











## Longitudinal Changes in Cognitive Function in a Nationwide Cohort Study of Patients With Lymphoma Treated With Chemotherapy

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### Abstract

**Background:** Cancer-related cognitive decline (CRCDD) is an important clinical problem, but limited research exists on assessment of cognitive function in patients with lymphoma. **Methods:** The overall objective of this nationwide, prospective, observational study conducted in the National Cancer Institute Community Clinical Oncology Research Program (NCORP) was to assess changes in memory, attention, and executive function in patients with lymphoma from pre- (A1) to postchemotherapy (A2) and to 6 months postchemotherapy (A3). Individuals without cancer served as noncancer controls, paired to patients by age and sex, and assessed at the same time-equivalent points. Longitudinal linear mixed models (LMM) including A1, A2, and A3 and adjusting for age, education, race, sex, cognitive reserve score, baseline anxiety, and depressive symptoms were fit. We assessed changes in patients compared with control participants without cancer and assessed differences in cognitive function in those patients with Hodgkin vs non-Hodgkin disease and by disease subtype. All statistical tests were 2-sided. **Results:** Patients with lymphoma (n = 248) and participants without cancer serving as controls (n = 212) were recruited from 19 NCORP sites. From pre- to postchemotherapy and from prechemotherapy to 6 months follow-up, patients reported more cognitive problems over time compared with controls (Functional Assessment of Cancer-Therapy-Cognitive Function [FACT-Cog] perceived cognitive impairment effect size (ES) = 0.83 and 0.84 for A1 to A2 and A1 to A3, respectively;  $P < .001$ ; single-item cognitive symptoms ES range = 0.55 to 0.70 inclusive of A1 to A2 and A1 to A3;  $P < .001$ ); the complaints were more pronounced in women with lymphoma compared with men with lymphoma (FACT-Cog Perceived Cognitive Impairment (PCI) score group-by-time-by-sex interaction,  $P = .007$ ). Patients with lymphoma also performed statistically significantly less well on tests of verbal memory and delayed recall, attention and executive function, and telephone-based category fluency. **Conclusion:** Patients with lymphoma experience worse patient-reported and objectively assessed cognitive function from prechemotherapy to 6-month follow-up compared with age- and sex-paired controls without cancer assessed at similar time intervals.

Cancer-related cognitive decline (CRCDD) is an important clinical problem with a negative impact on quality of life (1-5). CRCDD has been fairly well characterized in patients with common solid tumors, showing that chemotherapy exacerbates CRCDD (5-21); however, less is known about how chemotherapy affects cognitive function in patients with hematologic malignancies

(22). Post-treatment cross-sectional studies have shown that survivors of lymphoma have long-term cognitive deficits compared with individuals without cancer or normative scores (23-25). One longitudinal study in patients with lymphoma, without a pretreatment assessment or control group, has suggested that chemotherapy may negatively impact cognitive

function over time (26). Because the disease biology of lymphoma is systemic and affects the immune system, it is important to consider the pretreatment impact of disease on cognition (27,28). It is also not clear if CRCD affects men and women differently as few studies have been able to systematically address sex differences, although the results of a large study of patients with colorectal cancer showed that men had a greater risk of cognitive decline than women on some cognitive outcomes (21).

The primary aim of this study was to assess longitudinal changes in cognition in patients with lymphoma from pre- to postchemotherapy and from prechemotherapy to 6 months postchemotherapy compared with age- and sex-paired controls assessed at the same time intervals. We evaluated baseline effects and trajectories of cognitive complaints measured by self-report as well as performance on objective neurocognitive tests of memory, attention, and executive function.

We also investigated and controlled for several factors that are known or thought to influence cognitive function including age, sex, race, education (29), cognitive reserve (30), lymphoma type (31,32), chemotherapy regimen, and anxiety and depression symptoms (16,18–20,32). We hypothesized that patients with lymphoma scheduled to receive chemotherapy would experience more cognitive problems than noncancer controls at baseline and that these changes would persist up to 6 months postchemotherapy.

## Methods

### Participants

Patients with lymphoma and individuals without cancer serving as noncancer controls were recruited from 19 National Cancer Institute Community Oncology Research Program (NCORP) locations nationwide. Eligibility included the following: 1) diagnosis of intermediate or high-grade lymphoma defined by the treating physician, 2) scheduled for a standard course of chemotherapy (with or without biologics), 3) chemotherapy naïve, 4) 21 years of age or older and able to speak and read English, 5) no confirmed central nervous system disease, 6) no neurodegenerative disease diagnosis, 7) no recent major psychiatric illness leading to hospitalization within the past year, 8) life expectancy greater than 10 months, and 9) no plan to receive concurrent radiation during chemotherapy. Control participants without cancer were the same age (within 5 years) and sex as the patients and met eligibility criteria 3–8. This study was approved by the institutional review boards of each NCORP and the University of Rochester Cancer Center (URCC) NCORP Research Base; all participants provided written informed consent. This cohort study was conducted concurrently with another cohort of patients with breast cancer and control participants without cancer, which finished accrual prior to this cohort; we published the results of the breast cancer study previously (16,33). Additional details are provided in the [Supplementary Methods](#) (available online) and in previous reports (16,33). We are presenting for the first time the results of the lymphoma cohort study.

### Cognitive Assessments and Covariates

All cognitive assessments were completed predominately at the following timepoints for patients: 1) prechemotherapy baseline assessment within 7 days prior to the first chemotherapy administration (A1), 2) postchemotherapy assessment within 1

month of the last chemotherapy administration (A2), and 3) follow-up assessment at 6 months following assessment 2 (A3). Participants serving as controls also completed the same assessments at the same time intervals as patients.

All study staff were formally trained. A standardized cognitive assessment manual was used. Computerized testing was conducted, followed by paper-based testing, and then self-report measures. The phone-based measures were administered following the in-person assessments by URCC staff. We used the same testing paradigm as described in detail in our previous publication; these measures are summarized briefly (16,33).

**Computerized Neuropsychological Assessments.** Computerized tests were from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and included the Delayed Match to Sample test (12-second delay), verbal recognition memory (VRM), rapid visual processing, and One Touch Stockings of Cambridge (34).

### Paper-Based Neuropsychological Assessments

Paper-based assessments included the Hopkins Verbal Learning and Memory Test-Revised (HVLT-R) (35–37), the Trail Making Test (TMT) A (ie, Comprehensive TMT 1) and B (ie, Comprehensive TMT 5) (38–40), and the Controlled Oral Word Association test (COWA) (41,42).

### Phone-Based Cognitive Assessments

The Brief Test of Adult Cognition by Telephone included the Rey Auditory Verbal Learning Test (RAVLT) immediate and delayed (based on 1 list learning trial), digits backward, category fluency, and backward counting (43).

### FACT-Cog

Perceived cognitive function was assessed by the Functional Assessment of Cancer-Therapy-Cognitive Function (FACT-Cog) Version 2 (44). The FACT-Cog has 4 subscales: perceived cognitive impairment (PCI), perceived cognitive abilities, impact of perceived cognitive impairment on quality of life, and comments from others. Additionally, a total score can be computed summing all 4 subscales. Smaller values on these scales imply greater cognitive difficulties. A  $\frac{1}{2}$  SD as a cutoff for a minimal clinically important difference has been identified for this measure (45).

