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RESEARCH ARTICLE

Longitudinal changes of psychological distress among childhood cancer survivors: The Swiss Childhood Cancer Survivor Study

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Abstract

Background: Childhood cancer survivors may experience psychological distress due to the disease, cancer treatments, and potential late effects. Limited knowledge exists regarding longitudinal changes in psychological distress after childhood cancer. We aimed to determine changes in psychological distress over time and explore determinants of changes.

Methods: The Swiss Childhood Cancer Survivor Study collected data at baseline (2007–2009) and follow-up (2010–2012). Psychological distress was measured using the Brief Symptom Inventory 18 (BSI-18), including three symptom scales (somatization, depression, anxiety) and an overall distress index (Global Severity Index, GSI). Sum-scores were *T*-standardized (mean = 50; standard deviation [SD] = 10). Survivors with a score ≥57 on the GSI or two symptom scales were classified as cases with distress. We used linear mixed effects regression to identify potential sociodemographic and clinical determinants of change in psychological distress.

Results: We analyzed 696 survivors at baseline (mean age = 24 years [SD = 4], 49% females, mean time since diagnosis = 16 years [SD = 4]). On follow-up (2.4 years, SD = 1), 317 survivors were analyzed, including 302 participants with repeated measures. We found that 13% (39/302) were cases at baseline, and 25% (76/302) were cases on follow-up. Those older at study and longer since diagnosis, females, diagnosed with central nervous system (CNS) tumors, and those reporting late effects were more likely to experience higher levels of distress. Females and unemployed are at higher risk for developing or persisting psychological distress than males and those who are employed or in training.

Abbreviations: BMT, bone marrow transplant; BSI-18, Brief Symptom Inventory (short form) 18; CI, confidence interval; CNS, central nervous system; GSI, Global Severity Index; OR, odds ratio; SCCSS, Swiss Childhood Cancer Survivor Study; SD, standard deviation.

Conclusion: We observed an increase in psychological distress score over time, with higher proportion of psychological distress on follow-up. Anticipatory guidance and screening should be implemented in regular follow-up care.

KEYWORDS
adolescents and young adults, BSI-18, cancer, oncology, psychological distress, survivor, Switzerland

1 | INTRODUCTION

Childhood cancer survivors may experience psychological burden as a result of the cancer itself, cancer therapies, and the possibility of late effects.[1] Reviews have estimated that up to 40% of childhood cancer survivors suffer from anxiety and depression, respectively.[2–5] Female survivors and those older at diagnosis and at the time of study, were more likely to report depressive symptoms. Additionally, survivors who were unemployed, had lower education, lower household income, and were single, were more likely to report depression, anxiety, somatization, and overall distress.[6–8] Survivors of central nervous system (CNS) tumors reported higher overall distress scores,[9,10] as did those with more intensive therapy regimens.[11–14]

The emergence of late physical effects from cancer and its treatment or the experience of social difficulties after cancer may impact psychological wellbeing long after cancer has been cured.[4] Although some studies have examined long-term psychological distress at a single point in time,[3] there is limited knowledge regarding longitudinal changes of psychological distress after childhood cancer. Distress may increase due to onset of new late effects or decrease because of better adjustment to life as a cancer survivor. A previous longitudinal study in the United States showed that approximately one-third of survivors reported distress symptoms at any time over 16 years, with a significant proportion (15%–20%) demonstrating persistent or increasing distress.[15] To date, no other studies have been published on longitudinal psychological distress in long-term cancer survivors.

In the current study, we investigated the changes in psychological distress over time. We aimed to (a) describe the psychological distress of childhood cancer survivors at baseline and follow-up, (b) determine the changes in distress scores over time, and (c) identify determinants of changes in psychological distress.

2 | METHODS

This is a longitudinal study using data from the Swiss Childhood Cancer Survivor Study (SCCSS).[16] The SCCSS is registered at ClinicalTrials.gov (NCT03297034).

2.1 | Setting and population

The Swiss Childhood Cancer Registry is a population-based registry including all Swiss residents diagnosed with leukemia, lymphoma, CNS tumor, malignant solid tumor, or Langerhans cell histiocytosis before age 21 years.[17] From this, the SCCSS was set up as a nationwide, long-term cohort study of all registered patients who were diagnosed after 1976 and survived for at least 5 years.[16] For the current analysis, we used data collected from survivors diagnosed before 2005, who participated in the first wave of the SCCSS 2007–2009 (baseline, T1) and who received a follow-up questionnaire (T2) between 2010 and 2012.

2.2 | Study procedures

For the baseline questionnaire, at T1, between 2007 and 2009 (baseline), all survivors received an initial information letter about the SCCSS from their former treating institution asking them to report if they did not wish to participate, if their address had changed, or if they required the questionnaire in another language (T1). Two weeks later, all survivors received a paper-based questionnaire with a prepaid return envelope. Non-responders received another questionnaire after 2 months, and if they still did not answer, were then contacted by phone. Non-responders received another questionnaire after 2 months, and if they still did not answer, were then contacted by phone. Questionnaires were provided in the three national languages: German, French, and Italian.

