

## **Lifestyle behavior among lymphoma survivors after high dose therapy with autologous hematopoietic stem cell transplantation, assessed by patient-reported outcomes**

**Hanne Skjerven Bersvendsen<sup>1</sup>, Hege Sagstuen Haugnes<sup>2</sup>, Unn-Merete Fagerli<sup>3</sup>, Øystein Fluge<sup>4</sup>, Harald Holte<sup>5</sup>, Knut Bjørro Smeland<sup>6</sup>, Tom Wilsgaard<sup>7</sup>, Cecilie Esholt Kiserud<sup>8</sup>**

- <sup>1</sup> *Department of Oncology, University Hospital of North Norway, Tromsø, Norway; Department of Clinical Medicine, UIT- The Arctic University of Norway, Tromsø. Email: [hanne.bersvendsen@unn.no](mailto:hanne.bersvendsen@unn.no) Phone: +4741461771.*
- <sup>2</sup> *Department of Oncology, University Hospital of North Norway, Tromsø, Norway; Department of Clinical Medicine, UIT- The Arctic University of Norway, Tromsø. Email: [hege.sagstuen.haugnes@unn.no](mailto:hege.sagstuen.haugnes@unn.no)*
- <sup>3</sup> *Department of Oncology, St. Olav`s Hospital, Trondheim, Norway; Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. Email: [Unn.Merete.Fagerli@stolav.no](mailto:Unn.Merete.Fagerli@stolav.no)*
- <sup>4</sup> *Department of Oncology, Haukeland University Hospital, Bergen, Norway. Email: [oystein.fluge@helse-bergen.no](mailto:oystein.fluge@helse-bergen.no)*
- <sup>5</sup> *Department of Oncology, Oslo University Hospital, Radiumhospitalet, Oslo, Norway; K.G. Jebsen-Centre for B cell malignancies, Institute of Clinical Medicine, University of Oslo, Norway. Email: [hhe@ous-hf.no](mailto:hhe@ous-hf.no)*
- <sup>6</sup> *National Advisory Unit for Late Effects After Cancer, Department of Oncology, Oslo University Hospital, Radiumhospitalet, Oslo, Norway. Email: [knusme@ous-hf.no](mailto:knusme@ous-hf.no)*
- <sup>7</sup> *Department of Community Medicine, UIT- The Arctic University of Norway, Tromsø. Email: [tom.wilsgaard@uit.no](mailto:tom.wilsgaard@uit.no)*
- <sup>8</sup> *National Advisory Unit for Late Effects After Cancer, Department of Oncology, Oslo University Hospital, Radiumhospitalet, Oslo, Norway. Email: [ckk@ous-hf.no](mailto:ckk@ous-hf.no). Phone: +4722935434.*

Corresponding author: Hanne Skjerven Bersvendsen

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## **Abstract**

**Introduction:** High dose therapy with autologous stem cell transplantation (HD-ASCT) is associated with increased risk of late effects. Our aim was to assess lifestyle behavior and factors associated with unhealthy lifestyle among HD-ASCT-treated lymphoma survivors (HD-ASCT-LS).

**Material and methods:** We conducted a national cross-sectional study of HD-ASCT-LS treated during 1987-2008. Among 399 eligible participants, 312 (78%) completed patient-reported outcomes measures (PROMs) on lifestyle behavior (physical activity, overweight, smoking and alcohol consumption), chronic fatigue (CF) and somatic and mental illness. We assessed lifestyle according to WHO recommendations. Multivariable logistic regression models were used to study associations between variables. A comparison to the general population was performed.

**Results:** Mean age at survey was 54.6 years, 60% were men, 55% sedentary, 55% overweight, 18% smokers and 5% had unhealthy alcohol consumption. Being sedentary was positively associated with older age, low household income, CF and higher somatic burden ( $\geq 4$  self-reported somatic conditions). Overweight was positively associated with male gender and negatively associated with increased number of chemotherapy regimens prior to HD-ASCT. Current smoking was positively associated with living alone and CF, and negatively associated with older age. Male gender, CF and higher somatic burden increased the risk of an unhealthier lifestyle whereas increased number of chemotherapy regimens prior to HD-ASCT decreased the risk.

HD-ASCT-LS were significantly less sedentary, less overweight, and had a lower likelihood of smoking than the controls.

**Discussion:** Assessed by PROMs, unhealthy habits was frequent among HD-ASCT-LS and associated with comorbidity. Nevertheless, compared with controls significantly more HD-ASCT-LS met lifestyle recommendations. These results indicate that the HD-ASCT-LS may consist of two groups, the adhering group with less comorbidity and the non-adhering group with more comorbidity. Our findings illustrate the necessity of recommendations and support for improving health-related behavior in cancer survivorship and the need for personalized follow-up.

## **Introduction**

Lymphoma affects mostly elderly patients, but some types are also predominant in younger age groups. There is an increasing number of long-term lymphoma survivors (LS), due to increased incidence and treatment improvements [1]. For the majority of lymphoma subtypes, patients in complete remission 2-3 years after standard therapy, have a long-term survival of 80-90% or more compared with the normal population [2].

It is well documented that lymphoma therapy is associated with an increased risk of late effects such as fatigue, cardiovascular disease, secondary malignancies and reduced health-related quality of life (HRQoL) [3,4,5]. A healthy lifestyle may positively influence the presence and outcome of these late effects, especially cardiovascular disease [6]. Among cancer patients and survivors, a healthy lifestyle may in addition decrease fatigue, improve physical functioning and increase HRQoL [7, 8].

There are reports of a positive association between lifestyle behavior, especially physical activity (PA), on HRQoL in both non-Hodgkin (NHL) and Hodgkin lymphoma (HL) survivors [9, 10]. Presumably, a healthy lifestyle might have an even greater impact on health status for lymphoma survivors after high-dose chemotherapy with autologous hematopoietic

stem-cell transplantation (HD-ASCT), as the highly intensive treatment seems to be associated with a high risk of late effects [11].

Lifestyle recommendations for the general population are well established, and apply equally for cancer survivors [12]. Nevertheless, a large cross-sectional study on 9105 cancer survivors treated for different types of solid cancers reported 30-47% to be physically active, 83-92% were non-smokers and only 15-19% had a healthy diet containing fruit and vegetables (5-a-day) [7]. Adherence to all three recommendations assessed together (PA, non-smoking and 5-a-day) was only 5%. Results for NHL survivors are similar [9, 10]. In addition, female gender, lower perceived health competence and comorbid limitations were associated with a sedentary lifestyle [9].

