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Quality of life in long-term Hodgkin's disease survivors with chronic fatigue

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ABSTRACT

The prevalence of chronic fatigue (CF), elevated fatigue levels >six months, is 2.5–3 times higher in long-term Hodgkin disease survivors (HDSs) than in the general population (GP). This is the first study comparing the quality of life (QoL) of chronic fatigued survivors with that of chronic fatigued subjects in the GP. The fatigue questionnaire (FQ) and the SF-36 were mailed to 591 HDSs successfully treated at the Norwegian Radium Hospital from 1971 to 1997. Patient data were compared with nationally representative GP data, adjusted for age, gender and education. The response rate was 80% ($N = 475$), median follow-up 195 months (range 53–431), mean age 46 years (range 21–74), and 44% were females. HDSs reported significantly poorer QoL than the GP with lower scores on six of eight SF-36 scales ($P < 0.001$). The subgroup of HDSs with chronic fatigue however ($N = 142/475$, 30%) had better QoL on five of eight SF-36 scales than subjects with CF in the GP ($N = 224/2141$, 11%), particularly mental health and emotional role-functioning ($P = 0.005$ and <0.0001). No differences were found on the physical SF-36 domains. Overall, HDSs reported lower QoL than the GP, in particular the HDSs with CF. Their QoL was similar to that of GP subjects with CF, but with significantly better mental health status. This suggests that CF in long-term survivors may be associated with more physical than psychological aspects of long-term cancer survivorship.

1. Introduction

More than 80% of patients diagnosed with Hodgkin's disease are now expected to live free of disease for five years or more after diagnosis [1]. However, long-term survivors are at risk of developing various late medical complications [1,2]. Consequently, more research has been devoted to objective and subjective health in Hodgkin's disease survivors (HDSs).

Fatigue is frequent among cancer patients in general [3–6] and in survivors of Hodgkin's disease in particular [7–14]. The prevalence of chronic fatigue defined as elevated fatigue levels that has lasted for six months or longer [15], has been reported as 2.5–3 times higher in Hodgkin's

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disease survivors (HDSs) relative to the general population [14,16,17] as assessed by fatigue-specific questionnaires like the Multidimensional Fatigue Inventory (MFI) [18] and the Fatigue Questionnaire (FQ) [19]. Some reports have shown that the presence of fatigue is associated with reduced working capacity and lowered engagement in leisure activities [20]. However, the association between fatigue and self-reported health or Quality of Life (QoL), the latter conceptualized as a multi-dimensional construct including physical, mental and social dimensions [21] is rarely investigated.

Fatigue characteristics do not differentiate between fatigue of psychological or physical origin, and biological markers of fatigue have not been established [22]. Thus, the subjective experience of fatigue is probably associated with different causal factors [23]. In the general population fatigue is strongly associated with psychological distress, while this correlation is weak among cancer patients in palliative care [24,25]. For example, compared to chronic fatigued subjects in the general population, chronic fatigued survivors of Hodgkin's disease have lower levels of anxiety and depression [26,27]. The findings of higher levels of fatigue in survivors of Hodgkin disease than in survivors of testicular cancer might indicate that characteristics of the cancer or its treatment has an influence on the level of fatigue after cancer cure [10,28]. However, the relationship between persisting fatigue, disease and treatment characteristics remains unclear, partly because the close connection between disease stage and type of treatment renders separate analyses difficult. A prospective study on fatigue in HDSs showed that combination treatment with radiotherapy and chemotherapy resulted in higher levels of fatigue assessed by the QoL tool SF-36 during the first year as compared to radiation therapy alone, but with similar levels after two years [11], while QoL outcomes were similar at the one year assessment. A recent study from our centre in which considerable effort was put into a novel method for quantification of the total treatment burden, did not reveal any significant association between treatment modality or intensity and persisting fatigue [17]. Presence of B-symptoms at diagnosis however, was significantly associated with CF at follow-up.

The lack of consistent findings regarding the relationship between fatigue and disease and treatment related characteristics, has lead to the proposal of conducting a broader assessment of related constructs in the assessment of cancer-related fatigue [29]. A better understanding of this state has direct clinical implications with respect to follow-up and interventions directed towards this prevalent condition in HDSs.

As far as we know, this is the first study that specifically examines how HDSs with chronic fatigue perceive their quality of life. The major objective of the present study was to assess the QoL by the SF-36 in long-term HDSs with chronic fatigue, who were treated at the Norwegian Radium Hospital from 1971 to 1997, relative to age and gender adjusted data from the general population (GP). The underlying assumption was that there would be better self-reported mental health in HDSs with CF relative to chronic fatigued subjects in the GP.