At T2 (follow-up), after approximately 3 years, all participants who had completed the T1 questionnaire, were aged 18 years and older, and diagnosed with cancer at age ≤16 years, received a second questionnaire. Non-responders got a reminder letter with another questionnaire and prepaid return envelope 2 months later. Because of few Italian-speaking participants, the second questionnaire was provided only in German and French (two Italian-speaking survivors received the questionnaire in German, their second language).

The baseline questionnaire contained the following main domains: psychological distress, quality of life, somatic health, current medication, health service utilization, fertility, health behavior and socioeconomic information.[16] The main focus of the follow-up questionnaire was continuing care and psychological outcomes.[18,19]

2.3 | Outcome measurement

Psychological distress was measured using the Brief Symptom Inventory 18 (BSI-18),[20,21] validated in German,[22] French,[23] and Italian.[24] The 18 items can be summarized into three symptom scales of six items each (somatization, depression, and anxiety) and an overall Global

Severity Index (GSI), which indicates overall psychological distress. For each item, survivors expressed their distress during the previous week on a five-point scale (0 = not at all to 4 = extremely). Items of each scale are totaled to calculate the sum scores; all 18 items were summed up to calculate the GSI. For survivors who missed two or less items per scale, scale scores were calculated by imputing missing items with the scale average of the remaining items.[25]

We standardized scores of all three scales and GSI into *T*-scores (mean = 50, standard deviation [SD] = 1) according to the manual.[25] "Psychological distress" (case) was defined as $T \geq 57$ on at least two scales or the GSI, otherwise, was classified as "no distress."[25] This cutoff was validated and recommended by earlier publications.[26–28]

2.4 | Covariates

Sociodemographic characteristics were obtained through self-administered questionnaires. Baseline questionnaires included age (<25, 25–29, and 30 years), sex (male, female), migration background (no, yes; defined as non-Swiss, not born in Switzerland, or at least one non-Swiss parent), siblings (has siblings, single child), and civil status (single, married, divorced/separated). At both time points, participants reported employment status (employed, unemployed, in education/training), and highest educational attainment (primary: compulsory schooling; secondary: vocational training or high school degree; tertiary: college or university degree).[29]

Clinical data were obtained from the cancer registry, namely, age at diagnosis (0–4, 5–9, ≥10 years), time since diagnosis (5–15, ≥16 years), and relapse (no, yes). Diagnoses were classified according to the International Classification of Childhood Cancer - Third edition.[30] We aggregated diagnoses into four groups: leukemia, lymphoma, CNS tumors, and other solid tumors. Treatment was coded hierarchically as surgery only, chemotherapy (without radiotherapy but may have had surgery), radiotherapy (may have had surgery and/or chemotherapy), and bone marrow transplantation (BMT).[31] Finally, the questionnaire also assessed self-reported late effects (no, yes).

2.5 | Data analysis

For descriptive statistics, we used number and proportions for categorical variables, and means with SDs for continuous variables. We used a Sankey diagram and bivariate plot (baseline score at *x*-axis and follow-up score at *y*-axis) to visually describe survivors' change in the BSI scores. To describe the prevalence of cases with psychological distress, we used proportions, using respondents at respective time points as denominators.

We used linear mixed effects model for repeated measures, with random intercept and slope to determine the change in distress scale scores (somatization, depression, anxiety, and GSI) from baseline (T1) to follow-up (T2). The mixed model accounts for individual differences and the correlation between repeated measures within the same participant. Furthermore, this is a well-established method of accounting for all available information even if participants have not completed questionnaires at all possible time points.[32] Univariable linear mixed effect model was fitted with covariates as fixed effects. Each covariate was dichotomized: age (adolescent/young adult <25 years old-ref vs. older adult ≥25 years old), sex (male-ref vs. female), education (lower-ref vs. upper), employment (employed-ref vs. in education/training and unemployed), diagnosis (leukemia/lymphoma/others-ref vs. CNS tumors), treatment (chemotherapy/surgery-ref vs. radiotherapy/BMT), age at diagnosis (child <10 years old-ref vs. adolescent ≥10 years old), times since diagnosis (short-term survivor <15 years vs. long-term survivor ≥15 years), relapse (no-ref vs. yes), and self-reported late effects (no-ref vs. yes). Dichotomized covariates were used for associations with change in the distress score. For each covariate, we fitted a separate model with time*covariate interaction to allow for variation of the covariate–outcome association over time. Multivariable regression was fitted as fully-adjusted model using only covariates with *p*-value less than .05 in univariable regression.

We used the univariable logistic regression to assess the determinants at baseline of psychological distress at follow-up. Participants were classified as: (a) good outcome (no distress at T2); and (b) poor outcome (case with distress at T2). We fitted dichotomized covariates as previously mentioned.[8]

2.6 | Sensitivity analysis

To determine dropout bias, we compared the sociodemographic and clinical characteristics of participants with two measurement time points to those with only baseline information. We further performed subgroup analysis for all aims in participants with valid BSI scores at both time points only.

