

# Psychological risk in long-term survivors of childhood acute lymphoblastic leukemia and its association with functional health status: A PETALE cohort study

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## Abstract

**Background:** Recent research has suggested that long-term pediatric cancer survivors were at risk of important physical and psychological morbidities. To date, we do not know to what extent functional health status contributes to psychological risk and which domains are most important. The aim of this study was to systematically explore which functional domain could explain anxiety, depression, and distress symptoms.

**Procedure:** We used data available for 105 adolescents and 182 adults successfully treated for childhood acute lymphoblastic leukemia at two Canadian sites part of the PETALE cohort. Participants were  $\geq 5$  years postdiagnosis, aged  $22 \pm 6$  years, 52% female, and 49% acute lymphoblastic leukemia high-risk status. The contribution of health functional status (15D/16D questionnaires) to self-reported anxiety, depression, and distress (Beck scales and distress thermometer) was evaluated using adjusted logistic regression models.

**Results:** Prevalence rates found for mild-severe anxiety, depression, and distress were 14%, 21%, and 30% among adolescents and 27%, 20%, and 19% among adults. Frequent health domains associated with psychological risk were sleeping and breathing in adolescents, and vitality/fatigue, discomfort/symptoms, mental function, and sleeping in adults. Mental function was systematically associated with psychological risk across age groups (median OR = 10.00, 95% CI 3.01-33.71). Exploratory mediation bootstrapping analyses suggested that the effect on psychological risk of overall health status and mental function problems was partly explained by social/work/school functioning.

**Conclusion:** The results identified important functional health domains that could be targeted for interventions preventing psychological risk: vitality/fatigue, discomfort/symptoms, sleeping, and mental function issues. Health domains probably affect mood partly by limiting social/work/school functioning.

## KEYWORDS

childhood cancer, health status, late effects, psychological risk, survivorship

## 1 | INTRODUCTION

Significant treatment improvements in childhood acute lymphoblastic leukemia (cALL) have led to a 5-year survival rate reaching 91% in Canada.<sup>1</sup> Several studies have highlighted how radiation therapy exposure, chemotherapy toxicity, as well as sex and age at diagnosis may be contributing factors to late adverse effects (LAEs) for survivors.

LAEs include metabolic dysfunctions, musculoskeletal morbidities, cardiopulmonary, and neurocognitive impairments.<sup>2-14</sup> A report on the Childhood Cancer Survivor Study (CCSS) has estimated that 62% of surveyed adult survivors had at least one chronic health condition and 28% suffered from a severe condition.<sup>5</sup> Furthermore, the St-Jude Lifetime Cohort study found that the cumulative burden of chronic health conditions among adult childhood cancer survivors (CCS) compared

with a community sample was also significantly higher with a high frequency of secondary neoplasms, spinal disorders, and pulmonary function deficits.<sup>15</sup> Fewer reports are available in younger survivors exclusively but a study revealed 66% of children and adolescents will have at least one chronic condition 5 to 14 years after diagnosis.<sup>16</sup>

Studies exploring psychological status in adult survivors have shown higher levels of negative mood, anxiety, depression, suicide ideation, and global distress than siblings or healthy controls<sup>17–23</sup> and a risk for elevated, persistent emotional distress over time.<sup>17</sup> Although few studies have assessed mental health status of adolescents previously treated for cancer, a systematic review found 13% to 29% of this age group experienced distress.<sup>24</sup> Yet, several reports have described no heightened distress in comparison with controls<sup>25</sup> or mixed inconclusive results.<sup>26</sup> Collecting self-descriptions in younger samples is essential, as other informants' descriptions may deviate from self-reports.<sup>27</sup>

Importantly, the course of emotional distress seems to follow that of age and gradual expression of physical late effects.<sup>16,17</sup> Across age groups, poorer functional health status and physical symptoms were found to contribute to both emotional distress and poorer quality of life.<sup>20,28–32</sup> Key factors of emotional distress frequency or severity supported by the evidence in the CCS population include younger age or adolescent age at diagnosis, older age at recall, female sex, lower socioeconomic status, single or divorced status, lack of health insurance, poor social relationships, neurocognitive impairment, pain, fatigue, chronic condition, and an overall perception of health deterioration and physical health status.<sup>8,20,22,23,29,33–40</sup> Physical limitations may hinder age-appropriate activities, lead to difficulties in social relationships, and thus to psychological suffering.<sup>7,9,41–43</sup> Particularly, impaired neurocognitive speed and executive function may affect emotional wellbeing as they hinder social functioning and are associated with lower educational attainment, employment discrimination, and unemployment.<sup>9,44–46</sup> In summary, although it is widely recognized that LAEs may have a detrimental impact on quality of life and mental health, it is still unclear which domains are most important for psychological outcomes. This is especially true for adolescents where data are scarce.

The primary aim of this study was to describe psychological symptoms, specifically internalizing problems (anxiety, depression, and distress) in a homogeneous cohort of adolescent and young adult cALL survivors and identify which domains of functional health status domains were most associated with these psychological outcomes. A secondary aim was to explore to what extent perceived social functioning issues could explain these relationships.