This study is part of a cross-sectional national multicenter study assessing a wide range of late effects in an unselected population of HD-ASC- treated lymphoma survivors (HD-ASCT-LS) [13, 14]. The main purpose of the present study was to acquire information regarding lifestyle behavior in this group of survivors, which, to our knowledge, has not been studied previously. Our second purpose was to evaluate associations between adherence to lifestyle recommendations and 1) patient and treatment characteristics, and 2) somatic or mental comorbidity with special emphasis on chronic fatigue (CF).

We hypothesized that 1) HD-ASCT-LS are more likely to adhere to recommended lifestyle behavior than the general population and 2) that an unhealthy lifestyle is associated with a higher degree of comorbidity and / or CF in this group of survivors.

## **Patients and methods**

### *Study population*

All lymphoma survivors aged  $\geq 18$  years treated with HD-ASCT in Norway over two decades (1987-2008) were eligible. Identification of study participants was based on reports from

multidisciplinary meetings were HD-ASCT patients routinely were discussed and Oslo Lymphoma Registry (Oslo University Hospital), and registries dedicated for HD-ASCT treated patients only (the other University hospitals). Active cancer treatment was an exclusion criterion. Overall, 399 eligible survivors were invited by mail, 312 (78%) completed questionnaires and 274 (69%) attended an extensive clinical examination in the period 2012-2014 (Figure 1) [13, 14].

### *Lymphoma characteristics and treatment*

Information regarding lymphoma characteristics and treatment details were retrieved retrospectively from medical records or the lymphoma registry at Oslo University Hospital.

Treatment was given according to international guidelines, and with a consensus in the Norwegian lymphoma group. During 1987-1996, patients received total body irradiation and high-dose cyclophosphamide as myeloablative treatment, while BEAM (carmustine, etoposide, cytarabine and melphalan) was applied after 1996 (15). Survivors were categorized according to lymphoma entity before HD-ASCT (HL, indolent NHL (iNHL) and aggressive NHL (aNHL)), number of regimens prior to HD-ASCT (one, two or  $\geq$ three), whether they had received radiotherapy or not and if they had recurrent disease after HD-ASCT or not.

### *Patient reported outcome measures*

The participants completed a set of well-established patient reported outcome measures (PROMs) assessing PA, smoking, alcohol consumption and dietary habits [16], Type D personality (Type D Scale-14 (DS14)) [17], CF (Fatigue Questionnaire (FQ)) [18], post-traumatic stress disorder (PTSD) (The Impact of Event Scale (IES)) [19], anxiety and depression (Hospital Anxiety and Depression Score (HADS)) [20]. In addition, they reported on prior or present somatic illness (secondary malignancy, heart-, lung-, kidney-, liver-, thyroidal- or hematological disease, stroke, high blood pressure, diabetes mellitus, gastric

ulcer, arthritis, osteoarthritis, back pain or other diseases). In case of somatic illness, they were asked whether this affected activity of daily living (ADL) or not.

#### *Socio-demographic characteristics*

Socio-demographic information was obtained from questionnaires. Household income was dichotomized into groups with more or less than 600.000 NOK/year ( $\approx$ € 63.900). Education was dichotomized into  $\leq 12$  years of education or more. Being in a paired relationship was defined as being either married or cohabitant.

#### *Lifestyle behavior recommendations*

The lifestyle recommendations are according to Norwegian guidelines [12] and include: 1) Moderate PA for  $\geq 150$  min per week or strenuous PA for  $\geq 75$  min per week, 2) a normal weight defined as body mass index (BMI)  $< 25$ , 3) non-smoking, 4) an alcohol consumption less than 10g/day and 20g/day for women and men respectively and 5) a healthy diet. Due to the complexity of diet recommendations we decided to investigate adherence to 5-a-day [12].

#### *Main outcomes*

Participants reported PA in frequency, intensity and duration. Multiplying frequency and duration gave minutes (minimum-maximum) of physical activity/week. A time range that included recommended time with PA was defined as adherence. PA was dichotomized into physically active or sedentary according to whether the PA recommendation was met or not. Information on height and weight was based on clinical examination when this was available (n=271) and self-report for the remaining subjects (n=41). BMI was calculated as  $\text{kg/m}^2$  and categorized into BMI  $< 25$  (normal weight) or BMI  $\geq 25$  (overweight). Smoking was dichotomized into yes (current or occasionally) or no (never or prior). An unhealthy alcohol

consumption was defined by  $\geq 6$  units/week and  $\geq 12$  units/week for women and men, respectively. One alcohol unit was defined as 12g. Healthy diet was dichotomized into yes or no, with regard to eating 5-a-day or not.

In order to grade the unhealthy lifestyle, we analysed the total number of guidelines not met (PA, BMI  $< 25$ , non-smoking and alcohol consumption), as a summary score. This provided every participant with a score from 0-4, with four representing the most unhealthy lifestyle according to guidelines.

A respectively high and low number of participants were not adhering to diet (n=305) and alcohol (n=15) recommendations. Hence, we deliberately omitted separate analyses on these issues. We included the habit of alcohol consumption in the summary score on unhealthy lifestyle, and used BMI as a surrogate variable for energy balance.

#### *Comorbidity characteristics*

Operationalization of PROMs (Type D personality, CF and HADS) have been described earlier [14]. Internal consistency (Cronbach's alpha) in our study was; type D personality, 0.90 for negative affectivity and 0.44 for social inhibition; CF, 0.92, 0.93 and 0.80 for total, physical and mental fatigue and HADS, 0.82 for depression and 0.86 for anxiety.

Assessment for PTSD was performed using IES, which combines seven questions on intrusion and eight questions on avoidance to produce a sum score (0-77). We considered a cut-off  $\geq 35$  to be consistent with a probability of PTSD. Internal consistency was 0.92 for intrusion and 0.90 for avoidance.

