.02	134 (19)	0.95 (0.71–1.27)	0.82 (0.59–1.13)	0.04	0.03/0.20
36–40 Years	125 (12)	1.13 (0.86–1.50)	1.01 (0.76–1.36)		88 (12)	1.04 (0.73–1.46)	0.84 (0.58–1.20)		
41–45 Years	150 (15)	1	1		135 (19)	1	1		
46–50 Years	212 (20)	1.06 (0.82–1.36)	0.95 (0.73–1.23)		148 (21)	1.35 (1.01–1.82)	1.28 (0.95–1.75)		
51–55 Years	333 (32)	0.85 (0.67–1.08)	0.70 (0.54–0.92)		205 (29)	0.95 (0.71–1.27)	0.93 (0.67–1.29)		
Educational level									
Basic school/ high school	293 (28)	1.06 (0.88–1.27)	1.12 (0.93–1.35)	0.01	211 (30)	1.00 (0.79–1.27)	1.04 (0.82–1.33)	0.42	0.65/0.41
Vocational education	470 (46)	1	1		256 (36)	1	1		
Higher education	245 (24)	1.46 (1.21–1.75)	1.34 (1.11–1.63)		238 (33)	1.19 (0.95–1.48)	1.17 (0.92–1.48)		
Missing	23 (2)	–	–		5 (1)	–	–		
Household income									
Low (first quartile)	265 (26)	0.85 (0.71–1.02)	0.79 (0.65–0.97)	0.03	169 (24)	1.13 (0.87–1.42)	1.14 (0.88–1.49)	0.28	0.092/0.081
Medium (two to third quartiles)	512 (50)	1	1		356 (50)	1	1		
High (fourth quartile)	250 (24)	1.01 (0.84–1.21)	1.07 (0.88–1.30)		184 (26)	1.24 (0.99–1.56)	1.20 (0.94–1.53)		
Missing	4 (0)	–	–		1 (0)	–	–		
Etnicity									
Danish	966 (94)	1	1	0.79	650 (92)	1	1	0.46	0.28/0.86
Western	36 (3)	1.05 (0.69–1.59)	1.03 (0.67–1.58)		31 (4)	1.16 (0.75–1.81)	0.19 (0.74–1.92)		
Nonwestern	29 (3)	0.86 (0.55–1.34)	0.85 (0.52–1.39)		29 (4)	0.76 (0.47–1.24)	0.77 (0.46–1.29)		
Family type									
Couple with children	476 (46)	1	1	0.21	319 (45)	1	1	0.97	0.63/0.18
Couple without children	270 (26)	0.82 (0.69–0.99)	0.92 (0.74–1.14)		220 (31)	0.96 (0.77–1.20)	1.00 (0.77–1.30)		
Single with children	25 (3)	0.81 (0.48–1.36)	0.97 (0.57–1.66)		60 (8)	1.02 (0.72–1.45)	1.10 (0.74–1.66)		
Single without children	256 (25)	0.76 (0.63–0.91)	0.80 (0.65–0.98)		110 (16)	0.92 (0.70–1.22)	1.03 (0.75–1.43)		
Missing	4 (0)	–	–		1 (0)	–	–		
Housing tenure									
Owner-occupied	722 (70)	1	1	0.18	490 (69)	1	1	0.58	0.21/0.065
Rental	287 (28)	0.83 (0.70–0.98)	1.14 (0.94–1.37)		210 (30)	0.99 (0.80–1.22)	0.93 (0.73–1.19)		
Missing	22 (2)	–			10 (1)	–	–		

[a] All variables in the table are mutually adjusted

[b] Wald test for interaction (between all factors and gender)

[c] Wald test for interaction (between gender and each independent variable one at a time)

to work 2 years after diagnosis [8]. This proportion is similar to the results of this present study, where 60 % returned to work during the first 2 years after diagnosis.