## 2 | MATERIALS AND METHODS

### 2.1 | Participant eligibility and data collection procedure

The study population consisted of individuals treated for cALL from the PETALE cohort at Sainte-Justine University Health Center (SJUHC, Montreal, Canada) and the Laval University Health Center (CHUL,

Quebec, Canada). Eligibility was determined based on the following criteria: ALL diagnosis before the age of 19, DFCI treatment protocol,  $\geq 5$  years from diagnosis with no recurrence, have not undergone hematopoietic stem cell transplantation, French or English speaking, and ability to complete self-rated questionnaires.

Data were collected among adolescents (13–18 years) and young adults (19+ years). Participants were asked to complete the measures presented below on site or, if not possible, at home and returned by mail. Ethical approvals for this cohort recall were obtained through both sites' review boards. Full details on the study design are available in a previous report.<sup>10</sup>

### 2.2 | Sociodemographic and clinical data

Sociodemographic data were obtained using a study-specific questionnaire and included key descriptors such as current age and sex. Cancer-related data such as age at diagnosis and clinical history were collected from medical files.

### 2.3 | Assessment of anxiety, depression, and distress

The psychological status of participants was assessed using standardized instruments. To assess anxiety and depression symptoms, the Beck self-rated inventories were selected as they are widely used in clinical research to measure anxiety and depression symptom severity and offer opportunity of a consistent definition across ages. The Beck Youth Inventories for Anxiety and Depression (BYI-AD)<sup>47</sup> were administered to adolescents. These 20-item self-rated inventories assess anxiety and depression presence and severity in the past 2 weeks. Raw scores were converted to standardized *T* scores and interpreted as follows:  $T < 55$  (average symptoms),  $T = 55–59$  (symptoms mildly elevated),  $T = 60–69$  (symptoms moderately elevated), and  $T \geq 70$  (symptoms extremely elevated).

For young adults, the Beck Anxiety Inventory (BAI),<sup>48</sup> a 21-item self-rated inventory, was used to measure the presence and severity of anxiety symptoms. Scores range from 0 to 63 and are interpreted as follows: 0–7 (minimal anxiety symptoms), 8–15 (mild anxiety symptoms), 16–25 (moderate anxiety symptoms), and 26–63 (severe anxiety symptoms). Presence and severity of depression symptoms in the past 2 weeks were measured using the 21-item self-rated Beck Depression Inventory II (BDI-II).<sup>48</sup> Scores range from 0 to 63 with different levels being: 0–13 (minimal depression symptoms), 14–19 (mild depression symptoms), 20–28 (moderate depression symptoms), and 29–63 (severe depression symptoms). In further analyses, we defined significant anxiety as *T* score  $\geq 55$  (BYI-A) in adolescents and scores  $\geq 8$  (BAI) in young adults, and significant depression as *T* score  $\geq 55$  (BYI-D) in adolescents and scores  $\geq 14$  (BDI-II) in young adults.

Psychological distress was measured with the visual analogic scale of the distress thermometer (DT).<sup>49–52</sup> It is a 10-point self-rated screening tool assessing distress severity in the past 7 days. Scores range from 0 (absence of distress) to 10 (extreme distress). Participants who scored 4 or higher on the DT were coded as positive for distress.

## 2.4 | Assessment of functional health status

Functional health status was investigated using the self-rated 16D (adolescents) and 15D (adults).<sup>53,54</sup> These questionnaires measure current functional health status across 18 domains: mobility, vision, hearing, breathing, sleeping, eating, speech, usual activities, excretion, mental function, discomfort/symptoms, distress, depression, vitality, sexual activity, school, appearance, and friendship. Usual activities and sexual activity domains are measured among adults exclusively while appearance, friendship, and school domains are specific to adolescents. In addition, to avoid confounding associations, depression, and distress items were removed from the 15D and 16D. To reflect the current research, the health domain vitality will be referred to as vitality/fatigue. For each domain, scores range from 1 (best level of function) to 5 (worst level of function). Raw scores are converted to a set of utility weights generating an index score on a 0 (being dead) to 1 (perfect health) scale for each domain and a total score representing overall status. In further analyses, problems in specific health domains were defined as raw scores > 1. The overall status index score was reversed with higher scores indicating poorer overall status.

## 2.5 | Assessment of social functioning

To approach social functioning, we used two subscales of the Pediatric Quality of Life Inventory—4.0 Generic Core Scales for adolescents and adults (PedsQL),<sup>55</sup> i.e., social functioning, work/school functioning (5 items each). The PedsQL is a 23-item Likert scale evaluating subjective quality of life. Scores range from 0 (never) to 4 (almost always) and are transformed to a percentage scale where higher well-being is reflected by higher percentages.

## 2.6 | Data analysis

Anxiety, depression symptoms, and distress were considered as outcome variables and functional health domains and overall health status as explanatory variables. After describing frequencies for each measure, we computed multivariable binary logistic regression models in each age group to explain the odds of a psychological risk (first aim). Analyses were adjusted for sex, age, age at diagnosis, and treatment risk status. To adjust for multiple testing in the first objective, statistical significance was set at  $p < 0.01$ .

