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Sexual function in long-term male lymphoma survivors after high-dose therapy with autologous stem-cell transplantation

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Abstract

Reduced sexual function may have negative implications on health related quality of life among lymphoma survivors. A national cross-sectional study among long-term lymphoma survivors after high-dose therapy with autologous stem-cell transplantation auto-SCT treated during 1987-2008 was conducted in 2012-2014. The current study explored sexual functioning among these survivors. Sixty-six percent (n=159) of eligible men with complete questionnaire data were included, median age was 55 years. The Brief Sexual Function Inventory (BSFI) was used to assess sexual function and sexual satisfaction, compared with age-matched controls. In addition, sexual problems were defined based on predetermined cut-off values for BSFI domain scores. Sexual drive and erections firm enough to have sexual intercourse were reported to be present only a few days or less last month among 30% and 41% of survivors, respectively. Sexual satisfaction was reported by 39% of survivors. The survivors had significantly lower scores on all BSFI domains and an increased risk of problems with sexual drive and erection compared with controls. In multivariable models, cardiovascular disease was significantly associated with worse erectile function, while age >55 years, chronic fatigue, and physical inactivity were significantly associated with lower sexual functioning overall. Chronic fatigue and anxiety were related to lower sexual satisfaction.

Introduction

Lymphoma therapy, in particular high-dose therapy with autologous stem-cell transplantation (auto-SCT), is associated with multiple long-term adverse effects, including sexual problems [1], which is important for quality of life (QoL) in lymphoma survivors [2, 3]. After conventional chemotherapy, 22-50% of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) survivors report reduced sexual function [4, 5, 2]. Among 246 male lymphoma survivors , reduced sexual function was associated with increasing age, low testosterone levels, poor physical health and increased mental distress (mean 14.8 years post-treatment) [6]. Reduced sexual function in HL survivors (n=3208) with up to 27 months follow-up, was associated with advanced stage disease, older age, pre-treatment sexual function and reduced health related QoL [2].

In male stem-cell transplanted (SCT) cancer survivors, reduced sexual function is frequent, with lack of sexual drive, erectile dysfunction (ED) and sexual dissatisfaction being the most common problems median 3 years post-SCT [7, 8]. However, sexual problems related to graft-versus-host disease dominate the reports [9-12].

Thus, there is a need for studies on sexual function in large samples of auto-SCT male lymphoma survivors, with long follow-up time [1, 12-15]. In addition, lymphoma patients have increased risk of cardiovascular disease (CVD), of which ED is an independent predictor in the general population [16]. However, the association between sexual function and CVD has not previously been studied in male lymphoma survivors.

Our primary aim was to evaluate sexual functioning and sexual satisfaction among male long-term lymphoma survivors after auto-SCT, and to compare the findings to those of normative controls. Our secondary aim was to investigate the associations between survivors' characteristics, especially psychological and somatic status including CVD, and sexual outcomes.

Subjects and methods

Study sample

During 2012-2014, a cross-sectional study was conducted at all four centers responsible for auto-SCT of lymphoma patients in Norway. Eligible subjects were lymphoma survivors (≥18 years) treated with auto-SCT during 1987-2008, alive per 31.12.2012 [17, 18]. Pre-established exclusion criteria were active cancer treatment and unknown address. Overall, 242 eligible male survivors received postal invitation, of whom 77% (n=187) completed a questionnaire (Figure 1). Those also treated with allogeneic-SCT (n=16), total brain irradiation (n=1) or who delivered an incomplete Brief Sexual Function Inventory (BSFI) (n=9) were excluded. In addition, two males with active cancer treatment were identified during data preparation for the current study. The remaining 159 male participants represented the sample included in the analyses. Overall 148 (93%) of these men also participated in a clinical examination with height, weight and blood pressure measurement in addition to blood sampling. Information on lymphoma diagnosis and treatment was collected retrospectively from medical records [19].

Controls

Normative data on sexual function using the BSFI from a sample of Norwegian males aged 20-59 years were available (n=3494). The questionnaire was mailed and the respondents returned it anonymously. Total respondent rate was 34%, and among men without cancer a valid BSFI questionnaire was obtained from 27% (n=929) [20]. Response rate varied according to age and was lowest among 20-29 years old (19%) increasing to 50-59 years (37%) and decreased among those >70 years (29%).

Frequency matching was performed with 10-year intervals, with three times as many controls as survivors randomly drawn within each interval.

Measurements

Fasting blood samples were collected before 10.00 AM. Testosterone, sex hormone-binding globulin (SHBG) and luteinizing hormone (LH) were measured at one laboratory, using Roche E-platform. Free androgen index (FAI) was calculated: testosterone*10/ SHBG. We categorized gonadal hormonal status according to age-specific reference values [21] of FAI and LH: 1) normal FAI + normal LH, 2) normal FAI + elevated LH, 3) low FAI + any level of LH and 4) ongoing testosterone replacement therapy.

The participants completed a multi-instrument questionnaire (125-items), including information on educational level, relationship status, current medication, the BSFI [20], Type-D14 for type D personality [22], Fatigue Questionnaire (FQ) [23], Hospital Anxiety and Depression Score (HADS) [24] and items on physical activity [25] and smoking. Details on study questionnaire, instruments (Type-D14, FQ), physical activity) and operationalization related to the instruments in addition to data on prevalence of chronic fatigue and associated factors in auto-SCT lymphoma survivors of both gender have been presented previously [18, 26].

The BSFI is an 11-item questionnaire on sexual experiences the last 30 days. The instrument constitutes three functional domains (drive 2 items, erection 3 items, ejaculation 2 items), one problem assessment domain (one item on drive, erection and ejaculation, respectively), and one item on overall sexual satisfaction [27]. Participants rated their responses from 0-4, with 0 presenting the poorest function, biggest problem or least satisfaction, and 4 the opposites. We calculated domain scores by adding values for corresponding items divided by number of items (range 0-4), and a total BSFI score

(adding all values except sexual satisfaction, range 0-40) as a measure of overall sexual functioning. Due to some difference in answer alternatives on item 7 (Figure 1) between survivors and controls, score 2 and 3 were merged for controls. Caseness was not part of the original BSFI, but has been described as a method to compare sexual problems between cases and controls [28]. Total sum score for each domain was calculated, and cut-off values for caseness (problem) were defined as; drive ≤3, erection ≤7, ejaculation ≤5, satisfaction ≤1. In addition, a combined sum score for drive, erection and ejaculation (DEE) was created and problem defined as DEE ≤10. A problem with overall sexuality was defined as the presence of either a satisfactory problem and/or a DEE problem.

The HADS assess anxiety (seven items) and depression (seven items), item agreement scored 0-3 with a possible range 0-21. Cut-off for anxiety or depression caseness was ≥8 for both conditions.

Cronbach's coefficient alpha was calculated to assess internal consistency: BSFI 0.94, Type-D personality; negative affectivity 0.90 and social inhibition 0.88, FQ total score 0.93 and HADS anxiety 0.83, depression 0.81.

Cardiovascular comorbidity

Information about CVD and risk factors were based on physicians' report (transient ischemic attack, stroke, angina pectoris and myocardial infarction), examinations (height and weight for calculation of BMI), blood samples or medication (hypertension, diabetes type 1 or 2 and hypercholesterolemia) when available (n=149), and self-reported data for the remaining participants (n=12). Obesity was defined as body mass index ≥30, kg/m^2. Hypertension, hypercholesterolemia or diabetes were defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (three consecutive measurements, mean value of last two), low-density lipoprotein ≥4.1

mmol/L (160 mg/dL) and hemoglobin A1c ≥6.5% or fasting glucose ≥7.0 mmol/L, respectively as previously described [17].

In order to elaborate on cardiovascular risk and sexual function, we constructed a categorical variable with 4 groups: 1) neither cardiovascular risk factors (smoking, obesity, hypertension or hypercholesterolemia), diabetes type 1 or 2, nor CVD (angina pectoris, myocardial infarction, transient ischemic attack or stroke); 2) ≥1 cardiovascular risk factor, but no diabetes or CVD; 3) prevalent diabetes type 1 or 2; 4) prevalent CVD.

Medication interfering with sexual function

The following medications were considered to have possible adverse effects on sexual functioning: antidepressants, benzodiazepines, antipsychotics, morphine, beta-blockers, thiazide diuretics, and spironolactone [29, 30], while pro-erectile medication was sildenafil and tadalafil. A categorical variable with four groups was constructed; 1) no medication interfering with sexual function (none); 2) medication with possible adverse effects on sexual function; 3) testosterone replacement therapy; and 4) pro-erectile medication. Men who used testosterone replacement therapy were categorized as such, regardless of other medication interfering on sexual function.

Statistics

Descriptive characteristics were presented as numbers (percent) for binary variables, median (range) for age and time variables and mean (standard deviation) for the BSFI scores. Independent sample t-test with equal variances not assumed was used to compare means between normally distributed data. We performed age-stratified binary logistic regression, age-adjusted and multivariable analyses using linear regression

models to assess associations between independent and outcome variables, presented with odds ratio (OR) [95% confidence intervals] or unstandardized regression coefficient beta. We added a quadratic term of age and time to assess non-linearity. The multivariable models were adjusted for age, relationship status and level of education. Variables with a p-value ≤0.25 in age-adjusted models were included as independent variables in a multivariable model. A backward selection process was performed.

Effect sizes were used as a measure to evaluate clinical significance and were reported as standardized mean difference with standard deviations of the controls as denominator due to heteroscedacity, equation: $SMD = \frac{mean_{survivors} - mean_{controls}}{SD_{controls}}$ [31, 32]. Effect size was considered to have none (0-0.20), moderate (0.21-0.49) and considerable (ES ≥0.50) clinical significance [33].

