SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

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SZABADOS MÁRTON

Molekuláris és experimentális onkológia

című program

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IDENTIFYING RISK FACTORS FOR MENTAL HEALTH AND QUALITY OF LIFE AMONG CHILDHOOD CANCER SURVIVORS

Ph.D. Thesis

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"Life isn't about waiting for the storm to pass,
but about learning how to dance in the rain."

Vivian Greene

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1. LIST OF ABBREVIATIONS

BDI – Beck Depression Inventory

BSI-18 – Brief Symptom Inventory–18

BST – Bone and Soft Tissue Tumors

CBCL – Child Behavior Checklist

CDI – Children's Depression Inventory

CDI-2 – Children's Depression Inventory, Second Edition

CFA – Confirmatory Factor Analysis

CFI – Comparative Fit Index

CI – Confidence Interval

CNS – Central Nervous System

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ETT – Health Science Council (Egészségügyi Tudományos Tanács)

GAD – Generalized Anxiety Disorder

GFI – Goodness-of-Fit Index

HADS – Hospital Anxiety and Depression Scale

HRQoL – Health-Related Quality of Life

ICC – Intraclass Correlation Coefficient

INF – Infratentorial

MDD – Major Depressive Disorder

M_RAW – Raw Mean Score

MMQL – Minneapolis–Manchester Quality of Life Instrument

MMQL-AF – Minneapolis–Manchester Quality of Life Instrument, Adolescent Form

NF1 – Neurofibromatosis Type 1

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO – International Prospective Register of Systematic Reviews

PedsQL – Pediatric Quality of Life Inventory

PedsQL SF15 – Pediatric Quality of Life Inventory, Short Form 15

QUIPS-2 – Quality in Prognostic Studies Tool, Version 2

RMSEA – Root Mean Square Error of Approximation

SCARED – Screen for Child Anxiety Related Emotional Disorders

SD – Standard Deviation

SRMR – Standardized Root Mean Square Residual

SUP – Supratentorial

TARES – Test Adaptation Reporting Standards

TLI – Tucker–Lewis Index

WHO – World Health Organization

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is that childhood cancer patients and survivors will live fulfilling and meaningful lives. To realize this vision, my mission is to establish a multidisciplinary follow-up system that monitors and supports the neuropsychological well-being of these patients. The specific goals of this work are to implement structured, long-term follow-up care focused on quality-of-life outcomes; to identify and continuously monitor neuropsychological late effects of childhood cancer and its treatment facilitating early intervention and personalized supportive care for patients at increased risk.

2.2. Scientometrics

Number of all publications:	7
Cumulative IF:	26.1
Av IF/publication:	3.73
Ranking (SCImago):	D1: 1; Q1: 5; Q2: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.3
Av IF/publication:	3.65
Ranking (Sci Mago):	D1: 1 Q1: 1
Number of citations on Google Scholar:	21
Number of citations on MTMT (independent):	7
H-index:	3

The detailed bibliography of the student can be found on page 53.

2.3. Future plans

In the future, I aim to continue my research by identifying risk factors that influence the quality of life of childhood cancer patients and survivors and by developing targeted intervention strategies to support optimal long-term outcomes. Paralell with my research, I plan to expand my clinical expertise by completing my specialization in pediatric hematology–oncology and palliative care, with the goal of delivering comprehensive, patient-centered care for children with serious illnesses.

3. SUMMARY OF THE THESIS

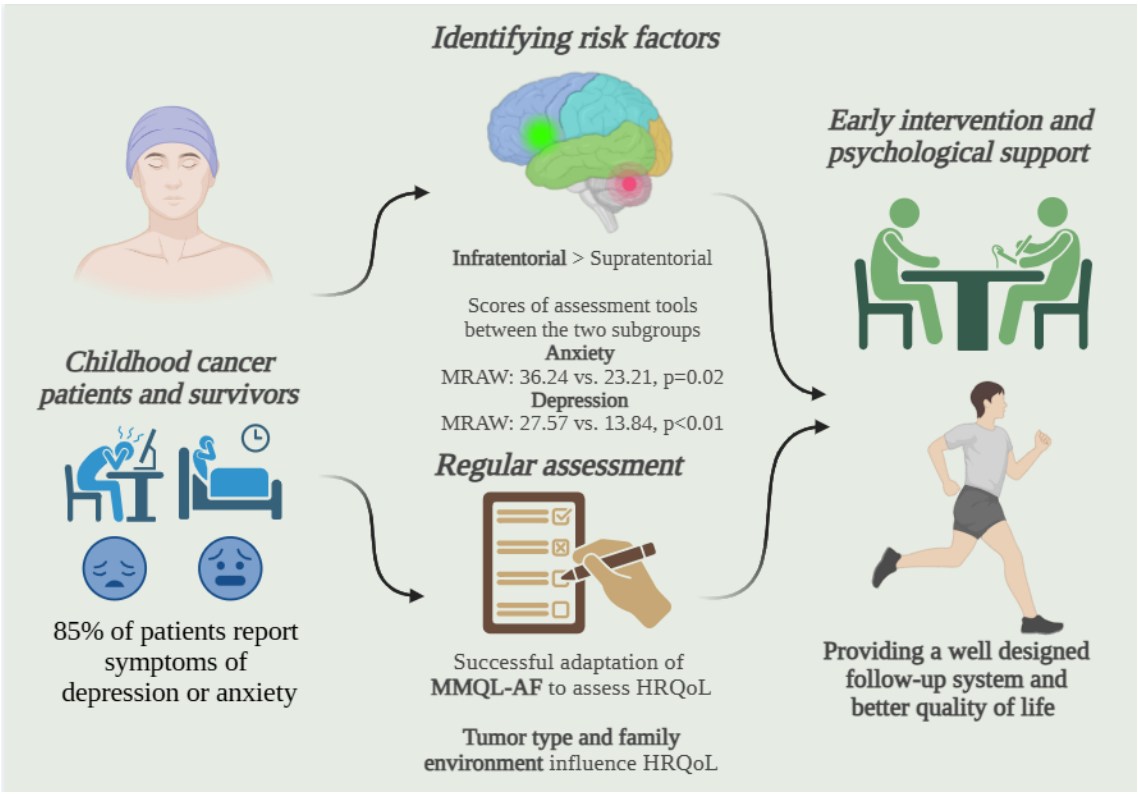
This thesis examines the neuropsychological welfare and health-related quality of life (HRQoL) of children, adolescents, and young adults diagnosed with cancer, particularly assessing patients with brain tumors. As survival rates enhance, psychological outcomes emerge as significant long-term issues. Neuropsychological side effects are common and severe consequences of pediatric cancer [1-3].

Study I is a systematic review and meta-analysis examining the association between brain tumor location and affective disorders among pediatric brain tumor survivors. Approximately 22% of survivors met diagnostic criteria for major depression and generalized anxiety disorder, confirming a high prevalence of emotional morbidity. Although no statistically significant difference was observed in the incidence of diagnosed illnesses between infratentorial and supratentorial tumors, survivors with infratentorial tumors had consistently elevated anxiety and depression scores on validated assessment tools. This indicates an increased symptomatic burden in this subgroup, and identifies infratentorial tumor survivors as a priority group for enhanced psychological surveillance.

Study II is the Hungarian cross-cultural adaption of the the Minneapolis–Manchester Quality of Life Instrument – Adolescent Form (MMQL-AF). The Hungarian MMQL-AF demonstrated good internal consistency, excellent test–retest reliability, acceptable structural validity after minor item reduction, and strong convergent validity with the Hungarian PedsQL 4.0 SF15. It clearly differentiated between cancer patients and healthy controls. Risk factor assessment showed, that family environment plays a signifant impact, as adolescents with parents who lived together exhibited more positive outlook on life and superior physical functioning.

The results highlight the necessity for a multidisciplinary, risk-stratified survivorship model that involves psychological assessment and quality-of-life monitoring into standard follow-up, facilitating early, and effective interventions that promote long-term well-being in childhood cancer survivors.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1 Overview of the topic

The thesis focuses on the neuropsychological welfare and health-related quality of life (HRQoL) of children, adolescents, and young adults with cancer. The studies investigate risk stratification according to tumor location, tumor specific and socioeconomic factors, as well as the necessary measuring methods for a systematic, long-term, multidisciplinary follow-up strategy.

5.2 Psychological and psychiatric symptoms among pediatric cancer patients

As survival rates improve, the focus in pediatric oncology has shifted from only survival data to ensuring that survivors may lead full and meaningful lives [1-3]. Survivors of pediatric cancer frequently face a variety of long-term physical complications resulting from both the illness and its treatment. This may include endocrinological disorders, musculoskeletal issues, like joint and bone anomalies, growth irregularities, and other organ-specific deficiencies [4]. While long-term follow-up care has traditionally prioritized physical late effects, increasing attention is now on the psychological impact of surviving childhood cancer. Anxiety, depression, and impaired HRQoL significantly impact academic performance, social integration, and overall long-term adaptation, as well as the autonomy of the individual [5]. Timely detection and management of these issues are crucial for high-quality survivorship care, since early intervention can mitigate symptom severity and duration, prevent relapse, and improve overall functioning [6]. Despite their clinical relevance, these outcomes are often insufficiently detected and monitored in routine care [7]. The relationship between specific clinical characteristics and the prevalence of anxiety and major depression in survivors has not been clearly quantified across studies. Survivors with brain tumors face a significantly elevated risk of cognitive and psychosocial late sequelae, due to the tumor biology, anatomical location, neurosurgical procedures, and additional treatment. Older age at diagnosis, intensive multimodal therapy, cranial irradiation, pre-existing neurodevelopmental difficulties, family stressors, and socioeconomic disadvantages are known risk factors for worse symptoms [8-10]. Emotional regulation depends on complex neural networks

involving the prefrontal cortex, amygdala, hippocampus, anterior cingulate cortex, basal ganglia, and thalamus. These regions are responsible for executive function, memory processing, stress response, fear conditioning, reward pathways, and impulse control. Cerebellar injury may therefore result in affective disturbances such as anxiety, depression, or emotional blunting, consistent with cerebellar cognitive-affective syndrome. [11, 12]. Supratentorial and infratentorial brain tumors vary in morphology and clinical manifestation. Supratentorial tumors, which arise in the cerebral hemispheres, may affect higher cognitive functions, executive control, and personality traits. Lesions in frontal or limbic regions may manifest as behavioral or attention deficits. Infratentorial tumors, located in the cerebellum and brainstem, are more frequently associated with coordination and balance problems, cranial nerve impairments, and cerebellar cognitive affective syndrome, characterized by emotional blunting, irritability, and reduced social cognition [13]. The degree to which tumor site affects the onset of anxiety and depression remains unclear. Understanding how tumor location is associated with the prevalence of anxiety and major depression can help identify subgroups that require intensified psychological monitoring and tailored interventions.

5.3 Evaluating the quality of life in pediatric cancer patients

Health-related quality of life (HRQoL) is an important outcome in pediatric oncology, as it reflects the multidimensional impact of cancer and its treatment on physical, emotional, social, and cognitive functioning [14]. Pediatric cancer and its therapies are frequently associated with psychological distress, disruptions in normal development, education, and social participation, all of which can adversely affect HRQoL. Children must cope with physical discomfort, developmental delay, and emotional stress, while families can face psychological distress and financial burderns also. Reduced HRQoL has been linked to poorer treatment cooperation, decreased motivation for rehabilitation, social isolation, and long-term mental health problems. Supportive psychosocial care, educational continuity, pain management, and family counseling have been shown to improve daily functioning and emotional adjustment [15, 16]. Systematic assessment of HRQoL provides patient-centred information that helps to identify and improve treatment-related problems, and guide interventions at optimizing both short- and long-term results [17]. In

Hungary, there was an absence of a validated HRQoL instrument specifically designed for cancer patients prior to this study. The Hungarian adaptation of the MMQL-AF helps facilitating standardized HRQoL assessment in Hungarian adolescents and young adults with cancer. This is essential for implementing coordinated, multidisciplinary follow-up and evaluating supportive interventions.

