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RESEARCH ARTICLE

Different subtypes of chronic fatigue in childhood cancer survivors: A DCCSS LATER study

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Abstract

Introduction: The aim of the current study was to investigate whether subtypes of chronic fatigue (CF) can be identified in childhood cancer survivors (CCS), and if so, to determine the characteristics of participants with a specific subtype.

Methods: Participants were included from the nationwide DCCSS LATER cohort. The Checklist Individual Strength (CIS) was completed to assess fatigue. Participants with CF (scored ≥35 on the *fatigue severity* subscale and indicated to suffer from fatigue for ≥6 months) were divided into subgroups using two-step cluster analysis

Abbreviations: BMI, body mass index; CCS, childhood cancer survivors; CF, chronic fatigue; CIS, Checklist Individual Strength; DCCSS LATER, Dutch Childhood Cancer Survivor Study Late Effect; PSQI, Pittsburg Sleep Quality Index.

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based on the CIS *concentration*, *motivation*, and *physical activity* subscales. Differences between groups on demographics, psychosocial, lifestyle, and treatment-related variables were determined using ANOVA and chi-square analyses (univariable) and multinomial regression analysis (multivariable).

Results: A total of 1910 participants participated in the current study ($n = 450$ with CF; $n = 1460$ without CF). Three CF subgroups were identified: Subgroup 1 ($n = 133$, 29% of participants) had *CF with problems in physical activity*; Subgroup 2 ($n = 111$, 25% of participants) had *CF with difficulty concentrating*; and Subgroup 3 ($n = 206$, 46% of participants) had *multi-dimensional CF*. Compared to Subgroup 1, Subgroup 2 more often reported sleep problems, limitations in social functioning, and less often have more than two comorbidities. Subgroup 3 more often reported depression, sleep problems, a lower self-esteem, and limitations in social functioning and a lower educational level compared to Subgroup 1.

Conclusion: Different subgroups of CCS with CF can be identified based on fatigue dimensions physical activity, motivation and concentration. Results suggest that different intervention strategies, tailored for each subgroup, might be beneficial.

KEYWORDS
childhood cancer survivors, chronic fatigue, fatigue severity, mental fatigue, physical fatigue, subgroup analyses

1 | INTRODUCTION

Chronic fatigue (CF) is often reported by childhood cancer survivors (CCS).[1] It is a persistent, subjective feeling of severe fatigue that can reduce quality of life.[2] Symptoms of fatigue can differ widely between subjects, varying from feeling too tired to participate in daily life activities to experiencing difficulties concentrating. Fatigue is multi-dimensional and can be measured in individuals using validated instruments.[3] A variation of questionnaires is available to capture the different aspects of fatigue. In research, CF is often used as a comprehensive term to describe all fatigue dimensions, but little is known about the heterogeneity in the appearance of CF. Identifying subgroups that experience different types of CF and characterize these different fatigue dimensions might help to tackle symptoms on a more personalized level. It is plausible that persons who experience physically related fatigue symptoms, that is, physical exhaustion or reduced physical activity, prefer interventions focused on this physical aspect opposed to persons who experience fatigue symptoms related to mental activities, that is, concentration or motivational problems. The aim of the current study was to investigate whether subtypes of CF could be identified in CCS, and if so, determine demographic, psychosocial, and/or diagnosis and treatment-related characteristics of participants with different fatigue subtypes.