2. Patients and methods

2.1. *Patients*

The majority (92%) of Norwegian cancer patients, in the age group between 15 and 39 years of age who were diagnosed with Hodgkin's disease before 1980, received their treatment at the Norwegian Radium Hospital (NRH). The corresponding percentages in the age groups 40–59 years and 60 years and above were 80% and 53%, respectively [30]. Although the treatment of Hodgkin's disease gradually became more decentralized after 1980, the patients in this report constitute a nationally representative sample as the hospital has had treatment responsibility for more than 50% of the national patient population.

For the patients included in this report, the therapeutic regimens for HD at the NRH can largely be divided into three time periods, 1971–1979, 1980–1986, 1987–1997 [17]. During the last period in particular, radiotherapy was modified to reduce long-term side effects by reducing the fractionation from 2 Gy × 20 to 1.8 Gy × 23 and making subcarinal or individual radiation field blocks. Chemotherapy was given with ABOD (adriamycin, bleomycin, vincristin, DTIC) as the preferred regimen from 1993 for patients with extensive disease; and EBVP (epirubicin, bleomycin, vinblastin, prednison) from 1988 for patients with limited disease with risk factors. Before 1987, stage IA–IIA patients without risk factors received irradiation only, stage I–IIB patients with risk factors received four cycles of chemotherapy prior to irradiation, while stage III–IV patients received eight cycles of chemotherapy, supplemented with radiotherapy when indicated. Before 1980, mantle field or inverted – Y field radiotherapy were given for stages I and II, while patients with stage III–IV disease were treated with eight cycles of chemotherapy supplemented by radiotherapy when indicated.

Full details of the treatment regimens are described in detail elsewhere [31–33].

For study inclusion, the patients should have a histologically verified diagnosis of Hodgkin's disease and should have received treatment between 1971 and 1997 at the NRH. Further requirements at the time of study were complete remission, no treatment for recurrent Hodgkin's disease the previous year, age between 18 and 76, no secondary cancer and sufficient language skills to fill in the questionnaires.

A total of 611 patients met the inclusion criteria. Ten patients were no longer registered at the Norwegian Census Bureau and could not be contacted. Ten patients who had received the majority of their treatment in another health region and who had recently participated in another postal survey on psychosocial late effects were not contacted.

The 591 eligible patients were contacted by mail. They received a questionnaire packet consisting of among others the fatigue questionnaire [19] and the SF-36 [34]. A total of 479 returned the questionnaire packets. However, four patients had failed to fill in the questionnaires, three for the FQ and one for the SF-36, and were excluded from analyses in this report. Thus, the response rate for the questionnaires in this study was 80%. The respondents had a median age of 46 years (21–74) and 44% were females ($N = 209$).

Missing items on the completed forms were less than 0.5%. To avoid omitting patients with partially incomplete data, mean-imputation was used for scale scores if the patient had completed at least 50% of the scale, according to the methods recommended by the EORTC Manual [35]. All clinical variables were retrieved from the lymphoma data base at the NRH.

All scores on the FQ and SF-36 were compared with reference values from a Norwegian general population survey after adjusting for age, gender and educational differences [36]. In 1996, a nationwide representative sample of 3500 Norwegian adults aged 19–80 years, had received these questionnaires by mail, yielding a response rate of 67%. Women reported higher levels of total fatigue than men, and the prevalence of chronic fatigue was 11%. Total fatigue and age were weakly correlated ($r < 0.2$). The physical health scales of the SF-36 were strongly affected by age. In all scales, with the exception of general health perception, women reported poorer health than men. Only subjects from the GP within the same age range as the patients were included in the analyses ($N = 2141$).

