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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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39	Abbreviation key:	
40	BYI-AD	Beck Youth Inventories- anxiety and depression
41	BYI-A	Beck Youth Inventory-Anxiety
42	BYI-D	Beck Youth Inventory -Depression
43	BAI	Beck Anxiety Inventory
44	BDI-II	Beck Depression Inventory-second edition
45	cALL	childhood Acute Lymphoblastic Leukemia
46	CCSS	Childhood Cancer Survivor Study
47	CCS	Childhood Cancer Survivors
48	CCs	Childhood Cancers
49	SJUHC	Sainte-Justine University Health Center
50	QUHC	Quebec Laval University Health Center
51	CRF	Cancer-Related Fatigue
52	DFCI	Dana-Farber Cancer Institute
53	DT	Distress Thermometer
54	LAEs	Late Adverse Effects
55	PETALE	Prévenir les Effets Tardifs des Traitements de la Leucémie Aiguë
56		Lymphoblastique chez l'enfant
57	PCA	Principal Components Analysis
58	PedsQL	Pediatric Quality of Life Inventory
59	15D	15 dimensions health-related quality of life instrument
60	16D	16 dimensions health-related quality of life instrument

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76 **Abstract**

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

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

88 **Results:** Prevalence rates found for mild-severe anxiety, depression and distress were 14%, 21%
89 and 30% among adolescents and 27%, 20% and 19% among adults. Frequent health domains
90 associated with psychological risk were sleeping and breathing in adolescents, and
91 vitality/fatigue, discomfort/pain, mental function, and sleeping in adults. Mental function was
92 systematically associated with psychological risk across age groups (median OR=10.00, 95% CI
93 3.01-33.71). Exploratory mediation bootstrapping analyses suggested that the effect on
94 psychological risk of overall health status and mental function problems was partly explained by
95 social/work/school functioning.

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

100 **INTRODUCTION**

101 Significant treatment improvements in childhood acute lymphoblastic leukemia (cALL) have led
102 to a 5-year survival rate reaching 91% in Canada¹. Several studies have highlighted how
103 radiation therapy exposure, chemotherapy toxicity, as well as sex and age at diagnosis may be
104 contributing factors to late adverse effects (LAEs) for survivors. LAEs include metabolic
105 dysfunctions, musculoskeletal morbidities, cardiopulmonary and neurocognitive impairments²⁻¹⁴.
106 A report on the Childhood Cancer Survivor Study (CCSS) has estimated that 62% of surveyed
107 adult survivors had at least one chronic health condition and 28% suffered from a severe
108 condition⁵. Furthermore, the St-Jude Lifetime Cohort study found that the cumulative burden of
109 chronic health conditions among adult childhood cancer survivors (CCS) compared to a
110 community sample was also significantly higher with a high frequency of secondary neoplasms,
111 spinal disorders, and pulmonary function deficits¹⁵. Fewer reports are available in younger
112 survivors exclusively but a study revealed 66% of children and adolescents will have at least one
113 chronic condition 5 to 14 years after diagnosis¹⁶.
114 Studies exploring psychological status in adult survivors have shown higher levels of negative
115 mood, anxiety, depression, suicide ideation, and global distress than siblings or healthy controls¹⁷⁻
116 ²² and a risk for elevated, persistent emotional distress over time¹⁷. Although few studies have
117 assessed mental health status of adolescents previously treated for cancer, a systematic review
118 found 13% to 29% of this age group experienced distress²³. Yet, several reports have described no
119 heightened distress in comparison with controls²⁴ or mixed inconclusive results²⁵. Collecting self-
120 descriptions in younger samples is essential, as other informants' descriptions may deviate from
121 self-reports²⁶.

122 Importantly, the course of emotional distress seems to follow that of age and gradual expression
123 of physical late effects^{16,17}. Across age groups, poorer functional health status and physical
124 symptoms were found to contribute to both emotional distress and poorer quality of life^{20,27-31}.
125 Key factors of emotional distress frequency or severity supported by the evidence in the CCS
126 population include younger age or adolescent age at diagnosis, older age at recall, female sex,
127 lower socioeconomic status, single or divorced status, lack of health insurance, poor social
128 relationships, neurocognitive impairment, pain, fatigue, chronic condition, and an overall
129 perception of health deterioration and physical health status^{8,20,22,28,32-39}. Physical limitations may
130 hinder age appropriate activities, lead to difficulties in social relationships and thus to
131 psychological suffering^{7,9,40-42}. Particularly, impaired neurocognitive speed and executive
132 function may affect emotional wellbeing as they hinder social functioning and are associated
133 with lower educational attainment, employment discrimination and unemployment^{9,43-45}. In
134 summary, although it is widely recognized that LAEs may have a detrimental impact on quality
135 of life and mental health, it is still unclear which domains are most important for psychological
136 outcomes. This is especially true for adolescents where data is scarce.