### Single-Item

On a Likert-type scale (0 to 10), participants rated their level of difficulty over 7 days on 3 single items for remembering things, paying attention, and multitasking as part of a modified symptom inventory (46).

### Covariate Measures

Participants self-identified age, sex, and race. Patient medical and treatment information was obtained from the medical record. Chemotherapy was categorized into 4 regimen types: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); bendamustine and rituximab (BR); doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); or other agents. Baseline reading ability, a proxy for cognitive reserve, was assessed with the Wide Range Assessment Test-4th Edition (WRAT-4) reading subscale (47). Anxiety was assessed with the Spielberger Trait Anxiety Inventory (48), and depressive

symptoms were measured by an item from the Multidimensional Fatigue Symptom Inventory (49).

## Statistical Analyses

For comparison of baseline characteristics for the patients and controls, *t* tests were used for continuous variables, and  $\chi^2$  tests were used for categorical variables.

The primary goal of this study was to assess trajectories of change in cognitive function from A1 to A2 and from A1 to A3 using longitudinal linear mixed modeling (LMM) adjusting for important a priori baseline covariates. We aimed to accrue 200 evaluable patients and 200 evaluable controls. Statistical computations were performed using R Version 3 ([www.r-project.org](http://www.r-project.org)) and SAS Version 9.4 (SAS Institute, Cary, NC). A 2-sided *P*-value of no more than .05 was considered statistically significant.

For LMM analyses, the fixed effects were time (assessments 1, 2, and 3 treated as nominal), group (patient or control), sex, age, education (less than high school, high school or general equivalency diploma [GED], college or graduate), race (Black, White, Other), cognitive reserve (WRAT), anxiety and depressive symptoms, and the following interactions: group-by-time, time-by-sex, group-by-sex, and group-by-time-by-sex. The random effect was subject-specific A1, A2, and A3 means with an unstructured covariance matrix. Based on graphical examination, for FACT-Cog total, we allowed group-specific covariance matrices; this was not necessary for the other measures. Estimation was performed using restricted maximum likelihood, and inferences were performed using the Kenward-Roger procedure (50). Appropriate contrasts were used to quantify the mean changes from A1 to A2 and from A1 to A3 (in addition to means for each time) by group and sex (for self-report measures). We provided estimates for both men and women computed from these models for those with statistically significant sex-related interactions.

We also fit similarly constructed models for the patients to assess the effects of lymphoma type and regimen type on cognitive outcomes. In women, we explored the effect of baseline menopausal status (ie, pre- vs peri- or postmenopausal) on cognitive outcomes.

All analyses were based on all available data. Missing data were assumed to be missing at random (51). We used general linear modeling to assess whether FACT-Cog PCI at A1 was predictive of dropout. The distribution of the TMT was highly skewed; values were  $\log_{10}$ -transformed. We also adjusted for multiple comparisons across all outcome measures with the Benjamini-Hochberg false discovery rate (FDR) and report the adjusted *P* values as indicated in the tables (52).

## Results

### Baseline Characteristics

In total, 460 eligible participants consented to the study including 248 patients (62.5% male) and 212 controls (59.0% male). The patient and control groups were balanced with respect to age, race, ethnicity, WRAT-4 reading score (cognitive reserve), and marital status (Table 1). Groups based on sex were balanced with respect to age, race, education, ethnicity, and WRAT-4 reading score, but female patients showed higher anxiety and depressive symptoms (Supplementary Table 1, available online). Retention from A1 to A2 was 86.4% in the lymphoma group and 95.7% in noncancer controls. Retention was 72.7% in the lymphoma patient group at A3 and 91.5% in the noncancer

control group (Figure 1). Baseline FACT-Cog PCI score was not predictive of those who dropped out at A2 or A3 by group or by sex. Of 248 patients with lymphoma, 186 had non-Hodgkin lymphoma, and of all lymphoma subtypes, 39.5% of patients had diffuse large B-cell lymphoma. The mean interval from A1 to A2 for those on ABVD was 113 (95% confidence interval [CI] = 99 to 127) days, BR was 132 (95% CI = 117 to 147) days, and R-CHOP was 103 (95% CI = 95 to 111) days.

### Perceived Cognitive Impairment

Cronbach  $\alpha$  values for FACT-Cog PCI scores were 0.96 and 0.94 for patients and controls, respectively, and 0.96 overall. Cronbach  $\alpha$  values for FACT-Cog total scores were 0.92 and 0.87 for patients and controls, respectively, and 0.91 overall. At baseline, patients with lymphoma self-reported statistically significantly more problems on the FACT-Cog (PCI and total scores) compared with sex-paired controls ( $P < .05$ ; Table 2). Patients reported statistically significantly more attentional difficulty compared with controls ( $P = .01$ ; Table 2). From A1 to A2 and from A1 to A3, patients with lymphoma reported statistically significantly greater perceived cognitive impairment (FACT-Cog PCI, FACT-Cog total, single item) compared with controls over time ( $P < .05$ ; Table 2). After adjusting for multiple comparisons, all associations remained statistically significant except for the associations of attention and multitasking ability single items from A1 to A3. The FACT-Cog PCI effect size (ES) was 0.83 and 0.84 for A1 to A2 and A1 to A3, respectively (FDR-adj.  $P < .001$ ), and the single item cognitive symptoms ES ranged from 0.55 and 0.70 inclusive of A1 to A2 and A1 to A3 (FDR-adj.  $P < .001$ ; Figure 2; Supplementary Table 2, available online).

### Memory

At baseline, we did not observe any statistically significant differences between patients and controls on the objective memory tests (Table 2). From A1 to A2, patients with lymphoma performed statistically significantly less well relative to controls on the CANTAB VRM immediate recall (ie, patients declined whereas controls improved;  $P = .01$ ). From A1 to A3, patients performed less well than controls, showing less of an improvement over time ( $P = .02$ ). From A1 to A2 and from A1 to A3, patients with lymphoma performed statistically significantly less well than controls on the phone-based RAVLT immediate and delayed recall (ie, patients declined, whereas controls improved;  $P < .001$ ). After adjusting for multiple comparisons, all statistically significant results remained significant ( $P < .05$ ) except VRM immediate recall from A1 to A3. The ES range for all statistically significant memory tests (after FDR adjustment) was 0.25 to 0.50 (Figure 2).

### Attention

At baseline, there were no statistically significant differences between patients and controls on any attention tests (Table 2). From A1 to A2, patients performed less well than controls, (ie, they did not change, whereas controls improved) on the TMT-A ( $P = .02$ ; ES = 0.22), even after controlling for multiple comparisons.