2.2. Questionnaires

2.2.1. Fatigue Questionnaire

The Fatigue Questionnaire (FQ) [19,24,37] asks about fatigue symptoms experienced during the last month compared with how the subjects felt when they were last well. It consists of 11 items that were generated to reflect physical and mental fatigue. Judged by inspection, the items correspond well with six of the proposed criteria for cancer-related fatigue [38]. The FQ was originally validated in primary care, has demonstrated good face and discriminant validity; and good and stable psychometric properties across populations [14,19,24,36,37,39]. Physical fatigue (PF) corresponds to the subjective feeling of being exhausted and lacking energy, while mental fatigue (MF) describes the subjective feeling of being mentally exhausted, encompassing items on concentration, memory and speech. The seven items on PF and the four items on MF all have four response categories (0: “better than usual”, 1: “no more than usual”, 2: ”worse than usual” and 3: “much worse than usual”). Thus, higher scores imply more fatigue and the sum score of all 11 items is designated total fatigue (TF) with a maximum score of 33. All 11 items are also scored on a dichotomized scale (0, 0, 1, 1) for the identification of chronic fatigue [19] with a cutoff point of 4 or higher on the dichotomized scale as the cutoff for a “case definition”. However, the FQ also contains an item about the duration of fatigue (<1 week, <3 months, 3–6 months, >6 months). In addition to a dichotomized score of 4 or higher, chronic fatigue also implies duration of 6 months or longer, according to a consensus definition [15]. We have preferred to use the concept chronic fatigue instead of fatigue ‘caseness’ in this report.

2.3. The SF-36

The SF-36 is a widely used generic QoL-measure [34,40]. The 36 items are grouped into eight scales: bodily pain, general health perceptions (general health), mental health, physical functioning, role limitations due to emotional problems (role emotional), role limitations due to physical problems (role physical), social functioning and vitality. These aspects cover three QoL dimensions; physical (physical function, role physical, bodily pain), mental (mental health, role emotional, social function) and intermediate (general health, vitality). The vitality scale was not included in the analyses due to the conceptual overlap with fatigue. The correlation was above 0.7 for survivors and the population sample taken together, as well as when analyzed separately. Standard scoring guidelines were followed [34]. The items were summarized and transformed to 0–100 scales (0: worst health state, 100: best health state). Missing values in half or less of the items within a scale were substituted with person-specific values according to the SF-36 algorithm [34].

2.4. Ethical considerations

Data collection were conducted according to the guidelines of the Helsinki Declaration. The Regional Committee for Medical Research Ethics, Health region I, Norway and the institutional review board at the NRH approved the study. In addition to the FQ and SF-36, the questionnaire packet mailed to the patients contained a consent form to be signed by participants. Thus, written informed consent was obtained from all respondents.

2.5. Statistical analyses

No gold standard exists as to what are the clinically significant numerical changes on the FQ or the SF-36. Differences of 10 points or more on 0–100 points scales as with the SF-36, are generally regarded to be clinically significant changes and perceptible to patients, whereas differences of 7–10 points represent questionable clinical importance [41].

To facilitate the judgment of the magnitude of the differences between patients and the general population, standard difference scores (s-scores) were calculated by subtracting the mean scale score of the patients from the mean scale score of the general population followed by dividing this deviation by each scale’s standard deviation (SD) in the GP [42]. This approach accounts for differences in means and SDs across scales, thus making possible comparisons across scales. Mean scale scores for the GP subjects without CF were used as the standard for the s-scores presented in Fig. 1, thus GP mean scores were subtracted from patient mean scores, yielding negative differences if patient health status was inferior to that of the GP without CF. To interpret effect sizes, we followed the suggestion of Cohen [43] and regarded effect sizes of 0.2–0.5 as being small, 0.5–0.8 as moderate and 0.8 and above as large.

Standard descriptive statistics were employed: χ_2 and Kruskal–Wallis (nominal categorical variables), Wilcoxon’s test (two-tailed) for independent samples or as appropriate, one-way ANOVA for differences in background characteristics and for variables relating to the specified study objectives after checking for multicollinearity. The significance level was set to P-values $\leqslant 0.01$ because of multiple testing. Analyses were performed by the SPSS statistical software version 12.0 (SPSS Inc., Chicago, IL, USA).

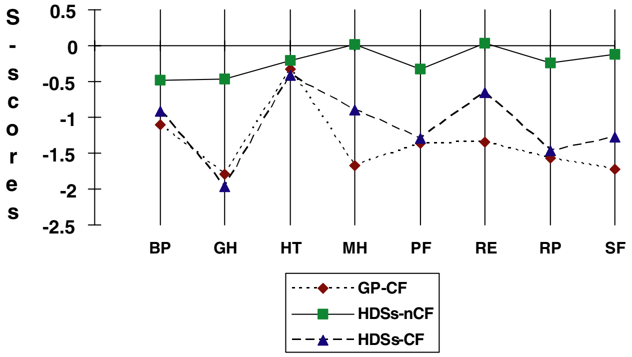

Fig. 1 – Health profiles for GP subjects with chronic fatigue (GP-CF), Hodgkin's disease survivors without chronic fatigue (HDSs-nCF) and Hodgkin's disease survivors with chronic fatigue (HDSs-CF). BP, bodily pain, GH, general health, HT, health transition, MH, mental health, PF, physical functioning, RE, role, emotional, RP, role, physical, SF, social functioning. 0-line represents GP subjects without chronic fatigue. Thus, mean scores for the GP without CF were subtracted from the mean scores of the three different groups, respectively, and the differences were divided by each scale's SD for GP subjects without CF.