To explore the second aim, a principal component analysis (PCA, parallel analysis<sup>56</sup>) was performed to determine the common variation among the three outcome variables and the principal component score was used as an outcome variable. We then tested mediation using bootstrapping techniques, where social and work/school functioning were tested as mediators in significant and consistent relationships identified in the first aim (PROCESS path analysis for SPSS<sup>57</sup>). We detected a mediation effect when zero was not included in the 95% CI and defined partial and complete mediation in line with current standards.<sup>58</sup> Percent mediation will be reported as the effect size of the indirect effect. Analyses were performed in the whole sample with age group as a control variable.

## 3 | RESULTS

### 3.1 | Cohort characteristics

Overall, 345 participants were contacted to participate in the study (Supplementary Information Figure S1). The participation rate was 83%, with a return rate of 89%. The final study cohort consisted of 105 adolescents aged 13–18 years and 182 adults aged 19+ years (Table 1). Adolescents had a mean age of 15.6 years ( $SD = 1.5$ ) and adults 25.4 years ( $SD = 4.7$ ). Mean time since diagnosis was 12 years ( $SD = 2.6$ ) for adolescents and 17 years ( $SD = 4.9$ ) for adults. The majority of participants were French speaking (96%) and Caucasian (97%). Significant statistical differences were found between both groups on treatment risk status and radiotherapy with younger participants being rated less frequently as high-risk treatment status. This translated into a lower frequency of radiation therapy in participants treated more recently. No significant difference was noted on other sociodemographic or clinical data across the two treatment sites.

### 3.2 | Psychological status

Most participants reported normative levels on psychological symptoms. Among adolescents, mean  $T$  scores and standard deviations for anxiety ( $47.9 \pm 9.2$ ) and depression ( $46.6 \pm 8.1$ ) were similar to matched control groups ( $48.2 \pm 7.0$ ,  $d = -0.04$  for anxiety) and ( $48.1 \pm 7.2$ ,  $d = -0.2$  for depression).<sup>47</sup> Among adults, means and standard deviations for anxiety ( $6.0 \pm 6.8$ ) and depression ( $6.7 \pm 7.5$ ) were slightly higher than a control group for anxiety ( $4.1 \pm 5.1$ ,  $d = 0.3$ ) but not for the depression ( $6.5 \pm 5.2$ ,  $d = 0.04$ ).<sup>59,60</sup> However, the control group for adults with anxiety symptoms were older (45.8 years old) and both scores are to be interpreted as minimal anxiety symptoms as scores ranged from 0 to 7.<sup>48</sup>

Subgroups were identified as reporting internalizing problems (Figure 1). Mild–severe levels of anxiety and depression were observed in 14% (adolescents) versus 27% (young adults) and 21% (adolescents) versus 20% (young adults), respectively. Significant distress was observed in 30% versus 19% of adolescent versus adult participants ( $\chi^2 = 4.25$ ,  $p < 0.05$ ).

### 3.3 | Functional health status

Overall, participants reported high functional health status on the 16D and 15D with a mean composite score close to 1 (perfect health) and low variability:  $0.91 \pm 0.08$  (adolescents) and  $0.92 \pm 0.08$  (adults). This indicates low severity of problems across health domains (Figure 2). Among adolescents, the most frequently reported issues (rate of occurrence > 25%) were appearance (55%), sleeping (50%), vitality/fatigue (37%), vision (33%), discomfort/symptoms (30%), speech (29%), and breathing (25%). In the adult group, issues with in sleeping (48%), vitality/fatigue, (41%), discomfort/symptoms (39%), breathing (37%), and mental function (29%) were most frequently reported. In contrast, very few participants from either group (< 10%) reported issues with mobility, eating, hearing, and friendship, with the latter domain assessed among adolescents only. When comparing