Certain subgroups may have different psychological distress trajectories. To account for these, we performed subgroup analysis for all aims, removing participants with relapse and those with CNS tumor to determine effect estimates in a more homogenous population.

All analyses were done using Stata 17.0 (StataCorp). All tests were performed using two-tailed tests, and *p*-values less than .05 were considered statistically significant. No adjustments for multiple testing were done.

2.7 | Ethical consideration

Ethics clearance for this study was provided through the general cancer registry permission (Swiss Federal Expert Commission for Professional Secrecy in Medical Research), and an updated ethics approval from the Ethics Committee of the Canton of Bern granted approval to the SCCR and SCCSS (KEK-BE: 166/2014, 2021-01462). The dataset was deidentified prior to analysis to maintain confidentiality.

3 | RESULTS

A total of 712 participants were included in the analysis, of whom 696 had valid BSI data at T1, 317 at T2; 302 survivors answered the

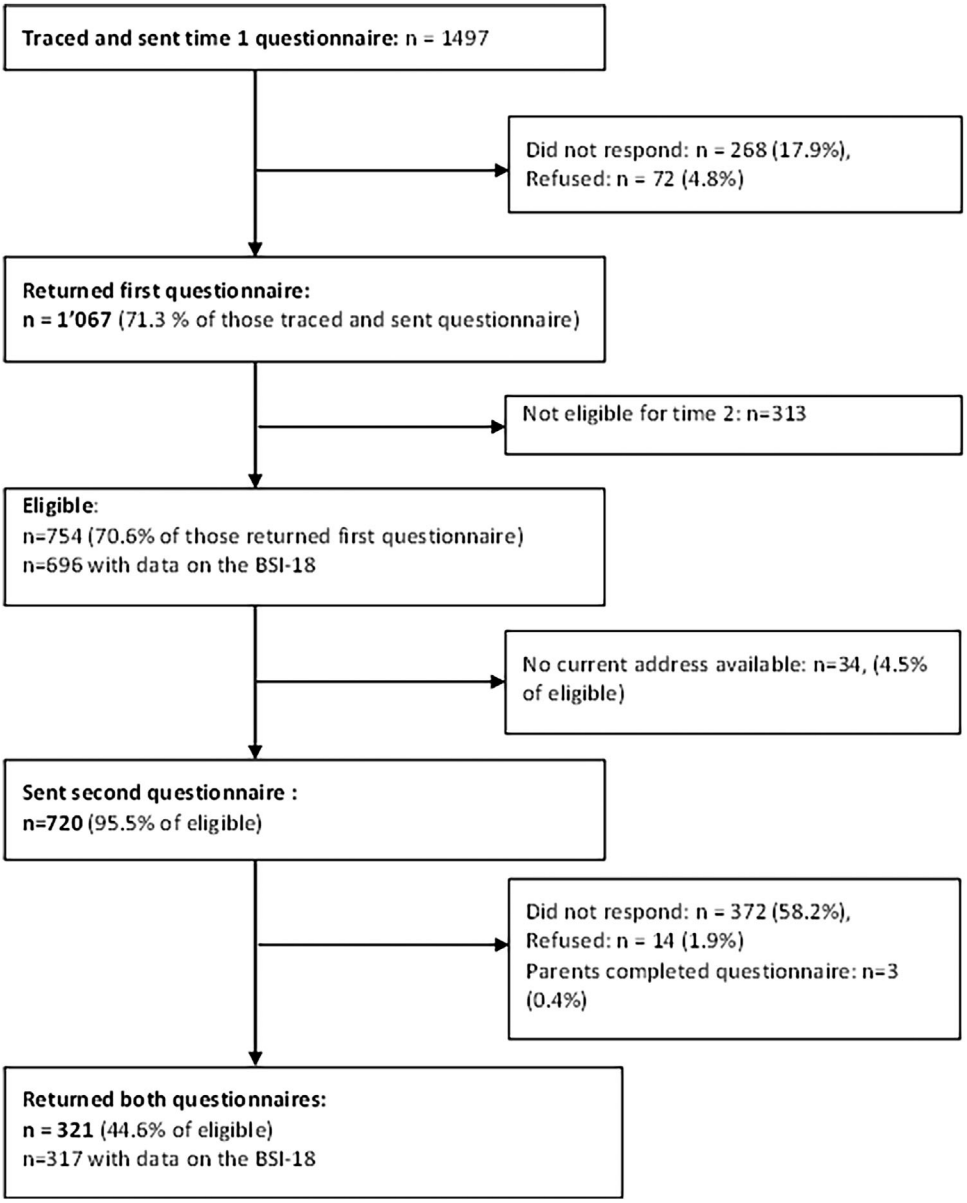

FIGURE 1 Flowchart of study participants. We included 712 survivors, of whom 696 had a valid Brief Symptom Inventory (BSI) measure at baseline and 317 at follow-up; 302 survivors had repeated measurements of BSI at both time points (see also Figure S1 for more details).