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

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146 **MATERIAL AND METHODS**

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148 **Participant Eligibility and Data Collection Procedure**

149 The study population consisted of individuals treated for cALL from the PETALE cohort at Sainte-
150 Justine University Health Center (SJUHC, Montreal, Canada) and the Laval University Health
151 Center (CHUL, Quebec, Canada). Eligibility was determined based on the following criteria: ALL
152 diagnosis before the age of 19, DFCI treatment protocol, ≥ 5 years from diagnosis with no
153 recurrence, have not undergone hematopoietic stem cell transplantation, French or English
154 speaking, and ability to complete self-rated questionnaires.

155 Data was collected among adolescents (13-18 years) and young adults (19+ years). Participants
156 were asked to complete the measures presented below on site or, if not possible, at home and
157 returned by mail. Ethical approvals for this cohort recall were obtained through both sites' review
158 boards. Full details on the study design are available in a previous report¹⁰.

159

160 **Sociodemographic and clinical data**

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

164

165 **Assessment of anxiety, depression, and distress**

166 The psychological status of participants was assessed using standardized instruments. To assess
167 anxiety and depression symptoms, the Beck self-rated inventories were selected as they are widely
168 used in clinical research to measure anxiety and depression symptom severity and offer
169 opportunity of a consistent definition across ages. The Beck Youth Inventories for Anxiety and
170 Depression (BYI-AD)⁴⁶ were administered to adolescents . These 20-item self-rated inventories

171 assess anxiety and depression presence and severity in the past two weeks. Raw scores were
172 converted to standardized T scores and interpreted as follows: T<55 (average symptoms); T=55-
173 59 (symptoms mildly elevated); T=60-69 (symptoms moderately elevated); T≥70 (symptoms
174 extremely elevated).

175 For young adults, the Beck Anxiety Inventory (BAI)⁴⁷, a 21-item self-rated inventory, was used to
176 measure the presence and severity of anxiety symptoms. Scores range from 0 to 63 and are
177 interpreted as follow: 0-7 (minimal anxiety symptoms), 8-15 (mild anxiety symptoms), 16-25
178 (moderate anxiety symptoms), 26-63 (severe anxiety symptoms). Presence and severity of
179 depression symptoms in the past two weeks were measured using the 21-item self-rated Beck
180 Depression Inventory II (BDI-II)⁴⁷. Scores range from 0 to 63 with different levels being: 0-13
181 (minimal depression symptoms); 14-19 (mild depression symptoms); 20-28 (moderate depression
182 symptoms); 29-63 (severe depression symptoms). In further analyses, we defined significant
183 anxiety as T score ≥ 55 (BYI-A) in adolescents and scores ≥ 8 (BAI) in young adults, and
184 significant depression as T score ≥ 55 (BYI-D) in adolescents and scores ≥ 14 (BDI-II) in young
185 adults.

186 Psychological distress was measured with the visual analogic scale of the distress thermometer
187 (DT)^{48,49}. It is a 10-point self-rated screening tool assessing distress severity in the past 7 days.
188 Scores range from 0 (absence of distress) to 10 (extreme distress). Participants who scored 4 or
189 higher on the DT were coded as positive for distress.

190 **Assessment of functional health status**

191 Functional health status was investigated using the self-rated 16D (adolescents) and 15D
192 (adults)^{50,51}. These questionnaires measure current functional health status across 18 domains:
193 mobility, vision, hearing, breathing, sleeping, eating, speech, usual activities, excretion, mental
194 function, discomfort/symptoms, distress, depression, vitality, sexual activity, school, appearance,

195 and friendship. Usual activities and sexual activity domains are measured among adults
196 exclusively while appearance, friendship, and school domains are specific to adolescents. In
197 addition, to avoid confounding associations, depression and distress items were removed from the
198 15D and 16D. For each domain, scores range from 1 (best level of function) to 5 (worst level of
199 function). Raw scores are converted to a set of utility weights generating an index score on a 0
200 (being dead) to 1 (perfect health) scale for each domain and a total score representing overall status.
201 In further analyses problems in specific health domains were defined as raw scores >1 . The overall
202 status index score was reversed with higher scores indicating poorer overall status.

203

204 **Assessment of social functioning**

205 To approach social functioning, we used two subscales of the Pediatric Quality of Life Inventory-
206 4.0 Generic Core Scales for adolescents and adults (PedsQL)⁵², i.e. social functioning, work/school
207 functioning (5 items each). The PedsQL is a 23-item Likert scale evaluating subjective quality of
208 life. Scores range from 0 (never) to 4 (almost always) and are transformed to a percentage scale
209 where higher well-being is reflected by higher percentages.