**TABLE 1** Sociodemographic and clinical characteristics of cALL survivors

Participants' characteristics	Adolescents (N = 105) M (SD) or N (%)	Adults (N = 182) M (SD) or N (%)	Total sample (N = 287) M (SD) or N (%)
<b>Sociodemographic characteristics</b>			
<b>Sex</b>			
Male	53 (50.5)	85 (46.7)	138 (48.1)
Female	52 (49.5)	97 (53.3)	149 (51.9)
Age at follow-up, years	15.6 (1.5)	25.4 (4.7)	21.9 (6.0)
<b>Marital status</b>			
Single	105 (100)	118 (64.8)	223 (77.7)
Married/Common law	0	64 (35.2)	64 (22.3)
<b>Ethnicity</b>			
Caucasian	103 (98.1)	174 (95.6)	277 (96.5)
Other	2 (1.9)	8 (4.4)	10 (3.5)
<b>Educational background</b>			
Pre-high school	81 (77.1)	22 (12.1)	103 (35.9)
High school	19 (18.1)	32 (17.6)	51 (17.8)
Graduate/PED <sup>a</sup>	4 (3.8)	39 (21.4)	43 (15.0)
CEGEP <sup>b</sup>	1 (1)	61 (33.5)	62 (21.6)
University (UG/PG <sup>c</sup> )	0 (0)	28 (15.2)	28 (9.8)
<b>Primary occupation</b>			
Student	73 (69.5)	20 (11.1)	93 (32.6)
Working full-time	1 (1.0)	108 (60)	109 (38.2)
Working part-time	29 (27.6)	47 (26.1)	76 (26.7)
Unpaid/unemployed	2 (1.9)	5 (2.8)	7 (2.5)
<b>First language</b>			
French	98 (93.3)	177 (97.8)	275 (96.2)
English	3 (2.9)	2 (1.1)	5 (1.7)
Other <sup>d</sup>	4 (3.8)	2 (1.1)	6 (2.1)
<b>Clinical characteristics</b>			
<b>Treatment site</b>			
CHU Sainte-Justine	90 (85.7)	153 (84.1)	243 (84.7)
CHU Quebec	15 (14.3)	29 (15.9)	44 (15.3)
Age at diagnosis, years	3.7 (2.3)	7.6(4.8)	6.2 (4.5)
Time since diagnosis, years	12 (2.6)	17.9 (4.9)	15.7 (5.1)
<b>ALL risk status</b>			
Standard risk	73 (69.5)	71 (39.4)	144 (50.3)
High risk	32 (30.5)	109 (60.6)	141 (49.3)
Unclassified	0	1 (0.6)	1 (0.3)

(Continues)

**TABLE 1** (Continued)

Participants' characteristics	Adolescents (N = 105) M (SD) or N (%)	Adults (N = 182) M (SD) or N (%)	Total sample (N = 287) M (SD) or N (%)
<b>Treatment protocol<sup>e</sup></b>			
87-01	0	21 (7.3)	21 (7.3)
91-01	0	55 (30.2)	55 (19.2)
95-01	27 (25.7)	61 (33.5)	88 (30.7)
2000-01	61 (58.1)	23 (12.6)	84 (29.3)
2005-01	17 (16.2)	16 (8.8)	33 (11.5)
<b>Radiotherapy</b>			
No	68 (64.8)	58 (31.9)	126 (43.9)
Yes	37 (35.2)	124 (68.1)	161 (56.1)

<sup>a</sup>PED, professional education diploma. <sup>b</sup>CEGEP is the first stage of higher education after high school, exclusively in province of Quebec, Canada. <sup>c</sup>UG/PG, undergraduate/postgraduate. <sup>d</sup>Other: Spanish, Vietnamese, Bulgarian, and Romanian. <sup>e</sup> Dana-Farber Cancer Institute ALL Consortium protocols for children. Each protocol is labeled by the year of the clinical trials detailing the treatment regimen during the 4 phases of therapy (remission induction, CNS-directed treatment, Intensification and continuation).

frequencies across groups, adolescents reported issues with vision more frequently than adults (33% vs. 8%,  $p < 0.001$ ).

### 3.4 | Contributors to psychological risk

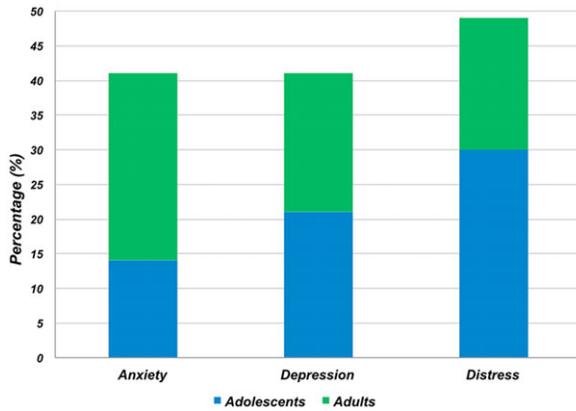
When exploring associations of potential controls (age, gender, age at diagnosis, and treatment risk status) with psychological status, no control variables were associated with the odds of reporting significant levels of anxiety, depression, or distress across the two age groups ( $p = 0.324$ ).

#### 3.4.1 | Anxiety

When adjusting for age, sex, age at diagnosis, and treatment risk status, we found significant associations of functional health status with anxiety. In adolescents, anxiety was associated with overall functional health status and specific issues with mental function, excretion, hearing, and sleeping (Table 2). The risk associated with issues with sleeping (OR = 10.27) is important as this issue was particularly frequently reported (> 25%). In adults, anxiety was also associated with overall functional status, and it was associated with issues on vitality/fatigue, discomfort/symptoms, usual activities, sexual activity, mobility, speech, mental function, and excretion (Table 3). Risks associated to issues of vitality/fatigue (OR = 8.49), discomfort/symptoms (OR = 8.18), and mental function (OR = 4.23) are also of importance as these issues were frequently reported (> 25%).