In order to grade mental burden, we constructed a summary score (0-3) based on presence of depression, anxiety and/or PTSD. Survivors were dichotomized according to scores 0-1 or 2-3 (high mental burden). We chose not to include CF in this summary score, as

we aimed to explore CF as an independent risk factor for not adhering to lifestyle recommendations. In addition, we chose not to include cognitive difficulties (memory and concentration problems) to avoid interaction with CF because of highly overlapping questions.

Based on self-report of somatic disease we constructed a summary score for the burden of somatic disease, and chose to dichotomize between 0-3 and  $\geq 4$  somatic conditions (high somatic burden), modified after a previous report [21]. We elaborated on consequences of somatic disease by dichotomizing into groups based on whether the somatic disease interfered on ADL or not.

#### *Control group*

We performed a comparison between our study group and the general population represented by age- and gender matched persons (1:5 matching) from the sixth survey of the Tromsø study (Tromsø 6) [22]. Tromsø 6 is a population-based study conducted during 2007-2008, consisting of questionnaires and clinical investigations. The Tromsø study population is considered representative of the Norwegian population [23]. PROMs regarding PA and smoking were identical to our study, whereas the wording of questions regarding alcohol consumption and diet were significant different from our study and a direct comparison was not applicable.

#### *Statistical analysis*

We used descriptive statistics to study population characteristics. The agreement between measured and self-reported BMI was calculated using kappa. To assess associations between variables predictive of a certain outcome, (non-adherence to guidelines) we performed age adjusted and multivariable analyses using binary and ordinal logistic regression. Ordinal



regression was used to assess the association between an increasing number of unhealthy lifestyle factors (later referred to as a more unhealthy lifestyle) and possible risk factors. Variables with a p-value  $\leq 0.25$  in age adjusted models were included as candidates in a multivariable model using a backward selection process. Level of education and income were included as covariates in the multivariable models, to adjust for socio-economical status. Associations are reported as odds ratios (OR) with 95% confidence intervals ([95% CI]). A p-value  $\leq 0.05$  (two-sided) was considered statistically significant. SPSS version 24 was used as statistical software (IBM Corporation, New York, USA).

### *Ethics*

The study was conducted according to the 1964 Helsinki declaration with amendments, and was approved by the Regional Ethics Committee. All participants gave a written informed consent prior to inclusion.

## **Results**

### *Patient characteristics*

There were no significant differences between respondents and non-respondents with regard to gender, lymphoma entity, myeloablative regimen, radiotherapy or age at diagnosis and HD-ASCT. There was a significant difference in mean age at survey, 55.0 vs. 51.6 years for respondents and non-respondents, respectively (p-value=0.02). There was a good agreement between measured and self-reported BMI, kappa 0.80.

The characteristics of the 312 participants are presented in Table 1. Median age at survey was 56 years (range 24-77) and median time from HD-ASCT to survey was 8.5 years (range 3.2-24.9). We found a high burden of comorbidity among the survivors as 31.1% had CF, 10.9% had high mental burden and 18.6% reported  $\geq 4$  somatic diseases.

### *Lifestyle variables compared to controls*

Among the HD-ASCT-LS, 54.8% were sedentary, 55.1% had a BMI  $\geq 25$  (61% among men and 46% among women) and 17.9% were smoking (23.8%, 21.5% and 7.3% among survivors 18-39, 40-64 and  $\geq 65$  years, respectively). Eating less than 5-a-day was reported by 98%, whereas only 4.8% had an alcohol consumption that exceeded recommendations (Table 1).

Among the controls from the Tromsø 6 study, 59% were sedentary, 67% were overweight, (73% among men and 58% among women) and 28% were smoking. Stratified into age groups 18-39 years, 40-64 years and  $\geq 65$  years, the prevalence of smoking in Tromsø 6 was 31%, 30% and 15.7%, respectively. Unhealthy alcohol consumption was found among 3.7%, whereas 74% reported an intake of less than 5-a-day.

Compared to the controls, the HD-ASCT-LS were significantly less sedentary (OR 0.77 [0.60-0.99]), less overweight (OR 0.61 [0.48-0.78]) and the likelihood of smoking was lower (OR 0.55 [0.41-0.75]) (Table 1).

### *Factors associated with each lifestyle behaviour*

The proportions of survivors being sedentary, overweight or smoking according to different characteristics is presented in Figure 2. The proportions of sedentary survivors were highest among those with type D personality, CF, or a high mental or somatic burden. Those treated with  $\geq 3$  regimens prior to HD-ASCT had the lowest frequency of overweight individuals.

#### Physical activity:

Being sedentary was significantly associated with a low household income (OR 2.12 [1.33-3.39]), Type D personality (OR 2.20 [1.21-4.00]), CF (OR 2.86 [1.69-4.83]), high mental burden (OR 2.97 [1.29-6.86]) and high somatic burden (OR 2.86 [1.51-5.45]) in age adjusted models (Table 2). In the multivariable model, older age at survey (OR 1.23 [1.00-1.51]), low

household income (OR 1.97 [1.18-3.29]), CF (OR of 2.30 [1.31-4.04]) and somatic burden  $\geq 4$  (OR 2.39 [1.21-4.74]) was significantly associated with a sedentary lifestyle.

#### Overweight:

In age adjusted models, higher age at survey (OR 1.21 [1.01-1.46], for every 10 years increase of age) and male gender (OR 1.78 [1.12-2.82]) were positively associated with increased risk of overweight, as opposed to a diagnosis of iNHL (OR 0.41 [0.19-0.90]) and treatment with  $\geq 3$  regimens prior to HD-ASCT (OR 0.31 [0.15-0.67]). In the multivariable model, men had an increased risk of being overweight in comparison to women (OR 2.03 [1.24-3.31]).

Survivors with  $\geq 3$  regimens prior to HD-ASCT had a 70% decreased risk of being overweight compared with those with fewer regimens (OR 0.31 [0.14-0.67]).

#### Smoking:

Smoking daily or occasionally was significantly related to age at survey (OR 0.72 [0.57-0.91], per 10 years increase) and with not being in a paired relationship (OR 2.12 [1.12-3.94]) in age adjusted models. In the multivariable model every 10 years increase of age reduced the risk of smoking by 30% (OR 0.70 [0.54-0.90]), whereas not being in a paired relationship (OR 2.38 [1.15-4.94]) and CF (OR 2.12 [1.10-4.06]) increased the risk of smoking.