Previous studies have documented that patients with hematological malignancies are at increased risk of having work-related problems compared to cancer-free control groups [4–6] and patients with other cancer types [7–9]. In this study, we found that the type of hematological malignancy also was strongly associated with RTW rates. Patients with MM or AML/ALL had the lowest incidence of RTW, and they had considerable lower RTW rates than patients with HL. To the best of our knowledge, this is the first study on work outcome for patients with hematological malignancies that have been large enough to stratify data into more than four subtypes of diagnosis. In earlier studies, patients diagnosed with hematological malignancies only comprised one to four minor subgroups of the total study population; hematological malignancies with different treatment and prognoses were mixed. Thus, different diseases like CLL, CML, and acute leukemias has often been grouped together as "leukemias"; FL, DLBCL, and lymphoblastic lymphomas has been grouped under the term "non-Hodgkin lymphomas". This may make sense from a biological view, and from the view of a pathologist, but it makes little sense when you look at the diseases from the point of prognosis or treatment. Based on our results, there is a clear need to distinguish between different types of leukemia and different lymphoproliferative diseases. Our choice of grouping the types of diagnoses is of course debatable, but this study has been able to divide hematological malignancies into comprehensive subgroups and we have clearly shown that RTW is highly dependent on the type of hematological malignancy.

Surprisingly, we did not find an association between comorbidity and RTW. To the best of our knowledge, this has not been investigated in previous studies on patients with hematological malignancies and RTW. Carlsen et al. have evaluated the association between comorbidity and unemployment and early retirement pension for cancer patients in general, and they found that comorbidity was associated with the risk of early retirement pension but not with unemployment [6, 27].

We also found that when patients were prescribed antidepressants or anxiolytics after diagnosis, their RTW rates became lower than the RTW rates for patients to whom these types of medication were not prescribed. Only a few studies have investigated this association. An American cohort study by Syrjala et al. included 263 patients with different types of hematological malignancies treated with hematopoietic cell transplantation and did not find an association between self-reported symptoms of depression and RTW [28]. The presence of depression was measured using a validated self-reporting scale, which might explain the diverging results. In contrast, we only had information on exposure to antidepressants or anxiolytics, and hence, our data must be interpreted with caution. First of all, we must consider bias by indication as some of the patients might have been prescribed these drugs due to mental distress by getting a cancer diagnosis. Secondly, patients treated with either antidepressants or anxiolytics are not necessarily suffering from clinical depression or anxiety and this possible misclassification may have led to an overestimation of the actual number of patients with a clinical diagnosis of anxiety and depression. Therefore, the information on use of antidepressants or anxiolytics used in this study can only be interpreted as an indicator of mental health status, not as an expression of presence of clinical diagnoses of depression or anxiety.

We found that female gender, high age, and vocational education were associated with low RTW rates. No associations were found for household income, ethnicity, family type, and housing tenure. Results on the association between RTW and socioeconomic and demographic factors are diverging in other studies on patients with hematological malignancies. Still, in previous cohort studies, female gender has been shown to be associated with low RTW rates [11]. Unlike the present study, however, earlier cohort studies did not find an association between neither age nor educational level and RTW among patients with different types of hematological malignancies. The diverging results are most likely due to different patient populations. Hence, two of the studies are limited to mixed populations of patients with hematological malignancies treated with autologous or allogeneic hematopoietic cell transplantation [28, 29]; this is a small subgroup to the population in our study, which complicates a comparison. The picture is also unclear when considering studies on factors associated with RTW for patients with cancer in general. However, similar to our results, several studies found young age, higher education, and male gender to be positively associated with RTW [26].

Similar to our study, a recent published study found gender to modify the association between age and RTW among patients diagnosed with various cancer sites. In that study, however, gender was also found to have influence on the association between cohabitation status and RTW as married men returned to work faster than married women. Like in our study, gender was not found to modify the association between neither educational level nor income and RTW [30].

Strengths and limitations of the study

One of the strengths of our study is the use of population-based registries with complete follow-up. This enabled us to describe RTW among patients with hematological malignancies in a relatively large unselected population. The design was prospective allowing us to evaluate temporal associations and, further, all patients between the age of 19 and 55 diagnosed between 2000 and 2007 were eligible for inclusion. Finally, the fact that information on all the variables

was obtained through registers reduced the risks of recall and selection bias.

However, the study also has some limitations. First, we defined RTW as not receiving welfare benefits for four consecutive weeks. This definition might have caused misclassification of the outcome in the study, since we could have misclassified individuals as returned to work, if they were supported by their partner or parents at least 4 weeks following a period of sick leave. We do consider this as a rare scenario and we are aware that a possible misclassification will have caused an overestimation of the proportion of RTW in our study.