5.4 Impact of the Research

These studies offer an empirically grounded foundation for developing a multidisciplinary, long-term follow-up system in Hungary that systematically evaluates HRQoL using a validated, culturally adapted instrument and integrates tumor-related and psychosocial risk factors into routine monitoring.

6. OBJECTIVES

6.1 Study I. – Association of Tumor Location with Anxiety and Depression in Childhood Brain Cancer Survivors: a Systematic Review and Meta-analysis

The aim of this meta-analysis was to examine how brain tumor location relates to the prevalence of anxiety and major depression, to support earlier diagnosis and targeted psychological interventions.

6.2 Study II. – The Hungarian Cross-cultural Adaptation of the MMQL-AF for Measuring Quality of Life in Adolescents with Cancer

The aim of this study was to validate the Hungarian version of the MMQL and support the development of a robust long-term follow-up system for children with cancer and survivors in Hungary. A secondary goal was to examine clinical and psychosocial factors influencing HRQoL.

7 METHODS

7.1 Study I.

7.1.1 Methodology and Protocol

Study I was conducted as a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the methodological recommendations of the Cochrane Handbook [18]. The study protocol was prospectively registered in the PROSPERO [19] international prospective register of systematic reviews under the registration number CRD42022370756, with the protocol title "Association of tumor location with anxiety and depression in childhood brain cancer survivors: a systematic review and meta-analysis."

7.1.2 Eligibility Criteria

Eligible studies included patients diagnosed with any type of intracranial malignancy before the age of 18 years and provided clear information on tumor location, supratentorial, infratentorial, or tumor types specific to one of these locations. Studies were required to report either a formal diagnosis of generalized anxiety disorder or major depression disorder based on DSM-IV or DSM-5 criteria, or quantitative data on anxiety and/or depressive symptoms measured with validated questionnaires (e.g. HADS, CDI, CDI-2, BSI-18, SCARED, CBCL). There were no language or publication date restrictions. We excluded case report studies, studies not specifying tumor location, and reports providing only qualitative statements about affective symptoms without extractable data.

7.1.3 Information Sources and Search Strategy

A systematic literature search was performed in five electronic databases: Medline (via PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. The last search was conducted on 22 November 2022. In

addition, reference lists of relevant articles were screened and citation tracking was performed using tool “citationchaser” [20] to identify further eligible studies. A comprehensive search key was composed of four domains, pediatric, brain cancer, localization and affective disorders as follows: (pediatric* OR paediatric* OR adolescent OR adolescence OR child* OR "young adult" OR "young adults" OR kids OR kid OR youth OR juvenile OR infant* OR infancy OR preschooler* OR teen OR teens OR teenager*) AND (“posterior fossa syndrome” OR astrocytoma OR glioblastoma OR DIPG OR “glioma” OR “HGG” OR “LGG” OR “ATRT” OR “PNET” OR medulloblastoma OR dysgerminoma OR oligodendroglioma OR xanthoastrocytoma OR astroblastoma OR ganglioglioma OR gangliocytoma OR "Lhermitte-Duclos disease" OR "neurocytoma" OR "cerebellar liponeurocytoma" OR ependymoma OR subependymoma OR "choroid plexus papilloma” OR pineocytoma OR pineoblastoma OR schwannoma OR neurofibroma OR perineurioma OR paraganglioma OR meningeoma OR "CNS hemangioma" OR "CNS vascular malformation" OR "meningeal melanocytosis" OR "meningeal melanomatosis" OR "meningeal melanocytoma" OR germinoma OR choriocarcinoma OR craniopharyngeoma OR pituicytoma OR oncocytoma OR "pituitary adenoma" OR "PitNET" OR "pituitary blastoma" OR "brain cancer" OR "brain cancers" OR “central nervous system tumor” OR “central nervous system tumour” OR “brain malignoma”) AND (localization OR localiz* OR "frontal lobe" OR frontal OR "temporal lobe" OR temporal OR "cerebellum" OR cerebellar* OR parietal OR "parietal lobe" OR "brain stem" OR "occipital lobe" OR occipital OR "supratentorial" OR "infratentorial" OR "thalamus" OR "hypothalamus" OR "pineal gland" OR pituitary OR amygdala OR "corpus callosum") AND ("mental health" OR mental health OR psychology OR psychologic* OR "mental issues" OR mental issue* OR mood* OR emotion* OR affective disorders OR affective OR "mental disorder" OR mental disord* OR depressi* OR "major depression" OR "anxiety" OR anxie* OR "unipolar depression" OR "bipolar depression" OR bipolar* OR dysthymia OR cyclothymia OR CDI OR CBCL OR SCARED OR BDI OR CDS).

7.1.4 Study Selection and Data Extraction

After removal of duplicates (manually and using EndNote X9 [21], two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially relevant articles, according to predefined eligibility criteria. Interrater agreement during study selection was quantified using Cohen's kappa coefficient, and any disagreements were resolved through discussion with a third reviewer. Data were extracted independently by two reviewers using a standardized data extraction form. Extracted variables included study characteristics (authors, year, design, study period), sample size, tumor location, number of patients with diagnosed anxiety or depression, mean scores and standard deviations of affective symptom questionnaires, and the length of follow-up.

7.1.5 Risk of Bias Assessment

Risk of bias in the included studies was assessed independently by two reviewers using the Quality in Prognostic Studies 2 (QUIPS-2) [22] tool, which evaluates potential bias across relevant domains (e.g. study participation, prognostic factor measurement, outcome measurement, confounding, statistical analysis and reporting). Any disagreements were discussed and resolved by a third investigator.

7.1.6 Data Synthesis and Analysis

Quantitative synthesis was conducted using R (version 4.1.2) [23]. For the prevalence of anxiety and depression, pooled proportions were estimated using random-intercept logistic regression models. Clopper–Pearson confidence intervals were calculated for individual studies [24], and between-study heterogeneity (τ^2) was estimated using maximum-likelihood methods. For symptom severity, raw CBCL T-scores were pooled directly, whereas scores from different anxiety and depression questionnaires were transformed to a common 0–100 scale and analyzed as standardized raw mean scores (M_RAW). All instruments measure depressive symptom severity as a continuous

construct, with higher scores consistently indicating greater symptom burden. Because the scoring systems are approximately linear and assess the same underlying construct, score transformation to a common linear scale was considered appropriate for pooled analysis [25]. Random-effects models with inverse variance weighting and maximum-likelihood estimation of τ^2 were applied, with Hartung–Knapp adjustments used due to the relatively low number of studies [26]. Heterogeneity was assessed using Cochrane's Q and Higgins and Thompson's I^2 statistics [27, 28]. Subgroup analyses were performed according to tumor location (supratentorial vs infratentorial) to evaluate differences in the prevalence and severity of anxiety and depression between these groups.

7.2 Study II.

7.2.1 Study design

Study II was a single-centre, observational study designed to perform the cross-cultural adaptation and psychometric validation of the Hungarian version of the Minneapolis–Manchester Quality of Life Instrument – Adolescent Form (MMQL-AF). The design was primarily cross-sectional, complemented by a short-term test–retest component to assess temporal stability. The study followed international TARES guideline [29], for patient-reported outcome measure adaptation and validation, including structured translation procedures [30] and comprehensive evaluation of reliability and validity.

7.2.2 Study setting

The study was conducted at the Pediatric Center of Semmelweis University, Hungary. Participants were recruited from both the pediatric oncology ward and the outpatient clinic, including patients currently receiving active treatment and patients after treatment on follow-up visit. Healthy controls were recruited from Babits Mihály Grammar School, Budapest, Hungary. Questionnaires were completed during routine clinical visits or during a class in a quiet, standardized setting, under the supervision of trained staff.

7.2.3 Ethics and patient consent

The study was approved by the Scientific and Research Ethics Committee (TUKEB) of the Health Science Council (ETT) (BM/16408-1/2023). The cross-cultural adaptation and validation were carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants aged 18 years or older, and from parents or legal guardians for minors, with assent obtained from adolescents as appropriate. Participation was voluntary, and respondents were informed about the anonymous handling and analysis of their data.

7.2.4 Participants

Participants were adolescents and young people aged 13–20 years, in line with the WHO definition of this age group [31]. The study population comprised three groups: patients with cancer undergoing active treatment, patients in complete remission or with stable disease, not receiving therapy and a healthy control group with no known chronic illness.

Inclusion criteria for the patient groups were: age 13–20 years, a diagnosis of malignant disease treated at the Pediatric Center, and being either on active treatment or in follow-up after completion of therapy. Healthy controls were required to have no self-reported or known chronic medical condition. Exclusion criteria included cognitive or developmental impairment that precluded completion of a self-administered questionnaire, critical clinical condition, inability to understand Hungarian, and refusal or withdrawal of consent. All participants completed a self-administered questionnaire package; a subsample received the same questionnaire again after a predefined interval of two weeks to assess test–retest reliability.

7.2.5 Variables and data sources

The primary outcome variable was health-related quality of life as measured by the Hungarian version of the MMQL-AF. The original version of the MMQL-AF was developed for participants between 13 and 20 years, who recovering from serious illnesses, including cancer, but designed to be applicable to both clinical and healthy population. The instrument includes 46 items covering 7 HRQoL domains: physical

functioning (9 items), psychological functioning (9 items), social functioning (6 items), cognitive functioning (9 items), body image (6 items), outlook on life (4 items), and intimate relations (3 items). The MMQL-AF is scored on a 4- or 5-point Likert scale from 1-4 and 1-5 with higher scores indicating greater HRQoL. The questionnaire helps clinicians and researchers to evaluate the long-term impact of illness and treatment, monitor recovery, and guide supportive care interventions [32].

For concurrent convergent validity, participants also completed the short-form 15-item Hungarian version of the Pediatric Quality of Life Inventory (PedsQL SF15) [33], which served as an external criterion measure.

Socio-demographic and clinical data were extracted from medical records and/or collected via a structured data sheet, including age, sex, diagnosis, tumor type, treatment status, time since treatment completion, and family characteristics.

7.2.6 Assessing confounding factors and variables

Potential confounding factors influencing HRQoL were evaluated using demographic, clinical, and psychosocial variables collected alongside MMQL-AF data. Predefined subgroup analyses were conducted to explore potential differences in HRQoL based on age group (13–16 vs. >16 years), parental education level, parental relationship status (parents living together vs. separately), and cancer diagnosis. Due to the lack of significant differences between patients on and off treatment, these groups were merged for selected diagnostic subgroup analyses to increase statistical power.

7.2.7 Statistical Methods

Statistical analyses were performed using R (version 4.3.2, R Core Team, 2023.) [22]. Descriptive statistics were used to summarize demographic and clinical characteristics and HRQoL scores.