#### *A more unhealthy lifestyle*

Figure 3a shows the distribution of survivors adhering to 0-4 lifestyle factors. The majority met 3-4 recommendations (57%). Figure 3b illustrates the proportion of HD-ASCT-LS not adhering to each lifestyle factor according to total number of recommendations not met. A sedentary lifestyle and overweight are frequent at all levels of non-adherence. Smoking and unhealthy alcohol consumption is more frequent together with another unhealthy factor, than as a single unhealthy habit.

### *Factors associated with a more unhealthy lifestyle*

In age adjusted models, there was a significant association between a more unhealthy lifestyle and male gender (OR 1.57 [1.02-2.41]) (Table 3). Survivors with a diagnosis of iNHL (vs. aNHL) and those with  $\geq 3$  regimens prior to HD-ASCT (vs.  $< 3$  regimens) were likely to have a more healthy lifestyle than compared groups (OR 0.44 [0.21-0.92] and OR 0.38 [0.19-0.75], respectively). Survivors with Type D personality, CF or high somatic burden were more likely to have a more unhealthy lifestyle (OR 1.91 [1.12-3.25]), OR 2.41 [1.52-3.83] and OR 2.50 [1.44-4.36], respectively).

In the multivariable adjusted model, male survivors had increased risk of a more unhealthy lifestyle (OR 1.79 [1.13-2.84]) while survivors with  $\geq 3$  regimens prior to HD-ASCT had lower risk (OR 0.28 [0.14-0.59]). The highest risk of unhealthier lifestyle was seen among survivors with CF and those with  $\geq 4$  somatic diseases (OR 2.37 [1.44-3.88] and OR 2.62 [1.45-4.75], respectively).

### **Discussion**

We report on lifestyle among an unselected group of adult lymphoma survivors treated with HD-ASCT nation-wide over two decades. The majority had a sedentary lifestyle and were overweight. Disappointingly, one quarter of younger survivors were smoking. Overall, increased comorbidity was associated with a more unhealthy lifestyle, consistent with results from a study on NHL survivors in general [10]. Since cancer survivors are at risk of several late effects, it is worrisome that unhealthy habits are present at this frequency. To the best of our knowledge, the existing literature on prevalence of lifestyle behavior in lymphoma survivors are limited and studies of factors associated with lifestyle behavior among HD-ASCT-LS are lacking.

Although the prevalence of unhealthy behavior is high, the HD-ASCT-LS were significantly less sedentary, less overweight and fewer were smoking compared with Tromsø 6 controls. Adjusting for comorbidity in the statistical models would presumably have increased the difference even further, as comorbidity is more frequent among HD-ASCT survivors than the normal population [24] and associated with a more unhealthy lifestyle. Unfortunately, this adjustment was not possible due to differences in reporting of comorbidity. Our finding of a healthier lifestyle among HD-ASCT-LS than controls are in contrast to a report on American cancer survivors in general, where these cancer survivors were less physically active and more overweight than persons without a cancer history [25]. In line with our finding, smoking was less frequent among cancer survivors than the general population [25].

A possible explanation for these differences could lie in the concept of teachable moments, which implies that a cancer diagnosis can be a driving force in adoption of health-promoting behavior [26]. Perhaps this effect is even stronger if one experiences relapse of cancer, as was the case for the majority of our study group. Selection by survival might be another explanation for the healthier lifestyle in our study group compared with the controls. One could argue that our study population is a highly selected portion of all lymphoma patients receiving HD-ASCT, because they are still alive and they might always have had a healthy lifestyle. In a recent publication better prognosis was reported among patients with aggressive lymphoma who were physically active, and among patients with indolent lymphoma obesity was associated with a worse prognosis [27], which supports this theory.

About half of the participants in our study reported to have a sedentary lifestyle, which is a lower proportion than reported among cancer survivors in general (70%) [28], whereas studies among non-HD-ASCT treated lymphoma survivors in particular report higher or similar

proportions (75% and 52%, respectively) [9, 10]. The difference in results between Bellizzi's study [9] and our, could be explained by a slightly less stringent definition of being sedentary, in addition to younger age and higher level of education among participants in our study. NHL survivors in Bellizzi's report were 3.7 times more likely to be physical inactive if they reported greater comorbid limitations [9]. This is comparable to our finding of a relationship between CF, burden of somatic comorbidity and a sedentary lifestyle.

Overweight or obesity are identified as late effects among cancer survivors [23, 25, 29]. However, the HD-ASCT-LS were less overweight than the controls, and less overweight than both NHL survivors (64%) and cancer survivors in general (66%) [10, 25]. A possible explanation might be that higher cumulative chemotherapy doses lead to physiological changes which results in decreased weight. A higher number of regimens was associated with a lower likelihood of overweight, and gives empirical support to this theory. Nonetheless, the 55% of overweight HD-ASCT-LS would presumably achieve health-benefits in case of weight reduction [6].

Based on our data it was not possible to explore whether the transplantation itself made a person more likely to live a healthy life, or whether the positive shift in lifestyle was a result of living with lymphoma and requiring chemotherapy treatment repeatedly. However, compared to previous studies on NHL survivors in general [9, 10] HD-ASCT-LS seems to have a lower prevalence of sedentary lifestyle and overweight. Hence, the transplantation experience might be influential on adherence to lifestyle recommendations.

The prevalence of smoking has been reported to be higher among younger than older cancer survivors [28], and a low prevalence of smoking has also been reported among older NHL survivors (6%) [10]. A similar pattern regarding smoking status was found among the HD-

ASCT-LS. Hence, it is highly relevant to increase focus on smoking cessation among younger HD-ASCT-LS.

Existing literature on long-term lymphoma survivors and diet is scarce. Two studies report 44-66% adherence to diet recommendations [10, 30] which is remarkably higher than the 2.2% eating 5-a-day in our study. At surveys people tend to present a favorable image of themselves, and the finding of only 5% reporting an unhealthy alcohol consumption might be underestimated due to this social desirability bias in self-reports [31]. Unfortunately, a comparison with Tromsø 6 controls could not be done due to differences in PROMs. These two latter aspects illustrate the difficulties with internal and external validity in assessing and comparing drinking and dietary habits. Still, the findings give a strong implication for integrating nutritional advice into follow-up as part of advice on a healthy energy balance.