2 | METHODS

2.1 | Study design and participants

This study is part of the Dutch Childhood Cancer Survivor Study on Late Effects (DCCSS LATER) part 2,[4] a cross-sectional study including participants from the nationwide DCCSS LATER cohort ($n = 6165$, baseline characteristics described elsewhere[5]). In total, 4735 eligible CCS were invited to participate (for flowchart of invitation process, see[4]). Participants were included if fatigue status could be determined (CF; yes or no): at least seven of the eight Checklist Individual Strength (CIS) fatigue severity items completed (with one missing value, the mean of the remaining completed items was imputed). If participants had severe fatigue (fatigue severity subscale score ≥ 35), the item assessing the duration of fatigue symptoms had to be completed. Participants who did not have sufficient data to determine fatigue status ($n = 326$) or participants who had missing data on one of the other CIS subscales ($n = 4$) were excluded. All participants were 18 years or older, were able to read and speak Dutch and gave written informed consent to participate. The DCCSS LATER fatigue study was approved by the Medical Research Ethics Committee of the Amsterdam University Medical Centers (registered at toetsingonline.nl, NL34983.018.10).

2.2 | Data collection

The CIS[6] was completed to assess fatigue and measures four fatigue dimensions, that is, *fatigue severity* (eight items), *concentration problems* (five items), *reduced motivation* (four items), and *problems with physical activity* (three items) on a seven-point Likert scale. Subscale items and information on how to score each item are presented in Table S1. A score of ≥35 on the *fatigue severity* dimension indicates the presence of severe fatigue. This cutoff score was validated in the general Dutch population[7] and the DCCSS LATER cohort.[8] To indicate whether participants scored elevated or problematic on the CIS fatigue dimensions *concentration problems*, *reduced motivation*, and *problems with physical activity*, we used the mean subscale values of the general Dutch population, presented by Worm-Smeitink et al.,[7] plus 1 or 2 standard deviations, respectively, as a threshold (≥18, ≥16, and ≥12 to indicate elevated subscale scores and ≥24, ≥20, and ≥16 to indicate problematic subscale scores on the respective subscales). Subsequently, an item assessing the duration of fatigue symptoms ("for how many weeks/months/years have you been fatigued?"), when applicable, was completed. CCS who reported severe fatigue and a duration of fatigue symptoms of 6 months or longer were indicated as having CF.

In addition to fatigue, other constructs were assessed through questionnaires completed at home or during a clinic visit between 2017 and 2022.

- The European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire was used as an indication for the participants' physical activity level (participants were categorized following the physical activity index as being active, moderately active, moderately inactive, or inactive).[9]
- The Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression, with subscale scores ≥8 to indicate (sub)clinical symptoms.[10,11]
- The Pittsburg Sleep Quality Index (PSQI) to determine if participants had sleep problems (PSQI total score ≥5).[12,13]
- The TNO (Netherlands Organisation for Applied Scientific Research) and AZL (Leiden University Medical Centre) Questionnaire for Adult's Quality of Life (TAAQOL) social functioning dimension (scored 0–100 after linear transformation), with higher scores reflecting better social functioning.[14]
- The Rosenburg Self-Esteem Scale (RSES) to assess self-esteem (scored 10–40, with higher score reflecting higher self-esteem).[15,16]
- The Illness Cognition Questionnaire (ICQ) helplessness subscale to reflect feelings of helplessness (scored 6–24, with higher scores reflecting more feelings of helplessness) related to the childhood cancer diagnosis.[17,18]
- A general questionnaire assessing level of education, employment status, relationship status, somatic comorbidities (categorized as having 0, 1–2, or >2 health issues of predefined organ systems[19]) and pain (six-point Likert scale, with higher scores reflecting more pain).
- Height and weight of the participant were manually assessed during the clinic visit and used to calculate body mass index (BMI).

Treatment and diagnosis data of primary cancer diagnoses and all recurrences of the participants were collected from medical records by data managers prior to the study.[20] A detailed description about participant inclusion and data collection has been previously published.[21]

2.3 | Statistical analyses

Participants who reported CF (severe fatigue for ≥6 months) were included in the two-step cluster analysis. Two-step cluster analysis[22] was conducted to group participants based on the total scores of the CIS fatigue *concentration*, *motivation*, and *physical activity* subscales. Silhouette measure of cohesion was used as an indication of the goodness-of-fit of the found clusters, with a score of greater than 0.2 considered fair.[23]

To compare subgroup characteristics (subgroups indicated by two-step cluster analysis), ANOVA (to compare means) and Pearson's chi-square (to compare category distributions) analyses were done. When applicable, that is, if overall Bonferroni adjusted *p*-value ($p = .05$/number of comparisons) for subgroup comparison was statistically significant, post hoc analyses, that is, Bonferroni tests for continuous variables and Bonferroni adjusted *z*-tests for categorical variables, were done to indicate which subgroups differed from each other.