A two-sided p-value ≤0.05 was considered statistically significant. SPSS version 25 was used as statistical software (IBM Corporation, Armonk, New York, USA).

Ethics

Approval from Regional Ethics Committee South East (no #2011/1353) and a written informed consent prior to inclusion from all study participants were obtained.

Results

Attrition analysis

Respondents were significantly older compared with non-respondents at diagnosis, at auto-SCT and at survey, (median age was 42 vs 38 years, 45 vs 41 years and 55 vs 49 years, respectively). No significant differences in lymphoma entities, number of

207 treatment regimes prior to auto-SCT, myeloablative regimen, or radiotherapy were
208 found.
209
210 ## Study sample characteristics
211 Median age at survey for included survivors was 55 years and median time from auto-
212 SCT to survey was 8.1 years (Table 1). Two participants were <18 years at diagnosis (10
213 and 13 years) and transplanted 29 and 19 years old, respectively. Low FAI was present
214 in 15% of the survivors and 5% received testosterone replacement treatment. Anxiety,
215 depression and chronic fatigue caseness were present in 14%, 14% and 27%,
216 respectively, 52% had ≥1 cardiovascular risk factor and 13% had CVD. Fifty-five percent
217 of survivors were sedentary with a level of physical activity below recommendations
218 [19]. In total, 18% of survivors were smoking daily or occasionally.
219 Among survivors, 75% were in a relationship (married or cohabitant) and 47%
220 had completed more than 12 years of education (primary and secondary school), the
221 corresponding numbers were 86% and 72% for controls.
222
223 ## Sexual outcomes
224 Thirty percent of survivors reported sexual drive only a few days or less last month, and
225 41% reported erections firm enough to have sexual intercourse only a few times or less
226 last month. Sexual satisfaction was reported by 39% of the survivors (Figure 2).
227 Survivors had lower score on all BSFI items and sexual domains compared with controls
228 (all p-values <0.001) (Figure 3, Table 2) and the differences in domain scores were
229 clinically significant. Effect size for overall sexual functioning declined with increasing
230 age, while the opposite was the case for sexual satisfaction. The two participants <18

231 years at diagnosis reported higher BSFI scores than mean of the 20-40 year old
232 survivors (data not shown).
233 Among the survivors, 43% had sexual drive problems, 54% had erectile
234 problems, and 40% overall sexual problems (Table 3). The corresponding proportions
235 among controls were 24%, 31% and 19%. The probability of a sexual problem among
236 survivors was 3-5 fold increased for all domains in comparison to controls (Figure 4,
237 Table 3). Age-stratified comparisons to controls showed greatest increased risk for
238 sexual drive problems among men 41-65 years old, and greatest increased risk of
239 erectile and satisfactory problems among men >65 years (Table 3).
240
241 ## Medication interfering on sexual function
242 In total, 127 men (80%) reported no current medication or no medication likely to
243 interfere on sexual function, 21 men (13%) used medication with a possible adverse
244 effect on sexual function and three men (2%) used pro-erectile medication. Eight men
245 (5%) used testosterone replacement therapy.
246
247 ## Factors associated with sexual outcomes
248 In age-adjusted analyses, longer time since auto-SCT, TBI or subdiaphragmal irradiation,
249 chronic fatigue, anxiety symptoms, diabetes type I or II, CVD, medication with possible
250 adverse effect on sexual function, testosterone replacement therapy, low FAI and being
251 sedentary were significantly associated with a lower sexual functioning overall, in
252 addition to age >55 years. Longer time since auto-SCT, subdiaphragmal irradiation,
253 type-D personality, chronic fatigue, anxiety, CVD and low FAI were significantly
254 associated with lower sexual satisfaction (Table 4).

In multivariable models age >55 years, chronic fatigue and presence of CVD was negatively associated with lower erectile function, while age >55 years, chronic fatigue, medication with possible adverse effect on sexual function, testosterone replacement therapy, and a sedentary lifestyle were significantly associated with a lower sexual functioning overall. Chronic fatigue was significantly associated with a lower overall sexual satisfaction (Table 4).

Discussion

In this considerable sample of male auto-SCT lymphoma survivors, 40% had overall sexual problems, and both functioning and satisfaction were reduced compared with age-matched controls.

There is a lack of studies comparing sexual function among auto-SCT lymphoma survivors with controls. However, supporting our findings are studies reporting on a sexual functioning inferior to controls in both lymphoma survivors who did not have auto-SCT and survivors of hematological malignancies after SCT [6, 10]. Compared with lymphoma survivors not treated with auto-SCT, sexual functioning might be even worse in our study group, as indicated by a comparison of effect sizes [6].

Stratified by age, we observed an increasing difference in erectile function and sexual satisfaction between survivors and controls with increasing age groups, despite the opposite trend for assessment of sexual problems. Expectations of normal sexual functioning are likely to differ between age groups, leading to a response shift where the older survivors report less problems related to a certain reduction in sexual function, than younger survivors. In addition, the younger survivors might have been more resilient to functional reductions before satisfaction was affected.

The associations found in age-adjusted models reflect the multifactorial (social, psychological and physiological) interactions on sexual function also described in the general population [34, 29].

In multivariable models, survivors aged 41-55 years did not differ in sexual outcomes compared with the reference group (survivors age 26-40 years), however a significant worsening was found for patients above the age of 55 years. A relationship between increasing age and reduced sexual functioning is well known in the general population [34] and from previous reports on lymphoma survivors [6, 2]. Reduced physical health, adverse effects of multipharmacy in the elderly, decrease in testosterone and lack of partner may contribute to this finding [35].

In this study, chronic fatigue was significantly associated with lower sexual functioning and satisfaction, in line with earlier findings [36], and this illustrates the detrimental effect chronic fatigue has on many aspects of life.

Thirteen percent of survivors had CVD with a significant negative association with erectile function. Atherosclerosis as well as endothelial dysfunction are common causes of both CVD and ED [37]. Hence, these conditions share many risk factors. ED precedes CVD by 2-5 years [16], and we believe this is of special importance as auto-SCT lymphoma survivors are at increased risk of fatal CVD [1, 38].

The majority of survivors were sedentary with reduced overall sexual functioning compared with the physically active survivors. Contrasting earlier reports, physical inactivity was not related to ED in particular [39]. Sedentary survivors had a reduced sexual function that they considered more problematic compared with the physically active. However, the sedentary survivors did not report lower sexual satisfaction than the physically active survivors.

In age-adjusted analyses, low FAI was related to lower sexual functioning overall and less sexual satisfaction. These significant associations were lost in multivariable models indicating that factors described above were more important than FAI for sexual outcomes. Our findings are diverging from previous reports describing associations between sexual function and testosterone levels [6, 40]. We present two plausible explanations: 1) Low FAI seems to be associated with CVD [41], a factor included in our multivariable analyses, and 2) a small proportion of survivors had gonadal dysfunction in our study, reducing the power to detect a significant association.

All auto-SCT lymphoma survivors treated in Norway until 2008 were accounted for and invited to participate in the survey. A high participation rate assures good representativeness, and external validity of our results. With long follow-up time, reversible aspects of sexual functions should be restored after treatment. In addition, long follow-up time enables us to examine the association between CVD and ED.

The BSFI is a validated instrument with good psychometric properties, and using a control group reporting on the same instrument is a considerable strength, especially in an area where a diversity of instruments have been used. The response rate in the control group was low, which is a problem with questionnaire studies of sexuality in the general population. Additionally, the representativeness was unknown [20]. However, the normative data resemble findings in a similar American study using the BSFI with better response rate [42]. Hence, we believe the control group was adequate, but we advise for careful interpretations. In addition, differences in education and relationship status between survivors and controls might represent selection bias.

Further limitations include the cross-sectional design that prevents us from addressing causality. Adding medication in the multivariable models in order to adjust for possible effects on sexual function might have diminished the associations between

both CVD and mental distress with the sexual outcomes as co-linearity between these variables are likely to be present. Our outcomes of interest were based on patient reported outcome measures, which are associated with recall difficulties [43]. The sample size of young survivors was small hence, statistical analyses on effect size are uncertain.

Clinical implications

Erectile dysfunction might be a symptom of silent CVD and addressing sexual function at consultations may reveal auto-SCT survivors in need of support for lifestyle changes or medical intervention in order to ameliorate cardiovascular risk factors and possibly avoid or delay CVD events [30, 44, 45]. In particular, physical activity might have positive implications for CVD, chronic fatigue and anxiety that are more prevalent in SCT survivors [15], and perhaps erectile function can be improved [39]. Treatment for sexual problems should be offered according to previously published guidelines [46]. First, assessment of gonadal function and testosterone replacement therapy should be considered. Second, in case of erectile dysfunction use of pro-erectile medication (assuming no contraindications) or use of a vacuum erectile device is recommended and finally survivors with relational or psychosocial problem should be referred to individual or couple counseling.

Conclusion

Our study identifies sexual dysfunction as a problem for many male auto-SCT survivors, however sexuality is a neglected issue during follow-up [47]. Hence, physicians should address sexual function before, during, and after treatment in order to identify sexual problems and their cause in auto-SCT survivors. By acknowledging the importance of sexual function after cancer, we believe that more auto-SCT male survivors will have sexual problems diagnosed, treated and hopefully improved.

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Competing interests statement

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Figure Legends

Figure 1 Flowchart. Auto-SCT, high-dose chemotherapy with autologous stem-cell transplantation; SCT, stem-cell transplantation; agg NHL, aggressive non-Hodgkin lymphoma; HL, Hodgkin lymphoma; TBI, total body irradiation; BSFI, Brief Sexual Function Inventory. *Two non-eligible survivors were identified during data assessment for the present study, hence they were excluded from analyses.