Structural validity was evaluated by confirmatory factor analysis (CFA) of the MMQL-AF domain structure. Model fit was assessed using standard indices, including the

Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), Goodness-of-Fit Index (GFI), Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean Square Residual (SRMR), with established thresholds for acceptable fit. Modification indices were inspected to identify items with substantial misfit; item removal was considered when theoretically justified to improve model parsimony and overall fit [34-36]

Internal consistency was assessed by Cronbach's alpha for each domain and for the total scale. Test–retest reliability was evaluated using intraclass correlation coefficients (ICC) for MMQL-AF domain and total scores between the initial and follow-up administrations. Concurrent convergent validity was examined by calculating correlations between MMQL-AF domains and corresponding PedsQL SF15 scales. Discriminant validity was assessed by comparing HRQoL scores between patient groups and healthy controls, and between clinical subgroups (e.g. different tumor types, treatment status, and time since treatment) using appropriate parametric or non-parametric tests depending on data distribution.

8 RESULTS

8.1 Study I: Association of tumor location with anxiety and depression in childhood brain cancer survivors: a systematic review and meta-analysis

8.1.1 Study Search and Selection

After conducting the search, we identified 6,692 records and 1,564 records through the references. A total of 42 studies were included in the quantitative analysis. The selection process is described in the PRISMA [37] flowchart (Figure 1).

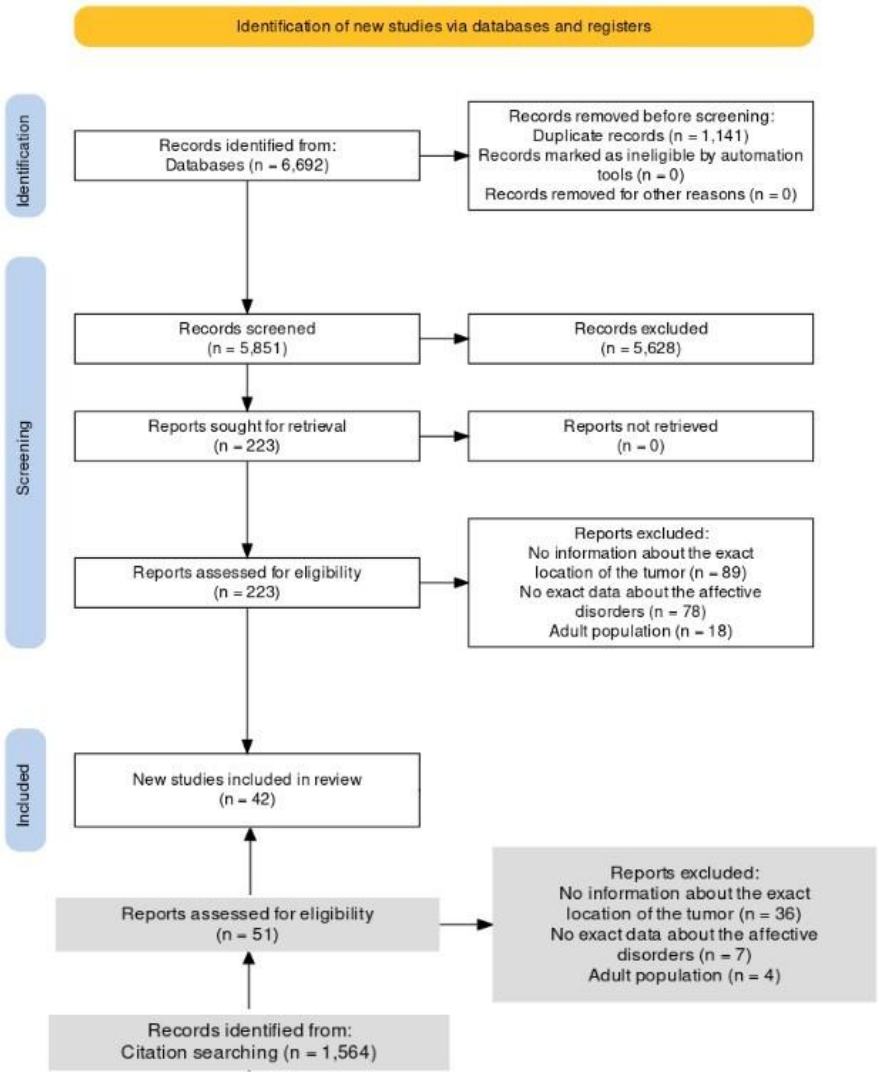


Figure 1 - PRISMA 2020 flowchart representing the detailed systematic search and study selection process [37].

Table 1 – Characteristics of included studies. All studies analyzed were cohort (retrospective and prospective), case-series, or cross-sectional. We included studies in our meta-analyses that showed clinical diagnosis of depression or anxiety or had data about the scores on different assessment tools (CBCL, CDI, CDI-2, BDI, BSI-18, HADS, SCARED)

	Author, year	Country	N°of patients	Major localization	Type of affective disorder	Assessed by*
1	Abla, 2010	United States	10	Supratentorial	MDD, GAD	Professional
2	Beckwitt, 2011	United States	14	Infratentorial	MDD	Professional
3	Brasme, 2012	France	166	Infratentorial	MDD	Professional
4	Fouda, 2019	United States	135	Supratentorial	MDD, GAD	Professional
5	Maddrey, 2005	United States	16	Infratentorial	MDD	Professional
6	Malbari, 2016	United States	7	Supratentorial	MDD	Professional
7	Zuzak, 2008	Schwitzerland	21	Infratentorial	MDD, GAD	Professional
8	Yano, 2016	Japan	26	Supratentorial	MDD	Professional
9	Chieffo, 2021	Italy	30	Infratentorial	MDD	Professional
10	Clopper, 1977	United States	20	Supratentorial	MDD	Professional
11	Laffond, 2012	France	22	Supratentorial	MDD	Professional
12	Mehren, 2018	Germany	35	Supratentorial	MDD	Professional
13	Memmesheimer, 2017	Germany	59	Supratentorial	MDD, GAD	Professional
14	Pedreira, 2006	Australia	10	Supratentorial	MDD, GAD	Professional
15	Szentes, 2018	Hungary	34	Infratentorial	MDD, GAD	Professional
16	Weissenberger, 2002	United States	12	Supratentorial	MDD, GAD	Professional
17	Pierre-Kahn, 2005	France	14	Supratentorial	MDD	Professional
18	Hargrave, 2005	Canada	17	Supratentorial	GAD	Professional
19	Aarsen, 2004	Netherlands	23	Infratentorial	GAD	Professional
20	Hirsch, 1979	France	59	Infratentorial	GAD	Professional
21	Kristiansen, 2019	Sweden	7	Infratentorial	GAD	Professional
22	Sands, 2005	United States	29	Supratentorial	Anxiety/Depression	CBCL

23	Duval, 2002	Canada	37	Supratentorial	Anxiety/Depression	CBCL
24	Y. Park, 2017	Republic of Korea	27	Supratentorial	Anxiety/Depression	CBCL
25	Patel, 2011	United States	70	Supratentorial and Infratentorial	Anxiety/Depression	CBCL
26	C. Park, 2012	United States	21	Supratentorial	Anxiety/Depression	CBCL
27	Mabbott, 2005	Canada	53	Infratentorial	Anxiety/Depression	CBCL
28	Dolson, 2009	United States	27	Supratentorial	Anxiety/Depression	CBCL
29	Ris, 2008	United States	54	Supratentorial	Anxiety/Depression	CBCL
30	Robinson, 2014	United States	13	Infratentorial	Anxiety/Depression	CBCL
31	Youn, 2022	Republic of Korea	46	Supratentorial and infratentorial	Anxiety/Depression	CBCL
32	Taddei, 2019	Italy	41	Supratentorial	Anxiety/Depression	CBCL
33	Schreiber, 2017	United States	32	Infratentorial	Anxiety/Depression	CBCL
34	Clark, 2016	United States	31	Supratentorial	Anxiety/Depression	CBCL
35	Ryden, 2022	Sweden	28	Supratentorial and infratentorial	Anxiety/Depression	HADS
36	Lv, 2022	China	64	Supratentorial	Anxiety/Depression	CDI, SCARED
37	Moitra, 2009	United States	10	Infratentorial	Anxiety/Depression	CDI, SCARED
38	Moitra, 2013	United States	42	Supratentorial	Anxiety/Depression	CDI, SCARED
39	Laliberté, 2021	Canada	27	Infratentorial	Anxiety/Depression	CDI-2, SCARED
40	Brackett, 2012	United States	109	Infratentorial	Anxiety/Depression	BSI-18
41	Zebrack, 2004	United States	202	Infratentorial	Depression	BSI-18
42	Waber, 2006	United States	10	Supratentorial	Depression	BDI

8.1.2 Results of the analysis, outcomes

8.1.2.1 Prevalence of major depression disorder and generalized anxiety based on brain tumor location

In the pooled analysis of 17 studies, there was no significant difference in the prevalence of major depression between infratentorial (INF) and supratentorial (SUP) brain tumor survivors. Prevalence was 0.21 (95% CI: 0.10–0.41) in the INF group and 0.23 (95% CI: 0.12–0.38) in the SUP group. Overall, the pooled prevalence of major depression among childhood brain tumor survivors was 22%. (Figure 2).

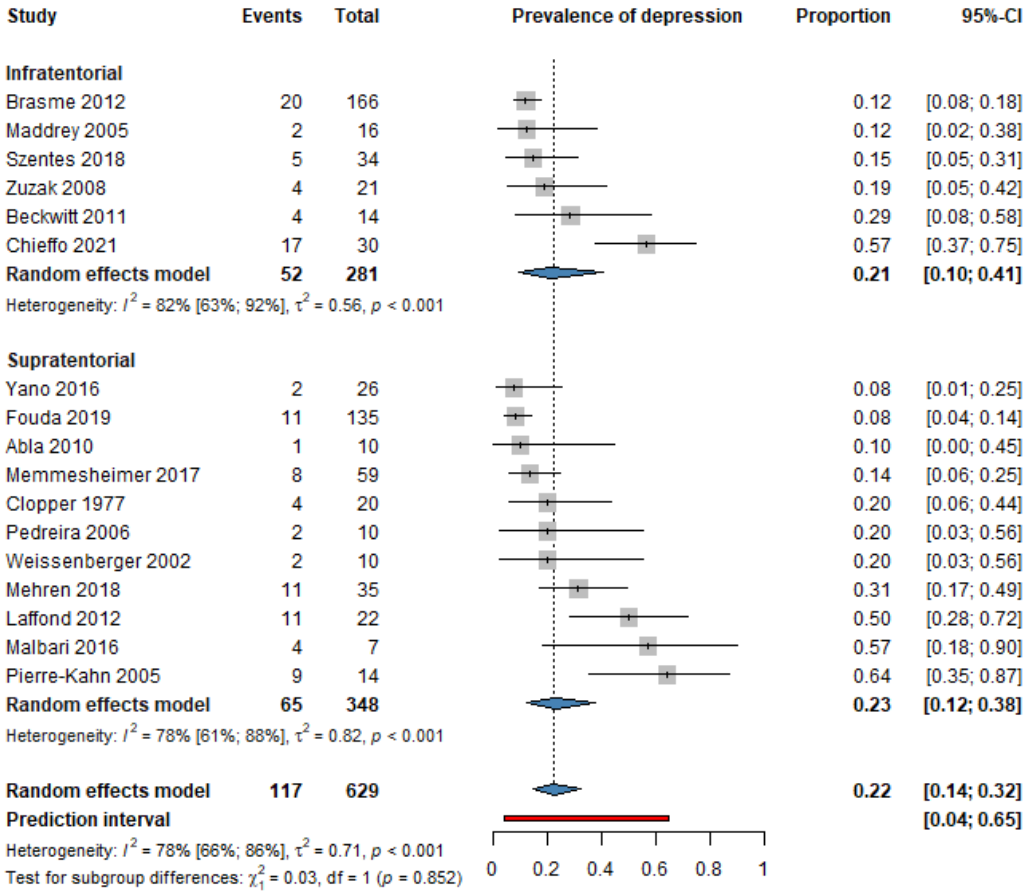


Figure 2 - Forest plot representing the prevalence of major depression among childhood brain tumor survivors, between supratentorial and infratentorial brain tumor patients. Events are the patients with major depressive disorder diagnosed by professional

psychiatrists based on DSM-IV or DSM-5 criteria. The pooled results represent prevalence with 95% confidence intervals (CIs).