BSI at both time points (Figure 1 and Figure S1). At T1, the mean age was 24 years (SD = 4) and 49% were female (Table 1). The mean time since diagnosis was 16 years (SD = 4). Most had been diagnosed with leukemia (33%) or lymphoma (21%). The mean time between T1 and T2 questionnaire was 2.4 years (SD = 1).

3.1 | Psychological distress of childhood cancer survivors

The mean values of *T*-scores at T1 (n = 696) were: somatization 47 (SD = 7), depression 47 (SD = 9), anxiety 46 (SD = 9), and GSI 46 (SD = 9). A total of 111 (16%, N = 696) survivors were considered cases (with psychological distress at T1).

The mean values of *T*-scores at T2 (n = 317) were: somatization 50 (SD = 9), depression 50 (SD = 9), anxiety 48 (SD = 9), and GSI 50 (SD = 10). A total of 79 (25%, N = 317) of the respondents at T2 were considered cases.

3.2 | Changes in psychological distress and its determinants

We used data from 302 participants with BSI measures at both time points to determine changes in prevalence over time. There were 39 cases at T1 (39/302, 13%). Of the 76 (76/302, 25%) cases at T2, 50 (50/302, 16%) were new cases and 26 (26/302, 9%) were persistent cases (Figure 2A). Thirteen cases have improved from T1 (case) to T2

TABLE 1 Sociodemographic and clinical characteristics at baseline and on follow-up.

	Baseline, T1 *N* = 696	Follow-up, T2 *N* = 317
Sociodemographic characteristics		
Sex		
Male	355 (51%)	138 (44%)
Female	341 (49%)	179 (56%)
Age (years)		
<25	558 (80%)	257 (81%)
25–30	113 (16%)	47 (15%)
≥30	25 (4%)	13 (4%)
Migration background		
No migration background	623 (90%)	286 (90%)
Migration background	73 (10%)	31 (10%)
Siblings		
Single child	74 (11%)	39 (13%)
Has siblings	622 (89%)	278 (87%)
Civil status		
Single	413 (94%)	180 (95%)
Married	21 (5%)	7 (4%)
Divorce/separated	3 (1%)	1 (1%)
Highest education attainment		
Primary	86 (20%)	32 (17%)
Secondary	286 (66%)	125 (68%)
Tertiary	58 (14%)	27 (15%)
Employment/education		
Employed	308 (44%)	191 (60%)
Unemployed	50 (7%)	20 (6%)
In education/training	338 (49%)	106 (34%)
Clinical characteristics		
Age at diagnosis (years)		
0–4	170 (24%)	86 (27%)
5–9	198 (28%)	80 (25%)
10+	328 (47%)	151 (48%)
Diagnosis		
Leukemia	229 (33%)	112 (35%)
Lymphoma	145 (21%)	59 (19%)
CNS tumor	96 (14%)	38 (12%)
Other tumors[a]	226 (32%)	108 (34%)
Treatment		
Chemotherapy	338 (49%)	157 (50%)
Surgery	100 (15%)	35 (11%)
Radiotherapy	210 (30%)	105 (33%)
BMT	44 (6%)	18 (6%)
Relapse		
No relapse	619 (89%)	278 (88%)
Had relapse	77 (11%)	39 (12%)
Time since diagnosis (years)		
5–15	296 (43%)	138 (44%)
16+	400 (57%)	179 (56%)
Late effects[b]		
No late effects	440 (63%)	186 (59%)
Reported late effects	256 (37%)	127 (40%)

Abbreviations: BMT, bone marrow transplantation; T1, baseline; T2, follow-up.

[a]Other tumors include renal tumors, soft tissue sarcomas, neuroblastoma, bone tumors, among others.

[b]Late effects obtained through self-report.

(non-case). Figure 2B shows the graphical plots of the score changes of each participant with complete data.

Using linear mixed model on the data from 712 participants (696 on T1 and 317 on T2), the mean changes from T1 to T2 showed increase in somatization score by 2.76 (95% confidence interval [CI]: 1.90–3.64, $p < .001$), of depression score by 2.10 (95% CI: 1.15–3.04, $p < .001$), of anxiety score by 1.63 (95% CI: 0.70–2.56, $p < .001$), and of GSI scores by 2.94 (2.01–3.89, $p < .001$).

Score changes in GSI were higher in those older at study (β 1.83, 95% CI: 0.34–3.32, $p = .016$), females (β 4.57, 95% CI: 3.21–5.93, $p < .001$), diagnosed with a CNS tumor (β 3.14, 95% CI: 1.12–5.15, $p = .002$), longer since diagnosis (β 1.76, 95% CI: 0.35–3.17, $p = .014$), and those reporting late effects (β 6.30, 95% CI: 4.91–7.69, $p < 0.001$), compared to their respective counterparts (Table 2). Determinants for score changes varied depending on the subscale measure (Table 2). The fully-adjusted model can be found in the Table S1.