Figure 2 Male lymphoma survivors treated with high-dose chemotherapy with autologous stem-cell transplantation response to the Brief Sexual Function Inventory items.

Figure 3 Brief Sexual Function Inventory (BSFI) mean item score in male lymphoma survivors treated with high-dose chemotherapy with autologous stem-cell transplantation (n=159) and controls (n=477).

Figure 4 Odds Ratio and 95% Confidence Interval [95%] for Brief Sexual Function Inventory (BSFI) problem* among male lymphoma survivors treated with high-dose chemotherapy with autologous stem-cell transplantation, reference = controls. *Categorized as problem (caseness) if total score on current domain: Sexual drive ≤3; erectile function ≤7; ejaculatory function ≤5; DEE (drive, erection, ejaculation) problems ≤10; sexual satisfaction ≤1; overall sexual problem= either DEE problem or overall satisfaction problem

Table 1 Characteristics of study sample at diagnosis and survey, and normative controls

	Auto-SCT male lymphoma survivors n=159	Controls n=477
SOCIODEMOGRAPHICS		
Age at diagnosis, years, median (range)	42.0 (10-65)	
Age at auto-SCT, years, median (range)	45.0 (18-67)	
Age at survey, years, median (range)	55.0 (26-77)	55.0 (20-79)
Time auto-SCT – survey, years, median (range)	8.2 (3.2-23)	
In a relationship[i]	119 (75)	412 (86)
Education >12 years	74 (47)	343 (72)
LYMPHOMA AND TREATMENT		
Lymphoma entity		
Aggressive Non-Hodgkin lymphoma[ii]	108 (68)	
Indolent Non-Hodgkin lymphoma[iii]	15 (9.4)	
Hodgkin lymphoma	36 (23)	
Stage at diagnosis:		
I-II	51 (32)	
III-IV	108 (68)	
Treatment regimes prior to auto-SCT		
1	56 (35)	
2	79 (50)	
≥3	24 (15)	
Radiotherapy		
None	61 (38)	
Other[iv]	1 (0.6)	
Supradiaphragmal[v]	37 (23)	
Total body irradiation[vi]	25 (16)	
Subdiaphragmal[vii]	35 (22)	
Myeloablative regime		
BEAM	132 (83)	
Total body irradiation	27 (17)	
Curable disease[viii]	102 (64)	
Relapse after auto-SCT	27 (17)	
HORMONAL STATUS AND THERAPY*		
Gonadal status[ix]		
Normal FAI and LH	79 (50)	
Normal FAI and elevated LH	32 (20)	
Low FAI and any level of LH	24 (15)	
Testosterone replacement therapy	8 (5.0)	
COMORBIDITY		
Type-D personality[x]	33 (21)	
Chronic fatigue	43 (27)	
Anxiety caseness	22 (14)	
Depression caseness	22 (14)	
Cardiovascular risk or disease[xi]		
None	44 (28)	
≥1 Cardiovascular risk factor[xii]	82 (52)	
Diabetes type 1 or 2	13 (8.2)	
Cardiovascular disease[xiii]	20 (13)	
MEDICATION INTERFERING WITH SEXUAL FUNCTION		
None	127 (80)	

Possible adverse effect on sexual function[xiv]	21 (13)
Testosteron replacement therapy[xv]	8 (5.0)
Pro-erectile medication[xvi]	3 (1.9)
LIFESTYLE BEHAVIOR	
Sedentary[xvii]	87 (55)
Smoking[xviii]	29 (18)

Abbreviations: Auto-SCT, high-dose chemotherapy with autologous stem-cell transplantation; BEAM, high-dose chemotherapy regime (carmustine, etoposide, cytarabine and melphalan); FAI, free androgen index; LH, luteinizing hormone.
Missing values among cases: In a relationship, n=1; income, n=3; gonadal hormonal status, n= 16; Type D personality, n=12; chronic fatigue, n=1; hypercholesterolemia, n=11; myocardial infarction, n=1; sedentary, n=3;
Missing values among controls: In a relationship, n=3; education, n=6.
*N=143 because 16 participants did not have blood samples available.
Data are presented as numbers (%) unless otherwise specified.

[i] Survivors: Married or cohabitant. Controls: Married or in an intimate relationship.
[ii] Includes: Lymphoblastic lymphoma, n=13; Burkitt lymphoma, n=8; diffuse large B-cell lymphoma, n=27; mantle cell lymphoma, n=30; T-cell lymphomas, n=16; transformed lymphoma, n=12, other (not specified), n=2.
[iii] Includes follicular or other indolent lymphomas.
[iv] Irradiated field unknown.
[v] Irradiated fields supradiaphragmal: ear/nose/throat/thyroideal, n=3; collum, n=9; supra/infraclavicular, n=12; axillar, n=9; columna, n=3, mediastinal, n=20; mantle field, n=4; other, n=8;
[vi] Two of the TBI treated participants also received subdiaphragmal irradiation and was categorized in that group, hence they do not appear in this group. Additional irradiated fields: collum, n=1; supra/infraclavicular, n=1, other, n=1.
[vii] Irradiated fields subdiaphragmal: Abdominal, n=20; paraaortal, n=1; reversed Y, n=2, pelvic, n=4, groin, n=5; spleen, n=1, lower extremities, n=2. Additional irradiated fields supradiaphragmal: ear/nose/throat, n=1; collum, n=5; supra/infraclavicular, n=6; columna, n=3; mediastinal, n=5, mantle field, n=4; other, n= 6. Total body irradiation, n=2.
[viii] Curable: lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma; palliative: follicular or other indolent lymphoma, mantle cell lymphoma, transformed lymphoma.
[ix] Survivors on testosterone replacement therapy excluded. According to age-specific reference values: FAI: 20-29, 4.8-13.6; 30-39 years, 3.8-11.0; 40-49 years, 3.1-9.1; 50-59 years, 2.7-7.7; 60-69 years, 2.3-6.5; 70-79 years, 2.1-5.5. LH IU/L: 20-29, 1.95-9.4; 30-39 years, 1.93-9.7; 40-49 years, 1.95-10.0; 50-59 years, 2.01-10.4; 60-69 years, 2.10-10.8; 70-79 years, 2.22-11.2.
[x] Type-D personality; negative affectivity and social inhibition.
[xi] Survivors with risk factors or diabetes type 1 or 2 in addition to disease were categorized as disease.
[xii] Risk factors: Obesity (body mass index >30) (n=18), smoking daily or occasionally (n=26, of note three smokers were categorized as cardiovascular disease hence do not appear here), hypertension (n=36), hypercholesterolemia (n=43, 5 missing).
[xiii] Disease: Stroke or transitory ischemic attack (n=10), angina pectoris (n=8) or myocardial infarction (n=7, 1 missing). Four males had >1 disease, hence appear in more than one group.
[xiv] Antidepressant (n=3), benzodiazepines (n=5), antipsychotics (n=1) morphine (n=1) beta-blocker (n=11), thiazide diuretics (n=6), spironolactone (n=1). Four males used more than one of these medications, hence appear in more than one group.
[xv] Four of these men used additional medication interfering with sexual function: case 1, thiazide diuretics and beta-blocker; case 2, beta-blocker, antidepressant and morphine; case 3, antidepressiva; case 4, tadalafil.
[xvi] Sildenafil (n=2), tadalafil (n=2), one male used both medications.
[xvii] Physical activity less than 150 min/week of moderate activity, or less than 75 min of strenuous activity
[xviii] Daily or occassionally.

Table 2 BSFI outcomes (sexual function domains, total BSFI score and sexual satisfaction) among male auto-SCT lymphoma survivors and normative controls, overall and age-stratified

	Sexual drive	Erectile function	Ejaculatory function	Problem assessment	Total BSFI score (overall sexual functioning)	Sexual satisfaction
TOTAL SAMPLE						
Auto-SCT survivors (n=159)	1.81 (0.95)	2.22 (1.36)	2.72 (1.41)	2.56 (1.27)	23.4 (10.8)	1.97 (1.22)
Controls (n=477)	2.24 (0.83)	2.94 (1.11)	3.46 (0.82)	3.21 (1.04)	29.9 (8.53)	2.61 (1.05)
p-value*	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
SMD[#]	**-0.52**	**-0.65**	**-0.90**	**-0.63**	**-0.76**	**-0.61**
YOUNG (20-40 years)						
Auto-SCT survivors (n=18)	2.47 (1.04)	3.17 (1.08)	3.53 (0.79)	2.93 (1.23)	30.3 (9.14)	2.11 (1.28)
Controls (n=55)	2.65 (0.80)	3.60 (0.57)	3.85 (0.34)	3.65 (0.68)	34.8 (4.60)	2.60 (1.05)
p-value*	0.50	0.12	0.11	**0.03**	0.06	0.15
SMD[#]	-0.23	**-0.75**	**-0.94**	**-1.06**	**-0.98**	-0.47
MIDDLE-AGED (>40-55 years)						
Auto-SCT survivors (n=65)	2.12 (0.77)	2.78 (1.13)	3.28 (0.95)	2.77 (1.25)	27.5 (9.39)	2.23 (1.14)
Controls (n=191)	2.52 (0.71)	3.40 (0.80)	3.77 (0.45)	3.57 (0.70)	33.5 (5.81)	2.78 (0.98)
p-value*	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**
SMD[#]	**-0.56**	**-0.78**	**-1.09**	**-1.14**	**-1.03**	**-0.56**
OLD (>55-65 years)						
Auto-SCT survivors (n=49)	1.50 (0.95)	1.80 (1.34)	2.16 (1.61)	2.35 (1.33)	19.8 (10.9)	1.86 (1.29)
Controls (n=128)	2.07 (0.74)	2.67 (1.04)	3.35 (0.86)	3.03 (1.13)	28.0 (8.43)	2.55 (1.10)
p-value*	**<0.001**	**<0.001**	**<0.001**	**0.002**	**<0.001**	**0.001**
SMD[#]	**-0.77**	**-0.84**	**-1.38**	**-0.60**	**-0.97**	**-0.63**
OLDEST (>65 years)						
Auto-SCT survivors (n=27)	1.19 (0.75)	0.99 (0.84)	1.85 (1.46)	2.16 (1.10)	15.5 (7.67)	1.44 (1.12)
Controls (n=103)	1.70 (0.82)	2.05 (1.22)	2.84 (1.04)	2.54 (1.22)	22.8 (9.21)	2.39 (1.10)
p-value*	**0.003**	**<0.001**	**0.002**	0.13	**<0.001**	**<0.001**
SMD[#]	**-0.62**	**-0.87**	**-0.95**	-0.31	**-0.79**	**-0.86**