#### 3.4.2 | Depression

After adjusting for controls in adolescents, depression was associated with overall functional status, and it was associated with issues with mental function, hearing, and breathing (Table 2). Risk associated with a breathing issue (OR = 9.62) is noteworthy as it was frequently reported (>25%). In adults, depression was associated with overall functional status and with issues with usual activities,

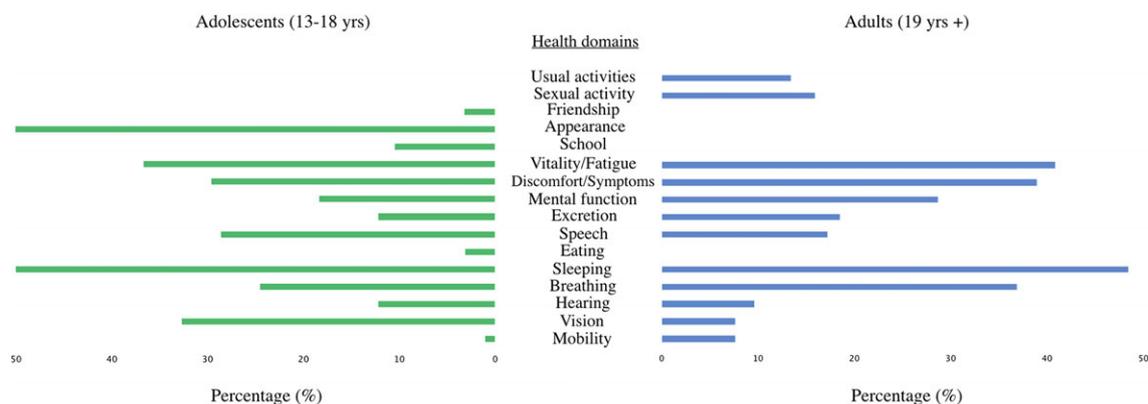


**FIGURE 1** Frequency of anxiety, depression, and distress symptoms in adolescent and adult cALL participants. For adolescents:  $N = 95$  for anxiety and depression,  $N = 98$  for distress. Positive cases for anxiety and depression were defined as  $T$  scores  $> 55$  (results obtained with BYI anxiety and depression inventories). For adults:  $N = 143$  for anxiety and depression,  $N = 157$  for distress. Positive cases for anxiety were defined as  $BAI > 7$ , positive cases for depression  $BDI-II > 13$ . For both groups, a cutoff point of 4 was used for distress (results obtained with DT)

discomfort/symptoms sexual activity, mental function, excretion, and sleeping (Table 3). Risks associated with vitality/fatigue ( $OR = 13.28$ ), discomfort/symptoms ( $OR = 7.44$ ), mental function ( $OR = 6.65$ ), and sleeping ( $OR = 3.91$ ) are noticeable as these issues were particularly frequent ( $>25\%$ ).

### 3.4.3 | Distress

When exploring the same models predicting for distress, we found an association with overall functional status in both age groups. Among adolescents, distress was associated with issues with mental function and sleeping (Table 2). Risk associated with issues with sleeping ( $OR = 5.07$ ) is meaningful, as this issue was particularly frequent ( $> 25\%$ ). Among adults, distress was associated with issues on mental function ( $OR = 5.13$ ), vitality/fatigue ( $OR = 3.92$ ), and sleeping ( $OR = 3.88$ ) (Table 3). All these health issues were frequently reported ( $> 25\%$ ).



**FIGURE 2** Frequency of issues with domains of health status in adolescent and adult cALL participants. For adolescents:  $N = 98$ . Results obtained from the 16D questionnaire. Domains exclusive to the 16D: appearance, friendship, and school. For adults:  $N = 157$ . Results obtained from the 15D questionnaire. Domains exclusive to the 15D: sexual activity, usual activities. Absence of eating issues for adults. For both questionnaires, scores range from 1 (best level of function) to 5 (worst level of function). Issues with health domains defined as scores  $> 1$

## 3.5 | Mediating role of social and work/school functioning

The main analyses revealed that the overall health status and mental function domains were consistently associated with anxiety, depression, and distress across age groups. Thus, the above-mentioned health domains were selected as predictors for two mediation model analyses. The PCA yielded one component summarizing 61% of the variance (raw data eigenvalue  $\geq 1.18$ ,  $KMO = 0.645$ ). Mediation analyses revealed a consistent pattern with the association of overall health status and mental function problems with psychological risk (component score) to be partially mediated by social and work/school functioning. Figure 3 provides an example of how mediation analyses were carried out. In the first model, with overall health status as a predictor, the indirect effect of social functioning was 0.01 ( $P_M = 0.17$ ), BootCI [0.01–0.03] and the direct effect was 0.07 ( $p < 0.0001$ ). For work/school functioning, the indirect effect was 0.02 ( $P_M = 0.28$ ), BootCI [0.01–0.04], the direct effect was 0.06 ( $p < 0.0001$ ). In the second mediation model, with mental function problems as a predictor, the indirect effect of social functioning was 0.25 ( $P_M = 0.22$ ), BootCI [0.12–0.44] and the direct effect was 0.89 ( $p < 0.0001$ ). The indirect effect of work/school functioning was 0.42 ( $P_M = 0.37$ ), BootCI [0.25–0.63] and the direct effect was 0.72 ( $p = 0.0001$ ). Importantly, there was no age-group effect suggesting results apply to both adolescents and adults alike.