To compare subgroup characteristics and CIS subscale scores with non-fatigued CCS (control group), ANOVA (to compare means) and Pearson's chi-square (to compare category distributions) analyses were done. Mean subgroup CIS subscale scores were compared with dimension scores reported by a healthy subgroup of the general Dutch population who reported no sick days in the past month ($n = 1923$), previously presented by Worm-Smeitink et al.,[7] using independent *t*-tests.

To determine whether subgroup characteristics remained different after mutual adjustment, multinomial regression analysis was done with the CF subgroups as dependent variable and age, sex, BMI, relationship status, employment status, educational level, anxiety, depression, sleep problems, physical activity index, pain, self-esteem, helplessness, social functioning, and number of comorbidities as independent variables.

Analyses were performed in participants with complete data, but sensitivity analyses were done using imputed data. Missing data (no pattern observed) were imputed using multiple imputation (Markov chain Monte Carlo method, 20 imputed datasets, using Rubin's rules to pool the analyses).[24–26] IBM SPSS (IBM Corp., released 2017, IBM SPSS Statistics for Windows, Version 25.0) was used for the analyses.

3 | RESULTS

3.1 | Prevalence CF subgroups

In total, 450 CCS with CF and 1460 CCS without CF (control group) participated in the current study (see flowchart in Figure S1). Two-step cluster analysis in the participants with CF identified three distinct CF subgroups. A Silhouette measure of cohesion of 0.4 indicated that subgroups could adequately be identified based on the CIS subscale scores. The following three subgroups were identified: Subgroup 1 contained 133 participants (29%), Subgroup 2 had 111 participants (25%), and Subgroup 3 was the largest with 206 participants (46%).

Subgroup 1 experiences the least difficulties, with no problematic CIS concentration scores and less than 1% problematic CIS motivation scores. This group also has the lowest prevalence of anxiety, depression, and sleeping problems, and scores best on self-esteem and social functioning. Still, half of this group has elevated CIS physical activity scores and one in four scores problematic on this dimension. Compared to the non-CF CCS, this subgroup scores worst on the CIS motivation and physical activity dimension. Compared to the general population, this subgroup scores worse on the CIS physical activity dimension. Hence, we labeled this CF subgroup as having "*fatigue with problems in physical activity*."

Subgroup 2 is characterized by a high score on the CIS concentration dimension, with every participant in this group having an elevated CIS concentration score and more than half scoring problematic on the concentration dimension. In addition, a high prevalence of anxiety and sleeping problems and, to a lesser extent, depression was seen in this group. This group had elevated scores on the physical activity dimension as well, when compared to non-CF CCS and the general population; however, compared to the other CF-subgroups, this subgroup seems to be scoring less problematic on the physical activity dimension. Hence, we labeled this CF subgroup as having "*fatigue with difficulty concentrating.*"

Subgroup 3 was characterized by high scores on all CIS dimensions, the highest fatigue severity score, a high prevalence of anxiety, depression and sleeping problems, feeling helpless, and scoring low on self-esteem, and this subgroup was also characterized by a lower educational level compared to the other subgroups and, although not statistically significant, a higher percentage of unemployment. Almost everyone in this group had elevated scores on all CIS dimensions and about half of this group scored problematic on all CIS dimensions, that is, 50.0%, 43.7%, and 57.8% for the dimensions concentration, motivation, and physical activity, respectively. As scores on all fatigue dimensions were elevated and/or problematic and worse compared to non-CF CCS and the general population, we labeled this CF subgroup as having "*multi-dimensional fatigue.*"

Subgroups did not differ on diagnosis and treatment-related factors, except that *CF subgroup multi-dimensional fatigue* less often received chemotherapy only compared to the non-CF group and the *CF subgroup with problems in physical activity*.