Regarding anxiety, the pooled analysis of 11 studies showed no statistically significant difference in the prevalence of anxiety between infratentorial and supratentorial tumor survivors. The estimated proportions were 0.26 (95% CI: 0.05–0.69) for the INF group and 0.18 (95% CI: 0.06–0.41) for the SUP group. The overall prevalence of anxiety disorders among childhood brain tumor survivors was 22% (Figure 3).

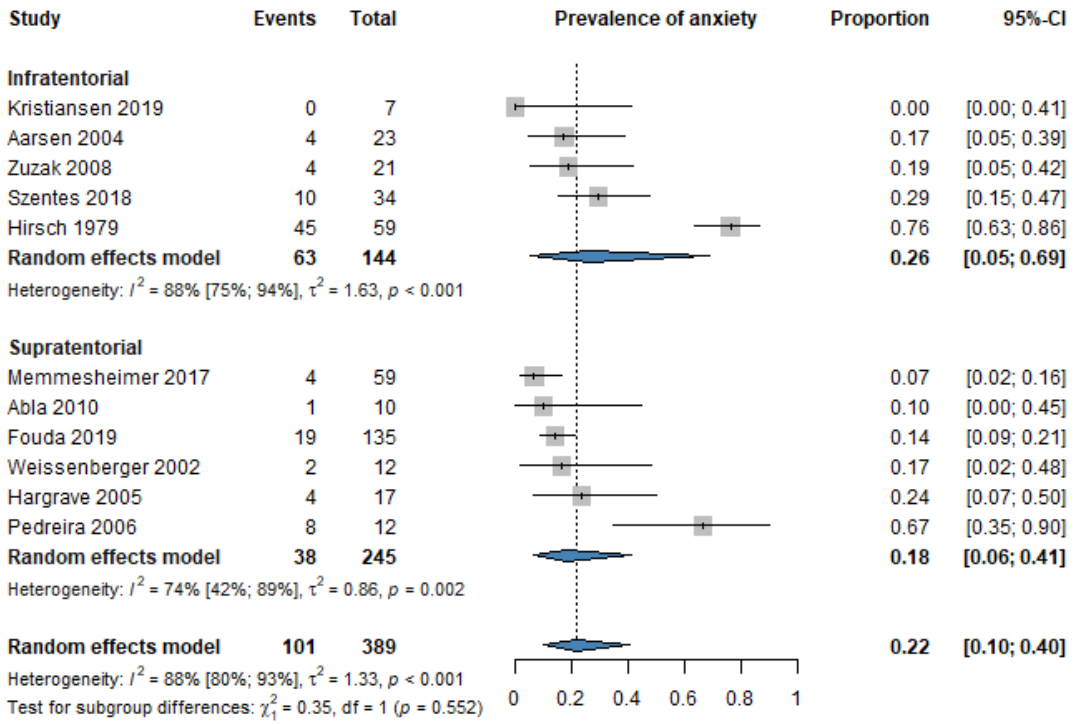


Figure 3 - Forest plot representing the prevalence of generalized anxiety disorder among childhood brain tumor survivor, between supratentorial and infratentorial brain tumor patients. Events are the patients with generalized anxiety disorder diagnosed by professional psychiatrists based on DSM-IV or DSM-5 criteria. The pooled results represent prevalence with 95% confidence intervals (CIs).

8.1.2.2. Impact of the brain tumor location on the scores of depression and anxiety assessment instruments

Nine studies reported quantitative data on depressive symptoms using various standardized instruments, including the Children's Depression Inventory (CDI), Children's Depression Inventory 2 (CDI-2), the Hospital Anxiety and Depression Scale (HADS), and the Brief Symptom Inventory-18 (BSI-18). To allow comparison across tools, main scores were converted and analyzed on a linear scale. Infratentorial tumor survivors tended to show higher levels of depressive symptoms than supratentorial survivors. The pooled raw mean scores (M_RAW) were 27.57 (95% CI: 14.35–40.78) for the INF group and 13.84 (95% CI: 11.43–16.26) for the SUP group, with a statistically significant difference between the groups ($p < 0.01$). (Figure 4)

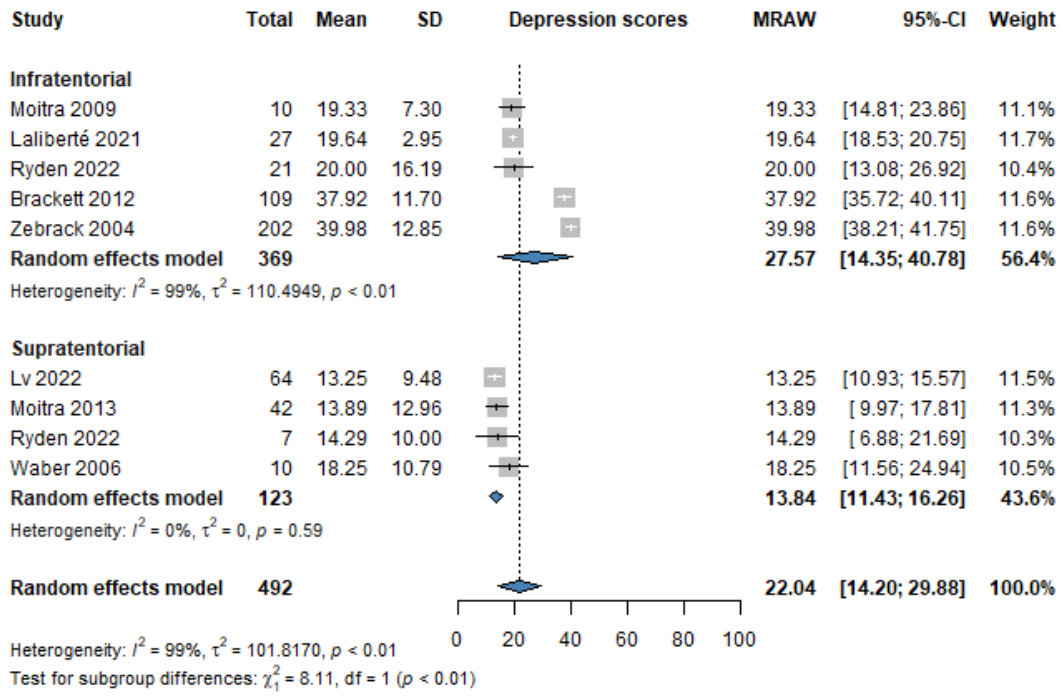


Figure 4 - Forest plot showing the mean scores on depression assessment tools (HADS, CDI, CDI-2, BSI-18), between patients with supratentorial and infratentorial brain tumor patients. Different measurement tools were put on a linear scale from 0-100. The pooled results represent MRAW scores with 95% confidence intervals (CIs).

Seven publications reported data from standardized anxiety assessment instruments, including the Screen for Child Anxiety Related Emotional Disorders (SCARED), the HADS, and the BSI-18. In analyses based on these tools, infratentorial survivors exhibited higher anxiety scores than supratentorial survivors. The pooled raw mean scores (M_RAW) were 36.24 (95% CI: 28.81–43.67) in the INF group and 23.21 (95% CI: 0.91–45.51) in the SUP group, indicating a significant difference between the two locations (p = 0.02). (Figure 5)

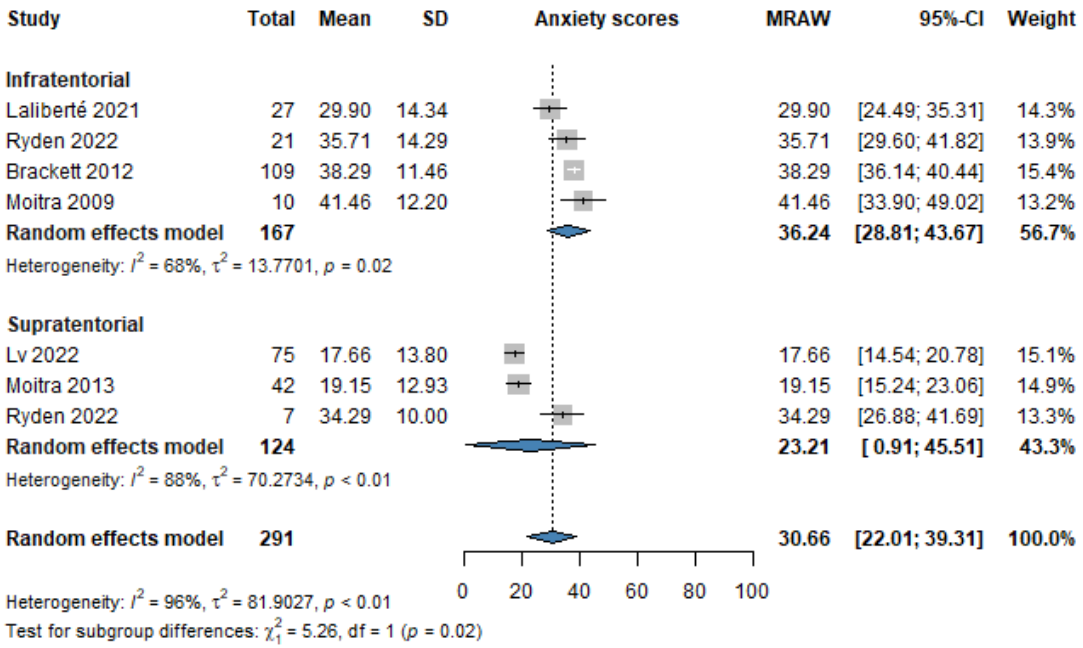


Figure 5 - Forest plot showing the mean scores on anxiety assessment tools (HADS, SCARED, BSI-18), between patients with supratentorial and infratentorial brain tumor patients. Different measurement tools were put on a linear scale from 0-100. The pooled results represent MRAW scores with 95% confidence intervals (CIs).

Fifteen studies reported outcomes on the Anxiety/Depression subscale of the Child Behavior Checklist (CBCL) among childhood brain tumor survivors, using T-scores for this domain. In contrast to the instrument-specific analyses above, no significant difference was observed between infratentorial and supratentorial survivors on this CBCL domain. The pooled T-scores were 55.37 (95% CI: 52.01–58.72) for the INF group and 55.67 (95% CI: 53.00–58.34) for the SUP group (Figure 6).