Another limitation is that the multivariable analyses were performed under the assumption that except for gender, there was no interaction between any other variables. It would have been relevant to perform analyses stratified on age groups and diagnoses. However, due to the limited number of individuals in each age group and diagnosis subgroup, we were not able to do this.

It is important to remember that this study focused on acute long-term sick leave following diagnosis. Long-term sick leave was here defined as 2 weeks of sick leave. This choice was conservative, i.e., as short as possible to include as many as possible with sick leave due to cancer. Sick leave periods shorter than 2 weeks were not registered in DREAM. However, the cause of sick leave is not registered in DREAM and some of the patients may have been listed as sick due to other reasons than cancer. Maybe such erroneous inclusion could have been reduced if longer sick leave periods had been used as inclusion criterion. However, we consider the risk of competing causes for 2 weeks sick leave as small within the 12 first weeks after cancer diagnosis. As mentioned earlier, some of the hematological malignancies causes sick leave for some of the patients later than within 12 weeks after diagnosis and these patients were not included in this study. However, our analyses with a prolonged inclusion period did not change the estimates.

Unfortunately, we had no access to data on disease status (complete or partial remission), which may also have an impact on work life. This was also the case for type of treatment; even though treatment clearly is related to the diagnosis, important associations may be overlooked. For instance, you would expect a difference in populations of patients with CLL or FL if there was a large difference in the use of aggressive first-line therapies versus a principle of wait and watch.

Similarly, we had no information on self-reported symptoms of late effects like physical impairments, fatigue, anxiety, and depression, which in several studies have shown to be endemic among patients with hematological malignancies [31–33]. Future studies might combine register-based data sources with data from questionnaires in order to explore the association between these factors and work outcome. Another task in future studies is to investigate work life situation for the entire population of patients with hematological malignancies, including those without a job at diagnosis. This could be done by determining the risk of long-term work disability in a cohort of patients diagnosed with hematological malignancies compared to a reference cohort without a history of these cancer types.

In conclusion, two thirds of patients with hematological malignancies on long-term sick leave RTW. A number of factors seem to herald a poor prognosis, the hematological diagnosis being the most important. These factors should be taken into account when performing studies on work-related issues in patients with hematological malignancies, and they may be exploited for early interventions aimed at RTW in this patient group.

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Paper IV

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

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60-word summary of policy implications and what is new in the paper
This is one of the first prospective studies to examine associations between self-reported fatigue, depression and anxiety and labour market participation among patients diagnosed with haematological malignancies. The study implies that clinicians should focus on fatigue in rehabilitation of patients with haematological malignancies. Further research is needed, before more comprehensive practical implications can be provided.

Running title: Haematological malignancies and labour market participation

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Abstract

Objectives:.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 one year follow-up, and to examine whether fatigue, depression and anxiety are associated with RTW and LTSA.

Methods: Questionnaire-based data on fatigue, depression and anxiety were obtained at baseline. In all, 196 patients returned the questionnaire and were followed prospectively for one 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 sickness absent patients returned to work during follow-up. 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. Ten (11%) working patients experienced LTSA.

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, taking time since diagnosis into account, are needed.

Key terms cancer, leukaemia, lymphoma, multiple myeloma, return to work, long-term sickness absence, mental health, risk factors, symptoms

Introduction

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 to 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 two to 12-fold higher risk of being granted disability pension compared to a reference cohort (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). However, in a recent Australian qualitative study, patients with haematological malignancies reported fatigue as the most frequent late-effect interfering in return to work (13). Two American cohort studies including 106 and 281 patients with haematological malignancies, respectively treated with hematopoietic cell transplantation found that psychological symptoms were not associated with future labour market participation (14, 15). On the other hand, two Danish register-based cohort studies including 3616 and 1741 patients diagnosed with haematological malignancies, respectively showed that need of treatment with antidepressants or anxiolytics was associated with both lower return to work rates and higher risk of being granted disability pension compared to 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.

The aims of this study were to: 1) examine levels of fatigue, depression and anxiety among sickness absent patients and patients working six to nine months following diagnosis of a haematological malignancy, 2) determine the cumulative incidence of return to work (RTW) during one year follow-up among the sickness absent patients, and to examine if fatigue, depression and anxiety are associated with RTW and 3) determine the cumulative incidence of long-term sickness absence (LTSA) during one year follow-up among the working patients, and examine if fatigue, depression and anxiety are associated with LTSA.