3. Results

There was a higher proportion of males than females among the non-responders (21% vs. 14.5%), but no significant differences were found with gender, age, observation time, primary treatment or relapse between responders and non-responders.

3.1. *Background and medical variables*

The patients were all Caucasian with a mean age of 46 years (range 21–74) and the majority (69%) were working or studying. There were more males among patients than in the population sample, 56% vs. 49%, $P < 0.01$. Mean age and the age distribution were significantly different when comparing patients to the GP (Table 1). A significantly higher proportion of the patients had higher education compared with the general population sample (37% vs. 30%, $P < 0.001$).

Sixty-three percent of the sample ($N = 300$) were diagnosed with stage I or II disease. Most patients (55%) had received combination treatment, while 149 patients (31%) were treated with radiotherapy only. Mantle field irradiation alone, in combination with other fields or as part of the multimodality treatment, was most frequently administered (73% of the patients who were irradiated). Fifteen patients had received autologous stem cell transplantation. Eleven percent (54 patients) had relapsed during follow-up.

3.2. *Fatigue – patients vs. the general population*

All aspects of fatigue, physical, mental and total, assessed by the FQ, were significantly elevated in the HDSs relative to the GP, with P values <0.001 after adjusting for age, gender and educational differences (Table 2). The prevalence of chronic fatigue was almost three times higher in patients compared with the population at large, $N = 142$, 30% vs. $N = 224$, 11% ($P < 0.001$, OR 3.6). s-Scores for the differences were moderate, being 0.5 for mental and physical fatigue and 0.7 for total fatigue respectively. None of the following medical or treatment related variables: observation time, stage of disease, presence of B-symptoms, period of treatment, treatment modality, or treatment intensity according to our previously described model [17] were associated with significantly higher levels of PF, MF, TF or a higher proportion of patients with CF.

Table 1 – Participant characteristics

	Patients (HDSs, N = 475)	Population sample (GP, N = 2141)	P
Age, mean (SD)	46 (11.6)	43 (14.9)	<0.001
Range	21–74	21–74	
Age-groups, N (%)			<0.001
19–29 yrs	36 (8)	440 (20)	
30–39 yrs	98 (21)	486 (23)	
40–49 yrs	153 (32)	446 (21)	
50–59 yrs	129 (27)	362 (17)	
60–74 yrs	59 (12)	407 (19)	
Gender, N (%)			<0.01
Male	266 (56)	1054 (49)	
Female	209 (44)	1087 (51)	
Educational level, N (%)	Missing 7	Missing 11	<0.001
⩽10 yrs	88 (19)	547 (26)	
11–12 yrs	205 (44)	952 (44)	
> 12 yrs	175 (37)	631 (30)	
Stage at diagnosis[a], N (%)			
IA/IIA	231 (49)	–	
IB/IIB	69 (14)	–	
IIIA/IVA	81 (17)	–	
IIIB/IVB	93 (20)	–	
B-symptoms at diagnosis, N (%)	Missing 1		
Yes	162 (34)	–	
No	312 (66)	–	
Median observation time (months), range	195 (53–431)	–	
Period of treatment[b], N (%)			
1971–1979	110 (23)	–	
1980–1987	141 (30)	–	
1987–1997	224 (47)	–	
Treatment, primary + salvage, N (%)			
Radiotherapy	149 (31)	–	
Chemotherapy	65 (14)	–	
Both	261 (55)	–	

[a] Including 6 patients with extension to extranodal tissue.
[b] Corresponds to the periodic division of the therapeutic regimens at the NRH as described in detail elsewhere [17].