## 4 | DISCUSSION

In a cross-sectional exploration of health status of 287 participants (105 adolescents and 182 adults) who were successfully treated for cALL and  $\geq 5$  years postdiagnosis, we found that approximately 1 in 5 survivors experienced mild–severe anxiety, depression, and distress. Unspecific distress was more frequent among adolescents than adults (30% vs. 19%). Domains that were frequently reported and associated with psychological risk across outcomes were vitality/fatigue, sleeping, discomfort/symptoms, and mental functioning. We also found from mediation analyses that the contribution of health status could be explained by its role on social functioning.

**TABLE 2** Odd ratios of significant levels of anxiety, depression, or distress as a function of health status issues reported by adolescent cALL survivors

Psychological status Health status domains	Anxiety (n = 94)			Depression (n = 94)			Distress (n = 96)		
	OR	95% CI	P value	OR <sup>a</sup>	95% CI <sup>b</sup>	P value	OR	95% CI	P value
Mobility <sup>a</sup>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Friendship <sup>b</sup>	0.95	0.75–12.11	0.970	N/A	N/A	N/A	0.71	0.05–2.11	0.803
Appearance <sup>b</sup>	2.72	0.75–9.85	0.128	N/A	N/A	N/A	2.81	0.96–8.23	0.059
School	4.88	1.07–22.31	0.041	0.64	0.08–5.01	0.673	1.17	0.25–5.37	0.842
Vision	0.60	0.17–2.06	0.410	0.68	0.15–3.03	0.613	0.25	0.17–1.58	0.524
Hearing	10.70	2.43–47.11	<b>0.002</b>	18.29	2.97–112.84	<b>0.002</b>	1.88	0.48–7.34	0.366
Breathing	4.04	1.11–14.75	0.035	9.62	1.87–49.46	<b>0.007</b>	1.82	0.61–5.45	0.284
Sleeping	10.27	2.39–44.03	<b>0.002</b>	3.94	0.84–18.52	0.083	5.07	1.70–15.17	<b>0.004</b>
Eating	11.09	0.87–141.56	0.064	6.66	0.45–98.82	0.168	1.14	0.91–14.26	0.919
Speech	4.43	1.40–14.06	0.011	2.84	0.73–10.99	0.131	1.19	0.43–3.28	0.734
Excretion	11.42	2.36–55.21	<b>0.002</b>	8.20	1.58–42.42	0.012	1.56	0.41–5.95	0.517
Mental function	15.55	3.43–70.47	<b>&lt;0.0001</b>	19.71	3.98–97.54	<b>&lt;0.0001</b>	13.48	3.62–50.28	<b>&lt;0.0001</b>
Discomfort/symptoms	2.19	0.68–7.03	0.187	2.34	0.61–8.96	0.214	3.45	1.28–9.31	0.014
Vitality/fatigue	2.53	0.79–8.10	0.117	7.35	1.40–38.74	0.019	3.32	1.21–9.09	0.019
16D total score <sup>c</sup>	1.36	1.16–1.60	<b>&lt;0.0001</b>	1.32	1.13–1.60	<b>&lt;0.0001</b>	1.17	1.07–1.30	<b>0.003</b>

ORs are adjusted for age, gender, age at diagnosis and treatment risk status in all analyses. P values in bold indicate  $p < 0.01$ .

<sup>a</sup>Analysis not applicable because the sample size for participants with mobility issues and presence of distress, anxiety and depression was equal to 1.

<sup>b</sup>Analysis not applicable as no participants with difficulties in this domain presented depression. <sup>c</sup>16D total score scale change by multiplying reversed score values by a factor of 100, excluding depression and distress item scores due to their shared variance with the outcomes.

Health status domains from the 16D questionnaire, scores range from 1 (best level of function) to 5 (worst level of function). Issue defined as scores  $> 1$ . Anxiety and depression scores from Beck Youth Inventories. Positive cases were defined as T scores  $> 55$ . Distress scores from distress thermometer. Positive cases defined as scores equal to or above 4.

**TABLE 3** Odd ratios of significant levels of anxiety, depression, or distress as a function of health status issues reported by adult cALL survivors