Being a case with distress at T2 was more likely in females (odds ratio [OR] 2.84, 95% CI: 1.11–7.29, $p = .030$), and survivors who were unemployed at T1 (OR 4.50, 95% CI: 1.03–19.7, $p = .046$) (Figure 3). Other sociodemographic and clinical characteristics were not clearly associated.

3.3 | Sensitivity analysis

We had a dropout rate of 57% (395/696) (Table S2, Figure S1). To detect bias from dropouts, we described the baseline sociodemographic and clinical characteristics of people who did not complete the second questionnaire and compared it with the analysis cohort (Table S2). No statistically significant differences were observed, except for sex and self-reported late effects. There were more females and survivors without late effects who completed both questionnaires. We refitted

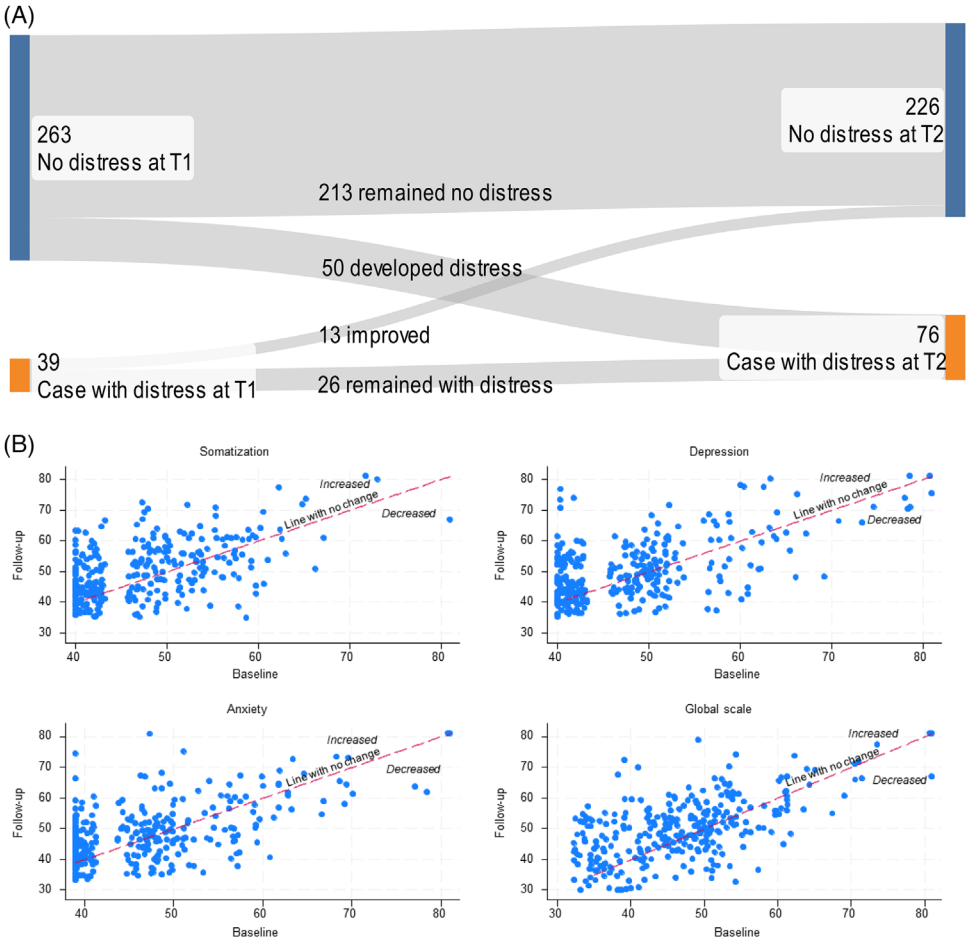

FIGURE 2 Changes in caseness and scores from T1 to T2. (A) The graph shows the number of individuals categorized as distressed and not distressed at both time points. Data were taken from 302 individuals with information on Brief Symptom Inventory (BSI) at both time points. (B) The bivariate plot on the changes of psychological distress. Each dot represents an individual. The T1 BSI score is plotted on the *y*-axis and the T2 score on the *x*-axis. The diagonal line denotes a line of no change. An individual who has a higher psychological score at follow-up occupies the right side of the diagonal line. An individual with a lower psychological score at follow-up occupies the left side of the diagonal line. The distance from the diagonal line is the magnitude of the difference. Data were taken from 302 individuals with data at both time points.

our models in those with complete data only (n = 302 with repeated measures) and found similar results (Table S3).

We performed restrictive analysis by excluding certain subgroups, which were expected to have different risks (those who had a CNS tumor or a relapse). Results are consistent with our main analysis (Tables S4 and S5).