Table 1. Lymphoma patient and noncancer control participant characteristics and demographics

Characteristic	Lymphoma/Chemotherapy (n = 248)	Control (n = 212)	Total (N = 460)	P
Age, y				.30 <sup>b</sup>
Mean (SD)	55.40 (14.70)	53.96 (14.98)	54.74 (14.83)	
Range	21.00-83.00	18.00-84.00	18.00-84.00	
Sex, No. (%)				.44 <sup>a</sup>
Female	93 (37.5)	87 (41.0)	180 (39.1)	
Male	155 (62.5)	125 (59.0)	280 (60.9)	
Race, No. (%)				.44 <sup>a</sup>
White	232 (93.6)	197 (92.9)	429 (93.3)	
Black	11 (4.4)	7 (3.3)	18 (3.9)	
Other	5 (2.0)	8 (3.8)	13 (2.8)	
Ethnicity, No. (%)				.84 <sup>a</sup>
Hispanic/Latino	5 (2.0)	6 (2.8)	11 (2.4)	
Not Hispanic/Latino	238 (96.0)	201 (94.8)	439 (95.4)	
Unknown	5 (2.0)	5 (2.4)	10 (2.2)	
Education, No. (%)				.02 <sup>a</sup>
< High school	7 (2.8)	1 (0.5)	8 (1.7)	
High school/GED	51 (20.6)	27 (12.7)	78 (17.0)	
Partial College and Higher	189 (76.2)	184 (86.8)	373 (81.1)	
Unknown	1 (0.4)	0 (0.0)	1 (0.2)	
Marital status, No. (%)				.48 <sup>a</sup>
Married	181 (73.0)	149 (70.3)	330 (71.7)	
Divorced	16 (6.4)	18 (8.5)	34 (7.4)	
Long-term relationship	18 (7.3)	9 (4.2)	27 (5.9)	
Separated	3 (1.2)	2 (0.9)	5 (1.1)	
Single	23 (9.3)	23 (10.8)	46 (10.0)	
Widowed	7 (2.8)	11 (5.1)	18 (3.9)	
WRAT 4 Reading, mean (SD)	62.86 (6.16)	63.67 (4.83)	63.24 (5.59)	.12 <sup>b</sup>
Anxiety (STAI), mean (SD)	34.95 (12.58)	27.46 (9.21)	31.48 (11.74)	<.001 <sup>b</sup>
Depression item, mean (SD)	0.64 (0.97)	0.30 (0.61)	0.48 (0.84)	<.001 <sup>b</sup>
Lymphoma type, No. (%)				
Hodgkin	51 (20.6)	—	—	
Non-Hodgkin	186 (75.0)	—	—	
Unknown	11 (4.4)	—	—	
Lymphoma subtype, No. (%)				
NHL subtypes				
DLBCL	98 (39.5)	—	—	
Follicular	41 (16.5)	—	—	
Other B cell	29 (11.7)	—	—	
T cell	8 (3.2)	—	—	
HL subtype				
Classical	45 (18)	—	—	
Lymphocyte predominant	3 (1.2)	—	—	
Unknown subtype	24 (9.7)	—	—	
Lymphoma regimen, No. (%)				
ABVD	42 (16.9)	—	—	
BR	35 (14.1)	—	—	
Other	26 (10.5)	—	—	
R-CHOP	116 (46.8)	—	—	
Unknown	29 (11.7)	—	—	

<sup>a</sup>Two-sided Pearson  $\chi^2$  test. ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BR = bendamustine and rituximab; DLBCL = diffuse large B-cell lymphoma; GED = general equivalency diploma; NHL = non-Hodgkin lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; STAI = Spielberger Trait Anxiety Inventory; WRAT-4 = Wide Range Achievement Test, 4th edition; — = not applicable.

<sup>b</sup>Welch t test. All tests were 2-sided.

## Executive Function

At baseline, there were no statistically significant differences between patients and controls on any executive function tests (Table 2). From A1 to A2, we observed that patients performed statistically significantly less well on the COWA compared with controls ( $P = .02$ ). From A1 to A2 and from A1 to A3, patients

performed statistically significantly less well than controls on the phone-based digits backward ( $P < .001$  for A1 to A2 and  $P = .01$  for A1 to A3) and category fluency tests (all  $P < .001$ ). All statistically significant results remained statistically significant after adjusting for multiple comparisons. The ES range on statistically significant executive function tests (after FDR adjustment) was 0.15 to 0.67 inclusive of A1 to A2 and A1 to A3.