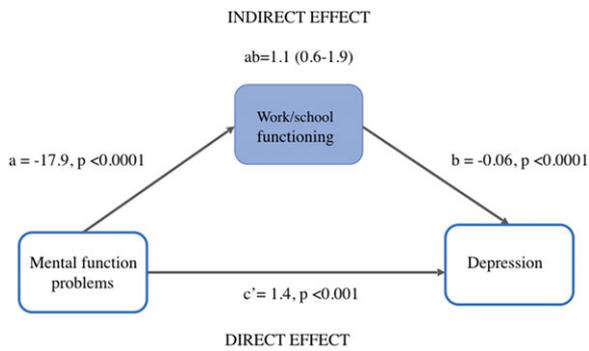
Psychological status Health status domains <sup>c</sup>	Anxiety (n = 142)			Depression (n = 142)			Distress (n = 156)		
	OR <sup>a</sup>	95% CI <sup>b</sup>	P value	OR <sup>a</sup>	95% CI <sup>b</sup>	P value	OR <sup>a</sup>	95% CI <sup>b</sup>	P value
Mobility	5.61	1.53–20.51	<b>0.009</b>	3.24	0.81–12.87	0.095	1.56	0.36–6.85	0.556
Vision	3.49	1.00–12.16	0.050	4.88	1.34–17.71	0.016	0.57	0.07–4.9	0.605
Hearing	3.05	0.99–9.42	0.052	1.78	0.49–6.44	0.378	1.33	0.32–5.57	0.690
Breathing	1.86	0.85–4.09	0.121	1.38	0.57–3.35	0.480	1.69	0.71–4.0	0.237
Sleeping	2.26	1.02–4.98	0.043	3.91	1.48–10.31	<b>0.006</b>	3.88	1.49–10.14	<b>0.006</b>
Eating <sup>d</sup>	N/A			N/A			N/A		
Speech	4.82	1.91–12.20	<b>0.001</b>	2.66	0.98–7.16	0.054	2.47	0.92–6.62	0.072
Excretion	3.79	1.56–9.19	<b>0.003</b>	4.48	1.68–11.95	<b>0.003</b>	1.03	0.36–2.96	0.964
Usual activities	6.68	2.36–18.95	<b>&lt;0.0001</b>	18.21	5.43–61.05	<b>&lt;0.0001</b>	3.58	1.15–11.14	0.027
Mental function	4.23	1.84–9.73	<b>0.001</b>	6.65	2.58–17.14	<b>&lt;0.0001</b>	5.13	2.04–12.91	<b>0.001</b>
Discomfort/symptoms	8.18	3.27–20.45	<b>&lt;0.0001</b>	7.44	2.63–21.07	<b>&lt;0.0001</b>	2.68	1.11–6.47	0.029
Vitality/fatigue	8.49	3.44–20.97	<b>&lt;0.0001</b>	13.28	4.09–43.11	<b>&lt;0.0001</b>	3.92	1.59–9.71	<b>0.003</b>
Sexual activity	6.22	2.40–16.27	<b>&lt;0.0001</b>	6.76	2.39–19.12	<b>&lt;0.0001</b>	2.91	1.04–8.15	0.043
15D total score <sup>e</sup>	1.18	1.10–1.25	<b>&lt;0.0001</b>	1.19	1.11–1.28	<b>&lt;0.0001</b>	1.10	1.04–1.17	<b>0.001</b>

P values in bold indicate  $p < 0.01$ .

<sup>a</sup>Odds ratio. <sup>b</sup>95% confidence interval. <sup>c</sup>ORs are adjusted for age, gender, age at diagnosis and treatment risk status. <sup>d</sup>Analysis not applicable because there were no participants with an eating issue. <sup>e</sup>15D total score scale change by multiplying reversed score values by a factor of 100. Total score excluding depression and distress item scores due to their shared variance with the outcomes.

Health status domains from the 15D questionnaire and scores range from 1 (best level of function) to 5 (worst level of function). Issue defined as scores  $> 1$ . Anxiety and depression scores from Beck Anxiety and Depression inventories. Positive cases define as BAI  $> 7$  and BDI-II  $> 13$ .

Distress scores from distress thermometer. Positive cases defined as scores equal to or above 4.



**FIGURE 3** Mediation analysis for cALL participants. Mediation analysis was conducted with path analysis—PROCESS macro for SPSS.<sup>57</sup> Sample consists of adolescent ( $n = 95$ ) and adult ( $n = 146$ ) cALL survivors with the age group included as a covariable. Mental function problems' score from the 16D and 15D questionnaires. Impairment is defined as scores  $> 1$ . Work/school functioning score from Pediatric Quality of Life Inventory (PedsQL). Higher scores indicate better work/school functioning. a, estimate of the effect of the predictor (mental function impairment) on the mediator (work/school functioning). b, estimate of the effect of the mediator on the outcome variable (component score representing psychological risk). ab, indirect effect which is the product of paths a and b representing the amount of mediation. Significance of the indirect effect determined with the bootstrapping method and to be interpreted as follows: if 0 is not included in the 95% CI, mediation has occurred and significant at the  $p < 0.05$ . c, direct effect of the predictor variable on the outcome variable controlling for the mediator

Regarding adolescents, the rate of distress found is fairly similar to that of other studies performed in aftercare and during treatment. The fact that subjective unspecific distress was far more frequent than anxiety and depression may reflect how younger participants were experiencing psychological issues and suggests these issues were probably not adequately captured in symptom-specific psychological scales. Supporting this hypothesis, it has been suggested that anxiety and depression symptoms are not sufficient to describe the adolescent's emotional burden associated with cancer as this can translate into a broader range of symptoms including anger or behavioral problems.<sup>61,62</sup>

Among adult survivors distress was much lower in our sample than in another mixed CCS cohort (19% vs. 28.6%),<sup>63</sup> which could be explained by heterogeneity of cancer types, treatment and older age found in the previous cohorts, possibly leading to more LAEs resulting in more distress.