210

211 **Data analysis**

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

218 To explore the second aim, a principal component analysis (PCA, parallel analysis⁵³) was
219 performed to determine the common variation among the three outcome variables and the principal
220 component score was used as an outcome variable. We then tested mediation using bootstrapping
221 techniques, where social and work/school functioning were tested as mediators in significant and
222 consistent relationships identified in the first aim (PROCESS path-analysis for SPSS⁵⁴). We
223 detected a mediation effect when zero was not included in the 95%CI and defined partial and
224 complete mediation in line with current standards⁵⁵. Percent mediation will be reported as the
225 effect size of the indirect effect. Analyses were performed in the whole sample with age group as
226 a control variable.

227

228 **RESULTS**

229 **Cohort characteristics**

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

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243 **Psychological status**

244 Most participants reported normative levels on psychological symptoms. However, subgroups
245 were identified as reporting internalizing problems (**Fig. 1**). Mild-severe levels of anxiety and
246 depression were observed in 14% (adolescents) vs. 27% (young adults) and 21% (adolescents)
247 vs. 20% (young adults) respectively. Significant distress was observed in 30% vs. 19% of
248 adolescent vs. adult participants ($\chi^2 = 4.25$, $p < 0.05$).

249

250 **Functional health status**

251 Overall, participants reported high functional health status on the 16D and 15D with a mean
252 composite score close to 1 (perfect health) and low variability: 0.91 ± 0.08 (adolescents) and
253 0.92 ± 0.08 (adults). This indicates low severity of problems across health domains (**Fig. 2**).
254 Among adolescents, the most frequently reported issues (rate of occurrence $>25\%$) were
255 appearance (55%), sleeping (50%), vitality (37%), vision (33%), discomfort/symptoms (30%)
256 speech (29%) and breathing (25%). In the adult group, issues with in sleeping (48%), vitality,
257 (41%), discomfort/symptoms (39%), breathing (37%) and mental function (29%) were most
258 frequently reported. In contrast, very few participants from either group ($<10\%$) reported issues
259 with mobility, eating, hearing, and friendship with the latter domain assessed among adolescents
260 only. When comparing frequencies across groups, adolescents reported issues with vision more
261 frequently than adults (33% vs. 8%, $p < 0.001$).

262

263 **Contributors to psychological risk**

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

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

277 *Depression.* After adjusting for controls in adolescents, depression was associated with overall
278 functional status and it was associated with issues with mental function, hearing, and breathing
279 (**Table 2**). Risk associated with a breathing issue (OR = 9.62) is noteworthy as it was frequently
280 reported (>25%). In adults, depression was associated with overall functional status and with
281 issues with usual activities, discomfort/symptoms, sexual activity, mental function, excretion,
282 and sleeping (Table 3). Risks associated with vitality (OR= 13.28), discomfort/symptoms
283 (OR=7.44), mental function (OR=6.65) and sleeping (OR=3.91) are noticeable as these issues
284 were particularly frequent (>25%).

285 *Distress.* When exploring the same models predicting for distress, we found an association with
286 overall functional status in both age groups. Among adolescents, distress was associated with

287 issues with mental function and sleeping (**Table 2**). Risk associated to issues with sleeping
288 (OR=5.07) is meaningful as this issue was particularly frequent (>25%). Among adults, distress
289 was associated with issues on mental function (OR=5.13), vitality (OR=3.92), and sleeping
290 (OR=3.88) (**Table 3**). All these health issues were frequently reported (>25%).

291

292 **Mediating role of social and work/school functioning**

293 The main analyses revealed that the overall health status and mental function domains were
294 consistently associated with anxiety, depression, and distress across age groups. Thus, the above-
295 mentioned health domains were selected for the present analysis. The PCA yielded one
296 component summarizing 61% of the variance (raw data eigenvalue ≥ 1.18 , KMO=0.645).

297 Mediation analyses revealed a consistent pattern with the association of overall health status and
298 mental function problems with psychological risk (component score) to be partially mediated by
299 social and work/school functioning (**Fig. 3**). Concerning overall health status, the indirect effect
300 of social functioning was 0.01 ($P_M = 0.17$), BootCI [0.01-0.03] and the direct effect was 0.07 (p
301 < 0.0001). For work/school functioning, the indirect effect was 0.02 ($P_M = 0.28$), BootCI [0.01-
302 0.04], the direct effect was 0.06 ($p < 0.0001$). For mental function problems, the indirect effect of
303 social functioning was 0.25 ($P_M = 0.22$), BootCI [0.12-0.44] and the direct effect was 0.89 ($p <$
304 0.0001). The indirect effect of work/school functioning was 0.42 ($P_M = 0.37$). BootCI [0.25-0.63]
305 and the direct effect was 0.72 ($p = 0.0001$). Importantly, there was no age-group effect
306 suggesting results apply to both adolescents and adults alike.