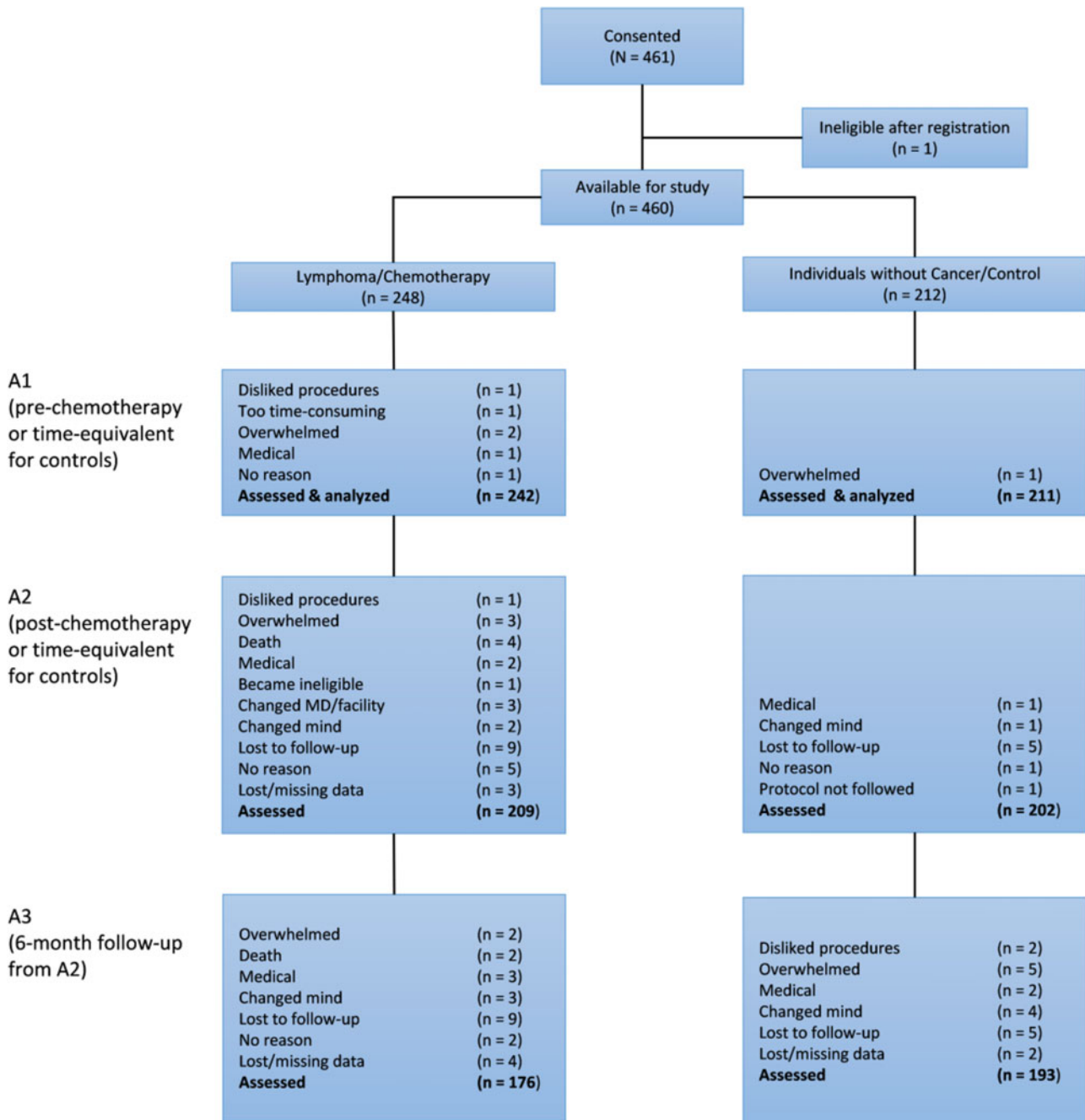


Figure 1. Participant flowchart. A = assessment.

### Predictors of Cognitive Change

The decrease in FACT-Cog PCI score, indicative of increased perceived impairment, was statistically significantly greater for women with lymphoma compared with men with lymphoma as compared with controls from A1 to A2 and from A1 to A3 revealed by a statistically significant group-by-time-by-sex interaction ( $P = .007$ ; Table 3 and Figure 3; Supplementary Table 3, available online). In women with lymphoma, 51.3% reported a perceived decline in FACT-Cog PCI scores compared with 14.5% of women who were controls ( $P < .001$ ; Figure 4). From prechemotherapy to 6 months follow-up, representing almost 1 year

later, 57.5% of women with lymphoma reported decline in FACT-Cog scores (based on  $1/2$  SD at A1) compared with 10.4% of female controls ( $P < .001$ ). In men with lymphoma, 51.9% reported a perceived decline in FACT-Cog scores compared with 20.5% of men who were controls ( $P < .001$ ; Figure 4). From prechemotherapy to 6 months follow-up, representing almost 1 year later, 37.8% of men with lymphoma reported decline in FACT-Cog scores compared with 15.1% of male controls ( $P < .001$ ). Similar patterns were observed for FACT-Cog total scores (Figure 3; Supplementary Figure 2, available online). Additionally, we observed a statistically significant group-by-sex interaction where women with lymphoma reported

**Table 2.** Self-report, memory, attention, and executive function measures at baseline (prechemotherapy [A1], postchemotherapy [A2], and 6 months follow-up [A3]) and changes from pre- to post-chemotherapy and changes from prechemotherapy to 6 months follow-up in patients with lymphoma and age- and sex-paired controls assessed at the same equivalent times

Domain and test/measure	Outcome	Better score	Chemotherapy			Control			Baseline: chemotherapy (A1) - control (A1)			Pre- to post-chemotherapy: chemotherapy (A2-A1) - control (A2-A1)			Pre-Chemotherapy to 6 months follow-up: chemotherapy (A3-A1) - control (A3-A1)		
			A1	A2	A3	A1	A2	A3	Adjusted $\mu$ (SE)	P <sup>a</sup>	(95% CI)	Adjusted $\mu$ (SE)	P <sup>a</sup>	(95% CI)	Adjusted $\mu$ (SE)	P <sup>a</sup>	(95% CI)
			Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted $\mu$ (SE)	P <sup>a</sup>	(95% CI)	Adjusted $\mu$ (SE)	P <sup>a</sup>	(95% CI)	Adjusted $\mu$ (SE)	P <sup>a</sup>	(95% CI)
<b>Self-reported cognitive problems</b>																	
FACT-Cog PCI	Perceived cognitive impairment	Higher	91.20 (2.82)	80.74 (2.89)	81.64 (2.94)	94.32 (2.87)	94.08 (2.93)	95.12 (2.97)	-3.12 (1.47)	.03	(-6.02 to -0.23)	-10.22 (1.31)	<.001	(-13.36 to -7.35)	-10.36 (1.53)	<.001	(-13.51 to -7.35)
FACT-Cog total score	Perceived cognitive difficulties	Higher	149.88 (4.28)	134.98 (4.54)	136.51 (4.69)	157.79 (4.17)	157.34 (4.18)	157.93 (4.20)	-7.91 (2.21)	<.001	(-12.24 to -3.59)	-14.45 (2.04)	<.001	(-18.45 to -10.44)	(2.46)	<.001	(-18.33 to -8.69)
Single item: memory	Perceived memory difficulty	Lower	2.46 (0.31)	3.54 (0.32)	3.31 (0.32)	2.14 (0.31)	2.27 (0.33)	2.19 (0.32)	0.32 (0.17)	.05	(0.00 to 0.65)	0.95 (0.18)	<.001	(0.59 to 1.31)	0.80 (0.20)	<.001	(0.41 to 1.19)
Single item: attention	Perceived attention difficulty	Lower	2.20 (0.30)	3.22 (0.32)	2.70 (0.32)	1.77 (0.31)	1.89 (0.32)	1.86 (0.32)	0.43 (0.17)	.01	(0.10 to 0.75)	0.90 (0.19)	<.001	(0.53 to 1.28)	0.41 (0.20)	.045	(0.01 to 0.80)
Single item: executive function	Perceived multitasking difficulty	Lower	2.23 (0.33)	3.31 (0.34)	2.83 (0.34)	1.91 (0.33)	2.01 (0.35)	1.98 (0.34)	0.33 (0.18)	.07	(-0.03 to 0.69)	0.97 (0.22)	<.001	(0.53 to 1.41)	0.52 (0.23)	.02	(0.07 to 0.97)
<b>Memory</b>																	
Computer: CANTAB delayed match to sample	Percent correct at the 12 second delay	Higher	78.99 (2.72)	81.60 (2.72)	78.18 (2.87)	79.97 (2.77)	83.56 (2.74)	76.72 (2.89)	-0.98 (1.73)	.57	(-4.39 to 2.42)	-0.98 (2.13)	.65	(-5.16 to 3.21)	2.44 (2.47)	.32	(-2.40 to 7.29)
Computer: CANTAB verbal recognition memory	Total correct (immediate recall)	Higher	7.40 (0.32)	7.35 (0.32)	7.60 (0.33)	7.12 (0.32)	7.54 (0.32)	7.79 (0.33)	0.28 (0.18)	.12	(-0.07 to 0.64)	0.19 (0.19)	.01	(-0.85 to -0.10)	-0.47 (0.20)	.02	(-0.86 to -0.07)
Computer: CANTAB verbal recognition memory	Recognition memory	Higher	23.25 (0.19)	23.36 (0.19)	23.23 (0.19)	23.14 (0.19)	23.48 (0.19)	23.40 (0.19)	0.11 (0.12)	.36	(-0.12 to 0.34)	-0.23 (0.14)	.09	(-0.50 to 0.04)	-0.28 (0.14)	.10	(-0.86 to -0.07)
Paper: Hopkins Verbal Learning Test-Revised	Total correct (immediate recall)	Higher	7.83 (0.29)	8.63 (0.29)	8.81 (0.29)	7.96 (0.29)	8.72 (0.29)	9.02 (0.29)	-0.13 (0.15)	.38	(-0.43 to 0.17)	0.05 (0.133)	.73	(-0.22 to 0.31)	-0.08 (0.138)	.58	(-0.56 to 0.00)
Paper: Hopkins Verbal Learning Test-Revised	Total correct (delayed recall)	Higher	8.16 (0.42)	9.05 (0.41)	9.14 (0.41)	8.35 (0.43)	9.10 (0.42)	9.19 (0.42)	-0.19 (0.24)	.44	(-0.67 to 0.29)	0.14 (0.20)	.47	(-0.25 to 0.54)	0.14 (0.21)	.52	(-0.35 to 0.19)
Phone: Rey Auditory Verbal Learning (Trial 1)	Total correct (immediate recall)	Higher	7.00 (0.37)	6.20 (0.38)	6.56 (0.38)	7.20 (0.38)	7.36 (0.38)	7.75 (0.39)	-0.19 (0.21)	.36	(-0.61 to 0.22)	-0.96 (0.24)	<.001	(-1.43 to -0.50)	-1.00 (0.25)	<.001	(-1.50 to -0.51)
Phone: Rey Auditory Verbal Learning (Trial 1)	Total correct (delayed recall)	Higher	4.03 (0.48)	3.51 (0.48)	3.94 (0.49)	4.28 (0.49)	4.92 (0.49)	5.51 (0.50)	-0.25 (0.27)	.35	(-0.77 to 0.27)	-1.16 (0.284)	<.001	(-1.72 to -0.60)	-1.33 (0.29)	<.001	(-1.90 to -0.75)