Abbreviations: BSFI, Brief Sexual Function Inventory; Auto-SCT, high-dose chemotherapy with autologous stem-cell transplantation; SMD, standardized mean difference.
Range score possible: sexual drive 0-4, erectile function 0-4, ejaculatory function 0-4, problem assessment 0-4, total BSFI score 0-40, sexual satisfaction 0-4.
Bold type indicating statistical significance (p-value <0.05) or considerable clinical significance (effect size ≥0.50).
Data are presented as mean (SD) unless otherwise specified.
*Independent sample t-test, equal variances not assumed.
[#] Equation: $SMD = \frac{mean_{survivors} - mean_{controls}}{SD_{controls}}$

Table 3 Age-stratified odds ratios for BSFI caseness (problem) comparing auto-SCT lymphoma survivors with normative controls using logistic regression models

	DOMAIN PROBLEM					
	Sexual drive	Erectile function	Ejaculatory function	DEE	Sexual satisfaction	Overall sexual problem
TOTAL SAMPLE, n=159 cases/477 controls						
Auto-SCT survivors	69 (43)	86 (54)	59 (37)	41 (26)	55 (35)	63 (40)
Controls	114 (24)	148 (31)	80 (17)	42 (8.8)	74 (16)	90 (19)
Odds Ratio [95%CI], reference = controls*	**2.96 [1.96, 4.47]**	**3.66 [2.39, 5.61]**	**3.96 [2.51, 6.26]**	**5.62 [3.20, 9.87]**	**2.97 [1.96, 4.50]**	**3.08 [2.05, 4.62]**
YOUNG SAMPLE (20-40 years) n=18 cases/55 controls						
Auto-SCT survivors	3 (17)	5 (28)	4 (22)	1 (5.6)	5 (28)	5 (28)
Controls	8 (15)	4 (7.3)	1 (1.8)	0	8 (15)	8 (15)
Odds Ratio [95%CI], reference = controls	NA	NA	NA	NA	NA	NA
MIDDLE-AGED SAMPLE (>40-55 years) n=65 survivors/191 controls						
Auto-SCT survivors	18 (28)	23 (35)	13 (20)	6 (9.2)	16 (25)	17 (26)
Controls	19 (9.9)	23 (12)	9 (4.7)	1 (0.5)	23 (12)	23 (12)
Odds Ratio [95%CI], reference = controls	**3.47 [1.69-7.13]**	**4.00 [2.05-7.81]**	**5.06 [2.05-12.5]**	NA	**2.39 [1.17-4.87]**	**2.59 [1.28, 5.23]**
OLD SAMPLE (>55-65 years) n=49 survivors/128 controls						
Auto-SCT survivors	28 (57)	34 (69)	24 (49)	19 (39)	20 (41)	24 (49)
Controls	36 (28)	55 (43)	27 (21)	12 (9.4)	23 (18)	25 (20)
Odds Ratio [95%CI], reference = controls	**3.41 [1.72, 6.76]**	**3.01 [1.49, 6.07]**	**3.59 [1.78, 7.25]**	**6.12 [2.68, 14.0]**	**3.15 [1.52, 6.51]**	**3.96 [1.94, 8.05]**
OLDEST SAMPLE (>65 years) n=27 survivors/103 controls						
Auto-SCT survivors	20 (74)	24 (89)	18 (67)	15 (56)	14 (52)	17 (63)
Controls	51 (50)	66 (64)	43 (42)	29 (28)	20 (19)	34 (33)

Odds Ratio [95%CI], reference= controls	**2.91 [1.13-7.48]**	**4.49 [1.27-15.9]**	**2.79 [1.15-6.80]**	**3.19 [1.33-7.63]**	**4.47 [1.82-11.0]**	**3.45 [1.43-8.34]**

Abbreviations: BSFI, Brief Sexual Function Inventory; auto-SCT, high-dose chemotherapy with autologous stem-cell transplantation; DEE, drive, erection and ejaculation; NA, not applicable.

*Age-adjusted.

Bold type indicating statistical significance (p-value <0.05).

Data are presented as numbers (%) unless otherwise specified.

Table 4. Association between BSFI outcomes (function domains, total BSFI score and sexual satisfaction) and characteristics of study sample (n=159), A) age-adjusted and B) multivariable linear regression models

	Mean Sum Sexual Drive	Mean Sum Erectile function	Mean Sum Ejaculatory function	Mean Sum Problem assessment	Total BSFI score (overall sexual functioning)	Sexual satisfaction
A) AGE-ADJUSTED MODELS						
SOCIODEMOGRAPHICS						
Age at auto-SCT, per 10 years	**-0.25 [-0.36, -0.14]**	**-0.43 [-0.58, -0.28]**	**-0.40 [-0.56, -0.25]**	*-0.14 [0.29, 0.00]*	**-3.02 [-4.23, -1.80]**	*-0.14 [-0.28, 0.00]*
Age at survey						
26 – 40 years	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
>40 – 55 years	*-0.36 [-0.81, 0.09]*	*-0.38 [-0.99, 0.22]*	-0.24 [-0.91, 0.42]	-0.16 [-0.81, 0.50]	-2.82 [-7.84, 2.21]	0.12 [-0.51, 0.75]
>55 – 65 years	**-0.97 [-1.44, -0.51]**	**-1.36 [-1.99, -0.74]**	**-1.37 [-2.05, -0.68]**	*-0.57 [-1.25, 0.11]*	**-10.5 [-15.7, -5.26]**	-0.25 [-0.91, 0.40]
>65 years	**-1.29 [-1.80, -0.77]**	**-2.18 [-2.87, -1.49]**	**-1.68 [-2.44, -0.92]**	**-0.77 [-1.51, -0.02]**	**-14.8 [-20.5, -9.02]**	*-0.67 [-1.39, 0.05]*
Time auto-SCT – survey, per 5 years	**-0.16 [-0.28, -0.04]**	**-0.21 [-0.37, -0.05]**	*-0.16 [-0.34, 0.02]*	**-0.18 [-0.35, 0.00]**	**-1.78 [-3.11, -0.45]**	**-0.18 [-0.35, -0.02]**
In a relationship[i]	*-0.23 [-0.54, 0.09]*	0.00 [-0.43, 0.42]	-0.11 [-0.57, 0.36]	-0.06 [-0.52, 0.41]	-0.84 [-4.38, 2.70]	-0.14 [-0.58, 0.30]
Education > 12 years	**-0.31 [-0.58, -0.04]**	-0.16 [-0.53, 0.21]	-0.09 [-0.50, 0.31]	-0.19 [-0.59, 0.21]	*-1.86 [-4.92, 1.20]*	*-0.24 [-0.62, 0.15]*
LYMPHOMA AND TREATMENT						
Lymphoma entity						
Aggressive NHL[ii]	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
Indolent NHL[iii]	*0.35 [-0.12, 0.82]*	0.20 [-0.43, 0.83]	0.31 [-0.38, 1.01]	0.08 [-0.60, 0.77]	2.19 [-3.06, 7.44]	0.11 [-0.55, 0.77]
Hodgkin lymphoma	-0.08 [-0.43, 0.27]	*-0.34 [-0.81, 0.13]*	-0.11 [-0.62, 0.41]	-0.17 [-0.68, 0.34]	-1.90 [-5.79, 1.99]	-0.02 [-0.51, 0.47]
Stage III-IV at diagnosis	0.11 [-0.19, 0.40]	-0.08 [-0.48, 0.33]	0.09 [-0.35, 0.53]	0.10 [-0.34, 0.53]	0.46 [-2.88, 3.79]	-0.09 [-0.50, 0.33]
Treatment regimes prior to auto-SCT						
1	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
2	0.00 [-0.30, 0.30]	-0.10 [-0.50, 0.31]	-0.20 [-0.65, 0.24]	-0.19 [-0.62, 0.24]	-1.24 [-4.60, 2.11]	0.06 [-0.36, 0.48]
≥3	0.05 [-0.37, 0.47]	-0.15 [-0.71, 0.42]	-0.05 [-0.66, 0.57]	0.36 [-0.25, 0.96]	0.64 [-4.04, 5.31]	0.25 [-0.34, 0.84]
TBI myeloablative regimen[iv]	*-0.26 [-0.62, 0.11]*	-0.17 [-0.66, 0.32]	-0.28 [-0.81, 0.26]	*-0.34 [-0.87, 0.19]*	*-2.59 [-6.65, 1.46]*	-0.15 [-0.66, 0.36]
Radiotherapy						
None	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.