307

308 **DISCUSSION**

309 In a cross-sectional exploration of health status of 287 participants (105 adolescents and 182
310 adults) who were successfully treated for cALL and ≥ 5 years post-diagnosis we found that

311 approximately 1 in 5 survivors experienced mild-severe anxiety, depression, and distress.
312 Unspecific distress was more frequent among adolescents than adults (30% vs. 18%). Domains
313 that were frequently reported and associated with psychological risk across outcomes were
314 vitality, sleeping, discomfort/symptoms, and mental functioning. We also found from mediation
315 analyses that the contribution of health status could be explained by its role on social
316 functioning.

317 Regarding adolescents, the rate of distress found is fairly similar to that of other studies
318 performed in aftercare and during treatment. The fact that subjective unspecific distress was far
319 more frequent than anxiety and depression may reflect how younger participants were
320 experiencing psychological issues and suggests these issues were probably not adequately
321 captured in symptom-specific psychological scales. Supporting this hypothesis, it has been
322 suggested that anxiety and depression symptoms are not sufficient to describe the adolescent's
323 emotional burden associated with cancer as this can translate into a broader range of symptoms
324 including anger or behavioral problems^{57,58}.

325 Among adult survivors distress was much lower in our sample than in another mixed CCS cohort
326 (19% vs. 28.6%)⁴⁸, which could be explained by heterogeneity of cancer types, treatment and
327 older age found in the previous cohorts possibly leading to more LAEs resulting in more distress.
328 .

329 Our results are consistent with the observation that anxiety is more salient than depression
330 among adult survivors^{40,60,61,62}. More generally, anxiety and depression have been found to be the
331 most common psychological complaints among CCS⁶³.

332 Functional health status was high and homogeneous in the cohort (total scores approaching
333 perfect health and minimal variation). However, our results revealed that cALL survivors

334 commonly reported vitality, sleeping, and discomfort/symptoms issues while several other health
335 domain issues were specific to either age subgroups (e.g. appearance in adolescents and mental
336 function in adults). The range of scores provided by the vitality health domain (feeling healthy
337 and energetic to feeling extremely weary, tired or feeble, totally exhausted) can be interpreted as
338 the level of fatigue. Cancer-related fatigue and sleep problems (sleep disturbance, sleep quality,
339 daytime sleepiness) are among the most common late effects following cancer^{48,60,61,63-67}. If left
340 unmanaged, they can yield important work or school performance difficulties which may lead to
341 significant distress, anxiety, depression, and impaired quality of life⁶⁸⁻⁷². In fact, sleeping issues
342 seemed to be key contributors to psychological health: both adolescents and adults in the present
343 study were 2 to 10 times more likely to report anxiety, depression or distress if they had sleeping
344 difficulty. Interestingly, despite similar percentages in reporting fatigue issues in both age
345 groups, it only seemed to be a key contributor to psychological risk among adults but not among
346 adolescents. It can be hypothesized that this issue did not significantly disrupt adolescents' daily
347 activities or lead to social constraints compared to adults. Therefore, perhaps the younger
348 group's coping strategies (adaptive health competence beliefs) were more effective in promoting
349 self-efficacy and preventing psychological burden.⁷³⁻⁷⁶

350 Discomfort/symptoms was also found to be frequent among adolescents (39%) and adults (50%)
351 . This health domain includes symptoms such as pain, aches, nausea, feeling sick, itching. Of
352 particular interest, the frequency of pain varies from 13% to 57% in similar CCS cohorts with
353 common complaints being abdominal, neuropathic, headaches and neck and back pain^{77,78}.

354 Clinicians and researchers identify pain and discomfort as major domains for future quality of
355 life. In long-term CCS, it has been associated with lower educational attainment, unemployment
356 and single status and could lead to psychological risk⁷⁷.

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

360 Alternatively, while issues with breathing were equally frequent in adolescents and adults (23%
361 vs. 32%), they were found to contribute to depression only in the former group. This could
362 reflect the importance of social limitations due to this health issue. In fact, studies have revealed
363 adolescent survivors with pulmonary issues to be less physically active than their siblings,
364 limiting their engagement in usual, age-appropriate activities and which could lead to impaired
365 quality of life and negative mood⁷⁹⁻⁸¹.

366 We focused on frequently reported health issues. However, less frequently reported difficulties,
367 such as mental function issues (reported in 17% and 25% of adolescents and adults,
368 respectively), might have pervasive impacts as well. Mental function issues were consistently
369 associated with psychological outcomes across age groups. Among adolescents, it was the
370 strongest key contributor of anxiety (95% CI 3.43-70.47), depression (95% CI 3.98-97.54), and
371 distress (95% CI 3.62-50.28). Mental function issues have been widely documented in CCS and a
372 strong hypothesis to account for its relation to psychological symptoms and school/work
373 achievement and social functioning^{9,43-45}. Given the close relationship between neurocognitive
374 functioning with fatigue^{68,69}, it is also possible that both interact to explain psychological risk.

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

380 own mental function difficulties on memory and attention may lead to lower self-esteem and
381 self-efficacy at school/work. Subsequent limitations on school achievements, and professional
382 goal attainments could contribute to social isolation, impaired social adjustments, and emotional
383 distress^{9,43-45}.