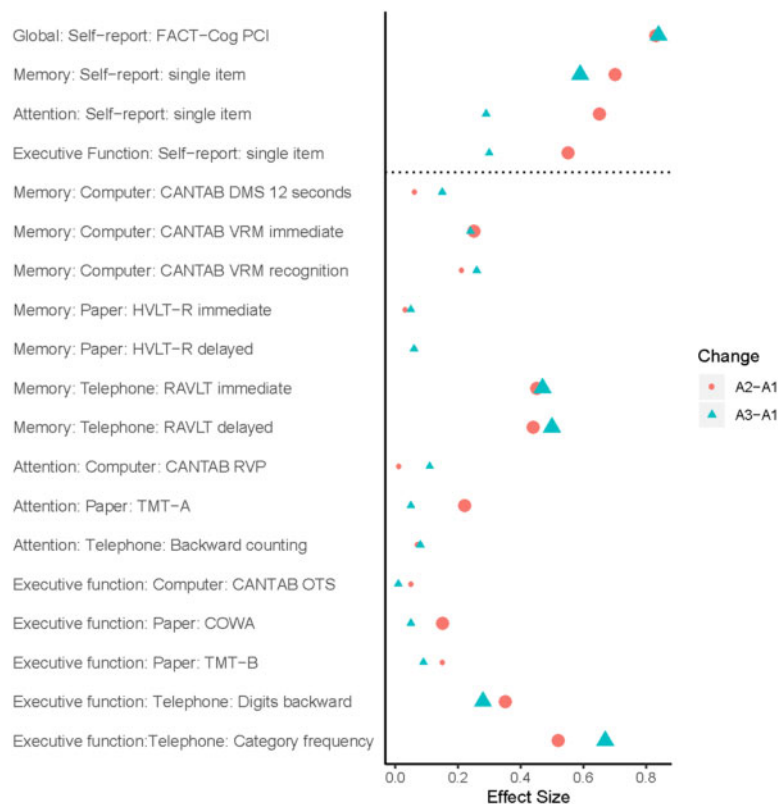
(continued)

Table 2. (continued)

Domain and test/measure	Outcome	Better score	Chemotherapy			Control			Baseline: chemotherapy (A1) - control (A1)			Pre- to post- chemotherapy: chemotherapy (A2-A1) - control (A2-A1)			Pre-Chemotherapy to 6 months follow-up: chemotherapy (A3-A1) - control (A3-A1)			
			A1 Adjusted mean (SE)	A2 Adjusted mean (SE)	A3 Adjusted mean (SE)	A1 Adjusted mean (SE)	A2 Adjusted mean (SE)	A3 Adjusted mean (SE)	Adjusted $\beta$ (SE)	(95% CI)	P <sup>a</sup>	Adjusted $\beta$ (SE)	(95% CI)	P <sup>a</sup>	Adjusted $\beta$ (SE)	(95% CI)	P <sup>a</sup>	FDR-adj. p <sup>b</sup>
<b>Attention</b>																		
Computer: CANTAB rapid visual processing speed	Total correct	Higher	242.63 (2.15)	246.39 (2.15)	246.84 (2.16)	241.44 (2.19)	245.40 (2.17)	247.25 (2.18)	1.19 (1.22)	(-1.21 to 3.58)	.33	-0.20 (1.13)	(-2.41 to 2.02)	.86	-1.60 (1.15)	(-3.85 to 0.66)	.17	.29
Paper: Trail Making Test-A (CTMT1)	Total time (note: values log transformed)	Lower	1.63 (0.02)	1.63 (0.02)	1.61 (0.02)	1.64 (0.02)	1.61 (0.02)	1.61 (0.02)	-0.01 (0.01)	(-0.04 to 0.01)	.40	0.03 (0.01)	(0.00 to 0.06)	.02	0.01 (0.01)	(-0.02 to 0.03)	.65	.69
Phone: backward counting	Final number	Lower	63.69 (2.17)	63.26 (2.19)	61.87 (2.21)	64.58 (2.20)	63.49 (2.22)	61.98 (2.24)	-0.88 (1.04)	(-2.92 to 1.16)	.40	0.66 (0.66)	(-0.65 to 1.96)	.32	0.77 (0.79)	(-0.78 to 2.32)	.33	.48
<b>Executive function</b>																		
Computer: CANTAB One Touch Stockings of Cambridge	Mean choice to correct response	Lower	1.58 (0.05)	1.49 (0.05)	1.45 (0.05)	1.63 (0.06)	1.52 (0.05)	1.50 (0.05)	-0.05 (0.03)	(-0.11 to 0.01)	.13	0.02 (0.03)	(-0.03 to 0.07)	.49	0.00 (0.03)	(-0.05 to 0.05)	.95	.95
Paper: Controlled Oral Word Association	Total correct words (Avg)	Higher	11.73 (0.62)	11.68 (0.62)	12.34 (0.63)	12.28 (0.63)	12.76 (0.63)	13.05 (0.64)	-0.55 (0.32)	(-1.19 to 0.08)	.09	-0.52 (0.23)	(-0.97 to -0.07)	.02	-0.16 (0.24)	(-0.63 to 0.31)	.51	.62
Paper: Trail Making Test-B (CTMT 5)	Total time (note: values log transformed)	Lower	1.87 (0.03)	1.85 (0.03)	1.84 (0.03)	1.88 (0.03)	1.84 (0.03)	1.84 (0.03)	-0.02 (0.02)	(-0.05 to 0.02)	.35	0.03 (0.02)	(-0.01 to 0.06)	.10	0.02 (0.02)	(-0.02 to 0.05)	.37	.50
Phone: digits backward	Total correct	Higher	4.37 (0.25)	4.34 (0.25)	4.35 (0.25)	4.27 (0.25)	4.71 (0.25)	4.64 (0.26)	0.10 (0.13)	(-0.16 to 0.36)	.46	-0.47 (0.15)	(-0.76 to -0.19)	.001	-0.39 (0.16)	(-0.70 to -0.08)	.01	.04
Phone: category fluency	Total correct	Higher	15.87 (0.51)	14.79 (0.52)	14.80 (0.52)	15.59 (0.52)	15.88 (0.52)	16.29 (0.52)	0.28 (0.30)	(-0.30 to 0.87)	.34	-1.37 (0.34)	(-2.04 to -0.70)	<.001	-1.77 (0.33)	(-2.43 to -1.12)	<.001	<.001