Material and methods

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

Administrative context

The welfare system in Denmark is tax-financed and covers all Danish citizens. If a resident is not able to work due to physical or mental disability, financial support is provided through public transfer payments (sickness absence benefits, disability pension etc.).

Subjects

All patients between 19 and 59 years of age in Denmark diagnosed with a haematological malignancy six to nine 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 1 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) (Figure 1).

Patients were identified through the Danish National Patient Register (NPR) including information on all hospital admissions in Denmark since 1977, and contacts to emergency or outpatient care since 1995. Since 1994, diagnostic information has been coded by physicians according to the ICD-10 at each contact (16). The type of haematological malignancy and date of diagnosis were validated using data from the Danish Cancer Register (CAR). This register contains highly valid data on the incidence of cancer in Denmark since 1943 (17).

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 two 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) (18) 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. Missing items were substituted by the mean of the non-missing items if no less than half of the items in the dimension were missing. Summary scores were divided into quartiles for analytic purposes (19).

The 14-item self-reported *Hospital Anxiety and Depression Scale* (HADS) (20) 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 HAD-D or HAD-A 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 (21). If one item was missing in a scale it was substituted by the mean of the non-missing items.

Covariates

Age and gender were retrieved from the Civil Registration System (CRS) (22) and comorbidity was measured using data from the NPR. A Charlson comorbidity index score was computed based on the diagnoses recorded in NPR for the five-year period before the patients were diagnosed with a haematological malignancy (23). In the Charlson index a

weight is assigned to defined categories of co-morbid diseases; the index is the sum of these weights (from 0 to 6). As only a few patients had high levels of comorbidity prior to diagnosis, 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 in weeks.

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 (24). Incidence of RTW was defined as the first period of four consecutive weeks without receiving sickness absence benefits or other social transfer payments (25, 26). 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 2 January 2012).

Statistical analyses

Baseline data on age, gender, comorbidity, diagnosis, time since diagnosis and levels of fatigue, depression and anxiety 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 one year follow-up, sickness absent patients were followed until RTW, death, emigration, permanent exit from the labour market or one year after baseline, whichever came first. To determine the cumulative incidence of LTSA during one year follow-up, working patients were followed until LTSA, death,

emigration, permanent exit from labour market or one year after baseline, whichever came first.

Using generalized linear regression models for pseudo observations (27), cumulative relative risks (RR) of RTW and LTSA including 95% confidence intervals (CI) one year after baseline were estimated for the levels of fatigue (quartiles), and depression and anxiety case classification (no case, possible case, 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 (28), 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. A RR > 1.00 indicates that patients are more likely to RTW or have an increased risk of LTSA compared to the reference, whereas a RR < 1.00 indicates that patients are less likely to RTW or have a decreased risk of LTSA.

Results

Baseline characteristics

A total of 451 patients aged 19 to 59 years were diagnosed with haematological malignancies in Denmark in the period from February 2011 to October 2011. 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 2). 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), though time since diagnosis was significantly shorter for non-responders (7.3 months) compared to responders (8.1 months).

At baseline 106 (54%) 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 to working patients. The same was observed for depression, and 15% of working patients were categorized as possible cases or subclinical cases of depression, compared to 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 to 61% among patients on sick leave ($p=0.13$) (Table 1).

Incidence of RTW

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 RTW

Patients with highest scores of Physical Fatigue were more than 50% less likely to RTW compared to 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 to 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 LTSA

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. Due to the small number of patients who experienced LTSA, we did not have sufficient power to examine associations between fatigue, depression and anxiety and LTSA.

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 (14, 15) 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 (15). The second prospective study found no association between mental health (according to SF-36) and RTW (14). 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). It is difficult to tell if the diverging results are caused by differences in study populations or study designs. With regard to the nature of the study design, the prospective design is more suitable for investigating associations than the cross-sectional study design, since exposure and outcome are measured at different time-points (32). As regarding study populations, the two previous prospective studies included populations of patients treated with hematopoietic cell transplantation, and the three cross-sectional studies, only comprised patients diagnosed with different types of lymphoma. These two patient groups differ and they are both subgroups of the study population in the present study making direct comparisons pointless.