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

394 In summary, our results offer new insights on levels and types of psychological risk in a
395 homogeneous cohort of young survivors treated for cALL, with emotional distress being reported
396 by 14% to 30% of our cohort. Our study further documents the important contribution of health
397 functions such as vitality, sleep, discomfort/symptoms, and mental function to psychological risk
398 in adolescent and adult cALL survivors as well as how social functioning impacts the relationship
399 found between functional health status and psychological risk. Future studies should explore
400 functional domains that are most often reported as problematic by young survivors as interventions
401 targeting these are increasingly available for the adult population who faces cancer and should be
402 adapted and proposed to CCS^{82,83}. Lastly additional research should be conducted to explore

403 cancer rehabilitation programs targeting vocational achievement⁸⁴ and social skills
404 interventions^{85,86} to promote social functioning.

405

406 **CONFLICT OF INTEREST**

407 The authors declare that there is no conflict of interests.

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634

635 LEGEND

636 **Figure 1** Frequency of anxiety, depression, and distress symptoms in adolescent and adult cALL
637 participants

638 For adolescents: N=95 for anxiety and depression, N= 98 for distress. Positive cases for anxiety
639 and depression were defined as T scores >55 (results obtained with BYI anxiety and depression
640 inventories).

641 For adults: N=143 for anxiety and depression, N=157 for distress. Positive cases for anxiety were
642 defined as BAI >7, positive cases for depression BDI-II >13

643 For both groups, a cut-point of 4 was used for distress (results obtained with DT).

644

645 **Figure 2** Frequency of issues with domains of health status in adolescent and adult cALL
646 participants

647 For adolescents: N= 98. Results obtained from the 16D questionnaire. Domains exclusive to the
648 16D: appearance, friendship and school

649 For adults: N=157. Results obtained from the 15D questionnaire. Domains exclusive to the 15D:
650 sexual activity, usual activities. Absence of eating impairment for adults.
651 For both questionnaires, scores range from 1 (best level of function) to 5 (worst level of
652 function). Issues with health domains defined as scores >1.

653

654 **Figure 3** Mediation analysis for cALL participants

655

656 Mediation analysis conducted with path analysis - PROCESS macro for SPSS (Hayes ref). Sample
657 consists of adolescent (n=95) and adult (n=146) cALL survivors with the age group included as a
658 covariable. Mental function problems' score from the 16D and 15D questionnaires. Impairment is
659 defined as scores >1. Work/school functioning score from Pediatric Quality of Life Inventory
660 (PedsQL). Higher scores indicate better work/school functioning.

661 a: estimate of the effect of the predictor (mental function impairment) on the mediator
662 (work/school functioning).

663 b: estimate of the effect of the mediator on the outcome variable (component score representing
664 psychological risk).

665 ab: indirect effect which is the product of path a and path b representing the amount of
666 mediation. Significance of the indirect effect determined with bootstrapping method and to be
667 interpreted as follows: if 0 is not included in the 95%CI, mediation has occurred and significant
668 at the $p < .05$.

669 c: direct effect of the predictor variable on the outcome variable controlling for the mediator.

670

671 **Supplementary Figure S1** Study structure and flow

672 Study structure and flow

673 Montreal treatment site: Sainte-Justine University Health Center (SJUHC, Montreal, Canada)

674 Quebec treatment site: Laval University Health Center (CHUL, Quebec, Canada)

675

TABLE 1 Socio-demographic 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 (%)
Socio-demographic characteristics			
Sex			
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)
Marital status			
Single	105 (100)	118 (64.8)	223 (77.7)
Married/Common law	0	64 (35.2)	64 (22.3)
Ethnicity			
Caucasian	103 (98.1)	174 (95.6)	277 (96.5)
Other	2 (1.9)	8 (4.4)	10 (3.5)
Educational background			
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 ^a	4 (3.8)	39 (21.4)	43 (15.0)
CEGEP ^b	1 (1)	61 (33.5)	62 (21.6)
University (UG/PG ^c)	0 (0)	28 (15.2)	28 (9.8)
Primary Occupation			
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)
First language			
French	98 (93.3)	177 (97.8)	275 (96.2)
English	3 (2.9)	2 (1.1)	5 (1.7)
Other ^d	4 (3.8)	2 (1.1)	6 (2.1)
Clinical characteristics			
Treatment site			
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)
ALL risk status			
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)
Treatment protocol ^e			
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)
Radiotherapy			
No	68 (64.8)	58 (31.9)	126 (43.9)
Yes	37 (35.2)	124 (68.1)	161 (56.1)

676

677 ^a PED, Professional Education Diploma.

678 ^b CEGEP is the first stage of higher education after high school, exclusively in province of
679 Quebec, Canada.

680 ^c UG/PG, Undergraduate/Postgraduate.