A comparison between the subgroups on CIS subscale scores is shown in Table 1. A comparison between subscale scores of the subgroups and the general population is shown in Table 2. A comparison between the subgroup characteristics and diagnosis and treatment-related factors is shown in Table S2. Differences between the groups remained when analyzed in a multivariable model (Table 3). A comparison with non-participants is shown in Table S3.

4 | DISCUSSION

The aim of the current study was to investigate whether subgroups of CF could be identified in CCS. Using two-step cluster analysis, three CF subgroups were identified based on the CIS dimensions *concentration*, *motivation*, and *physical activity*: (i) *fatigue with problems in physical activity*, (ii) *fatigue with difficulty concentrating*, and (iii) *multi-dimensional fatigue*.

4.1 | Comparison with existing literature

Previous studies mostly aimed at identifying subgroups in cancer survivors focusing on the severity of fatigue, including both fatigued and non-fatigued participants.[27,28] Although this approach is interesting, the current study aimed to identify subgroups based on the different dimensions of fatigue rather than the severity of symptoms. Some studies did focus on dimensions of fatigue, for example, in the review of de Raaf et al., physical and mental fatigue were suggested to be separate concepts in cancer patients.[29] Also in people with chronic diseases, physical and mental fatigue are frequently present, where they often occur simultaneously, but they can also occur separately.[30] This suggests that different fatigue subtypes exist; however, these subtypes had not been identified in CCS yet. Identifying subgroups based on fatigue dimensions could be of particular interest when choosing an optimal intervention strategy. Several fatigue interventions exist, all aimed at different fatigue-related factors. Determining whether subgroups can be identified that are characterized by specific fatigue-related factors might help to choose a matching intervention.

Based on the current results, that is, differences in CIS dimension scores and subgroup characteristics between the three identified subgroups, we can conclude that subtypes of CF are present in CCS. It should be emphasized that all subgroups reported CF, and thus all subgroups experience severe fatigue symptoms; however, CF is characterized differently across the three subgroups. All subgroups showed fatigue symptoms regarding physical activity, but the *subgroup with difficulty concentrating* and the *multi-dimensional fatigue* subgroup also showed fatigue regarding concentration and/or motivation. In the latter groups, psychosocial outcomes were present, suggesting there is a relation between the fatigue dimensions concentration and motivation and psychosocial outcomes. This makes us believe that the dimensions concentration and motivation represent a psychological or mental fatigue.

TABLE 1 CIS dimension scores of the non-CF control group and the CF subgroups.

CIS dimension	Non-CF group ($n = 1460$)	CF with problems in physical activity ($n = 133$)	CF with difficulty concentrating ($n = 111$)	Multi-dimensional fatigue ($n = 206$)
CIS fatigue severity				
Mean dimension score (SD)	19.4 (8.5)[c,d,e]	41.2 (4.8)[d]	42.1 (5.0)[e]	44.7 (6.3)[c,d]
CIS concentration				
Mean dimension score (SD)	12.6 (6.6)[d,e]	12.0 (4.1)[d,e]	25.6 (3.9)[c,e]	23.6 (5.8)[c,d]
Proportion scoring elevated[a]	23.3%[c,d,e]	11.3%[d,e]	100%[c,e]	87.4%[c,d]
Proportion scoring problematic[b]	7.9%[c,d,e]	0%[d,e]	60.4%[c]	50.0%[c]
Number of missing values	–	–	–	–
CIS motivation				
Mean dimension score (SD)	8.5 (4.1)[c,d,e]	11.8 (3.7)[e]	11.0 (2.9)[e]	19.4 (3.6)[c,d]
Proportion scoring elevated[a]	7.1%[c,e]	18.0%[d,e]	5.4%[c,e]	87.9%[c,d]
Proportion scoring problematic[b]	1.9%[d]	0.8%[e]	0%[e]	43.7%[c,d]
Number of missing values	–	–	–	–
CIS physical activity				
Mean dimension score (SD)	5.0 (2.9)[c,d,e]	12.3 (4.2)[e]	11.5 (4.5)[e]	16.1 (3.6)[c,d]
Proportion scoring elevated[a]	3.8%[c,d,e]	54.9%[e]	48.6%[e]	91.7%[c,d]
Proportion scoring problematic[b]	0%[c,d,e]	24.1%[e]	21.6%[e]	57.8%[c,d]
Number of missing values	–	–	–	–