<sup>a</sup>Adjusted means, standard errors, 95% confidence intervals (CI), and  $\beta$  estimates are from the longitudinal linear mixed models after adjustment for age, education, race, reading score, baseline anxiety, and baseline depression. Estimates are based on group-by-time interaction. All P values are based on 2-sided tests. A = assessment; adj. = adjusted; CANTAB = Cambridge Neuropsychological Test Automated Battery; CTMT = Comprehensive Trail Making Test; FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; FDR = false discovery rate; PCI = perceived cognitive impairment.

<sup>b</sup>FDR-adjusted P values are adjusted for all cognitive outcomes. All P values are based on 2-sided tests.



**Figure 2.** Effect sizes for changes on cognitive measures in patients compared to controls. To determine the effect size (ES), we used a Cohen  $d$  approach, where the effect estimates ( $\beta$ ) were divided by the estimated standard deviation of the population (ie, all subjects at baseline). Statistically significant effect sizes (after FDR adjustment) are expressed as larger circles for assessment 1 (A1) to assessment 2 (A2) and larger triangles for assessment 1 (A1) to assessment 3 (A3). CANTAB = Cambridge Neuropsychological Test Automated Battery; COWA = Controlled Oral Word Association Test; DMS = delayed match to sample; FACT-Cog = Functional Assessment of Cancer-Therapy-Cognitive Function; HVLt-R = Hopkins Verbal Learning and Memory Test-Revised; RAVLT = Rey Auditory Verbal Learning Test; RVP = Rapid Visual Processing; TMT = Trail Making Test; VRM = verbal recognition memory.

statistically significantly more difficulty compared with men on the memory and attention difficulty items. We also observed an overall group effect where men performed less well than women on verbal memory tests (VRM, RAVLT, and HVLt-R) regardless of group.

On a majority of assessments, older age was statistically significantly associated with worse performance on objective tests as well as perceived cognitive impairment (Supplementary Table 3, available online). In general, those with a some college or greater education were associated with statistically significantly better performance on a majority of tests. In general, lower WRAT-4 reading score was associated with worse performance. Higher baseline anxiety and depressive symptoms were associated with worse performance on some cognitive tests as well as perceived cognitive impairment.

In additional exploratory LMMs, we did not observe any consistent pattern in differences in cognitive outcomes in those with Hodgkin compared with non-Hodgkin lymphoma or any consistent differences in cognitive performance by those receiving R-CHOP, BR, or ABVD chemotherapy regimens (data not shown). We also did not observe differences in those who were pre- vs peri- or postmenopausal at baseline (data not shown).

## Discussion

In this nationwide study, we showed that patients with lymphoma perform statistically significantly worse over time on objective assessments of cognitive function compared with sex-

and age-paired participants serving as noncancer controls assessed at the same time intervals as patients. Based on ES estimates, these mean changes of group differences are in the mild to moderate range. Additionally, patients with lymphoma report statistically significantly more perceived impairments over time compared with controls. Of note, we found that women with lymphoma report statistically significantly more perceived impairment compared with men with lymphoma and controls.

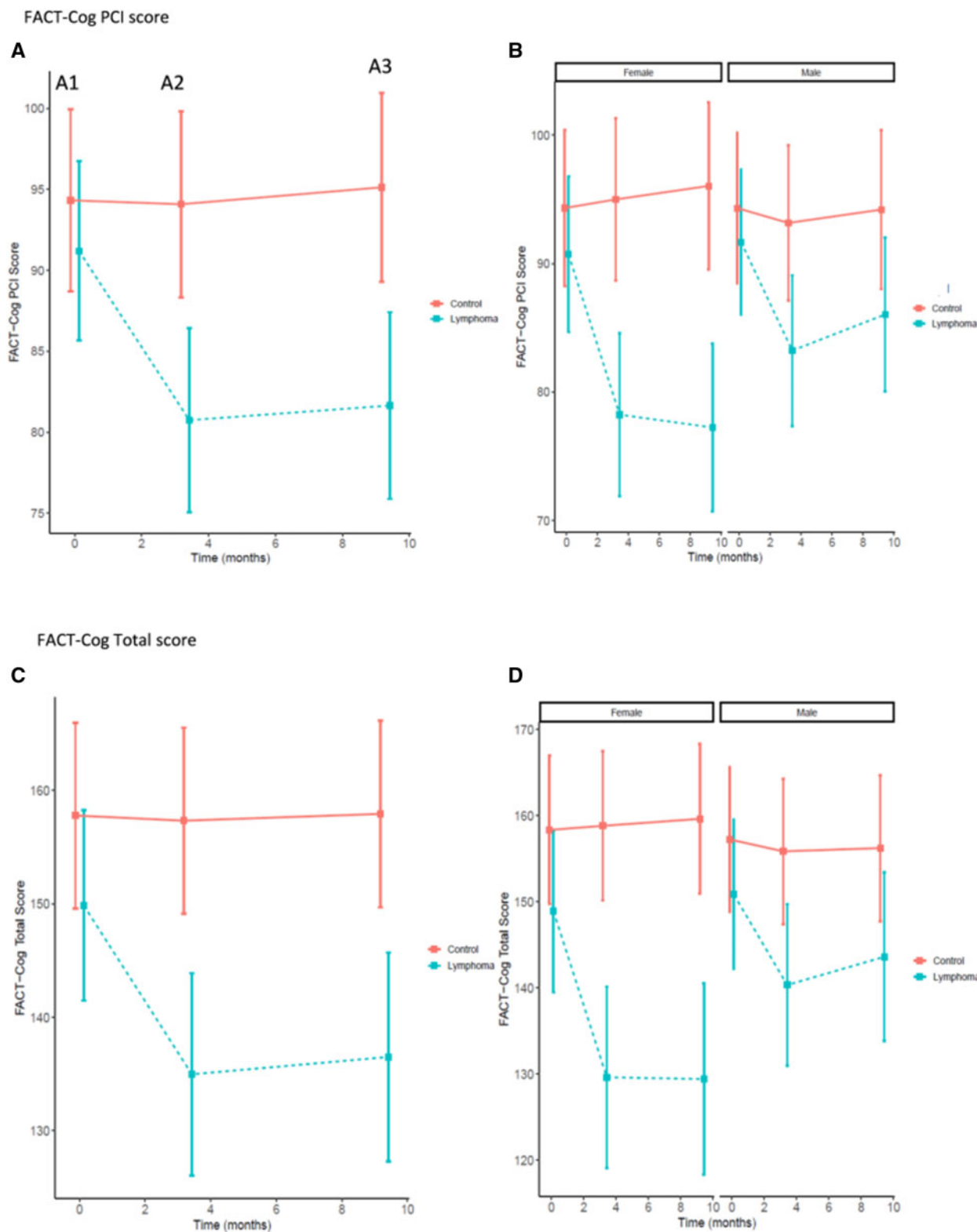
The overall trajectory of cognitive complaints assessed by the FACT-Cog in patients with lymphoma is similar to the pattern of those in our breast cancer study (16) and other studies (53). Also, similar to the breast cancer study, in this study, we observed overall similar trajectories of cognitive function scores on objective tests in patients with lymphoma who performed less well over time compared with controls from A1 to A2 and from A1 to A3 demonstrating either decline over time relative to controls or less improvement over time (33). With the smaller sample size of the lymphoma cohort, we did not have the same power to detect longitudinal group differences on some measures as we did with the larger breast cancer study. For example, in the breast cancer study, we saw statistically significantly worse performance on the rapid visual processing sustained attention test over time in patients compared with controls, with patients improving less over time compared with controls (33). In the current lymphoma study, patients show the same overall pattern compared with controls; however, these were not statistically significant.