Our results are consistent with the observation that anxiety is more salient than depression among adult survivors.<sup>41,64-66</sup> More generally, anxiety and depression have been found to be the most common psychological complaints among CCS.<sup>67</sup>

Functional health status was high and homogeneous in the cohort (total scores approaching perfect health and minimal variation). However, our results revealed that cALL survivors commonly reported vitality/fatigue, sleeping, and discomfort/symptoms issues while several other health domain issues were specific to either age subgroups (e.g., appearance in adolescents and mental function in adults). Cancer-related fatigue and sleep problems (sleep disturbance, sleep quality, and daytime sleepiness) are among the most common late effects

following cancer.<sup>63-65,67-71</sup> If left unmanaged, they can yield important work or school performance difficulties, which may lead to significant distress, anxiety, depression, and impaired quality of life.<sup>72-76</sup> In fact, sleeping issues seemed to be key contributors to psychological health: both adolescents and adults in the present study were 2 to 10 times more likely to report anxiety, depression or distress if they had sleeping difficulty. Interestingly, despite similar percentages in reporting vitality/fatigue issues in both age groups, it only seemed to be a key contributor to psychological risk among adults but not among adolescents. It can be hypothesized that this issue did not significantly disrupt adolescents' daily activities or lead to social constraints compared with adults. Therefore, perhaps the younger group's coping strategies (adaptive health competence beliefs) were more effective in promoting self-efficacy and preventing psychological burden.<sup>77-80</sup>

Discomfort/symptoms was also found to be frequent among adolescents (39 %) and adults (50%). This health domain includes symptoms such as pain, aches, nausea, feeling sick, and itching. Of particular interest, the frequency of pain varies from 13% to 57% in similar CCS cohorts with common complaints being abdominal, neuropathic, headaches, and neck and back pain.<sup>81,82</sup> Clinicians and researchers identify pain and discomfort as major domains for future quality of life. In long-term CCS, it has been associated with lower educational attainment, unemployment, and single status and could lead to psychological risk.<sup>81</sup>

However, we found this domain to contribute to psychological risk only in adults. It is possible that discomfort or pain was not recognized or reported similarly across age groups or that adolescents had lesser pain-related disability compared with their adult counterparts.

Alternatively, although issues with breathing were equally frequent in adolescents and adults (25% vs. 32%), they were found to contribute to depression only in the former group. This could reflect the importance of social limitations due to this health issue. In fact, studies have revealed that adolescent survivors with breathing problems may be less likely to engage in typical physically active recreation with friends, possibly leading to impaired quality of life and negative mood.<sup>83-85</sup>

We focused on frequently reported health issues. However, less frequently reported difficulties, such as mental function issues (reported in 17% and 25% of adolescents and adults, respectively), might have pervasive impacts as well. Mental function issues were consistently associated with psychological outcomes across age groups. Among adolescents, it was the strongest key contributor of anxiety (95% CI, 3.43-70.47), depression (95% CI, 3.98-97.54), and distress (95% CI, 3.62-50.28). Mental function issues have been widely documented in CCS and a strong hypothesis to account for its relation to psychological symptoms and school/work achievement and social functioning.<sup>9,44-46</sup> Given the close relationship between neurocognitive functioning with fatigue,<sup>72,73</sup> it is also possible that both interact to explain psychological risk.

When exploring the role of overall health status and mental function, we found that social and work/school functioning partially accounted for the association of overall health status and psychological risk. It could be argued that health status limitations prevented participants from engaging in usual activities, interacting with peers or colleagues and decreased ability to meet one's goals, thereby

contributing to psychological symptoms. Indeed, the recognition of one's own mental function difficulties on memory and attention may lead to lower self-esteem and self-efficacy at school/work. Subsequent limitations on school achievements and professional goal attainments could contribute to social isolation, impaired social adjustments, and emotional distress.<sup>9,44–46</sup>

This study presents a unique exploration of functional status and psychological risk in a young cohort including a subsample of adolescents with a French-speaking cultural background. However, as analyses were performed separately in both age groups, this limited statistical power. The comparison between both age groups can also be biased as the older group received more radiation therapy, which is a known risk factor for LAEs. Furthermore, as the design was cross-sectional we could not draw causal inferences on observed associations as there is no certainty that physical health issues preceded psychological risk. It is possible that health functional status would partly reflect negative mood. Although we did control symptom overlap in contributors and outcomes, a longitudinal study design would be required to further confirm our results.

In summary, our results offer new insights on levels and types of psychological risk in a homogeneous cohort of young survivors treated for cALL, with emotional distress being reported by 14% to 30% of our cohort. Our study further documents the important contribution of health functions such as vitality/fatigue, sleep, discomfort/symptoms, and mental function to psychological risk in adolescent and adult cALL survivors as well as how social functioning impacts the relationship found between functional health status and psychological risk. Future studies should explore functional domains that are most often reported as problematic by young survivors as interventions targeting these are increasingly available for the adult population who faces cancer and should be adapted and proposed to CCS.<sup>86,87</sup> Lastly, additional research should be conducted to explore cancer rehabilitation programs targeting vocational achievement<sup>88</sup> and social skills interventions<sup>89,90</sup> to promote social functioning.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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## SUPPORTING INFORMATION

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

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