Note: Differences between the groups are shown as follows (with superscript letters [c, d,] and [e], using Bonferroni post hoc test for continuous variables and Bonferroni adjusted *z*-tests for categorical variables). Between group differences did not change after multiple imputation (significant difference remained in majority of 20 imputed datasets).

Abbreviations: CF, chronic fatigue; CIS, Checklist Individual Strength; non-CF group, CCS participants without CF.

[a]To indicate whether participants scored elevated on the CIS fatigue dimensions concentration, motivation and physical activity, we used the mean subscale values of the general Dutch population + 1 standard deviation (presented by Worm-Smeitink et al.[7]) as a threshold (≥18, ≥16, and ≥12, respectively).

[b]To indicate whether participants scored problematic on the CIS fatigue dimensions concentration, motivation and physical activity, we used the mean subscale values of the general Dutch population + 2 standard deviations (presented by Worm-Smeitink et al.[7]) as a threshold (≥24, ≥20, and ≥16, respectively).

[c]Significant difference with CF subgroup with problems in physical activity (Subgroup 1).

[d]Significant difference with CF subgroup with difficulty concentrating (Subgroup 2).

[e]Significant difference with CF subgroup multi-dimensional fatigue (Subgroup 3).

TABLE 2 CIS dimension scores of CF subgroups compared to population controls.

CIS dimension	General population[a]	CF with problems in PA ($n = 133$)	CF with difficulty concentrating ($n = 111$)	Multi-dimensional fatigue ($n = 206$)
CIS concentration				
Mean scale score (SD)	12.44 (5.96)[c,d]	12.0 (4.1)	25.6 (3.9)	23.6 (5.8)
CIS motivation				
Mean scale score (SD)	11.14 (4.74)[d]	11.8 (3.7)	11.0 (2.9)	19.4 (3.6)
CIS physical activity				
Mean scale score (SD)	8.28 (4.29)[b,c,d]	12.3 (4.2)	11.5 (4.5)	16.1 (3.6)

Note: Significant difference: p-value < .05 calculated with independent t-test.

Abbreviations: CF, chronic fatigue; CIS, Checklist Individual Strength; PA, physical activity.

[a]General Dutch population controls, that is, group of healthy population controls who reported no sick days in past month ($n = 1923$), previously presented by Worm-Smeitink et al.[7]

[b]Significant difference between general population and CF subgroup with problems in physical activity (Subgroup 1).

[c]Significant difference between general population and CF subgroup with difficulty concentrating (Subgroup 2).

[d]Significant difference between general population and CF subgroup multi-dimensional fatigue (Subgroup 3).

TABLE 3 Results of the multinomial regression analyses to compare CF subgroup characteristics.