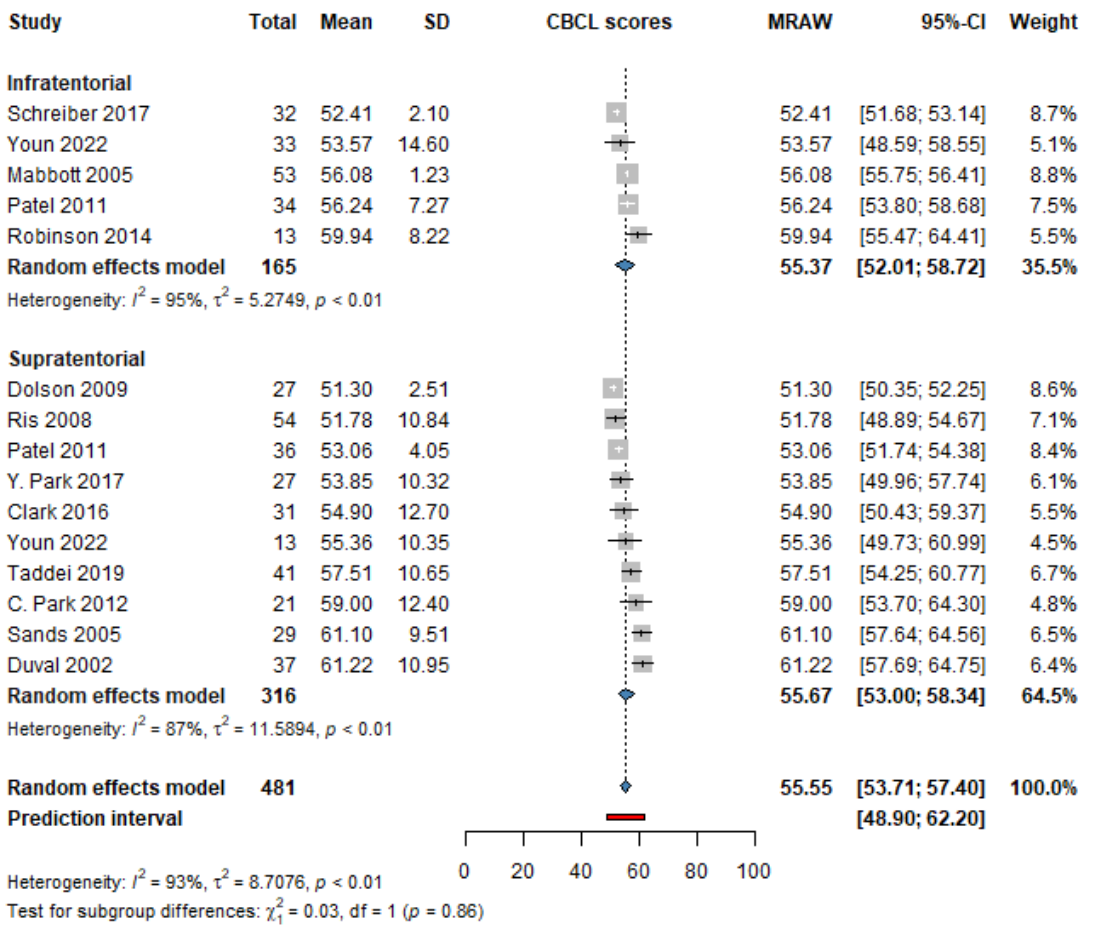


Figure 6 - Forest plot showing the T-scores supratentorial and infratentorial brain tumor patients achieved on the anxiety/depression domain of the CBCL questionnaire. The pooled results represent MRAW scores with 95% confidence intervals (CIs).

8.1.2.3. Impact of follow-up duration regarding depression and anxiety

Because follow-up time is a key factor that may influence the occurrence and severity of affective disorders, we initially planned to perform a meta-regression using follow-up duration as a predictor. However, the included studies showed marked heterogeneity in follow-up times, with assessments conducted at widely varying intervals after treatment. Methodologically, it would not have been appropriate to treat these heterogeneous time intervals as comparable time points in a meta-regression model.

To address this, we attempted to dichotomize follow-up time into two subgroups using a cut-off of 48 months (±12 months tolerance). We chose the cut-off value based on both clinical and methodological decision. After this dichotomization, the number of studies contributing usable data to each subgroup was too low to allow a meaningful subgroup analysis. Consequently, we were unable to draw valid conclusions regarding the impact of time since treatment completion on the prevalence or severity of depression and anxiety among childhood brain tumor survivors. (Figure 7)

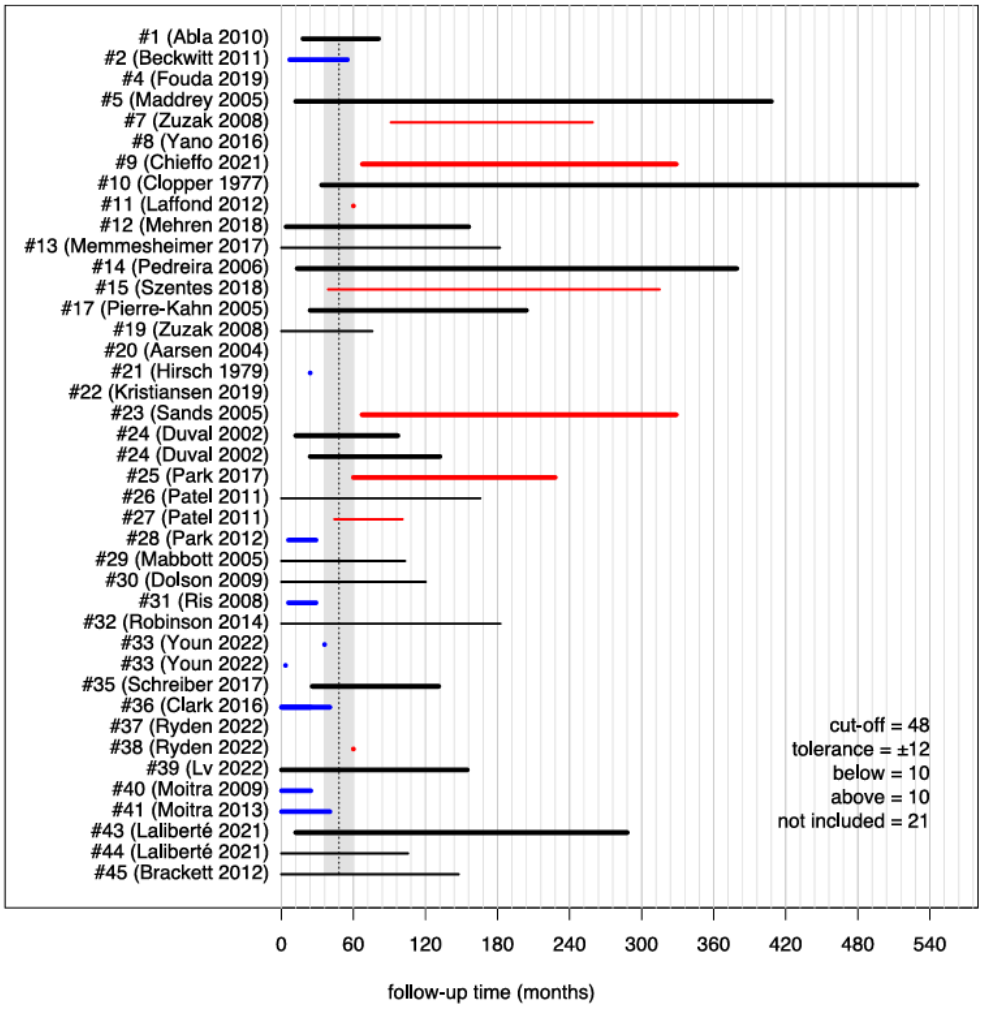
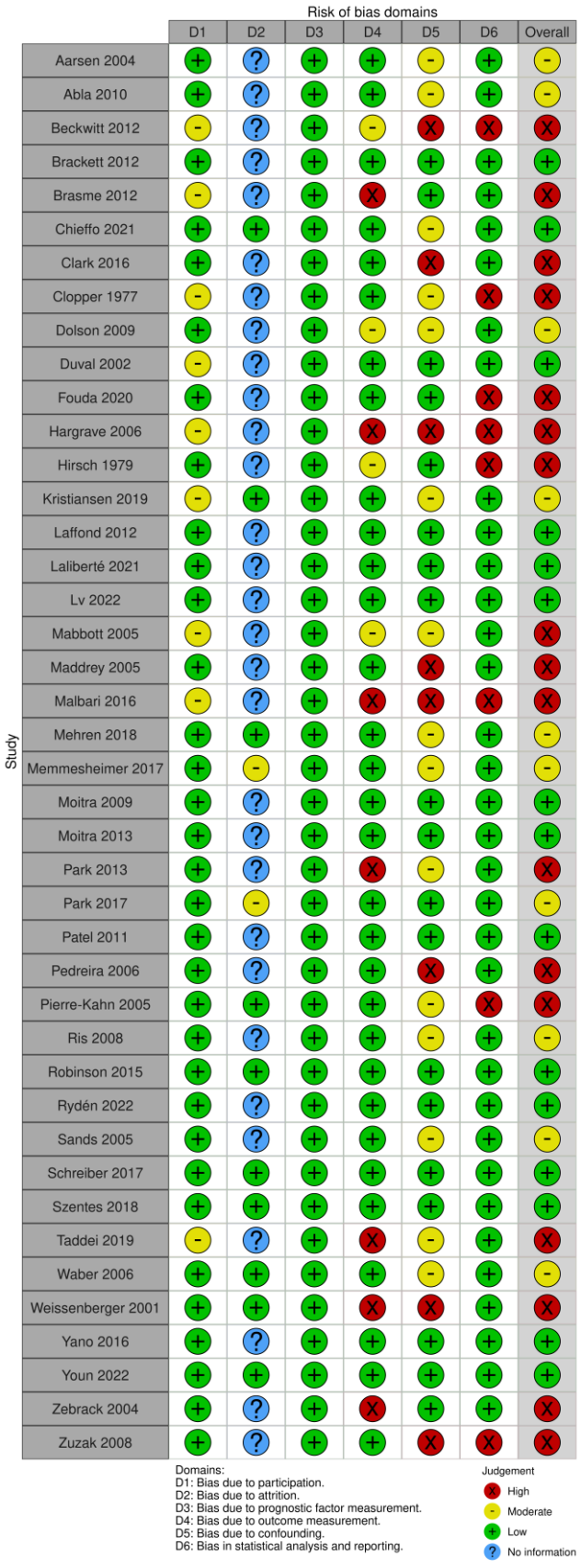


Figure 7 - Follow-up durations used in different studies. The time intervals are given in months. Follow-up under- 48+12 months: short-term follow-up (blue lines) Follow-up above months: long-term follow-up (red lines). Studies crossing the cut-off values were not included in the analyzis.

8.1.3. Risk of bias assessment

Overall, 36% of the included studies were judged to have a low risk of bias, 24% a moderate risk, and 40% a high risk of bias. The most frequent sources of substantial bias were insufficient reporting of potential confounding factors and incomplete or unclear descriptions of methodology and statistical analyses. Detailed ratings for each domain and study are presented in Figure 8.

Figure 8 – Risk of bias assessment based on QUIPS-2 tool.



8.1.4. Assessment of heterogeneity

Marked statistical heterogeneity was present in all pooled analyses. A major reason appeared to be the wide variation in follow-up durations across studies. To address this, we conducted subgroup analyses according to follow-up time; however, as discussed above, these analyses did not reveal significant differences between shorter- and longer-term follow-up groups. In addition, heterogeneity may partly reflect the subjective nature of clinical diagnoses of anxiety and depression, as well as differences in assessment procedures (DSM-IV and DSM-5) and diagnostic thresholds between studies.