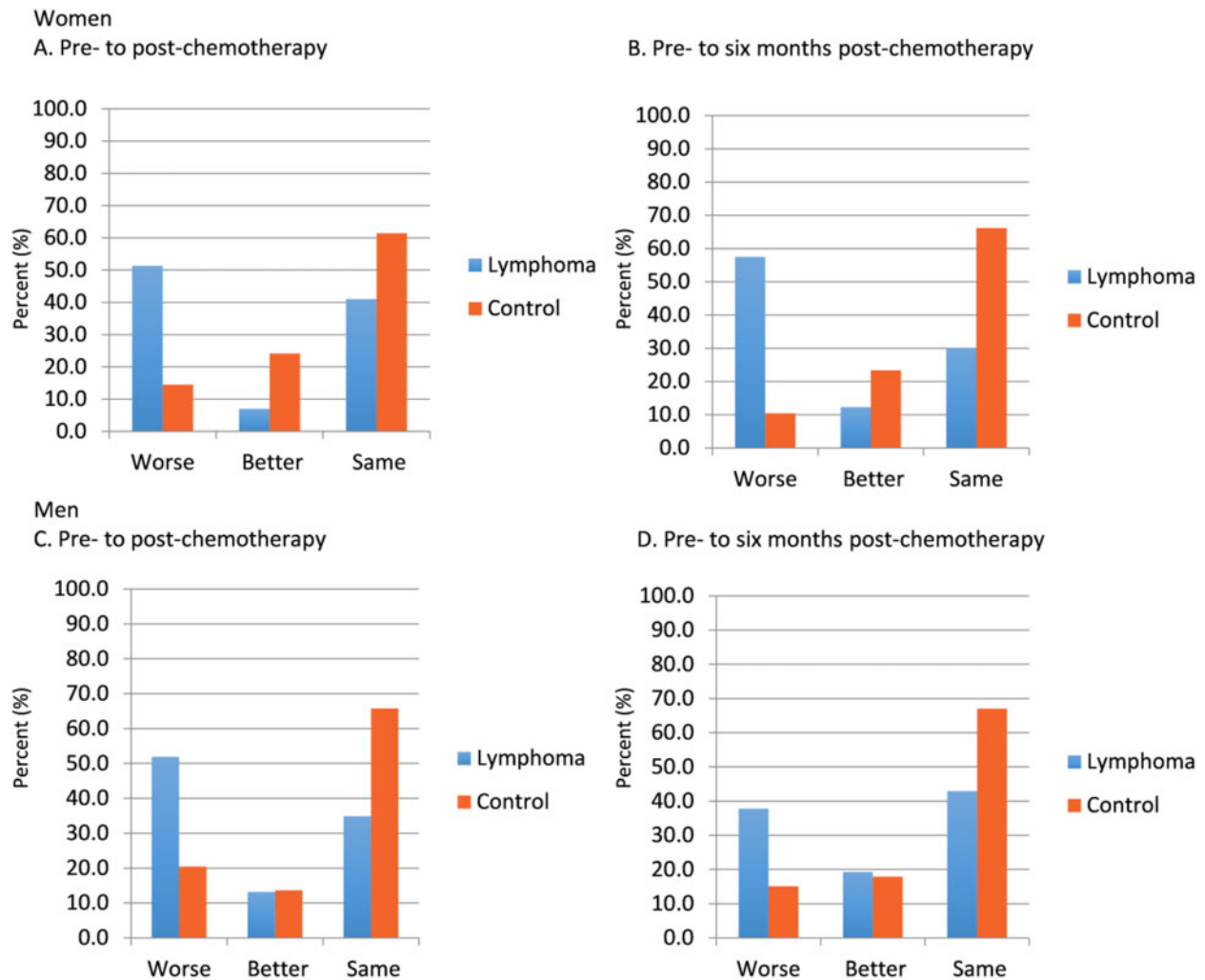
**Table 3.** Self-report measures at baseline (prechemotherapy [A1], post-chemotherapy [A2], and 6 months follow-up [A3]) and changes from pre- to postchemotherapy and changes from prechemotherapy to 6 months follow-up in men and women with lymphoma and age- and sex-paired controls assessed at the same equivalent times