An increased risk of an unhealthier lifestyle was found among men, corroborating previous reports showing that male cancer survivors are less likely to adopt health-promoting behaviors [10, 26]. CF and a high somatic burden were independent predictors of a more unhealthy lifestyle, and together with the higher adherence among HD-ASCT-LS vs. controls to lifestyle recommendations, this indicate that the HD-ASCT-LS may consist of two groups. The adhering, not fatigued group with less somatic comorbidity in contrast to the group who do not adhere to guidelines, experience CF and/or have a high somatic burden. As PA may reduce CF, it is important to recognize these survivors and initiate support to improve level of PA.

About 20% of HD-ASCT-LS had a high somatic burden. Even though we report past and present comorbidity, this seems remarkably higher than the 2.5% incidence of  $\geq 3$  late-effects

previously reported [32]. Another report on health problems after hematopoietic stem cell transplantation (HSCT) found on average 3.5 medical problems after HD-ASCT or allogeneic-HSCT [24]. The numbers are not directly comparable due to differences in methodology and study population. Nonetheless, HD-ASCT-LS are at risk of many late effects [32] and more health problems than the normal population [24], which our findings support.

The major strength of our study is the completeness of the study population. Due to the Norwegian public health system, personal identification number and national collaboration, all eligible HD-ASCT-LS were invited to participate. A high number of survivors returned the questionnaire (78%), assuring representativeness. In order to compare lifestyle behavior with the normal population we matched survivors with subjects from Tromsø 6 study, which is considered to be representative for the general population [22-23].

Outcome data in our study were based on PROMs, which are associated with recall bias and represents a weakness in our study. However, we believe this bias was similar to subjects from the Tromsø 6 study because identical PROMs were used. Self-reported BMI was used for a minority of HD-ASCT-LS (13%), which might have introduced a bias due to differences in self-reported and measured BMI. Nevertheless, we believe the potential bias is minor based on good agreement between the two methods and a sensitivity analysis that did not alter the main results.

Our study is unable to address causality, because of the cross-sectional design. Nevertheless, we assume somatic illness and health-related behavior affects each other mutually, and the cause of both are probably multifactorial.



**In conclusion,** HD-ASCT-LS have a high risk of late effects and the high prevalence of a somatic burden reported herein is more pronounced than reported earlier. Our results raise the attention to HD-ASCT-LS with CF and high somatic burden, and illustrate the necessity of incorporating recommendations and support for improving health-related behavior into cancer survivorship plans. The patient-doctor meeting is a great opportunity to increase awareness, provide knowledge, initiate support for lifestyle changes and thereby empower survivors in their life beyond cancer.

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### **Disclosure of interest**

The authors report no conflicts of interest.

### **Figure legends**

Figure 1 Flowchart of study population.

Figure 2 Proportion of lymphoma survivors after high dose therapy with autologous hematopoietic stem cell transplantation not adhering to lifestyle recommendations, by different characteristics of the study-population. Abbreviations: HD-ASCT, high dose chemotherapy with autologous hematopoietic stem cell transplantation; iNHL, indolent non-Hodgkin lymphoma; aNHL, aggressive non-Hodgkin lymphoma; HL, Hodgkin lymphoma.

Figure 3a Proportion of lymphoma survivors after high dose therapy with autologous hematopoietic stem cell transplantation adhering to a number of lifestyle recommendations (physical activity:  $\geq 150$  min/week of moderate physical activity or  $\geq 75$  min/week of strenuous activity, body mass index  $< 25$ , non-smoking and alcohol consumption  $\leq 6$  or  $\leq 12$  alcohol units per week for women and men, respectively).

Figure 3b Proportion of lymphoma survivors after high dose therapy with autologous hematopoietic stem cell transplantation not adhering to each lifestyle recommendation,

according to total number of recommendations not met (sedentary: <150 min/week of moderate physical activity or <75 min/week of strenuous physical activity, body mass index  $\geq 25$ , smoking, alcohol consumption >6 or >12 alcohol units per week for women and men, respectively).

**Table 1. Characteristics of study population at survey and age- and gender matched controls from the Tromsø 6 study**

	<b>HD-ASCT lymphoma</b>	<b>Tromsø 6 study</b>
	<b>survivors</b>	<b>controls</b>
	<b>N=312</b>	<b>N=1560</b>
<b>SOCIODEMOGRAPHICS:</b>		
Age at diagnosis, median (range)	42 (10-65)	
Age at HD-ASCT, median (range)	46 (18-67)	
Age at survey, median (range)	56 (24-77)	56 (30-79)
Time HD-ASCT - survey in years, median (range)	8.5 (3.2-24.9)	
Gender:		
Female, n (%)	125 (40)	625 (40)
Male, n (%)	187 (60)	935 (60)
In a relationship <sup>i</sup> , n (%)	227 (73)	966 (62)
Education >12 years, n (%)	141 (45)	618 (40)
Household income high <sup>ii</sup> , n (%)	133 (43)	707 (45)
<b>LYMPHOMA AND TREATMENT:</b>		
Lymphoma entity:		
Aggressive Non-Hodgkin lymphoma <sup>iii</sup> , n (%)	209 (67)	-
Indolent Non-Hodgkin lymphoma <sup>iv</sup> , n (%)	31 (9.9)	-
Hodgkin lymphoma, n (%)	72 (23)	-
Stage III-IV at diagnosis, n (%)	214 (69)	-
Treatment regimes prior to HD-ASCT:		
1, n (%)	92 (29)	-
2, n (%)	176 (56)	-
≥3, n (%)	44 (14)	-
Radiotherapy <sup>v</sup> , n (%)	201 (64)	-
Relapse after HD-ASCT, n (%)	70 (22)	-
<b>COMORBIDITY:</b>		
Type D personality, n (%)	64 (21)	-

Chronic fatigue, n (%)	97 (31)	-
Mental burden $\geq 2$ , n (%)	34 (11)	-
Somatic burden $\geq 4$ , n (%)	58 (19)	-
Somatic illness with interference on ADL, n (%)	121 (39)	-

**LIFESTYLE VARIABLES:**

Sedentary <sup>vi</sup> , n (%)	171 (55)	918 (59)
Body mass index $\geq 25$ , n (%)	172 (55)	1042 (67)
Smoking <sup>vii</sup> , n (%)	56 (18)	437 (28)
Unhealthy alcohol consumption <sup>viii</sup> *, n (%)	15 (4.8)	57 (3.7)
Diet less than 5-a-day <sup>ix</sup> *, n (%)	305 (98)	1146 (74)

Abbreviations: HD-ASCT, high dose chemotherapy with autologous hematopoietic stem cell transplantation; ADL, activity of daily living.