8.2. Study II: The Hungarian Cross-cultural Adaptation of the MMQL-AF for Measuring Quality of Life in Adolescents with Cancer

8.2.1. Study population

Study II included adolescents and young people aged 13–20 years, recruited between November 2023 and January 2024 at the Pediatric Center, Tűzoltó street Department, Semmelweis University, Budapest. The study population consisted of three groups: adolescents receiving active oncological treatment (Group A), patients who had completed cancer treatment at least one year earlier and were in complete remission or stable disease (Group O), and healthy controls with no history of chronic illness (Group C). Each group comprised 46 participants, resulting in a total sample of 138 individuals. Patients represented a heterogeneous range of tumor diagnoses, with central nervous system tumors, bone- and soft-tissue tumors, malignancies associated with neurofibromatosis type 1, and thyroid cancer being the most frequent. Healthy controls were recruited from a secondary school after confirmation of the absence of chronic diseases. Study population characteristics is shown in Table 2.

Table 2 – Demographic characteristics and diagnoses of the study population.

	Patients on active treatment (Group A)	**Patients off treatment (Group O)**	**Healthy controls (Group C)**
Sex			
Female (%)	22 (47.83)	27 (58.70)	24 (52.17)
Male (%)	24 (52.17)	19 (41.30)	22 (47.83)
Age			
Mean (SD)	15.33 (1.85)	17.14 (2.20)	16.87 (1.03)
Diagnoses			
Central nervous system (CNS) tumors (%)	**14 (30.43)**	**19 (41.30)**	
Pilocytic astrocytoma	5 (10.87)	2 (4.35)	
Ganglioglioma	5 (10.87)	3 (6.52)	

Medulloblastoma	2 (4.35)	8 (17.39)	
Low-grade glioma	1 (2.17)	3 (6.52)	
High-grade glioma	1 (2.17)	-	
Craniopharyngioma	-	1 (2.17)	
Germinoma	-	2 (4.35)	
Bone- and soft-tissue tumors (%)	**11 (23.91)**	**3 (6.52)**	
Ewing's sarcoma	4 (8.7)	1 (2.17)	
Rhabdomyosarcoma	5 (10.87)	-	
Osteosarcoma	2 (4.35)	-	
Giant-cell tumor	-	1 (2.17)	
Teratoma	-	1 (2.17)	
Neurofibromatosis (%)	**13 (28.26)**	**6 (13.04)**	
Thyroid cancer (%)	**6 (13.04)**	**11 (23.91)**	
Non-Hodgkin lymphoma (%)	**2 (4.35)**	**-**	
Neuroblastoma (%)	**-**	**5 (15.22)**	

8.2.2. Reliability assessment

The reliability of the Hungarian version of the MMQL-AF was evaluated through analyses of internal consistency, questionnaire adequacy, and test–retest reliability. Internal consistency, assessed using Cronbach's alpha, was excellent for the total questionnaire score ($\alpha = 0.92$; 95% CI: 0.86–0.94). All seven domains demonstrated satisfactory to excellent reliability, with Cronbach's alpha coefficients ranging from 0.73 (95% CI: 0.65–0.91) to 0.90 (95% CI: 0.87–0.92), supporting the internal coherence of the scale. (Table 3).

Table 3 - Cronbach's alpha coefficient with 95% CI for the Hungarian version of the MMQL-AF.

	Cronbach's alpha coefficient	CI (95%)
Total score	0.92	0.86, 0.94
Physical functioning	0.76	0.71, 0.81
Psychological functioning	0.82	0.77, 0.86
Social functioning	0.80	0.75, 0.84
Cognitive functioning	0.90	0.87, 0.92
Body Image	0.73	0.65, 0.79
Outlook on life	0.87	0.82, 0.91
Intimate relations	0.75	0.65, 0.82

Questionnaire adequacy was examined using confirmatory factor analysis. The initial model showed suboptimal fit indices (RMSEA = 0.074; 90% CI: 0.070–0.080; CFI = 0.748; TLI = 0.731; SRMR = 0.086; GFI = 0.94). After removing items with high modification indices (C1d, C1e, D1d, E6, and G2), model fit improved (RMSEA = 0.062; 90% CI: 0.055–0.069; CFI = 0.828; TLI = 0.814; SRMR = 0.079; GFI = 0.962). Although CFI and TLI values remained below the commonly accepted thresholds, RMSEA, SRMR, and GFI indicated acceptable model fit. Given the complexity of the instrument and the cross-cultural adaptation process, the model was considered adequate for exploratory validation. Factor loadings were evaluated before and after item removal, with values above 0.70 interpreted as excellent, between 0.50 and 0.69 as acceptable, and below 0.49 as weak indicators of the underlying constructs. Table 4 shows the factor loadings after item removal.

Table 4 - Standardized factor loadings of the MMQL domains obtained from confirmatory factor analysis (CFA) after item removal. The table presents unstandardized (Estimate) and standardized (Std.all) factor loadings, standard errors (Std.Err), and significance values (p-values) for remaining items within each latent construct.
All reported loadings are statistically significant ($p < 0.05$) unless otherwise noted.

	Estimate	Std. Err	z-value	P(>IzI)	Std. lv.	Std. all
Physical functioning						
MMQL_B1	0.056	0.017	3.312	0.001	0.056	**0.299**
MMQL_B2	0.132	0.103	1.279	0.201	0.132	**0.125**
MMQL_C1a	0.762	0.087	8.805	0.000	0.762	**0.712**
MMQL_C1b	0.808	0.114	7.062	0.000	0.808	**0.591**
MMQL_C1c	0.951	0.101	9.398	0.000	0.951	**0.742**
MMQL_C1f	0.828	0.116	7.112	0.000	0.828	**0.595**
MMQL_D1c	0.674	0.084	8.021	0.000	0.674	**0.653**
MMQL_D1g	0.702	0.096	7.311	0.000	0.702	**0.608**
Social functioning						
MMQL_F3	0.633	0.067	9.499	0.000	0.633	**0.730**
MMQL_F4	0.531	0.085	6.242	0.000	0.531	**0.525**
MMQL_F5	0.818	0.069	11.826	0.000	0.818	**0.848**
MMQL_F6	0.961	0.096	9.990	0.000	0.961	**0.757**
MMQL_F7	0.792	0.092	8.640	0.000	0.792	**0.681**
MMQL_F8	0.357	0.072	4.986	0.000	0.357	**0.429**
Psychological functioning						
MMQL_D1a	0.546	0.064	8.528	0.000	0.546	**0.680**
MMQL_D1b	0.254	0.081	3.120	0.002	0.254	**0.282**
MMQL_D1e	0.417	0.060	6.946	0.000	0.417	**0.576**
MMQL_D1f	0.925	0.088	10.530	0.000	0.925	**0.792**
MMQL_D1h	0.424	0.102	4.173	0.000	0.424	**0.368**
MMQL_D1i	0.573	0.104	5.517	0.000	0.573	**0.477**
MMQL_D1j	0.989	0.097	10.183	0.000	0.989	**0.776**
MMQL_D1k	0.727	0.099	7.319	0.000	0.727	**0.604**
Cognitive functioning						
MMQL_G1	0.854	0.079	10.772	0.000	0.854	**0.788**
MMQL_G3	0.590	0.073	8.049	0.000	0.590	**0.636**
MMQL_G4	0.846	0.079	10.738	0.000	0.846	**0.786**
MMQL_G5	0.803	0.086	9.362	0.000	0.803	**0.726**
MMQL_G6	0.794	0.076	10.483	0.000	0.794	**0.785**
MMQL_G7	0.846	0.085	9.902	0.000	0.846	**0.755**
MMQL_G8	0.760	0.099	7.696	0.000	0.760	**0.626**

MMQL_G9	0.882	0.079	11.103	0.000	0.882	**0.816**
Intimate relations						
MMQL_F1	0.956	0.094	10.146	0.000	0.956	**0.797**
MMQL_F2	0.928	0.103	9.047	0.000	0.928	**0.723**
MMQL_H1	0.609	0.101	6.015	0.000	0.609	**0.521**
MMQL_H2	0.727	0.103	7.025	0.000	0.727	**0.593**
Body image						
MMQL_E1	0.863	0.103	8.344	0.000	0.863	**0.709**
MMQL_E2	0.733	0.092	7.958	0.000	0.733	**0.682**
MMQL_E3	0.399	0.098	4.092	0.000	0.399	**0.381**
MMQL_E4	0.898	0.104	8.635	0.000	0.898	**0.731**
MMQL_E5	0.321	0.102	3.150	0.002	0.321	**0.300**
Outlook on life						
MMQL_I1	0.953	0.074	12.868	0.000	0.953	**0.900**
MMQL_I2	0.810	0.075	10.808	0.000	0.810	**0.801**
MMQL_I3	0.910	0.081	11.244	0.000	0.910	**0.819**

Test–retest reliability was assessed using intraclass correlation coefficients (ICCs), with a high retest response rate of 90% (124 out of 138 participants). The results demonstrated excellent stability across most domains, with ICC values above 0.90. The body image domain showed a lower ICC of 0.78, indicating good to moderate reliability (Table 5).

Table 5 - Test-retest reliability of the Hungarian version of the MMQL-AF questionnaire. Table legend - Test retest reliability results for each domain of the questionnaire, assessed using Intraclass Correlation Coefficients (ICCs).

	First measurement	**Second measurement**		
MMQL domains	**Mean (SD)**	**Mean (SD)**	**ICC**	CI (95%)
Total score	3.66 (0.53)	3.74 (0.52)	**0.96**	0.94, 0.97
Physical functioning	3.14 (0.69)	3.22 (0.68)	**0.90**	0.86, 0.93
Psychological functioning	3.80 (0.68)	3.93 (0.63)	**0.90**	0.86, 0.93
Social functioning	3.86 (0.75)	3.93 (0.73)	**0.90**	0.86, 0.93
Cognitive functioning	3.72 (0.85)	3.80 (0.8)	**0.94**	0.91, 0.96
Body image	3.84 (0.74)	3.85 (0.73)	**0.78**	0.7, 0.84
Outlook on life	3.79 (0.95)	3.99 (0.86)	**0.90**	0.86, 0.93
Intimate relations	3.69 (0.92)	3.71 (0.88)	**0.92**	0.88, 0.94

8.2.3. Validity assessment

Assessment of content validity indicated that respondents found the items of the Hungarian version of the MMQL-AF clear, understandable, and age-appropriate. During pilot testing, adolescents completed the questionnaire in an average of 11 minutes. Comprehensibility was evaluated directly with adolescent participants, while a comprehensive content validity review was conducted by an onco-psychologist working in the neuro-oncological ward. Reliability analyses were repeated on the final version of the questionnaire after item removal, confirming the adequacy of the revised instrument.

Concurrent convergent validity was assessed by calculating Spearman's correlation coefficients between MMQL-AF subscale scores and corresponding domains of the PedsQL 4.0 SF-15 questionnaire. Strong correlations were observed between the corresponding domains of the two questionnaires, with Spearman's coefficients ranging from 0.76 to 0.85 ($p < 0.001$). Additionally, intimate relations strongly correlated with social functioning, while body image and outlook on life showed moderate associations with related PedsQL domains as shown in Table 6.

Table 6 - Spearman's correlation coefficients between the Hungarian version of the MMQL-AF and the PedsQL 4.0 SF questionnaires. $p<0.001$ in all results.