681 ^d Other: Spanish, Vietnamese, Bulgarian, Romanian.

682 ^e Dana-Farber Cancer Institute ALL Consortium protocols for children. Each protocol is labeled
683 by the year of the clinical trials detailing the treatment regimen during the 4 phases of therapy
684 (remission induction, CNS-directed treatment, Intensification and continuation).

685

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	Anxiety (n= 94)			Depression (n= 94)			Distress (n= 96)		
	OR	95%CI	P-value	OR ^a	95%CI ^b	P-value	OR	95%CI	P-value
Mobility ^a	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Friendship ^b	0.95	0.75-12.11	0.970	N/A	N/A	N/A	0.71	0.05-2.11	0.803
Appearance ^b	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	0.002	18.29	2.97-112.84	0.002	1.88	0.48-7.34	0.366
Breathing	4.04	1.11-14.75	0.035	9.62	1.87-49.46	0.007	1.82	0.61-5.45	0.284
Sleeping	10.27	2.39-44.03	0.002	3.94	0.84-18.52	0.083	5.07	1.70-15.17	0.004
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	0.002	8.20	1.58-42.42	0.012	1.56	0.41-5.95	0.517
Mental function	15.55	3.43-70.47	<0.0001	19.71	3.98-97.54	<0.0001	13.48	3.62-50.28	<0.0001
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	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 ^c	1.36	1.16-1.60	<0.0001	1.32	1.13-1.60	<0.0001	1.17	1.07-1.30	0.003

ORs are adjusted for age, gender, age at diagnosis and treatment risk status in all analyses.

P-values in bold indicate $p < 0.01$.

^a Analysis not applicable because the sample size for participants with mobility impairment and presence of distress, anxiety and depression was equal to 1.

^b Analysis not applicable as no participants with difficulties in this domain presented depression.

^c 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). Impairment defined as scores >1 .

Anxiety and depression scores from Beck Youth Inventories for anxiety and depression. Positive cases were defined as T scores >55.
Distress scores from Distress Thermometer. Positive cases define as scores equal or above to 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 ^c	Anxiety (<i>n</i> = 142)			Depression (<i>n</i> = 142)			Distress (<i>n</i> = 156)		
	OR ^a	95% CI ^b	P-value	OR ^a	95% CI ^b	P-value	OR ^a	95% CI ^b	P-value
Mobility	5.61	1.53-20.51	0.009	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	0.006	3.88	1.49-10.14	0.006
Eating ^d		N/A			N/A			N/A	
Speech	4.82	1.91-12.20	0.001	2.66	0.98-7.16	0.054	2.47	0.92-6.62	0.072
Excretion	3.79	1.56-9.19	0.003	4.48	1.68-11.95	0.003	1.03	0.36-2.96	0.964
Usual activities	6.68	2.36-18.95	<0.0001	18.21	5.43-61.05	<0.0001	3.58	1.15-11.14	0.027
Mental function	4.23	1.84-9.73	0.001	6.65	2.58-17.14	<0.0001	5.13	2.04-12.91	0.001
Discomfort/symptoms	8.18	3.27-20.45	<0.0001	7.44	2.63-21.07	<0.0001	2.68	1.11-6.47	0.029
Vitality	8.49	3.44-20.97	<0.0001	13.28	4.09-43.11	<0.0001	3.92	1.59-9.71	0.003
Sexual activity	6.22	2.40-16.27	<0.0001	6.76	2.39-19.12	<0.0001	2.91	1.04-8.15	0.043
15D total score ^e	1.18	1.10- 1.25	<0.0001	1.19	1.11-1.28	<0.0001	1.10	1.04-1.17	0.001

P values in bold indicate $p < 0.01$.

^a Odds Ratio.

^b 95% confidence interval.

^c ORs are adjusted for age, gender, age at diagnosis and treatment risk status.

^d Analysis not applicable because there were no participants with an eating impairment.

^e 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, scores range from 1 (best level of function) to 5 (worst level of function). Impairment 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 define as scores equal or above to 4.