	CF with difficulty concentrating ($n = 111$)	Multi-dimensional fatigue ($n = 206$)
Characteristic	**OR [95% CI]**	**OR [95% CI]**
Mean age in years	1.01 [0.97–1.05]	1.02 [0.98–1.05]
Sex (ref = female)	1.24 [0.68–2.26]	1.20 [0.68–2.13]
BMI		
Underweight	0.52 [0.12–2.22]	0.28 [0.06–1.23]
Healthy weight	ref	ref
Overweight	1.01 [0.53–1.94]	1.15 [0.60–2.18]
Obesity	0.92 [0.40–2.08]	1.76 [0.82–3.77]
In a relationship (ref = not in a relationship)	0.93 [0.46–1.91]	1.06 [0.53–2.12]
Not employed (ref = employed)	0.59 [0.28–1.23]	0.79 [0.40–1.57]
Educational level		
Low	1.38 [0.51–3.70]	**2.46 [1.01–5.98]**
Middle	1.68 [0.89–3.19]	1.55 [0.84–2.85]
High	ref	ref
Clinically relevant anxiety (ref = no)	1.62 [0.83–3.17]	1.33 [0.71–2.48]
Clinically relevant depression (ref = no)	2.60 [0.72–9.38]	**5.53 [1.88–16.3]**
Sleeping problems (ref = no)	**2.23 [1.21–4.11]**	**2.38 [1.43–4.25]**
Physical activity index		
Inactive	0.69 [0.18–2.62]	1.00 [0.28–3.54]
Moderately inactive	1.13 [0.54–2.37]	1.68 [0.84–3.38]
Moderately active	1.75 [0.79–3.86]	1.59 [0.73–3.48]
Active	ref	ref
Pain (continuous)	1.04 [0.83–1.30]	0.97 [0.78–1.20]
Self-esteem (continuous)	0.97 [0.90–1.03]	**0.90 [0.84–0.97]**
Helplessness (continuous)	1.08 [0.97–1.20]	1.11 [1.00–1.22]
Social functioning (continuous)	**0.98 [0.97–0.99]**	**0.98 [0.97–0.99]**
Number of comorbidities		
0	ref	ref
1–2	1.00 [0.54–1.86]	1.31 [0.70–2.44]
>2	**0.37 [0.14–0.96]**	0.55 [0.23–1.33]

Note: Table shows results of multinomial regression analysis with CF subgroup 1 (problems with physical activity; $n = 133$) as reference group. Bold odds ratios show statistically significant difference with the reference group.
Abbreviations: CF, chronic fatigue; CI, confidence interval.

Results showed that all subgroups experience problems with physical activity (elevated physical activity dimension scores compared to non-CF CCS and the general population), but differ on concentration/motivation dimensions (mental fatigue). With Subgroup 1 showing the least problems on the psychosocial characteristics, we believe this group to predominantly experience fatigue problems regarding physical activity. Compared to Subgroup 2, which predominantly experiences concentration problems, Subgroup 1 more often has more than two comorbidities, which might be related to the fatigue symptoms these CCS experience regarding physical activity.

One explanation for the differences in symptoms experienced by the subgroups might be the therapy received during childhood cancer. In a previous study, we found that type of childhood cancer treatment was not associated with CF[31]; however, the current results indicate that whenever CCS have CF, type of treatment might be associated with the type of fatigue that CCS experience. The *multi-dimensional fatigue* subgroup less often received chemotherapy only compared to the non-CF group and the *CF subgroup with problems in physical activity*, indicating that the *multi-dimensional* subgroup more often received radiotherapy (with or without chemotherapy). Radiotherapy has been associated with a higher risk for various comorbidities, for example, cardiovascular, neurocognitive, and fertility problems,[32–35] and might therefore be a plausible cause for the multi-faceted problems that CCS in this group experience.