3.3. *Quality of life – patients vs. the general population*

There was a significant association between better QoL scores and treatment in the last treatment period (1987–1997) on four scales; general health, health transition, physical functioning and role physical. When adjusted for the significantly younger age of the patients who were treated in this period, no such association was found. None of the other medical

Table 2 – Fatigue and SF-36 scores, patients vs. general population

	Patients ($N = 470–474$)	General population ($N = 2029–2120$)	P[a]	s-Score[c]
Chronic fatigue, N (%)	142 (30%)	224 (11%)	<0.001	[b]
Mental fatigue, mean (SD)	5.0 (1.8)	4.3 (1.4)	<0.001	0.5
Physical fatigue, mean (SD)	9.6 (3.9)	7.9 (3.1)	<0.001	0.5
Total fatigue, mean (SD)	14.6 (5.1)	12.2 (3.9)	<0.001	0.7
SF-36, bodily pain	70 (28)	88 (17)	<0.001	0.2
SF-36, general health	64 (27)	77 (22)	<0.001	0.6
SF-36, health transition	57 (21)	60 (17)	<0.001	0.2
SF-36, mental health	78 (17)	79 (16)	NS	
SF-36, physical functioning	81 (22)	88 (17)	<0.001	0.4
SF-36, role emotional	82 (33)	83 (32)	NS	
SF-36, role physical	66 (42)	79 (35)	<0.001	0.4
SF-36, social functioning	81 (25)	86 (22)	<0.001	0.2

a For differences in mean scores, adjusted for age, gender and educational differences.

b OR 3.5, patients vs. age and gender adjusted population scores.

c *s*-Scores were calculated by subtracting patients' mean scale scores from GP mean scale scores and dividing the differences by the GP standard deviation for each scale.

or treatment-related variables that were used in the analyses for fatigue, were associated with lower scores indicating impaired QoL.

When analyzing the scores for the entire patient sample ($N = 475$), patients reported lower QoL mean scores relative to the GP on six of the eight scales assessed in this report (Table 2). After adjusting for age, gender and educational differences, results reached statistically significant differences for all six scales ($P < 0.001$), while mental health, HDSs: mean 78 (SD 17) vs. GP: mean 79 (SD 16); and role functioning emotional, HDSs: 82 (33) vs. GP: 83 (32) showed no differences across groups. The greatest numerical differences in mean scores (13) were found with the role physical and general health perception scales. *s*-Scores were small to moderate, going from 0.2 for bodily pain and social function to 0.6 for general health perception.

3.4. *Chronic fatigued subjects, patients vs. the general population*

When comparing HDSs with CF ($N = 142$) with the 224 GP subjects with CF, there was better QoL in the HDSs, with higher mean scores on five of eight scales (data not shown). Statistically significant differences were found in the mental health dimension with role emotional, HDSs: 68 (SD 40) vs. GP 49 (SD 43), $P < 0.001$; mental health: HDSs: 69 (SD 40) vs. 58 (SD 20), $P < 0.0001$; and social function: HDSs: 66 (SD 27) vs. GP: 58 (SD 28), $P = 0.01$, after adjusting for age, gender and education. *s*-Scores were moderate to small being 0.4, 0.6 and 0.3 for these three scales, respectively. The only scale score being slightly higher in the GP was general health perception: HDSs: 44 (SD 25) vs. GP: 48 (SD 25).

The *s*-scores of the four subgroups are shown in Fig. 1: HDSs with chronic fatigue, HDSs without chronic fatigue, GP subjects with chronic fatigue and GP subjects without chronic fatigue. The scores of latter group represent the 0-line. The chronic fatigued HDSs had the lowest scores in general health perception (−1.96), role physical (−1.46) and physical function (−1.30). The chronic fatigued subjects from the GP had the lowest scores in general health perception (−1.80), social function (−1.72) and mental health (−1.68). The pattern shows that HDSs without fatigue have relatively similar scores to GP subjects without fatigue, although they regard their general health status as poorer. Both HDSs and GP subjects with CF have impaired QoL compared with those in the population without CF, with relatively similar curves, except for the mental health dimension (mental health/role emotional) that is significantly better in HDSs with chronic fatigue than in fatigued GP subjects.

4. Discussion

In this study, we have shown for the first time that HDSs with chronic fatigue report better QoL in the mental health dimension than GP subjects with chronic fatigue. Patient QoL however, was significantly impaired relative to the GP as a whole, and was at the same level as GP subjects with chronic fatigue.

When comparing the entire group of HDSs with the general population sample, fatigue and QoL in HDSs were significantly impaired, in line with previous reports [9,11,14,16] and studies employing the SF-36 [11,13,44]. Mental health however, conceptualised in the SF-36 mental health scale as 'being nervous', 'being down in the dumps', 'feeling calm and peaceful', 'feeling blue', 'being happy' and emotional role function (how emotional problems interfere with daily activities) were at the same level as in the GP.