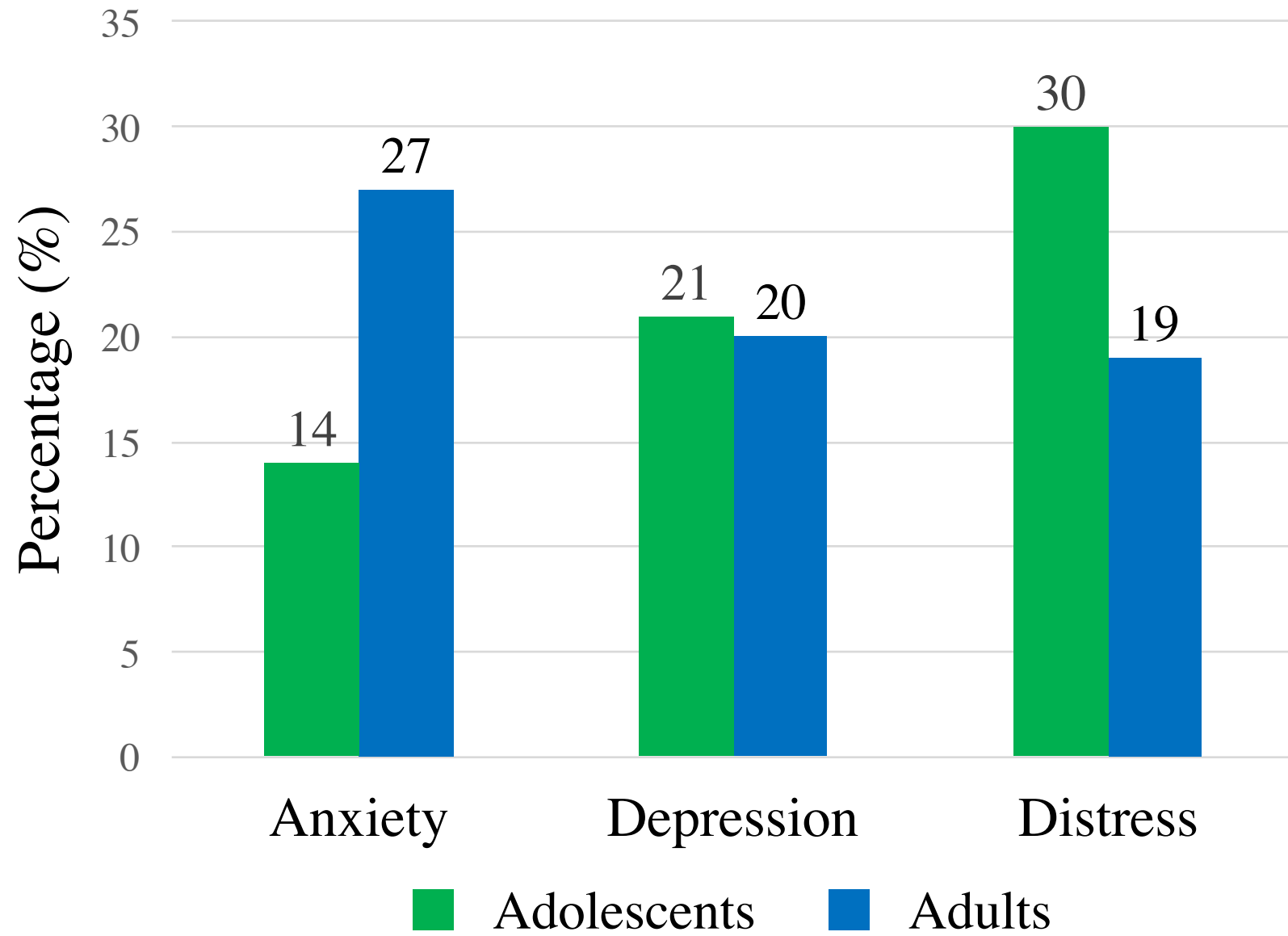


Figure 1.