MMQL questionnaire	**PedsQL 4.0 SF questionnaire**				
	Total score	**Physical functioning**	**Emotional functioning**	**Social functioning**	**School functioning**
Total score	**0.84**	0.58	0.65	0.59	0.56
Physical functioning	0.71	**0.76**	0.4	0.35	0.31
Psychological functioning	0.65	0.43	**0.8**	0.46	0.26
Social functioning	0.61	0.32	0.44	**0.85**	0.32
Cognitive functioning	0.61	0.34	0.27	0.33	**0.85**
Body Image	0.37	0.21	0.39	0.19	0.25
Outlook on life	0.47	0.36	0.43	0.33	0.25
Intimate relations	0.48	0.26	0.39	0.51	0.29

Discriminant validity was examined by comparing MMQL-AF subscale scores between adolescents with cancer and healthy controls. Adolescents receiving ongoing treatment had significantly lower total MMQL-AF scores than healthy controls (mean 3.58, SD 0.46, 95% CI 3.44–3.72 vs. mean 3.81, SD 0.45, 95% CI 3.68–3.94; p = 0.012). Patients over treatment scored significantly lower on the physical functioning scale compared to healthy controls (mean 3.01, SD 0.79, 95% CI 2.78–3.24 vs. mean 3.32, SD 0.54, 95% CI 3.16–3.48; p = 0.025). Social functioning scores were also significantly lower in the patient group after treatment (mean 3.71, SD 0.81, 95% CI 3.47–3.95) compared to controls (mean 4.05, SD 0.53, 95% CI 3.89–4.21; p = 0.048). No significant group differences were observed in the remaining domains. Results can be seen in Table 7.
Results from the PedsQL 4.0 Short Form further supported these findings, as healthy controls scored significantly higher in the total score, as well as in the physical functioning and school functioning domains.

Table 7 - Discriminant validity of the Hungarian version of the MMQL-AF questionnaire (mean + SD). Table legend - Comparison of MMQL-AF subscale scores among adolescents with cancer - both actively treated (group A) and post-treatment (group O) - and healthy controls (group C) to assess discriminant validity.

	Group A	**Group O**	**Group C**	A vs. C (p)	O vs. C (p)	A vs. O (p)
Total score	3.58 (0.46)	3.59 (0.46)	3.81 (0.45)	**0.012**	0.083	0.7
Physical functioning	3.08 (0.71)	3.01 (0.79)	3.32 (0.54)	0.083	**0.025**	0.7
Psychological functioning	3.79 (0.64)	3.80 (0.76)	3.80 (0.64)	0.9	0.8	0.8
Social functioning	3.81 (0.83)	3.71 (0.81)	4.05 (0.53)	0.2	**0.048**	0.6
Cognitive functioning	3.64 (0.80)	3.57 (1.05)	3.95 (0.61)	0.053	0.2	0.9
Body image	3.69 (0.80)	3.86 (0.81)	3.98 (0.58)	0.15	0.6	0.4
Outlook on life	3.63 (0.97)	3.78 (0.96)	3.96 (0.91)	0.085	0.4	0.4
Intimate relations	3.47 (1.03)	3.72 (0.96)	3.87 (0.71)	0.073	0.6	0.2

8.2.4. Socioeconomic factors influencing HRQoL in pediatric cancer patients and survivors

Comparative analyses were conducted to examine the associations between HRQoL outcomes and socioeconomic as well as treatment-related characteristics of the study population. No significant differences in MMQL-AF scores were observed between age groups. Similarly, parental education level, analyzed separately for mothers and fathers, showed no significant association with reported quality of life across any domain. Family structure was associated with differences in specific quality-of-life domains. As shown in Table 8, patients whose parents lived together reported significantly higher scores in the outlook on life domain compared to those whose parents lived separately (mean 3.97, SD 0.86, 95% CI 3.79–4.15 vs. mean 3.39, SD 1.01, 95% CI 3.08–3.70; $p < 0.001$). Similarly, physical functioning scores were significantly higher among patients whose parents lived together (mean 3.22, SD 0.66, 95% CI 3.09–3.36) compared to those with separated parents (mean 2.97, SD 0.73, 95% CI 2.75–3.19; $p = 0.044$). Differences in MMQL-AF scores were also observed across diagnostic groups. Significant group effects were identified for the total mean score (3.45, SD 0.47 vs. 3.48, SD 0.57 vs. 3.48, SD 0.56 vs. 3.77, SD 0.47 vs. 4.08, SD 0.50; $p = 0.015$), outlook on life (2.95, SD 0.91 vs. 3.71, SD 0.91 vs. 3.82, SD 0.85 vs. 3.88, SD 1.03 vs. 4.19, SD 0.94; $p = 0.021$), and social functioning domains (3.69, SD 0.74 vs. 3.43, SD 0.94 vs. 3.86, SD 0.73 vs. 4.11, SD 0.51 vs. 4.24, SD 0.64; $p = 0.013$). Adolescents and young adults diagnosed with bone and soft tissue tumors or central nervous system tumors reported lower scores compared to those in other diagnostic categories. Detailed pairwise comparisons between diagnostic groups are presented in Table 9. Analysis of treatment status revealed no significant association between time since completion of treatment and health-related quality of life outcomes across any MMQL-AF domain.

Table 8 - Exploratory comparison of mean scores (SD) of MMQL-AF scores based on parental relationship status.

	Together (n=94)	Separate (n=44)	p-value
MMQL Questionnaire	**Mean (SD)**		
Total score	3.72 (0.52)	3.54 (0.55)	0.1
Physical functioning	3.22 (0.66)	2.97 (0.73)	**0.044**
Psychological functioning	3.85 (0.66)	3.68 (0.70)	0.2
Social functioning	3.92 (0.71)	3.73 (0.82)	0.3
Cognitive functioning	3.72 (0.81)	3.71 (0.93)	0.8
Body image	3.91 (0.72)	3.69 (0.77)	0.080
Outlook on life	3.97 (0.86)	3.39 (1.01)	**<0.001**
Intimate relations	3.72 (0.91)	3.61 (0.95)	0.5

Table 9 - Exploratory comparison of mean scores (SD) of MMQL-AF across different cancer diagnostic groups (Bone- and soft tissue tumors (BST), central nervous system tumors (CNS), neurofibromatosis 1 (NF1), thyroid cancer (TC), others) to assess the impact of disease type on QoL.

	BST (n=13)	CNS (n=34)	NF1 (n=19)	TC (n=17)	Other (n=9)	p-value
Total score	3.45 (0.47)	3.48 (0.57)	3.48 (0.56)	3.77 (0.47)	4.08 (0.50)	**0.015**
Physical functioning	3.04 (0.74)	2.94 (0.71)	2.9 (0.81)	3.14 (0.72)	3.58 (0.67)	0.200
Psychological functioning	3.59 (0.73)	3.8 (0.64)	3.63 (0.69)	3.88 (0.78)	4.28 (0.58)	0.150
Social functioning	3.69 (0.74)	3.43 (0.94)	3.86 (0.73)	4.11 (0.51)	4.24 (0.64)	**0.013**
Cognitive functioning	3.54 (0.75)	3.49 (0.96)	3.41 (1.02)	3.88 (0.76)	4.03 (1.02)	0.300
Body image	3.78 (0.81)	3.77 (0.72)	3.49 (0.899	3.8 (0.92)	4.39 (0.55)	0.300
Outlook on life	2.95 (0.91)	3.71 (0.91)	3.82 (0.85)	3.88 (1.03)	4.19 (0.94)	**0.021**
Intimate relations	3.39 (0.80)	3.35 (1.18)	3.63 (0.89)	3.96 (0.78)	4.11 (0.90)	0.120

9 DISCUSSION

9.1. Summary and interpretation of findings

This thesis investigated two interrelated dimensions of pediatric oncology survivorship: the impact of brain tumor localization on emotional outcomes in childhood brain tumor survivors, and the psychometric and cultural adaptation of the MMQL-AF instrument for assessing health-related quality of life (HRQoL) in adolescents and young adults with cancer in Hungary. The results collectively augment the understanding of psychological risk in survivorship and provide an academic basis for systematic psychosocial follow-up.

In Study I, the meta-analysis indicated that a very high proportion of children brain tumor survivors meet the diagnostic criteria for major depressive disorder or an anxiety disorder, with aggregated prevalences approaching 22% for each disease. The rates are considerably higher than among the general pediatric population [38-40], confirming emotional morbidity as a common and clinically relevant late consequence of pediatric brain tumors. No statistically significant differences were observed in the prevalence of diagnosed major depression or generalized anxiety disorder between survivors of infratentorial and supratentorial tumors, individuals with infratentorial tumors reported significantly higher levels of depressive and anxiety symptoms on standardized self-report measures. This result suggests that the location of infratentorial tumors is associated with an increased prevalence of subclinical or clinically significant emotional symptoms, even in the absence of exceeding diagnostic thresholds.

There are several possible reasons for these observations. Infratentorial tumors are frequently associated with motor coordination deficits, balance disturbances, and persistent neurological symptoms, all of which can inhibit daily activities and social interactions. These functional impairments may increase emotional distress and contribute to the development of depressive and anxiety symptoms over time [41]. Treatment-related characteristics may vary according to the location of the tumor. Radiotherapy for infratentorial cancers sometimes requires complex planning for preserving essential tissues, and in some cases may involve more localized dosages, increasing the risk of cognitive and psychological effects [42]. The difference between

elevated symptom scores and comparable diagnostic prevalence rates may indicate subthreshold affective illnesses, variations in help-seeking behavior, or inconsistencies in diagnostic methodologies between research. Self-report instruments might demonstrate heightened sensitivity to subjective distress compared to classification diagnoses, highlighting the clinical importance of symptom-level assessment [43].

The follow-up lengths differed significantly among the studies and were frequently inadequately recorded, limiting meaningful meta-regression or comprehensive time-based subgroup analysis. Affective symptoms and psychiatric illnesses may vary throughout the survival trajectory , the absence of defined follow-up intervals constrains inferences about the timing, persistence, or advancement of depressive and anxiety symptoms [44].

Study II demonstrated that the Hungarian adaptation of the MMQL-AF is a reliable and valuable instrument for assessing HRQoL in adolescents and young adults with cancer. The questionnaire exhibited remarkable internal consistency for the overall score and adequate reliability across domains, along with robust test-retest reliability, indicating temporal stability. The Hungarian adaptation of the PedsQL SF15 exhibited strong convergent validity, so confirming the construct validity of the instrument. Known-group validity was demonstrated, as adolescents with cancer had significantly inferior health-related quality of life (HRQoL) relative to their healthy peers, particularly in physical and social functioning.

Confirmatory factor analysis originally suggested inadequate model fit, which enhanced subsequent to the elimination of five components exhibiting persistently elevated modification indices. The removal of these questions was primarily motivated by conceptual inadequacies, which clarified the observed psychometric inconsistencies. The removed items displayed cross-loadings or residual correlations that suggested redundancy, ambiguity, or cultural variances in interpretation, which were not aligned with the proposed factor structure in the Hungarian context. Various international versions of the MMQL-AF used item or domain level modifications, highlighting the challenges inherent in cross-cultural validation of multidimensional HRQoL metrics [45-

47]. After item reduction, the model fit indices reached satisfactory levels for exploratory validation, supporting the seven-domain structure while improving interpretability.

The justification for the exclusion of each item is detailed below. C1d: “I cannot do many activities because of my health”. C1e: “I cannot do many activities because of my arms or legs”. The current study revealed that both items had consistently higher, so better scores relative to other items evaluating physical performance. We propose that their negatively stated wording may have created challenges for teenagers, potentially resulting in an underestimating or distortion of the intended concept. Moreover, recent advancements in Hungarian physical education, which prioritize inclusion for children with physical challenges, may affect adolescents' perceptions and reports of physical limitations.