4 | DISCUSSION

Longitudinal studies of psychological distress in childhood cancer survivors remain scarce.[3] In our longitudinal assessment, we noted an increase by double in the prevalence of psychological distress from 13% to 25% over 2.4 years of observation. Moreover, 9% were persistently distressed at T2. Those older at study, females, diagnosed with CNS tumors, longer since diagnosis, and those reporting late effects were more likely to experience higher levels of distress. Females and those unemployed were at higher risk for developing or persisting psychological distress than males and those who are employed or in training. These factors can be used by clinicians to stratify those at increased risk for psychological distress in their survivorship clinics.

Our findings are consistent with a previous longitudinal study showing a relatively low burden of psychological distress, and identified risk factors similar to what we found.[15] The previous study, in contrast, used a different approach by using class membership analysis (into different trajectories).[15] Because of our smaller cohort size, we used linear mixed models to prevent loss of statistical power. We validated our approach using different statistical techniques. Likewise, our findings were still consistent and were supported by those from the previous study.

We found unemployment to have an association with psychological distress, which is the only modifiable risk factor we identified. Our cohort showed 9.1% were unemployed, which declined in the follow-up assessment to 6.3%. These unemployment figures are high, as the national unemployment rate is at 4%–5%.[33] Unemployment of childhood cancer survivors could be due to the lower or delayed educational

TABLE 2 Association of clinical and sociodemographic variables with longitudinal changes (expressed as beta coefficients on the changes of standardized scores, and 95% CI)*.

	Somatization ($n = 712$)		Depression ($n = 712$)		Anxiety ($n = 712$)		GSI ($n = 712$)	
	Beta coefficient (95% CI)	*p*-Value	Beta coefficient (95% CI)	*p*-Value	Beta coefficient (95% CI)	*p*-Value	Beta coefficient (95% CI)	*p*-Value
Sociodemographic characteristics								
Older age[a]	0.22 (−0.98, 1.41)	.723	**1.82 (0.43, 3.21)**	**.010**	**1.47 (0.12, 2.83)**	**.033**	**1.83 (0.34, 3.32)**	**.016**
Being female[b]	**3.21 (2.12, 4.30)**	**<.001**	**2.94 (1.65, 4.22)**	**<.001**	**3.85 (2.61, 5.09)**	**<.001**	**4.57 (3.21, 5.93)**	**<.001**
Having migration background[c]	0.25 (−1.13, 1.63)	.722	1.21 (−0.40, 2.81)	.141	**1.66 (0.09, 3.23)**	**.038**	1.19 (−0.53, 2.92)	.176
Being single child	−0.01 (−1.79, 1.78)	.994	1.32 (−0.76, 3.39)	.214	0.50 (−1.53, 2.53)	.628	0.33 (−1.89, 2.56)	.769
Having a partner[d]	1.00 (−0.12, 2.11)	.079	−0.48 (−1.76, 0.80)	.460	1.26 (0.01, 2.51)	.048	0.82 (−0.52, 2.16)	.232
Having university degree[e]	−1.02 (−2.94, 0.89)	.296	0.29 (−1.90, 2.49)	.793	0.48 (−1.66, 2.61)	.660	−0.13 (−2.42, 2.17)	.914
Education/employment[f]								
Being on training/education	−0.21 (−1.31, 0.89)	.704	−1.12 (−2.37, 0.12)	.077	−0.99 (−2.22, 0.23)	.112	1.50 (−1.11, 4.11)	.260
Being unemployed	0.38 (−1.77, 2.54)	.724	**3.09 (0.64, 5.56)**	**.014**	0.85 (−1.57, 3.27)	.492	−1.15 (−2.47, 0.16)	.086
Clinical characteristics								
Diagnosed at adolescence[g]	**−1.17 (−2.28, −0.05)**	**.040**	−0.34 (−1.65, 0.96)	.605	−0.33 (−1.60, 0.94)	.606	−0.83 (−2.23, 0.57)	.245
Had CNS tumor[h]	0.90 (−0.71, 2.52)	.273	**3.13 (1.26, 5.01)**	**.001**	2.20 (0.37, 4.03)	.019	**3.14 (1.12, 5.15)**	**.002**
Underwent radiotherapy and BMT[i]	0.22 (−0.90, 1.35)	.699	0.62 (−0.69, 1.93)	.355	0.92 (−0.36, 2.20)	.161	0.85 (−0.56, 2.27)	.236
Had relapse[j]	0.01 (−1.77, 1.79)	.991	0.32 (−1.76, 2.39)	.765	−0.16 (−2.19, 1.86)	.874	−0.05 (−2.28, 2.18)	.968
Long-term survivor (≥15 years since diagnosed)[k]	**1.57 (0.45, 2.70)**	**.006**	1.24 (−0.07, 2.56)	.063	1.21 (−0.08, 2.49)	.065	**1.76 (0.35, 3.17)**	**.014**
Self-reported late effects[l]	**3.78 (2.65, 4.91)**	**<.001**	**5.30 (4.00, 6.60)**	**<.001**	**4.88 (3.60, 6.16)**	**<.001**	**6.30 (4.91, 7.69)**	**<.001**

Note: Univariable linear mixed effects regression with covariate–time interaction. Fully adjusted model can be found in Table S1.