Other	NA	NA	NA	NA	NA	NA
Supradiaphragmal	-0.20 [-0.59, 0.18]	*-0.40 [-0.91, 0.12]*	*-0.54 [-1.10, 0.02]*	*-0.38 [-0.95, 0.18]*	*-3.83 [-8.10, 0.43]*	-0.27 [-0.81, 0.27]
Total body irradiation	**-0.49 [-0.90, -0.08]**	*-0.52 [-1.07, 0.03]*	**-0.79 [-1.39, -0.20]**	*-0.57 [-1.17, 0.03]*	**-5.84 [-10.4, -1.32]**	*-0.49 [-1.06, 0.09]*
Subdiaphragmal	*-0.30 [-0.66, 0.06]*	*-0.46 [-0.94, 0.02]*	**-0.58 [-1.10, -0.06]**	*-0.36 [-0.88, 0.17]*	**-4.21 [-8.16, -0.25]**	**-0.54 [-1.04,- 0.04]**
COMORBIDITY						
Type-D personality[v]	*-0.25 [-0.60, 0.11]*	*-0.44 [-0.91, 0.03]*	*-0.28 [-0.80, 0.24]*	*-0.51 [-1.01, 0.00]*	*-3.89 [-7.78, 0.00]*	**-0.56 [-1.04, -0.07]**
Chronic fatigue caseness	*-0.19 [-0.50, 0.11]*	**-0.53 [-0.94, -0.13]**	*-0.44 [-0.88, 0.01]*	**-0.46 [-0.90, -0.02]**	**-4.23 [-7.58, -0.88]**	**-0.64 [-1.05, -0.22]**
Anxiety caseness	-0.16 [-0.56, 0.23]	**-0.62 [-1.15, -0.10]**	**-0.64 [-1.22, -0.07]**	**-0.60 [-1.17, 0.03]**	**-5.26 [-9.62, -0.91]**	**-0.78 [-1.32, -0.23]**
Cardiovascular risk or disease[vi]						
None	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
Cardiovascular risk	0.07 [-0.25, 0.38]	-0.07 [-0.49, 0.34]	-0.01 [-0.47, 0.44]	-0.16 [-0.61, 0.30]	-0.59 [-4.03, 2.85]	-0.02 [-0.46, 0.42]
Diabetes type 1 or 2	*-0.41 [-0.96, 0.13]*	**-0.79 [-1.49, -0.08]**	*-0.70 [-1.48, 0.09]*	-0.47 [-1.25, 0.32]	**-5.99 [-11.9, -0.09]**	*-0.44 [-1.20, 0.31]*
Cardiovascular disease	*-0.27 [-0.73, 0.19]*	**-1.02 [-1.62, -0.43]**	**-0.91 [-1.58, -0.25]**	**-0.86 [-1.55, -0.22]**	**-7.84 [-12.8, -2.91]**	**-0.81 [-1.44, -0.17]**
MEDICATION						
None	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
Noxious on sexual functioning	**-0.53 [-0.92, -0.13]**	**-0.80 [-1.33, -0.27]**	**-0.70 [-1.29, -0.12]**	*-0.55 [-1.12, 0.03]*	**-6.49 [-10.9, -2.12]**	*-0.37 [-0.93, 0.19]*
Testosteron substitution	*-0.37 [-0.99, 0.25]*	*-0.80 [-1.63, 0.02]*	**-0.92 [-1.83, -0.01]**	**-1.28 [-2.17, -0.39]**	**-8.84 [-15.6, -2.04]**	*-0.88 [-1.76, -0.01]*
Pro-erectile medication	NA	NA	NA	NA	NA	NA
GONADAL HORMONAL STATUS[vii]						
Hormonal groups[viii]						
Normal FAI and LH	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
Normal FAI, elevated LH	0.19 [-0.20, 0.57]	0.08 [-0.47, 0.62]	-0.15 [-0.71, 0.42]	-0.16 [-0.67, 0.35]	-0.17 [-4.51, 4.17]	-0.02 [-0.51, 0.46]
Low FAI, any level of LH	*-0.27 [-0.70, 0.15]*	**-0.69 [-1.30, -0.08]**	*-0.60 [-1.23, 0.04]*	*-0.40 [-0.97, 0.17]*	**-5.02 [-9.87, -0.17]**	**-0.74 [-1.29, -0.20]**
LIFESTYLE BEHAVIOR						
Sedentary[ix]	**-0.29 [-0.56, -0.02]**	**-0.39 [-0.76, -0.03]**	**-0.63 [-1.03, -0.24]**	**-0.53 [-0.92, -0.14]**	**-4.60 [-7.59, -1.62]**	-0.19 [-0.57, 0.19]
B) MULTIVARIABLE MODELS[x]						
SOCIODEMOGRAPHICS						
Age at survey						
26 – 40 years	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
>40 – 55 years	-0.23 [-0.69, 0.22]	-0.09 [-0.68, 0.50]	-0.04 [-0.73, 0.64]	0.08 [-0.60, 0.75]	-0.14 [-5.18, 4.89]	0.31 [-0.32, 0.95]
>55 – 65 years	**-0.88 [-1.35, -0.41]**	**-1.13 [-1.74, -0.51]**	**-1.27 [-1.98, -0.56]**	*-0.38 [-1.08, 0.32]*	**-8.91 [-14.1, -3.73]**	*-0.20 [-0.85, 0.46]*
>65 years	**-1.07 [-1.57, -0.56]**	**-1.92 [-2.57, -1.26]**	**-1.46 [-2.22, -0.70]**	*-0.57 [-1.32, 0.18]*	**-12.6 [-18.2, -7.01]**	*-0.58 [-1.29, 0.13]*
In a relationship	*-0.22 [-0.53, 0.08]*	-0.03 [-0.44, 0.38]	-0.13 [-0.59, 0.33]	-0.07 [-0.46, 0.45]	-0.94 [-4.36, 2.47]	-0.12 [-0.55, 0.32]

Education > 12 years	**-0.28 [-0.55, -0.01]** **Ble sign**	-0.07 [-0.42, 0.29]	-0.10 [-0.51, 0.30]	-0.11 [-0.51, 0.29]	-1.16 [-4.13, 1.82]	*-0.17 [- 0.55, 0.21]*
COMORBIDITY						
Chronic fatigue		**-0.53 [-0.91, -0.14]**			**-3.75 [-7.01, -0.47]**	**-0.66 [-1.08, -0.24]**
Cardiovascular risk or disease[viii]						
None		0 Ref.				
Cardiovascular risk		-0.02 [-0.43, 0.38]				
Diabetes type 1 or 2		*-0.57 [-1.26, 0.13]*				
Cardiovascular disease		**-0.87 [-1.48, -0.26]**				
MEDICATION INTERFERING WITH SEXUAL FUNCTION						
None	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.	0 Ref.
Possible adverse effect on sexual function	**-0.47 [-0.86, -0.09]**	**-0.69 [-1.21, -0.17]**	**-0.62 [-1.21, -0.04]**	-0.48 [-1.06, 0.10]	**-6.42 [-10.7, -2.14]**	-0.44 [-0.99, 0.11]
Testosteron substitution	-0.23 [-0.83, 0.38]	-0.51 [-1.32, 0.30]	-0.82 [-1.72, 0.09]	**-1.20 [-2.09, -0.30]**	**-7.90 [-14.5, -1.25]**	*-0.79 [-1.66, 0.07]*
Pro-erectile medication	NA	NA	NA	NA	NA	NA
LIFESTYLE BEHAVIOR						
Sedentary[x]	**-0.29 [-0.56, -0.03]**		**-0.62 [-1.02, -0.22]**	**-0.49 [-0.88, -0.09]**	**-4.02 [-6.97, -1.07]**	

Abbreviations: BSFI, Brief Sexual Function Inventory; auto-SCT, high-dose chemotherapy with autologous stem-cell transplantation; TBI, total body irradiation; NA, not applicable; FAI, free androgen index; LH, luteinizing hormone.

Range score possible: sexual drive 0-4, erectile function 0-4, ejaculatory function 0-4, problem assessment 0-4, total BSFI score 0-40, sexual satisfaction 0-4.

Bold type indicating statistical significance (p-value <0.05).

Italic type indicating p-value <0.25.

Data are presented as unstandardized coefficient beta [95% Confidence Interval], unless otherwise specified.

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[i] Married or cohabitant.

[ii] Includes: Lymphoblastic lymphoma, n=13; Burkitt lymphoma, n=8; diffuse large B-cell lymphoma, n=27; mantle cell lymphoma, n=30; T-cell lymphomas, n=16; transformed lymphoma, n=12, other (not specified), n=2.

[iii] Follicular or other indolent lymphomas.

[iv] TBI vs. BEAM (high-dose chemotherapy regime (carmustine, etoposide, cytarabine and melphalan)).

[v] Type-D personality; negative affectivity and social inhibition.

[vi] None, neither risk nor disease; Cardiovascular risk, either obesity (body mass index >30), smoking, hypertension, or hypercholesterolemia; diabetes type 1 or 2; cardiovascular disease, either transitory ischemic attack, stroke, angina pectoris or myocardial infarction.

[vii] Age was omitted as covariate in order to avoid over-adjustment as hormonal status was operationalized based on age-specific reference values.
[viii] Survivors on testosterone replacement therapy excluded. According to age-specific reference values: FAI: 20-29, 4.8-13.6; 30-39 years, 3.8-11.0; 40-49 years, 3.1-9.1; 50-59 years, 2.7-7.7; 60-69 years, 2.3-6.5; 70-79 years, 2.1-5.5. LH IU/L: 20-29, 1.95-9.4; 30-39 years, 1.93-9.7; 40-49 years, 1.95-10.0; 50-59 years, 2.01-10.4; 60-69 years, 2.10-10.8; 70-79 years, 2.22-11.2.
[ix] Physical activity less than 150 min/week of moderate activity, or less than 75 min of strenuous activity.
[x] Adjusted for age, relationship, education and medication interfering with sexual function performed backward selection were variables with p-value<0.25 were included. Only variables that remained statistically significant (p-value<0.05) are reported.