Self-report	Outcome	Better score	Chemotherapy			Control			Baseline: chemotherapy (A1) - control (A1)			Pre- to postchemotherapy: chemotherapy (A2-A1) - control (A2-A1)			Prechemotherapy to 6 months follow-up: chemotherapy (A3-A1) - control (A3-A1)					
			A1	A2	A3	A1	A2	A3	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	Adjusted $\beta$ (SE)	P <sup>a</sup>	P <sup>a</sup>	P <sup>a</sup>
			Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
<b>Women</b>																				
FACT-Cog PCI	Perceived cognitive impairment	Higher	90.72 (3.08)	78.25 (3.23)	77.25 (3.33)	94.32 (3.09)	95.00 (3.22)	96.04 (3.31)	-3.60 (2.24)	(-7.99 to 0.79)	.11	-13.15 (2.04)	(-17.16 to -9.15)	<.001	-15.20 (2.38)	(-19.87 to -10.53)	<.001			
FACT-Cog total score	Perceived cognitive difficulties	Higher	148.92 (4.81)	129.62 (5.36)	129.40 (5.66)	158.34 (4.39)	158.82 (4.41)	159.63 (4.43)	-9.43 (3.37)	(-16.04 to -2.81)	.005	-19.77 (3.21)	(-26.07 to -13.47)	<.001	-20.80 (3.86)	(-28.38 to -13.22)	<.001			
Single item: memory	Perceived memory difficulty	Higher	2.53 (0.34)	3.93 (0.37)	3.72 (0.36)	2.12 (0.34)	2.18 (0.37)	2.22 (0.36)	0.41 (0.25)	(-0.08 to 0.90)	.10	1.34 (0.28)	(0.78 to 1.89)	<.001	1.09 (0.31)	(0.48 to 1.70)	.002			
Single item: attention	Perceived attention difficulty	Higher	2.33 (0.33)	3.75 (0.36)	3.00 (0.36)	1.78 (0.34)	1.86 (0.36)	1.83 (0.36)	0.55 (0.25)	(0.05 to 1.04)	.03	1.34 (0.30)	(0.75 to 1.92)	<.001	0.63 (0.32)	(0.01 to 1.25)	.045			
<b>Men</b>																				
FACT-Cog PCI	Perceived cognitive impairment	Higher	91.67 (2.87)	83.23 (2.98)	86.04 (3.05)	94.32 (2.99)	93.16 (3.08)	94.20 (3.15)	-2.65 (1.79)	(-6.17 to 0.87)	.14	-7.28 (1.64)	(-10.50 to -4.06)	<.001	-5.51 (1.92)	(-9.28 to -1.74)	.004			
FACT-Cog total score	Perceived cognitive difficulties	Higher	150.84 (4.41)	140.33 (4.79)	143.61 (4.99)	157.24 (4.28)	155.86 (4.30)	156.23 (4.32)	-6.40 (2.66)	(-11.62 to -1.19)	.02	-9.12 (2.51)	(-14.06 to -4.19)	<.001	-6.22 (3.04)	(-12.18 to -0.26)	.04			
Single item: memory	Perceived memory difficulty	Higher	2.39 (0.31)	3.16 (0.34)	2.91 (0.33)	2.16 (0.33)	2.36 (0.35)	2.17 (0.34)	0.24 (0.20)	(-0.16 to 0.63)	.13	0.56 (0.23)	(0.11 to 1.01)	.02	0.50 (0.25)	(0.01 to 0.99)	.04			
Single item: attention	Perceived attention difficulty	Higher	2.08 (0.31)	2.70 (0.33)	2.39 (0.33)	1.77 (0.32)	1.92 (0.34)	1.90 (0.34)	0.31 (0.20)	(-0.09 to 0.71)	.21	0.47 (0.24)	(-0.01 to 0.94)	.05	0.18 (0.26)	(-0.32 to 0.69)	.48			

<sup>a</sup> Adjusted means, standard errors, 95% confidence intervals (CI), and  $\beta$  estimates are from the longitudinal linear mixed models after adjustment for age, education, race, reading score, baseline anxiety, and baseline depression. Estimates are based on group-by-time-by-sex interaction. All P values are based on 2-sided tests. FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; PCI = perceived cognitive impairment.



**Figure 3.** Fact-Cog self-report scores in women and men with lymphoma and controls. Assessments (A) are prechemotherapy (A1), postchemotherapy (A2), and 6 months following chemotherapy (A3; or time equivalent for control participants). Smaller values imply greater perceived cognitive impairment. Mean adjusted scores on each test and the corresponding 95% confidence intervals are presented for A1 (0 months; approximately within 7 days prior to chemo), A2 (approximately 3.3 months from A1; postchemotherapy), and A3 (approximately 9.3 months from A1; 6-month follow-up) in panels A and C (stratified by patients with lymphoma receiving chemotherapy (dashed blue line) vs control participants (solid red line)) and panels B and D (additionally stratified by female vs male). Panels A and B include adjusted PCI scores, and panels C and D include adjusted total scores. Unadjusted plots are provided in [Supplementary Figure 1](#) (available online). FACT-Cog = Functional Assessment of Cancer-Therapy-Cognitive Function.



**Figure 4.** Prevalence of overall perceived cognitive impairment on the FACT-Cog PCI score based on clinically important differences from pre- to postchemotherapy and prechemotherapy to 6 months following completion of chemotherapy in women (A and B) and men (C and D). “Better” is defined as a minimal clinically important difference (based on  $\frac{1}{2}$  SD of controls at baseline) increase of 6.19 or more in the FACT-Cog, and “worse” is defined as a decrease of 6.19 or more. The y axis represents the percentage of participants meeting each threshold or who stayed the same. FACT-Cog = Functional Assessment of Cancer Therapy-Cognitive Function; PCI = perceived cognitive impairment. Blue bars = lymphoma and orange bars = control.

Of note, in the breast cancer cohort from our previous publication (16), there was only a trending difference in patients compared with controls on the FACT-Cog total score after controlling for covariates at baseline. Herein, we observed statistically significant baseline effects on the FACT-Cog total score in patients with lymphoma compared with controls even after controlling for covariates suggesting that there may be an impact of disease from lymphoma at the prechemotherapy time point on perceived functioning. There were also trending baseline differences in executive function in patients with lymphoma compared with noncancer controls. It is possible that the biology of lymphoma and other hematologic malignancies may play a unique role in CRCD. Indeed, those with higher risk chronic lymphocytic leukemia have greater problems in verbal memory and executive function, irrespective of treatment status (54). However, many factors can contribute to pretreatment cognitive functioning including comorbid conditions (55) and coping ability (56). The interaction of these factors and their impact on CRCD in lymphoma and other diseases needs to be further studied.

Although exploratory, we did not see differences in cognitive function outcomes between patients by lymphoma type or treatment regimen, possibly because of the small relative sample sizes in these subgroups. Future studies should be designed to address differences of the impact of disease subtypes and treatment on cognitive function, including those receiving more targeted therapies and immunotherapy. We also did not observe changes in cognitive function between women who were premenopausal vs peri- or postmenopausal at baseline. We did not assess changes in menopausal status during chemotherapy and how that influences cognitive function, which is worthy of further study. A limitation of our research is that we only included a single item to assess depression, which did not allow for a comprehensive assessment. Another limitation is that our study lacked racial and ethnic diversity.

This study is, to our knowledge, the first comprehensive longitudinal study assessing the impact of chemotherapy on cognitive function in patients with lymphoma. Our nationwide study increases generalizability on diverse factors such as geographic location and individuals with varying levels of education. The

use of a study-specific control group was critical to identifying changes over time between groups, particularly for the objective assessments, where practice effects were observed on some assessments. Having both age- and sex-paired controls also allowed us to precisely assess sex effects. Our results are limited to 6 months postchemotherapy; research on more long-term cognitive effects of chemotherapy is needed as has been investigated in other studies. Interventions to alleviate cognitive problems in patients with lymphoma should be developed.

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## Notes

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**Author contributions:** Conceptualization: MJ, GM, TA, CH. Data curation: MJ, MM, SD, JG, TA, GM, MM. Formal analysis and investigation: MJ, MM, LP, AM, EB, CK, LM, PR, SM, GM, TA, CH. Writing—original draft: MJ, CH. Writing—review and editing: All authors.

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## Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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