Abbreviations: BMT, bone marrow transplantation; CI, confidence interval; CNS, central nervous system; GSI, Global Severity Index.

[a]Age is dichotomized to <25 and ≥25 years

[b]Sex: males as reference group.

[c]Immigration history dichotomized as those with no immigration background (reference), and those who migrated to Switzerland.

[d]Civil status dichotomized into non-married as single, widow/er, separated and divorced (reference), or married.

[e]Education was dichotomized into lower (basic, mandatory, high school, vocational training, and apprenticeship) (reference) and upper education (bachelor, masteral, doctorate, and continuing education).

[f]Employment/education was classified as those with full-time or part-time employment (reference), and those who are unemployed seeking employment, or in education. *p*-Values for trends were as follows: somatization $p = .045$; depression $p < .001$; anxiety $p = .083$; and Global Severity Index $p = .002$.

[g]Survivors' age at the diagnosis of cancer dichotomized into 10 years (reference) and ≥10 years.

[h]Survivors' diagnosis dichotomized into leukemia/lymphoma/others (reference) and CNS tumors.

[i]Survivors' past cancer therapy dichotomized into chemotherapy or surgery (reference) and radiotherapy or bone marrow transplantation.

[j]Presence of relapse (reference) or its absence.

[k]Time since diagnosis dichotomized into <15 years (reference) and ≥15 years.

[l]Self-reported late effects of cancer and chemotherapy.

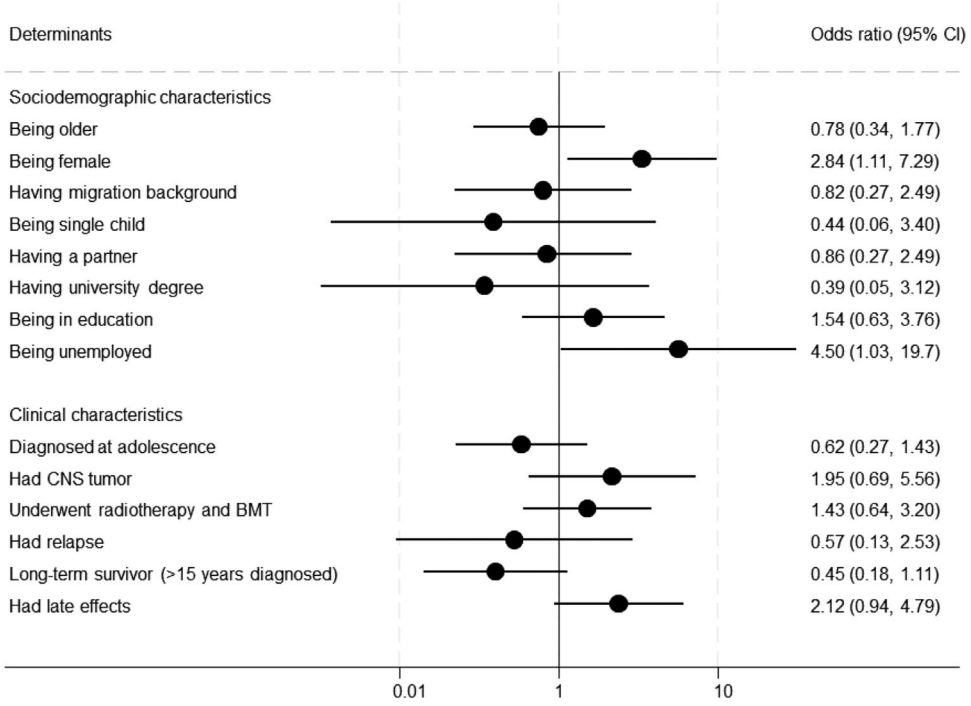

FIGURE 3 Determinants for being a case with distress (cases at T2) (univariable logistic regression) based on 302 with available data at both time points (good outcome, $n = 226$ vs. poor outcome, $n = 76$).

attainment[34,35] or lower health status that prevents them from joining the workforce. However, reverse causation is also possible, with psychological distress resulting in unemployment. Low motivation, poor self-efficiency, and low energy from psychological distress may collectively lead to unemployment.[36] This makes the causality between unemployment and mental health difficult to disentangle. Nevertheless, our findings highlighted the importance of a multidisciplinary team and a holistic approach to long-term follow-up clinics. Survivors could be included in training and integration programs for them to attain new skills, assist them in finding employment, and thereby help to prevent or improve psychological distress.[34–36]

A systematic review showed higher psychological distress in females, in those having a relapse, and self-reported late effects across different cross-sectional studies.[1–3,5] These determinants were also seen in our longitudinal study. Females, in general, are at higher risk for poorer psychological outcomes.[5] This sex/gender difference is multifactorial, from hormonal fluctuations (biological), societal pressures accorded to female gender (sociocultural), and differences in self-reporting of psychological distress in questionnaires.[37,38] More notably, stress reaction is different, with females' higher levels of psychological distress in response to stress compared to males.[39] On the other hand, male survivors exhibit more risky behaviors compared to females, such as smoking, binge-drinking, and illicit drug use, which may be a red flag for a mental health problem.[40]