\*Patient-reported outcome measures were different in our study and Tromsø 6. Direct comparison between groups was not applicable.

Missing values, study group: In a relationship, n=1; education, n=2; income, n=9; stage at diagnosis, n=1; Type D personality, n=26; chronic fatigue, n=1; somatic burden  $\geq 4$ , n=12; mental burden  $\geq 2$ , n=2; somatic illness with interference on ADL, n=72; sedentary, n=5; smoking, n=2; unhealthy alcohol consumption, n=4.

Missing values, control group: Education, n=17; income, n=90; sedentary, n=68; body mass index, n=1; smoking, n=29; unhealthy alcohol consumption, n=20; diet less than 5-a-day, n=93.

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<sup>i</sup> Married or cohabitant.

<sup>ii</sup> High/Low income:  $>/\leq 600.000$  nkr/year  $\approx \text{€ } 62.900$  (study population) and  $>/\leq 551.000$  nkr/year  $\approx \text{€ } 57700$  (Tromsø 6).

<sup>iii</sup> Includes: Lymphoblastic lymphoma, n=21; Burkitt lymphoma, n=11; diffuse large B-cell lymphoma, n=69; mantle cell lymphoma, n=41; T-cell lymphomas, n=32; transformed lymphoma, n=33.

<sup>iv</sup> Includes follicular or other indolent lymphomas.

<sup>v</sup> Radiotherapy part of treatment, prior to HD-ASCT or as consolidation to such.

<sup>vi</sup>  $<150$  min/week of moderate physical activity or  $<75$  min/week of strenuous physical activity.

<sup>vii</sup> Smoking current or occasionally.

<sup>viii</sup> Alcohol consumption  $>6$  or  $>12$  alcohol units per week for women and men, respectively.

<sup>ix</sup> Three vegetables and two fruits per day.



<b>TREATMENT:</b>																	
<b>Lymphoma entity:</b>																	
aNHL <sup>iv</sup>	1	Ref.															
iNHL <sup>v</sup>	0.97	0.54-1.75	0.91														
HL	0.59	0.28-1.27	0.18														
<b>Number of regimes prior to HD-ASCT:</b>																	
1 regimen	1	Ref.															
2 regimes	1.02	0.61-1.72	0.94														
≥3 regimens	0.64	0.31-1.32	0.23														
<b>Radiotherapy<sup>vi</sup>:</b>																	
No	1	Ref.															
Yes	1.22	0.75-1.98	0.42														
<b>COMORBIDITY:</b>																	
<b>Type D personality<sup>vii</sup>:</b>																	
No	1	Ref.															
Yes	2.20	1.21-4.00	0.01														
<b>Chronic fatigue:</b>																	
No	1	Ref.		1	Ref.							1	Ref.				
Yes	2.86	1.69-4.83	<0.001	2.30	1.31-4.04	0.004						1.61	0.88-2.95	0.12	2.12	1.10-4.06	0.02
<b>Mental burden ≥2<sup>viii</sup>:</b>																	
No	1	Ref.															
Yes	2.97	1.29-6.86	0.01														
<b>Somatic burden ≥4<sup>ix</sup>:</b>																	



No	<b>1</b>	Ref.		<b>1</b>	Ref.		<b>1</b>	Ref.		<b>1</b>	Ref.	
Yes	<b>2.86</b>	<b>1.51-5.45</b>	<b>0.001</b>	<b>2.39</b>	<b>1.21-4.74</b>	<b>0.01</b>	1.34	0.74-2.42	0.33	1.66	0.81-3.43	0.17
<b>Somatic illness with interference on ADL:</b>												
No	1	Ref.					1	Ref.		1	Ref.	
Yes	1.63	0.96-2.74	0.07				0.93	0.56-1.55	0.78	1.12	0.57-2.22	0.74

Bold type indicates statistical significance, p-value <0.05.

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; Ref., reference; iNHL, indolent non-Hodgkin lymphoma; aNHL, aggressive non-Hodgkin lymphoma; HL, Hodgkin lymphoma; HD-ACST, high dose chemotherapy with autologous hematopoietic stem cell transplantation; ADL, activity of daily living.

\*Multivariable model from a backward selection process additionally adjusted for age at survey, gender, education and household income.

<sup>i</sup> <150 min/week of moderate physical activity or <75 min/week of strenuous physical activity.

<sup>ii</sup> Married or cohabitant.

<sup>iii</sup> 600.000 nkr/year ≈ € 62.900/year.

<sup>iv</sup> Includes: Lymphoblastic lymphoma, n=21; Burkitt lymphoma, n=11; diffuse large B-cell lymphoma, n=69; mantle cell lymphoma, n=41; T-cell lymphomas, n=32; transformed lymphoma, n=33.

<sup>v</sup> Includes follicular or other indolent lymphomas.

<sup>vi</sup> Radiotherapy part of treatment, prior to HD-ASCT or as consolidation to such.

<sup>vii</sup> Type D personality; negative affectivity and social inhibition.

<sup>viii</sup> Presence of post traumatic stress syndrome, depression caseness and/or anxiety caseness

<sup>ix</sup> Based on self report of secondary malignancy, heart disease (heart failure, myocardial infarction, angina pectoris), hypertension, stroke, asthma, COPD, diabetes mellitus, gastric ulcer, anemia, blood-, thyroid-, liver or kidney disease, arthritis, osteoarthritis, back pain or other disease.