Recently, we have published two register-based cohort studies showing that need of treatment with antidepressants or anxiolytics following diagnosis of a haematological malignancy is associated with both 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 confidence intervals and hence, we cannot entirely rule out the risk of type 2 errors. Further, it is well known that antidepressants and particularly 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 fully 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 also 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, due to the nature of both disease and treatment 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

A strength of our study is the use of self-reported data on fatigue, depression and anxiety obtained with validated scales in combination with 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). Therefore, we cannot entirely rule out residual confounding.

Forty-two of the eligible patients did not receive the questionnaire due to impaired accuracy of the NPR or because they lived at undisclosed addresses. Most likely these misrepresentations occurred at random and did not cause selection bias (33). However, 43 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 simultaneous associated with RTW rates, the selection might have biased the results towards or against the null hypothesis (32).

Finally, time since diagnosis was found to be an important confounder in this study. Time since diagnosis varied between the patients, and we found that RTW, fatigue, depression and

anxiety were associated with this variable. 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.

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 one-year follow-up. 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. Future studies should be conducted in larger populations of patients with haematological malignancies. 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 self-reported symptoms should be measured at the same time-point following diagnosis for all patients.

Ethics Statements

The study was approved by the Danish Data Protection Agency (journal number 2013-41-1921).

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We are grateful to all the patients for their participation in the study.

Conflicts of interest

None to declare

Contributions

All authors contributed to the designing of the study. T.A.H. obtained the data, and carried out the statistical analyses. N.T.A supervised the statistical analyses. T.A.H. and U.B. drafted the manuscript and C.V.N., B.N., N.T.A., and A.T. contributed with reviews and comments. All authors made significant contributions to the final manuscript.

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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 leukemia	3	(3)				15	(14)				
Chronic myeloid leukemia	5	(6)				2	(2)				
Chronic lymphoid leukemia	14	(16)				6	(6)				
Others	21	(23)				22	(21)				
Fatigue (MFI-20)											
General Fatigue (GF)			9.8	4.1	(4-19)			13.2	4.3	(4-20)	**< 0.001**
Physical Fatigue (PF)			10.1	4.4	(4-19)			13.5	4.3	(4-20)	**< 0.001**
Mental Fatigue (MF)			8.7	3.5	(4-16)			11.2	4.2	(4-20)	**< 0.001**
Reduced Activity (RA)			9.0	4.2	(4-18)			12.7	4.7	(4-20)	**< 0.001**
Reduced Motivation (RM)			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)				

Table 2 Return to work TW one 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														
1st quartile	16	(15)	1	.	0.62	1	.	0.82	1	.	0.62	1	.	0.63
2nd 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)	
3rd 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)	
4th 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														
1st quartile	14	(13)	1	.	**0.023**	1	.	**0.02**	1	.	**0.01**	1	.	**0.004**
2nd 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)	
3rd 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)	
4th 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														
1st quartile	24	(23)	1	.	0.27	1	.	0.74	1	.	0.60	1	.	0.69
2nd 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)	
3rd 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)	
4th 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														
1st quartile	17	(16)	1	.	0.07	1	.	0.19	1	.	0.21	1	.	0.19
2nd 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)	
3rd quartile	26	(25)	0.93	($0^{.6}$1-1.41)		1.05	(0.70-1.57)		1.01	0.66-1.54)		1.03	(0.61-1.75)	
4th 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														
1st quartile	28	(26)	1	.	0.73	1	.	0.89	1	.	0.85	1	.	0.90
2nd 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)	
3rd 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)	
4th 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 one year after diagnosis according to HAD-D and HAD-A case classification (N=105)

			Model 1			Model 2			Model 3		
	N	**(%)**	**RR[f]**	**(95 % CI)**	**P**	**RR[g]**	**(95 % CI)**	**P**	**RR[h]**	**(95 % CI)**	**P[i]**
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

[f] Crude estimates
[g] Adjusted for time since diagnosis
[h] Adjusted for time since diagnosis, age and gender
[i] Test for trend

Figure 1 Inclusion process

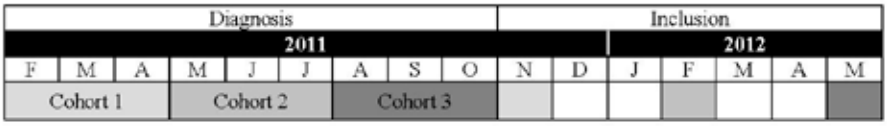

Figure 2 Flowchart of inclusion