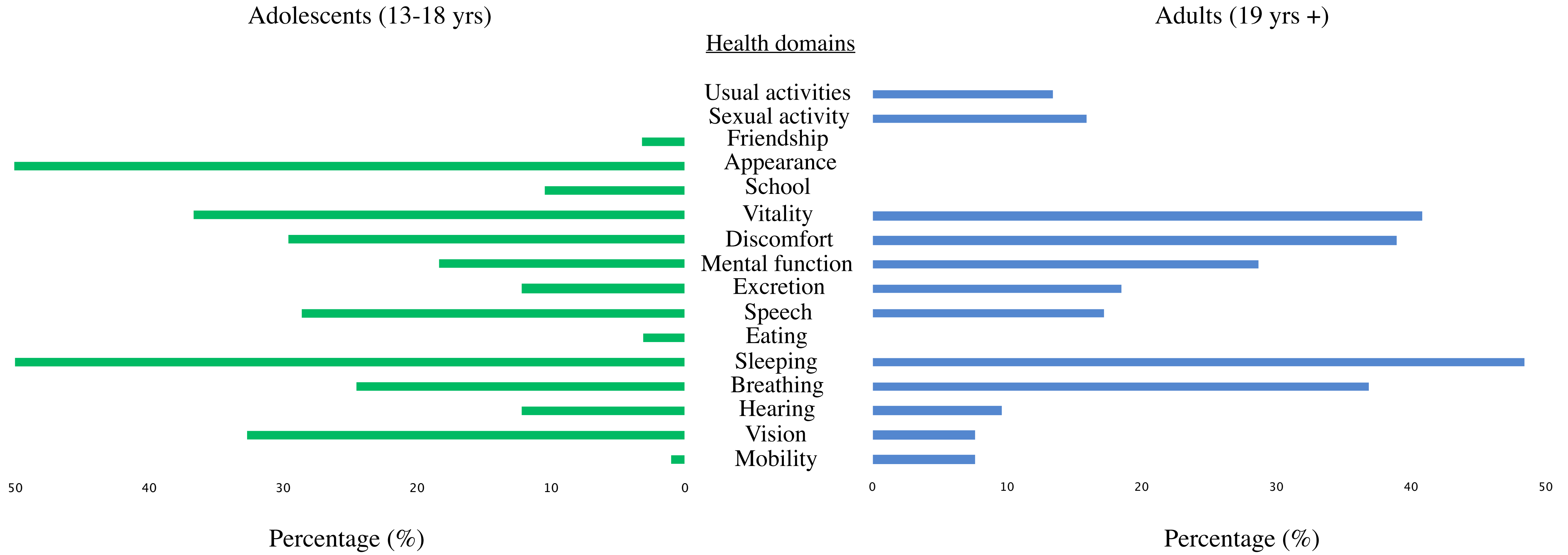


Figure 2.

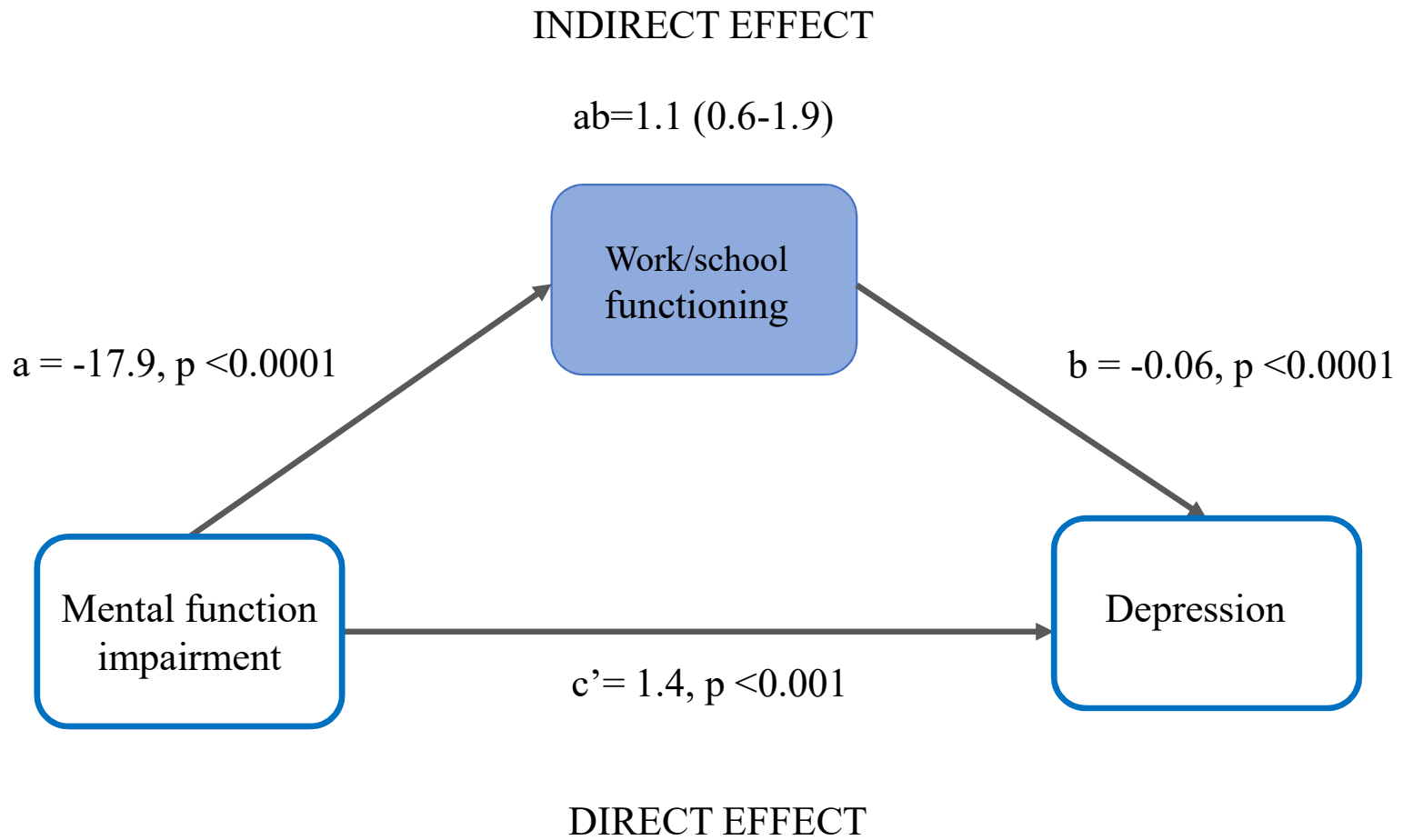


Figure 3