**Table 3. Odds ratios for a more unhealthy lifestyle<sup>i</sup> in age adjusted and multivariable adjusted models\*, assessed by ordinal logistic regression**

	Age adjusted model			Multivariable model*		
	OR	95% CI	p-value	OR	95% CI	p-value
<b>SOCIO- DEMOGRAPHICS:</b>						
Age at survey, 10 years	1.09	0.92-1.30	0.29	1.13	0.94-1.35	0.20
<b>Gender:</b>						
Female	<b>1</b>	Ref.		<b>1</b>	Ref.	
Male	<b>1.57</b>	<b>1.02-2.41</b>	<b>0.04</b>	<b>1.79</b>	<b>1.13-2.84</b>	<b>0.01</b>
<b>In a relationship<sup>ii</sup>:</b>						
Yes	1	Ref.				
No	1.25	0.77-2.01	0.37			
<b>Education:</b>						
>12 years	1	Ref.		1	Ref.	
≤12 years	1.11	0.73-1.70	0.61	1.05	0.66-1.66	0.84
<b>Household income<sup>iii</sup>:</b>						
>600.000 nkr	1	Ref.		1	Ref.	
≤600.000 nkr	1.48	0.97-2.28	0.07	1.44	0.91-2.28	0.12
<b>LYMPHOMA AND TREATMENT:</b>						
<b>Lymphoma entity:</b>						
aNHL <sup>iv</sup>	<b>1</b>	Ref.				
iNHL <sup>v</sup>	<b>0.44</b>	<b>0.21-0.92</b>	<b>0.03</b>			
HL	0.78	0.45-1.34	0.36			
<b>Number of regimes prior to HD-ASCT:</b>						
1 regimen	<b>1</b>	Ref.		1	Ref.	
2 regimes	0.79	0.49-1.26	0.32	0.78	0.47-1.29	0.33
≥3 regimens	<b>0.38</b>	<b>0.19-0.75</b>	<b>0.006</b>	<b>0.28</b>	<b>0.14-0.59</b>	<b>0.001</b>
<b>Radiotherapy<sup>vi</sup>:</b>						
No	1	Ref.				
Yes	0.82	0.53-1.28	0.39			
<b>COMORBIDITY:</b>						
<b>Type D personality<sup>vii</sup>:</b>						
No	<b>1</b>	Ref.				
Yes	<b>1.91</b>	<b>1.12-3.25</b>	<b>0.02</b>			
<b>Chronic fatigue:</b>						
No	<b>1</b>	Ref.		<b>1</b>	Ref.	
Yes	<b>2.41</b>	<b>1.52-3.83</b>	<b>&lt;0.001</b>	<b>2.37</b>	<b>1.44-3.88</b>	<b>0.001</b>
<b>Mental burden ≥2<sup>viii</sup>:</b>						
No	1	Ref.				
Yes	1.64	0.83-3.23	0.15			
<b>Somatic burden ≥4<sup>ix</sup>:</b>						
No	<b>1</b>	Ref.		<b>1</b>	Ref.	
Yes	<b>2.50</b>	<b>1.44-4.36</b>	<b>0.001</b>	<b>2.62</b>	<b>1.45-4.75</b>	<b>0.001</b>
<b>Somatic illness with interference on ADL:</b>						
No	1	Ref.				
Yes	1.21	0.74-1.98	0.44			

Bold type indicates statistical significance, p-value <0.05.

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; iNHL, indolent non-Hodgkin lymphoma; aNHL, aggressive non-Hodgkin lymphoma; HL, Hodgkin lymphoma; HD-ASCT, high dose chemotherapy with autologous hematopoietic stem cell transplantation; ADL, activity of daily living.

\* Multivariable model from a backward selection process additionally adjusted for age at questionnaire, gender, education and income.

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<sup>i</sup> Sedentary: <150 min/week of moderate physical activity or <75 min/week of strenuous physical activity, BMI  $\geq 25$ , smoking, alcohol consumption >6 or >12 alcohol units per week for women and men, respectively.

<sup>ii</sup> Married or cohabitant.

<sup>iii</sup> 600.000 nkr/year  $\approx$  € 62.900/year.

<sup>iv</sup> Includes: Lymphoblastic lymphoma, n=21; Burkitt lymphoma, n=11; diffuse large B-cell lymphoma, n=69; mantle cell lymphoma, n=41; T-cell lymphomas, n=32; transformed lymphoma, n=33.

<sup>v</sup> Includes follicular or other indolent lymphomas.

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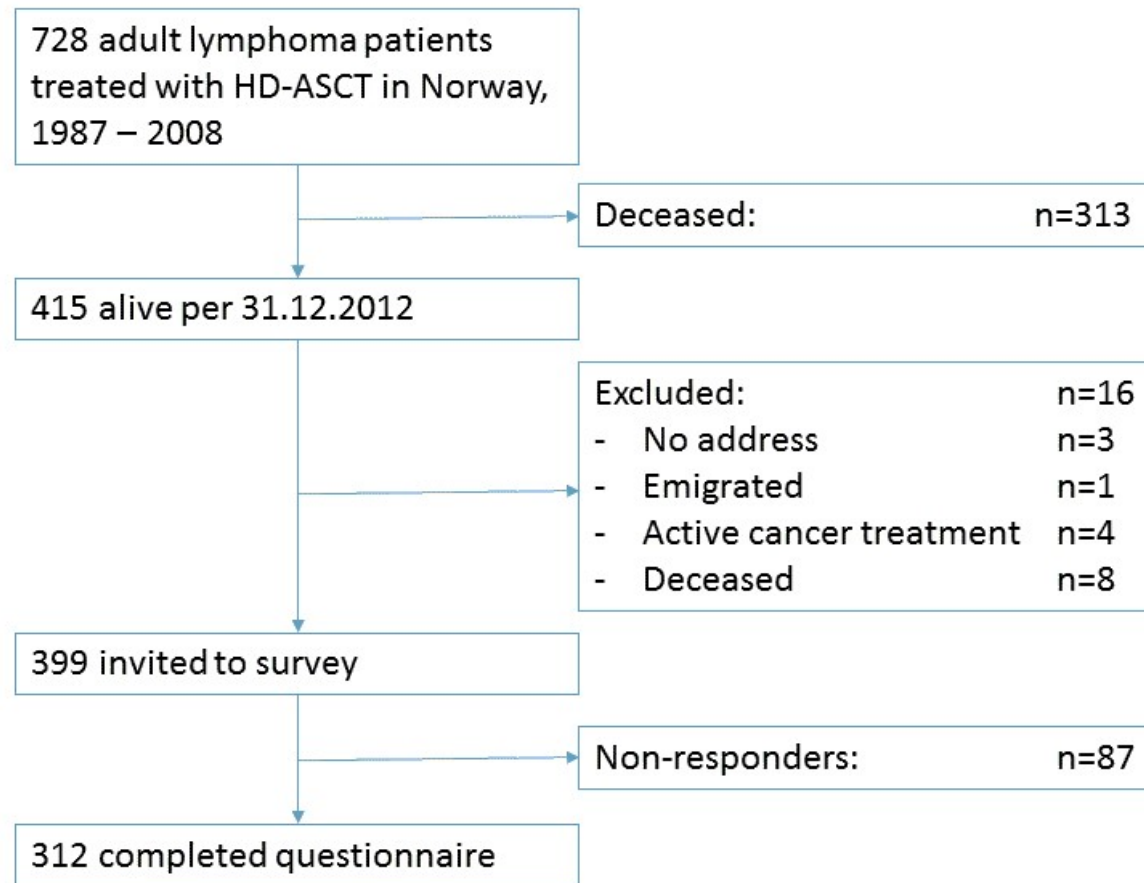