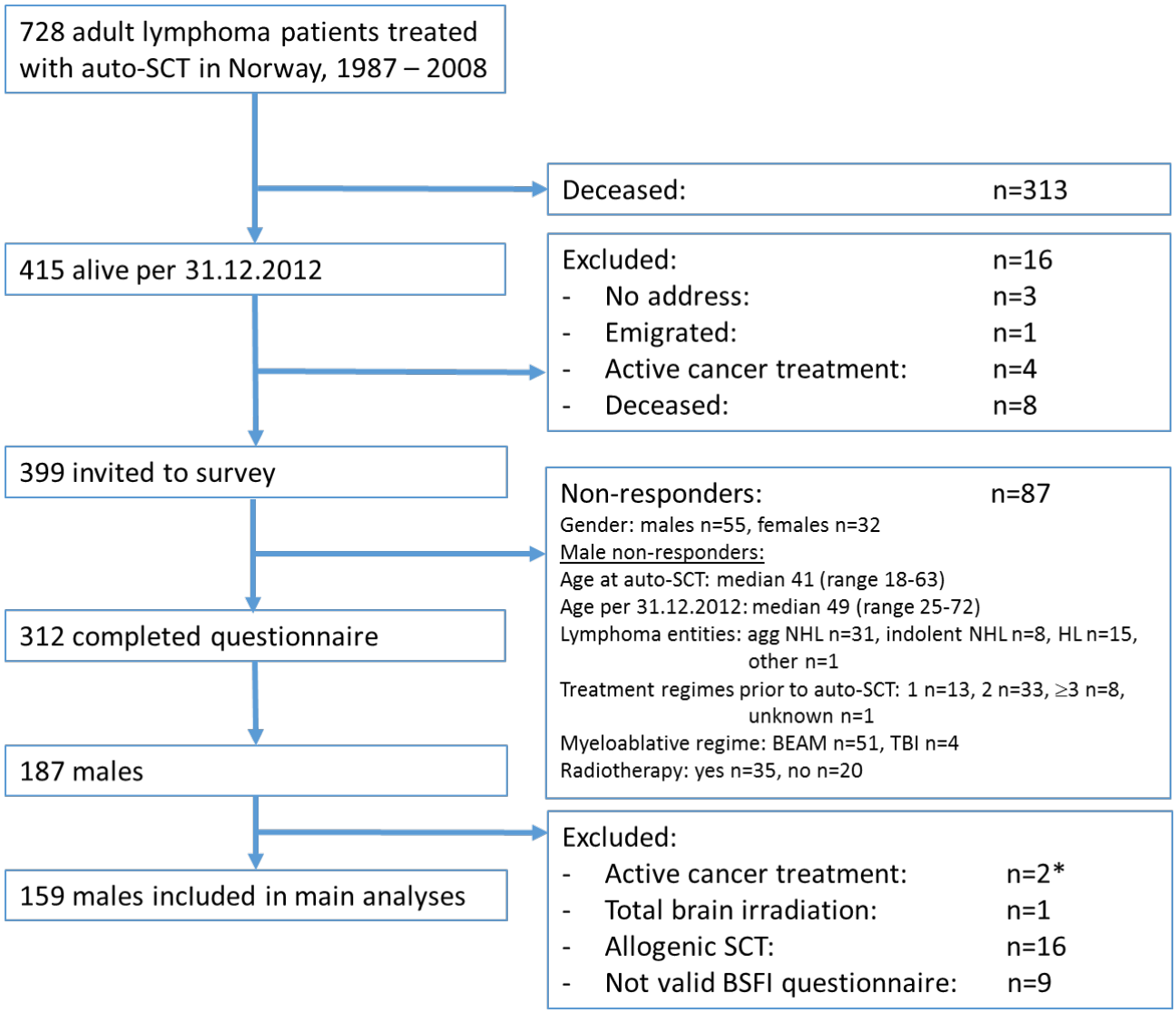

728 adult lymphoma patients treated with auto-SCT in Norway, 1987 – 2008
Deceased: n=313
415 alive per 31.12.2012
Excluded: n=16
- No address: n=3
- Emigrated: n=1
- Active cancer treatment: n=4
- Deceased: n=8
399 invited to survey
Non-responders: n=87
Gender: males n=55, females n=32
Male non-responders:
Age at auto-SCT: median 41 (range 18-63)
Age per 31.12.2012: median 49 (range 25-72)
Lymphoma entities: agg NHL n=31, indolent NHL n=8, HL n=15, other n=1
Treatment regimes prior to auto-SCT: 1 n=13, 2 n=33, ≥3 n=8, unknown n=1
Myeloablative regime: BEAM n=51, TBI n=4
Radiotherapy: yes n=35, no n=20
312 completed questionnaire
187 males
Excluded:
- Active cancer treatment: n=2*
- Total brain irradiation: n=1
- Allogenic SCT: n=16
- Not valid BSFI questionnaire: n=9
159 males included in main analyses

Figure 1

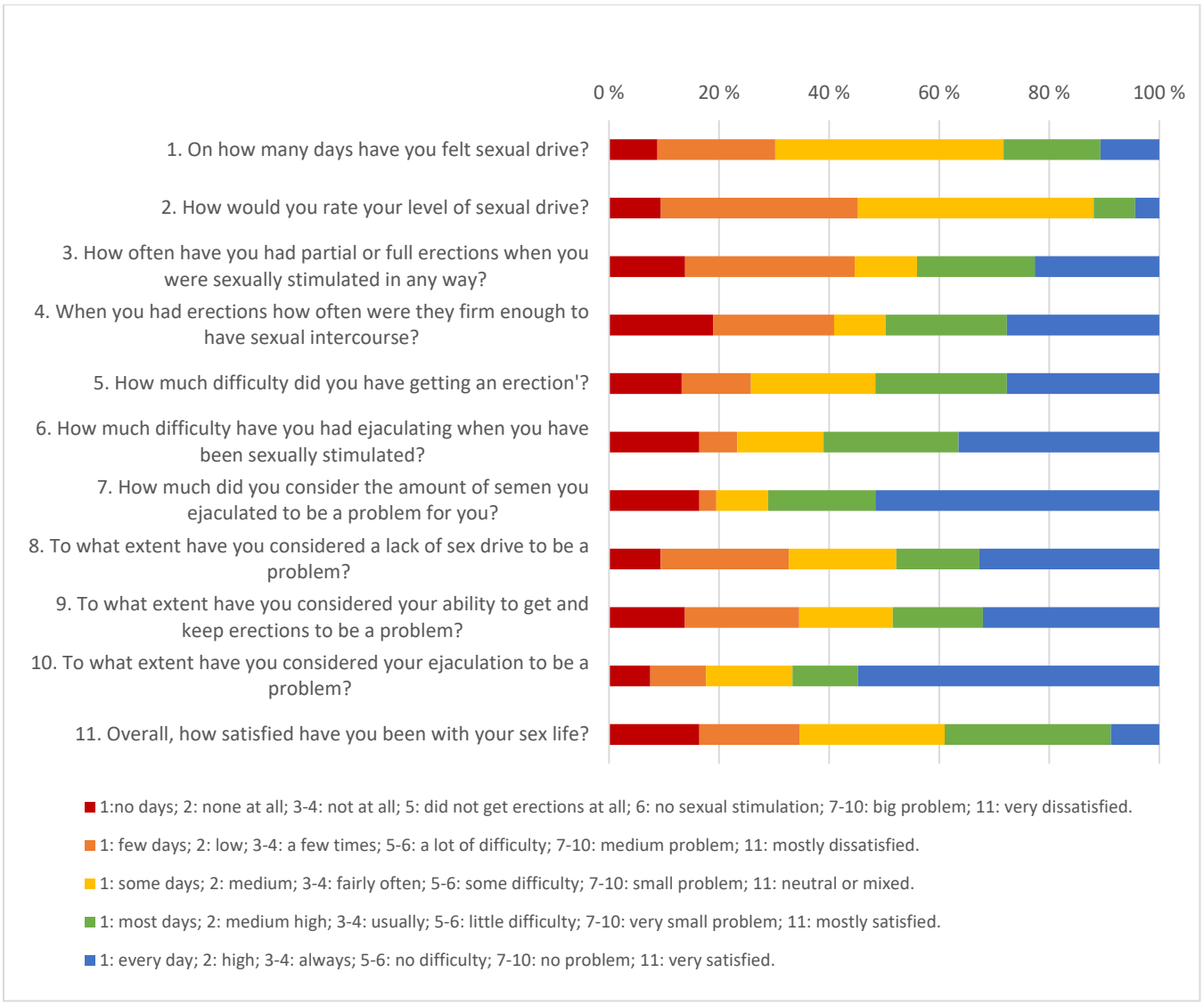

0 %
20 %
40 %
60 %
80 %
100 %
1. On how many days have you felt sexual drive?
2. How would you rate your level of sexual drive?
3. How often have you had partial or full erections when you were sexually stimulated in any way?
4. When you had erections how often were they firm enough to have sexual intercourse?
5. How much difficulty did you have getting an erection'?
6. How much difficulty have you had ejaculating when you have been sexually stimulated?
7. How much did you consider the amount of semen you ejaculated to be a problem for you?
8. To what extent have you considered a lack of sex drive to be a problem?
9. To what extent have you considered your ability to get and keep erections to be a problem?
10. To what extent have you considered your ejaculation to be a problem?
11. Overall, how satisfied have you been with your sex life?
1:no days; 2: none at all; 3-4: not at all; 5: did not get erections at all; 6: no sexual stimulation; 7-10: big problem; 11: very dissatisfied.
1: few days; 2: low; 3-4: a few times; 5-6: a lot of difficulty; 7-10: medium problem; 11: mostly dissatisfied.
1: some days; 2: medium; 3-4: fairly often; 5-6: some difficulty; 7-10: small problem; 11: neutral or mixed.
1: most days; 2: medium high; 3-4: usually; 5-6: little difficulty; 7-10: very small problem; 11: mostly satisfied.
1: every day; 2: high; 3-4: always; 5-6: no difficulty; 7-10: no problem; 11: very satisfied.