4.2 | Clinical implications

Exploring how to distinctly tackle CF in different subgroups might result in more effective intervention strategies. Several studies in various patient populations have shown that fatigue can be experienced on different dimensions, whether or not simultaneously.[29,30,36] It might therefore be plausible that tailored interventions focusing on different fatigue dimensions might be beneficial in reducing fatigue symptoms. For example, the *CF subgroup with problems in physical activity* (Subgroup 1) might benefit most from interventions focusing on the physical activity dimension, such as exercise therapy, a promising intervention to tackle fatigue in CCS.[37] CCS who experience *fatigue with difficulty concentrating* (Subgroup 2) might benefit most from interventions addressing psychological aspects that were related to this subgroup, such as cognitive behavioral therapy (CBT) or mindfulness. A pilot study in CCS showed CBT to be a promising intervention to reduce fatigue and psychological distress.[38] However, compared to CCS without CF, both subgroups score worse on all characteristics; therefore, all these aspects need to be taken into account when determining the best interventions strategy. Still, it might be beneficial to focus on the fatigue dimension that is predominantly affected. Future intervention studies should investigate whether using different strategies based on fatigue dimensions could indeed be helpful in decreasing symptoms on specific dimensions of fatigue.

Subgroup 3 shows *multi-dimensional fatigue*; therefore, tackling one specific fatigue dimension might not be the preferred strategy. This group also shows high prevalence rates of anxiety, depression, and sleeping problems, and scores low on psychosocial outcomes such as self-esteem and social functioning. In addition, this subgroup was lower educated compared to the non-CF group and the other subgroups and also seemed to be more often unemployed (although the latter was not statistically significant), which suggests that this group might experience difficulties regarding educational and/or employment-related demands. Therefore, as there seems to be multi-factorial issues to be present in this group, a multi-dimensional approach might be most beneficial here.

4.3 | Strengths and limitations

The current study is part of a nationwide collaboration, including a cohort that includes CCS with all childhood cancer diagnoses and treatments, contributing to the generalizability of the results. A limitation of the current study is that data are cross-sectional. Therefore, we can determine associations between subgroups and certain characteristics; however, we cannot determine causality. For example, we assume that the *muti-dimensional fatigue* subgroup is experiencing difficulties regarding educational and/or employment-related demands, which might be a consequence of the multi-dimensional problems that they experience. However, due to the cross-sectional nature of the data, we can only speculate. A longitudinal study where CCS are followed from the end of cancer therapy into survivorship might provide information regarding the origin and the course of the symptoms and what the consequences are. In addition, it would be interesting to compare subgroups on characteristics that were not included in the current study, for example, social determinants or genetic factors. Future studies might include these factors.

5 | CONCLUSION

To conclude, three different CF subtypes were identified in CCS. A subgroup presenting with *CF and problems with physical activity*, a second group with *CF and difficulty concentrating*, and a third group presenting with *multi-dimensional fatigue*. This indicates that different intervention strategies, focused at the fatigue dimension most affected in each subgroup, might be beneficial.

AUTHOR CONTRIBUTIONS

Adriaan Penson: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing—original draft. Iris Walraven: writing—original draft, and writing—review and editing. Ewald Bronkhorst: formal analysis, writing—review and editing. Heleen Maurice-Stam: resources, writing—review and editing. Martha Grootenhuis, Wim Tissing, Helena van der Pal, Andrica de Vries, Sebastian Neggers, Birgitta Versluys, Marloes Louwerens, Dorine Bresters, Cécile Ronckers, Saskia Pluijm, Eline van Dulmen-den Broeder: investigation, methodology, resources, writing—review and editing. Margriet van der Heiden-van der Loo: data curation, software, writing—review and editing. Nicole Blijlevens: supervision, writing—review and editing. Marry van den Heuvel-Eibrink and Leontien Kremer: investigation, methodology, funding acquisition, resources, writing—review and editing. Hans Knoop: conceptualization, methodology, project administration, supervision, writing—original draft, writing—review and editing. Jacqueline Loonen: conceptualization, methodology, project administration, supervision, funding acquisition, writing—original draft, writing—review and editing

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study we provided by the DCCSS LATER Consortium under license. Data are available from the corresponding author upon reasonable request with permission of the DCCSS LATER consortium.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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