Figure 1

Figure 2

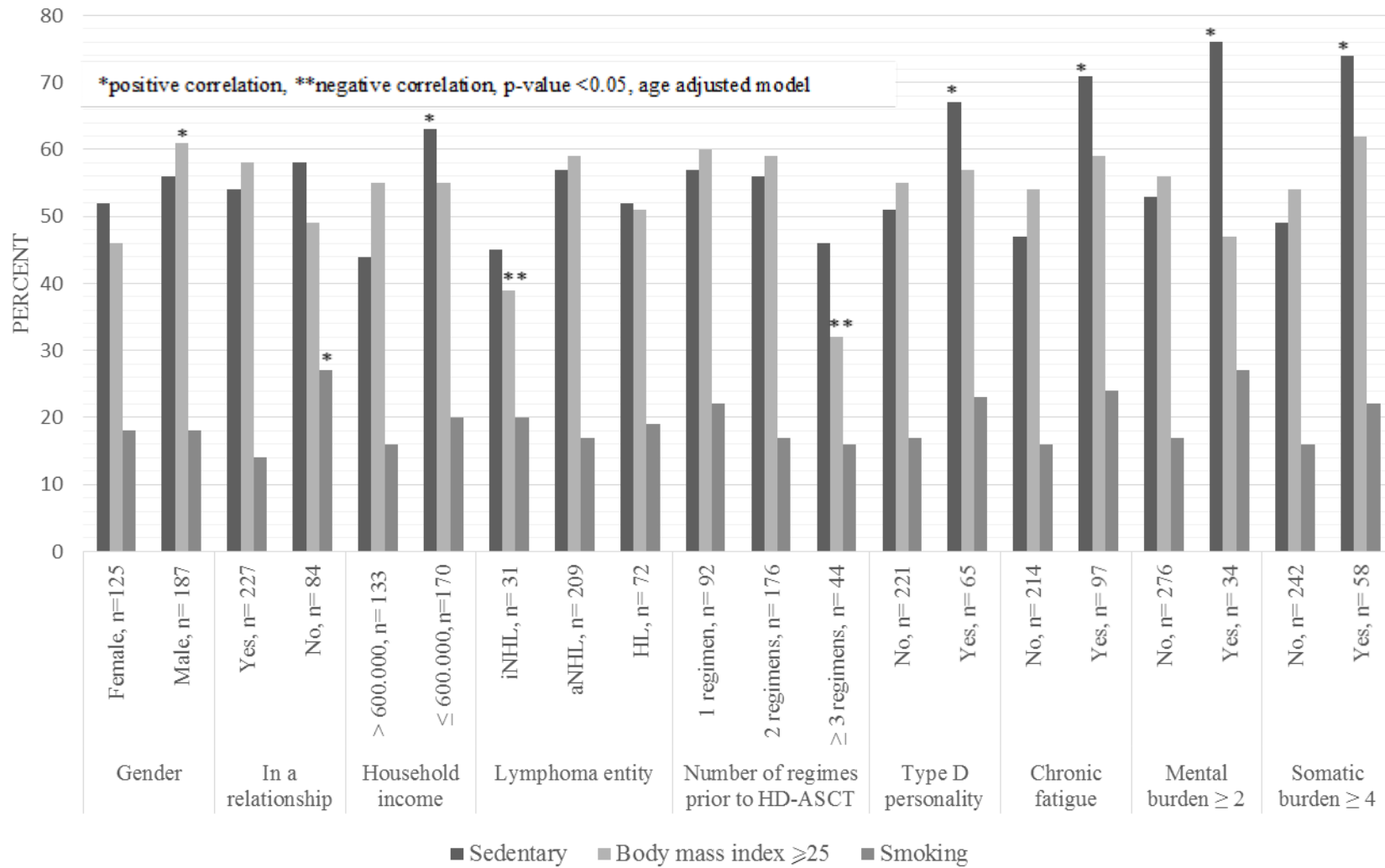


Figure 3a

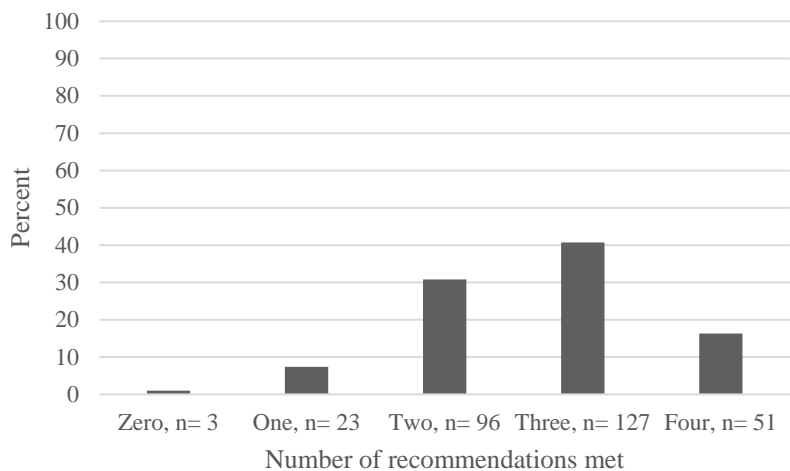


Figure 3b