Figure 2

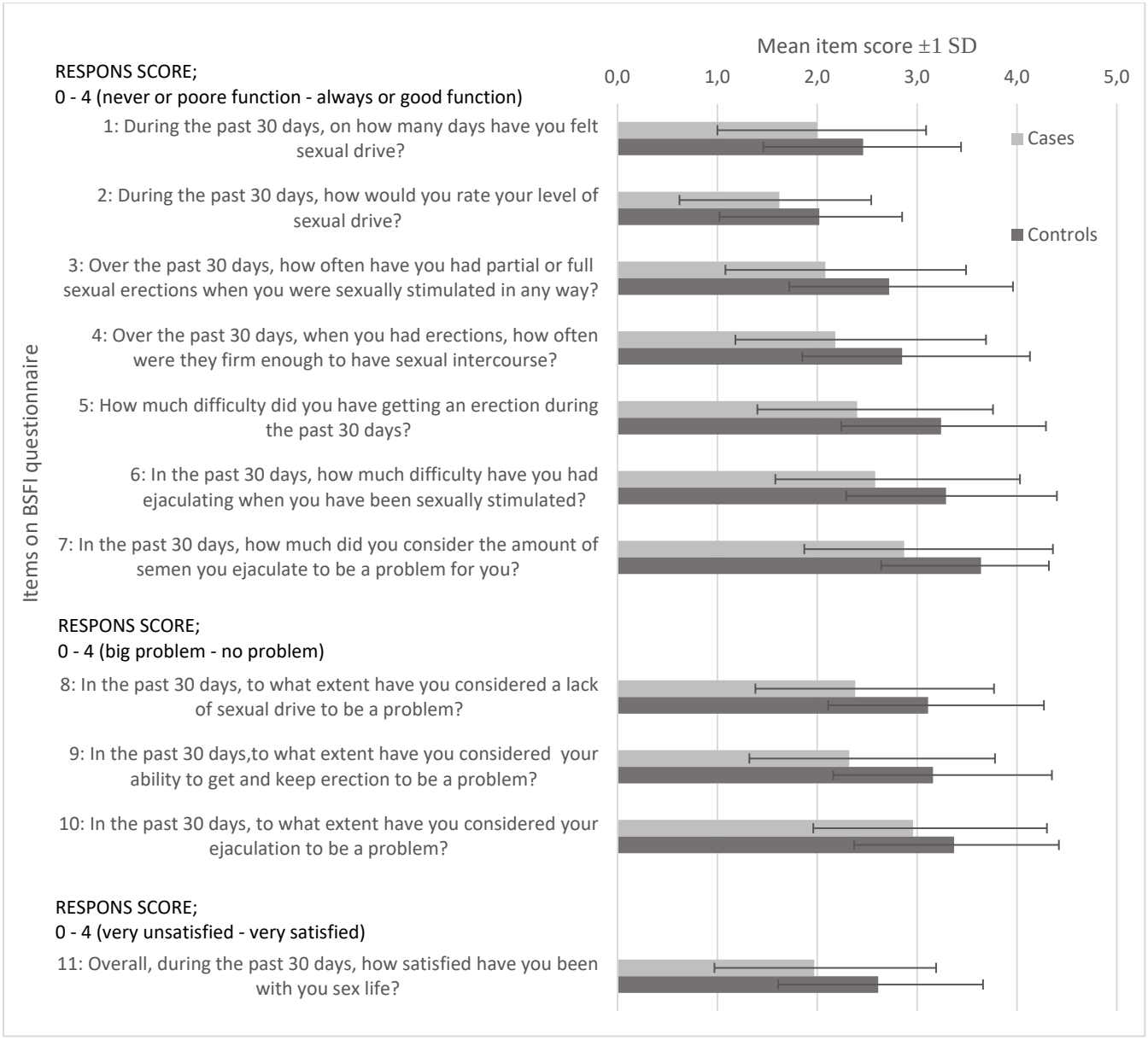
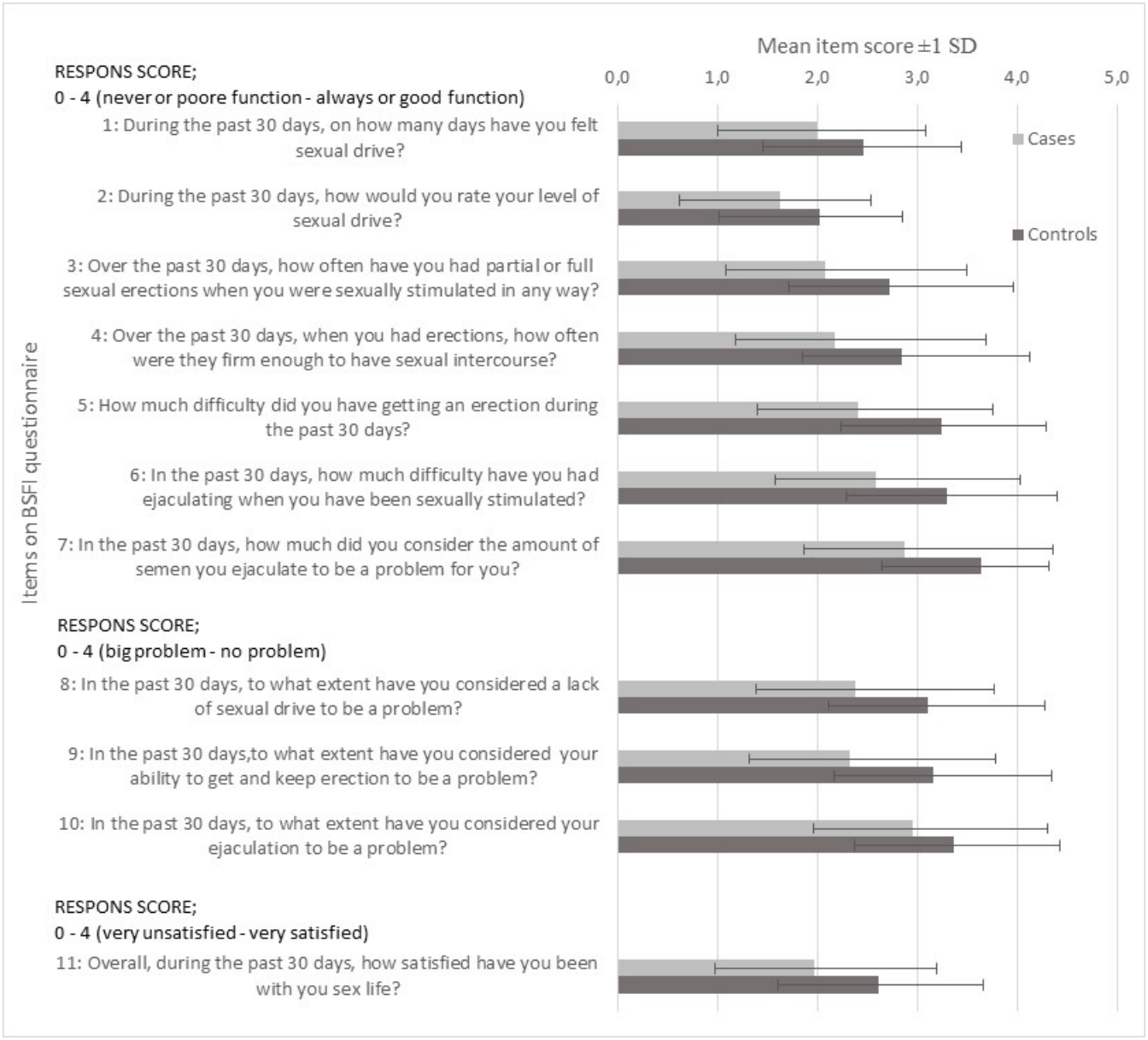
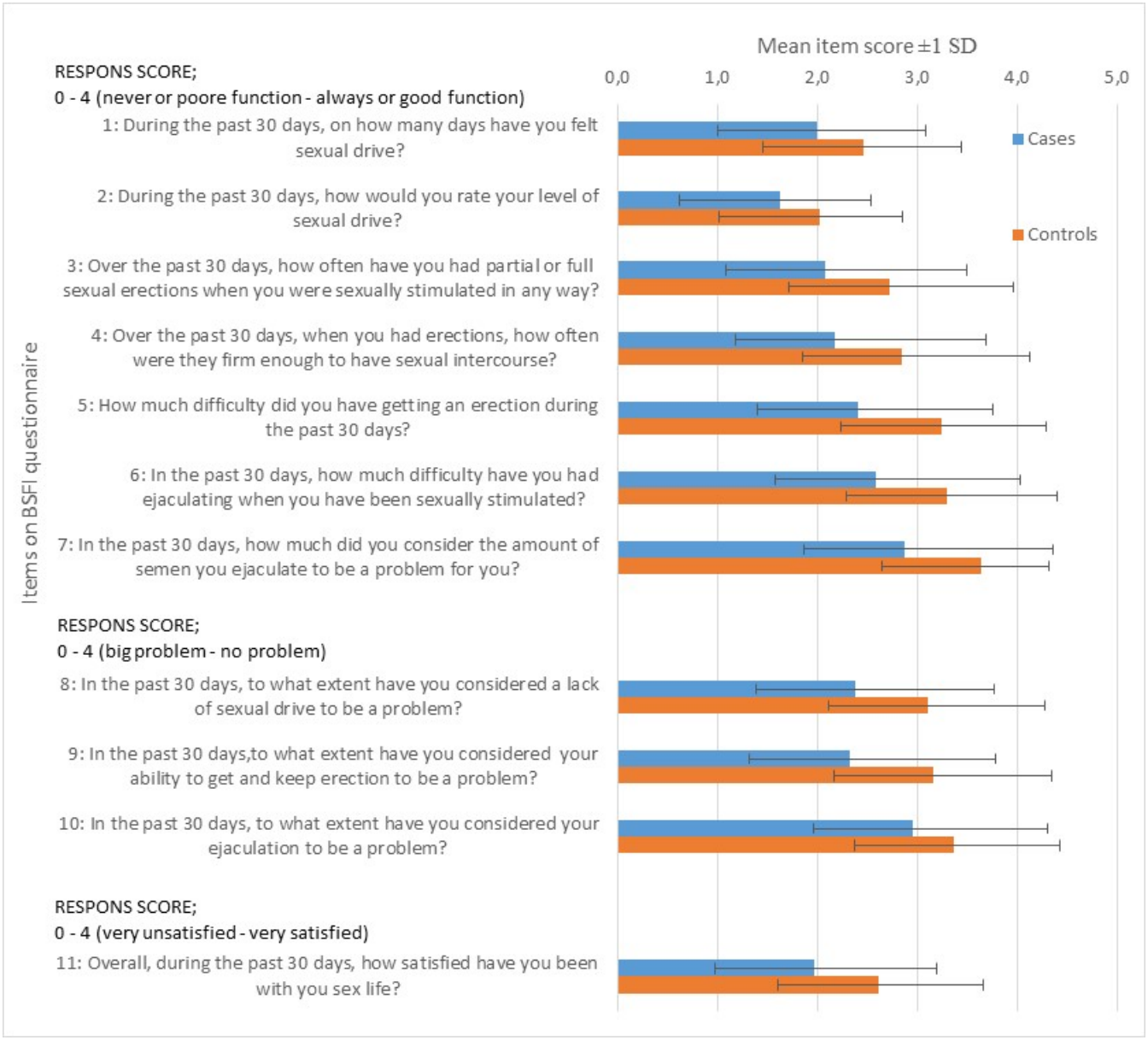