Previous studies were inconsistent for CNS tumors as a risk factor for psychological distress. This was due to low sample sizes in the cross-sectional studies.[41] Our findings showed the association of the previous diagnosis of neurologic tumors and psychological distress that can be explained by the neuropsychiatric sequelae of the cancer or the therapy.[42] In addition, the permanent and visible scars of previous surgery and the higher likelihood of cognitive or physical disabilities, could have contributed to the development of psychological distress in this group.[42,43]

A childhood cancer diagnosis, with its sometimes long and impactful treatment, also allows children to grow and become resilient when confronted with future stressful events.[44] Overall, our data show that while there is a significant number of survivors with psychological problems, which need to be addressed, most survivors fare well in the long-term.

4.1 | Strengths and limitations

Our study is one of the few population-based studies on childhood cancer survivors investigating longitudinal psychological distress.[3] Some longitudinal studies have focused on early survivorships or immediately after cancer therapy.[45,46] A huge number of studies in the literature used cross-sectional surveys, which only captured a snapshot of psychological distress in their respective population.[2,3] Longitudinal studies are an essential piece of evidence in causal association, as they consider the temporality of psychological status of an individual capturing the dynamic nature of mental health. Our analysis also considered individual differences, alongside group differences, which were a more accurate depiction of mental and emotional development. Finally, unlike other assessments, we used mixed effects linear regression models for repeated measures to account for dropouts. The result

was confirmed by fitting a model using the complete dataset, showing consistency in the estimates.

However, several caveats need to be considered for the interpretation of our findings. First, the questionnaire we used is not a diagnostic tool, but rather to screen for distress. Estimates we provided identified high-risk individuals, which should be followed by a more detailed clinical assessment. This limitation is shared by other population-based studies. Second, self-selection may have happened during the study enrollment. This occurs when the participant, who has high psychological distress, opts out of our survey. However, we compared the baseline scores of those who dropped out with those who had complete participation and found no difference between the two, making self-selection bias less likely (Tables S2.1-3 and S3). Third, almost half of our baseline population had no measurement on follow-up. High dropout rates are likewise seen in a previous longitudinal study[15] and an established limitation in any longitudinal analyses. But a prior analysis of our cohort indicated that the non-response bias may be minimal for psychological outcomes.[47] Moreover, we employed multiple statistical strategies to investigate and address this issue.

Fourth, we reported a smaller sample size compared to the previous longitudinal study.[15] Childhood cancer is rare, and in Switzerland there are only about 240 new cases or 200 survivors per year.[48] We therefore optimized our models to mitigate issues for smaller sample sizes. Fifth, we observed an increase in somatization scores on follow-up, yet the interpretation of this subscale may be difficult for survivors of childhood cancer. Cancer survivors undergo surveillance and follow-up checkup to screen for recurrence or treatment sequelae. One cannot distinguish whether these clinical symptoms are due to long-term consequences of the cancer or treatment, or with no organic cause so it could be considered a psychological problem (somatization).[49] The association of self-reported late effects with global score index (composite score) and somatization score may have demonstrated this bias. Although the BSI-18 is validated and widely used for childhood cancer survivors, the interpretation of the somatization subscale remains a contentious topic in this field.[50]

Finally, our findings suffer a publication lag of a decade after data collection, potentially compromising its current applicability. Nonetheless, cancer diagnosis remains a significant source of stress. Moreover, risk factors for psychological distress remain consistent and independent of treatment outcomes, with age, sex (or gender in social contexts), unemployment status, and especially late effects serving as perennial and persistent predictors of adverse psychological health.

4.2 | Clinical implications and future research

Current clinical guidelines underscore the importance of mental health screening and anticipatory guidance for childhood cancer survivors during their long-term follow-up.[4] However, studies show that mental health screening is lacking even with previous evidence on its importance.[51,52] Our findings continue to reiterate this need. Clinicians should be aware of the risk for mental health problems during follow-up visits.

Future research should focus on longitudinal, population-based studies using clinical diagnoses of anxiety and depression in survivors and comparison with the general population. With the aging survivor population and increasing number of late effects, prevalence of psychological distress might further increase. Multiple time points should be included, and non-linear growth trajectory explored. Most studies of mental health progression over time have used linear models, yet practical and clinical experience proved non-linear development over time.[53]

5 | CONCLUSION

We found increasing psychological distress in long-term childhood cancer survivors over 2.4 years of observation. Survivors who were older, females, had CNS tumors, longer time since diagnosis, and those reporting late-effects have higher increase in psychological distress. Females and survivors unemployed at baseline were at higher risk for developing or persisting psychological distress. Continuous psychosocial screening and anticipatory guidance is advised even after the cancer therapy and long into their survivorship.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are accessible through the corresponding author upon reasonable request.

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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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