It was interesting that despite the finding of better mental health, the HDSs perceived themselves as having impaired health with lower scores on the general health perception scale. This may be explained by the wordings in one of the items asking for a comparison of health perception relative to others. Some patients may compare themselves to others of the same age, while some will be considering how they were before they became ill. A response shift, a change in the subjects' criteria for responses over time, occurs in most populations with serious or chronic disease due to a change of expectations or as a part of adaptation process [45]. It should be kept in mind though, that this is true for subjects with chronic diseases in the GP as well. Thus, we think that HDSs with CF is a heterogeneous group including subjects with CF unrelated or related to having had Hodgkin's disease.

We believe that the better mental health of the chronic fatigued HDSs indicates that other underlying mechanisms cause the fatigue in HDSs than in GP subjects with CF. One strategy for future research should therefore be to look for differences between HDSs with CF with and without reduced mental health. Few studies have examined the relationship between late medical complications, fatigue and impaired QoL after HD. More knowledge is warranted in this area, in particular with regard to myocardial infarction, cardiac, pulmonary and endocrinological dysfunction [46] as the use of self-report for prevalence estimates of common chronic conditions does not yield valid results.

The cross-sectional design implies some limitations, in particular the limited possibility to draw inferences of causality. A prospective design could better answer relevant questions about the causality of fatigue and impaired QoL in HDSs. In this respect, it may be regarded as a limitation of our study that we could not include a measure of psychological distress that might aid in the interpretation of our findings. On the other hand, no association between CF and self-reported psychiatric symptoms before diagnosis or during treatment was found in a previous report [26], and the SF-36 mental health scale has been shown to detect psychiatric conditions such as major depression and generalized anxiety disorder very well [47]. The FQ clearly separated fatigue from depression, thus we feel confident that our finding of better mental health among HDSs with CF relative to the GP subjects with CF refers to a true difference in the perception of chronic fatigue, as shown by others [26,27].

Although there were no significant differences in the background variables between responders or non-responders, a possible response bias can not be ruled out. A previous study has demonstrated a tendency to select patients with a favourable prognosis for survival (i.e., younger patients) for treatment at the Norwegian Radium Hospital [30]. Such a selection bias may exert an influence in studies in which survival is an outcome. In follow-up studies of long-term survivors however, such a selection bias is of less relevance because the mortality among the unselected is high (i.e., older patients with an unfavourable prognosis). Thus, in studies like the present, such a bias represents an underestimation of the fatigue levels in long-term survivors, rather than the opposite. In this respect however, it should be remembered that the reference population consisted of individuals who suffered from the normal spectrum of physical and psychological conditions and that fatigue is the final common end-point of a variety of conditions and life events for all people and not only for cancer survivors. This was controlled for by performing adjusted comparisons.

It might be that survivors after a life-threatening disease become more actively engaged in health-promoting activities relative to GP subjects with CF. In this respect, the lack of companion data on various adaptation strategies undertaken by the patients to overcome the feeling of fatigue and improve their general health is a limitation of the study. In smaller studies or in sub-groups of patients, this may be explored further by other methods such as objective measures of physical function or in-depth interviews. Our impression from clinical experience is that many patients engage in physical exercise as a means to increase their physical capacity and reduce the sensation of fatigue. A recent study however, showed that this was the case for lymphoma survivors as the only group among six groups of cancer survivors [48].

The strengths of the present study is related to the large patient and population sizes, good representation of GP data with response rates comparable to other population surveys [36,49–51], the adjusted comparisons with the GP data, the low amount of missing data and the use of well known instruments, in addition to the originality of the study objectives.

In conclusion our results combined with previous studies support the hypothesis of a multifactorial etiology of fatigue after HDSs. The over-all picture is that the CF survivors report reduced QoL [36]. However, the most prominent difference between the CF survivors and CF normal controls was the better mental health of the survivors. Nevertheless, their general health perception was lower than in the GP, even several years after treatment. We were not able to show any association with their physical health, and we can only hypothesise about their reduced health perception being a result of an adaptation process after a life-threatening disease and intensive treatment. The direct clinical implication of these findings is the need to assess QoL and fatigue in HDSs in order to implement strategies for symptom relief. Furthermore, future research in this group of cancer survivors should examine fatigue and QoL in relation to immunological, endocrinological, respiratory and circulatory alterations, as well as examine co-morbid conditions and life-style activities, preferably in a prospective design.

Conflict of interest statement

None declared.

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