Figure 3

Abbreviations: BSFI, Brief Sexual Function Inventory; Auto-SCT, high-dose chemotherapy with autologous stem-cell transplantation.

The difference between survivors and controls was statistically significant ($p<0.001$) on all items.


Mean item score ±1 SD
0,0
1,0
2,0
3,0
4,0
5,0
Cases
Controls
Items on BSFI questionnaire
RESPONS SCORE;
0 - 4 (never or poore function - always or good function)
1: During the past 30 days, on how many days have you felt sexual drive?
2: During the past 30 days, how would you rate your level of sexual drive?
3: Over the past 30 days, how often have you had partial or full sexual erections when you were sexually stimulated in any way?
4: Over the past 30 days, when you had erections, how often were they firm enough to have sexual intercourse?
5: How much difficulty did you have getting an erection during the past 30 days?
6: In the past 30 days, how much difficulty have you had ejaculating when you have been sexually stimulated?
7: In the past 30 days, how much did you consider the amount of semen you ejaculate to be a problem for you?
RESPONS SCORE;
0 - 4 (big problem - no problem)
8: In the past 30 days, to what extent have you considered a lack of sexual drive to be a problem?
9: In the past 30 days,to what extent have you considered your ability to get and keep erection to be a problem?
10: In the past 30 days, to what extent have you considered your ejaculation to be a problem?
RESPONS SCORE;
0 - 4 (very unsatisfied - very satisfied)
11: Overall, during the past 30 days, how satisfied have you been with you sex life?


Mean item score ±1 SD
0,0
1,0
2,0
3,0
4,0
5,0
Cases
Controls
Items on BSFI questionnaire
RESPONS SCORE;
0 - 4 (never or poore function - always or good function)
1: During the past 30 days, on how many days have you felt sexual drive?
2: During the past 30 days, how would you rate your level of sexual drive?
3: Over the past 30 days, how often have you had partial or full sexual erections when you were sexually stimulated in any way?
4: Over the past 30 days, when you had erections, how often were they firm enough to have sexual intercourse?
5: How much difficulty did you have getting an erection during the past 30 days?
6: In the past 30 days, how much difficulty have you had ejaculating when you have been sexually stimulated?
7: In the past 30 days, how much did you consider the amount of semen you ejaculate to be a problem for you?
RESPONS SCORE;
0 - 4 (big problem - no problem)
8: In the past 30 days, to what extent have you considered a lack of sexual drive to be a problem?
9: In the past 30 days,to what extent have you considered your ability to get and keep erection to be a problem?
10: In the past 30 days, to what extent have you considered your ejaculation to be a problem?
RESPONS SCORE;
0 - 4 (very unsatisfied - very satisfied)
11: Overall, during the past 30 days, how satisfied have you been with you sex life?

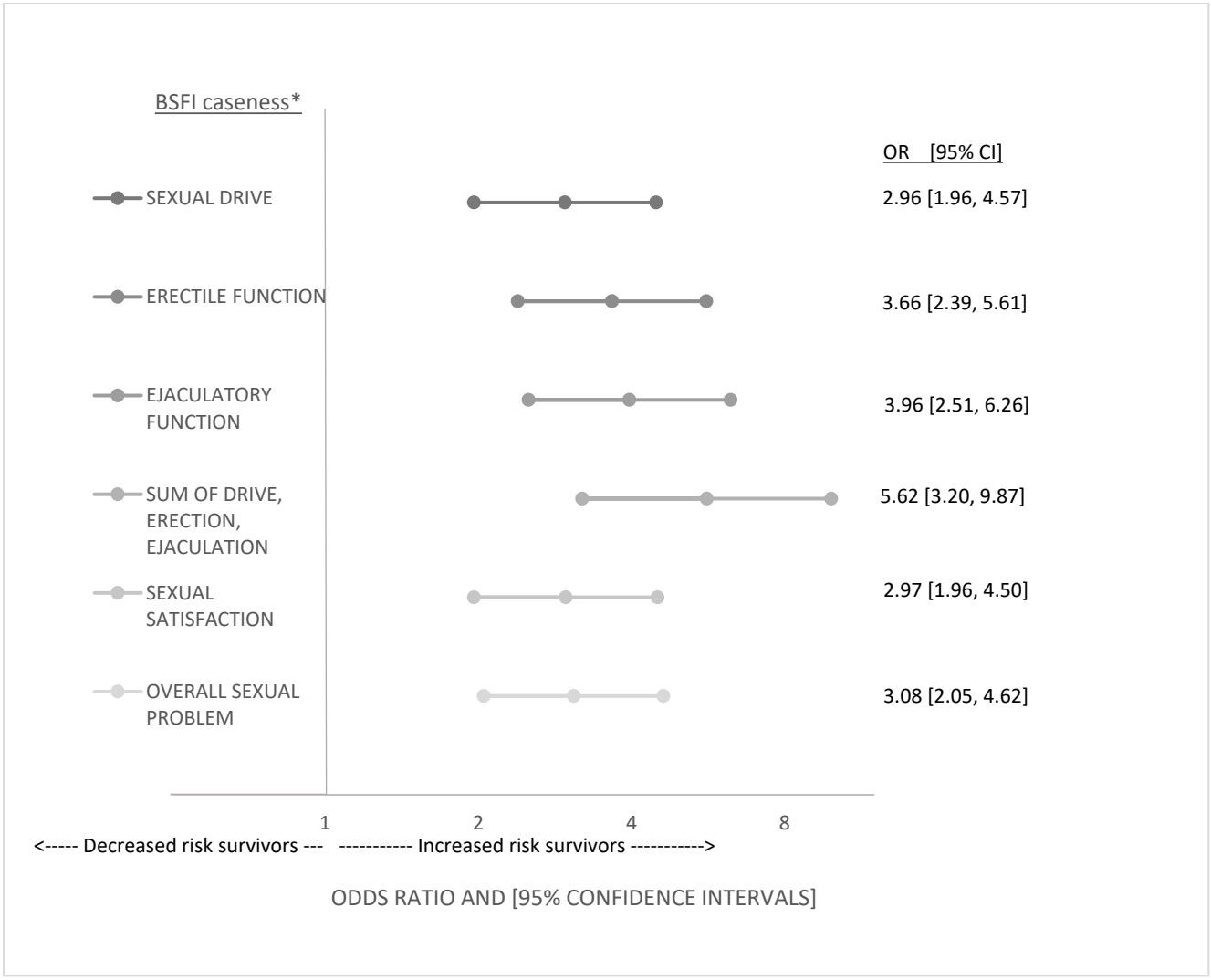

BSFI caseness*
OR [95% CI]
SEXUAL DRIVE
2.96 [1.96, 4.57]
ERECTILE FUNCTION
3.66 [2.39, 5.61]
EJACULATORY FUNCTION
3.96 [2.51, 6.26]
SUM OF DRIVE, ERECTION, EJACULATION
5.62 [3.20, 9.87]
SEXUAL SATISFACTION
2.97 [1.96, 4.50]
OVERALL SEXUAL PROBLEM
3.08 [2.05, 4.62]
1
2
4
8
<----- Decreased risk survivors --- ---------- Increased risk survivors ---------->
ODDS RATIO AND [95% CONFIDENCE INTERVALS]

Figure 4