D1d: “I feel lonely.” This item exhibited unexpectedly high modification indices, indicating poor fit within the emotional functioning domain, with patients scoring higher than on other emotional items. Loneliness is a complex and subjective construct that children and adolescents may find difficult to assess accurately. Furthermore, increased access to online communities and digital communication may mitigate feelings of social isolation, potentially altering how loneliness is perceived and reported in this age group.

E6: “I am uncomfortable with the way my body is developing.” This item, concerning body image within the framework of physical growth, exhibited response patterns that diverged from those of other body image items. The wording refers to a gradual and multifaceted developmental process. The combination of negative phrasing and conceptual complexity likely contributed to inconsistent measurement and reduced model fit.

G2: “Do you have difficulty concentrating at other times (e.g., playing cards, computer games, or reading)?” This question primarily addresses concentration during leisure activities, in contrast to other cognitive functioning issues. Within the relatively structured Hungarian school system, children often have limited free time during the school day and may perceive recreational activities as enjoyable or relaxing. As a result,

respondents may be less likely to report concentration difficulties in these contexts, making it harder to detect impairments and contributing to elevated modification indices and poor model fit.

In addition to validation, Study II offered insights into the clinical and psychosocial factors related to HRQoL, conducting an exploratory analysis. Adolescents diagnosed with central nervous system tumors and bone or soft-tissue malignancies demonstrated worse outcomes across various domains, particularly in life perspective and social functioning. These results can be attributed to the aggressive nature of the treatment protocols, which may include high-dose chemotherapy, cranial irradiation, and radical surgical interventions, frequently resulting in long-term physical disabilities and functional impairments. [48-51]. Moreover, family structure emerged as an important factor. Adolescents whose parent lived togethers, had better physical functioning and a more positive outlook on life. Cohabiting parents are more likely to provide a consistent source of emotional support, daily stability, and practical assistance, which can buffer the psychological burden of illness and enhance overall adjustment. This suggests that a stable family environment may have a positive emotional impact on cancer and its treatment, highlighting the need of integrating family context in follow-up assessment. [52-54]

9.2 Strengths

A major strength of this thesis is the approach that combines a rigorous evidence synthesis on affective outcomes after childhood brain tumors with the development of a practical measurement tool for HRQoL in Hungarian pediatric oncology.

Study I is, to our knowledge, the first comprehensive meta-analysis specifically examining the association between pediatric brain tumor location and anxiety and depression. It followed PRISMA and Cochrane recommendations and a prospectively registered protocol. The search was conducted in five major databases, and a standardized methods for risk-of-bias assessment (QUIPS-2) was applied.

Study II followed internationally accepted guidelines for cross-cultural adaptation (TARES), including forward–backward translation [30], expert review, and pilot testing. The psychometric evaluation used a broad set of indices - internal consistency, test–retest reliability, confirmatory factor analysis, concurrent convergent validity, and known-group comparisons with healthy controls. This comprehensive approach is comparable to, and in several respects aligned with the earlier international MMQL-AF validation studies.

Another important strength is the linkage between clinical and psychosocial risk factors and patient-reported outcomes across both studies. The meta-analysis highlights infratentorial tumor survivors as a group with elevated affective symptom burden, while the second study identifies diagnostic categories (CNS and bone and soft-tissue tumors) and family structure as correlates of poorer HRQoL. This convergence supports a risk-stratified, biopsychosocial model of survivorship care that is directly relevant for clinical practice in Hungary, where structured long-term follow-up and HRQoL assessment have not yet been systematically implemented.

9.3 Limitations

Despite these strengths, several limitations must be acknowledged. In Study I, most included studies were retrospective cohorts or cross-sectional designs, often with small sample sizes and incomplete reporting of confounders such as treatment modality, neurocognitive status or socio-economic factors. Approximately 40% of the studies were judged to have a high risk of bias, mainly due to insufficient information on confounding, methodology and statistical analyses.

Substantial statistical heterogeneity was present in the analyses, mainly due to widely varying follow-up times and diagnostic approaches. Planned meta-regression on follow-up duration could not be performed because follow-up was typically reported as broad intervals rather than precise time points, and even after dichotomisation of follow-up length, the number of studies per subgroup was insufficient for meaningful analysis.

Moreover, the use of published aggregate data, rather than individual patient data, limited the ability to adjust for confounders or to explore interactions between tumor location, treatment, and psychosocial factors.

In Study II, the main limitations relate to sample size, design and generalizability. The validation was conducted in a single center with 138 participants for 46 items, resulting in a participant-to-item ratio of approximately 3:1, which is below the commonly recommended 5–10:1 range for CFA.

Although model fit improved after removing five items, this modification may reduce cross-cultural comparability with other MMQL-AF versions and suggests that some aspects of the original factor structure may not fully generalize to the Hungarian context. The cross-sectional design prevents causal inference between clinical or family factors and HRQoL, and excluding patients with severe cognitive or developmental impairments may underestimate HRQoL deficits in the overall survivor population. In addition, all psychosocial data were self-reported, which introduces potential information bias related to response style, mood at the time of assessment or social desirability.

Across both studies, important domains such as neurocognitive functioning, school performance, and specific anxiety subtypes, for example social anxiety, panic disorder could not be evaluated in depth. Treatment-related variables, such as cumulative radiation dose and chemotherapy regimen, were not systematically analyzed, limiting the ability to fully clarify the mechanisms linking tumor characteristics with affective and HRQoL outcomes.

10 CONCLUSIONS

This thesis demonstrates that affective disorders are common and clinically relevant late effect among survivors of childhood brain tumors. The findings support the incorporation of systematic psychological screening and long-term mental health monitoring into the standard follow-up care for all pediatric brain tumor survivors, particularly those with infratentorial tumors. The Hungarian MMQL-AF tool offers a systematic, patient-focused approach for recognizing unmet requirements and tracking HRQoL outcomes over time. Collectively, these findings call for the establishment of a risk-stratified, multidisciplinary survivorship model which includes psychological evaluation and quality-of-life assessment.

11 IMPLICATIONS FOR PRACTICE

The results support the regular inclusion of rigorous psychological screening in follow-up regimens for all pediatric brain tumor survivors, rather than depending exclusively on clinical impressions. Survivors with infratentorial brain tumors should be classified as a high-risk group and prioritized for increased frequency of psychological evaluation and reduced criteria for referral to mental health services.

The validation of the Hungarian MMQL-AF offers a practical tool for the ongoing assessment of HRQoL in adolescents and young adults diagnosed with cancer. Integrating the MMQL-AF into routine follow-up visits, utilizing results to inform personalized care, and pinpointing areas such as academic performance, emotional health, or social connections that necessitate specific assistance will enhance the survivorship program. Both studies emphasize that survivorship care must extend beyond medical observation. Implementation in practice should encompass organized multidisciplinary teams of pediatric oncologists, neurologists, psychologists/psychiatrists, neuropsychologists, social workers, and educational specialists.

The HRQoL study demonstrated that family structure (e.g., cohabiting parents) correlates with improved outcomes in certain domains. For practice, this implies the regular evaluation of familial situations, provision of family-centered interventions and parental assistance, especially for families experiencing separation or significant stress, and the inclusion of caregivers in psychoeducation about emotional and health-related quality of life late effects.

12 IMPLICATIONS FOR RESEARCH

Future work should prioritize prospective, multicentre cohort studies with clearly defined and standardized follow-up time points regarding psychosocial outcomes of childhood cancer patients. We recommend that psychological follow-up be done at key points in the treatment, at every regular check-up after treatment, and once a year as long-term follow-up. We suggest using standardized, validated, and harmonized tools for anxiety, depression, and HRQoL. These would provide more accurate estimations of the incidence and trajectories of emotional disorders, neurocognitive consequences, and psychosocial outcomes.

The meta-analysis was limited to aggregate published data. Future research should focus on developing international collaborations to do individual patient data meta-analyses, facilitating the adjustment for significant confounders such as age at diagnosis, treatment intensity, socioeconomic status, and comorbidities.

Subsequent research ought to employ the MMQL-AF instrument longitudinally to monitor HRQoL trajectories from diagnosis through treatment, and the transition to adult care. Regular HRQoL evaluations would facilitate the identification of crucial intervals of increased risk, such as the conclusion of treatment, reintegration into educational settings, the transition to adulthood, and the assessment of whether initial impairments forecast subsequent educational, occupational, and social results.

13 IMPLICATIONS FOR POLICY MAKERS

This thesis shows that approximately one in five childhood brain tumor survivors meet criteria for major depression or generalized anxiety disorder, with infratentorial survivors showing particularly elevated symptom levels. This justifies treating childhood brain tumor survivors as a clearly defined high-risk population for affective disorders.

Both studies highlight the need for organized, lifelong follow-up beyond the end of oncological treatment. Policy makers should support development and funding of standardized survivorship pathways that extend into adolescence and young adulthood.

The finding that family environment is associated with HRQoL underscores the importance of social context. Policy measures could include incorporating family assessment and family-focused support into survivorship service packages, facilitating access to parenting programmes, family counseling and social benefits for families affected by childhood cancer.

14 FUTURE PERSPECTIVES

In the upcoming years, I would like to continue investigating the neuropsychiatric well-being of childhood cancer patients and survivors. In particular, I aim to conduct prospective and longitudinal studies that integrate clinical and psychosocial variables in order to better understand individual vulnerability to affective disorders and impaired quality of life across different phases of survivorship. By identifying specific risk factors, I hope to contribute to the development of targeted preventive and therapeutic interventions.

I would also like to further adapt and validate the MMQL questionnaires for additional pediatric age groups, including younger children and adults. I plan to implement these instruments more systematically in routine clinical care, enabling early identification of difficulties, individualized follow-up planning, and evaluation of supportive interventions.

Beyond that, I would like to extend my research focus to the assessment of neurocognitive functioning in children with cancer. Cognitive impairments related to both the disease and its treatment can seriously affect academic achievement, social integration, yet they are often under-recognized in routine survivorship care. By integrating standardized neurocognitive assessments alongside psychological and HRQoL measures, I aim to contribute to a more comprehensive understanding of survivorship outcomes and to support early neuropsychological and educational interventions.

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Szabados, Márton; Farkas, Nelli; Fleisz, Andrea; Takács, Kata; Juhász, Orsolya; Hernádfői, Márk; Teutsch, Brigitta; Csóka, Monika; Hegyi, Péter; Garami, Miklós The hungarian cross-cultural adaptation of the MMQL-AF for measuring quality of life in adolescents with cancer. SCIENTIFIC REPORTS 15 Paper: 45119, 11 p. (2025) Publication: 36594503 | Journal Article (Article) | Scientific Scopus - Multidisciplinary Rank: Q1 IF: 3,9

16.2 Publications not related to the thesis

Erdős Sándor, Papik Flóra, Dorottya Nyáry, Schlosser Károly, Topa Kristóf, András Mátyás, Jakus Gábor, Juhász Orsolya, Koch Dóra, Korponay Zsuzsanna, Hauser Balázs, Papp Szilveszter, Petró Anna, Pásztor Borbála, Szabados Márton, Varga Edit, Szabó Attila, Horváth Klára Comparing virtual reality-based simulation, booklet-based and standard preparation methods for pediatric magnetic resonance imaging (MR-VR): study protocol for a randomized clinical trial VIRTUAL REALITY 29: 3 Paper: 95, 13 p. (2025) Publication: 36195428 | Validated Core | Journal Article (Article) | Scientific Scopus - Computer Graphics and Computer-Aided Design Rank: Q1 Scopus - Human-Computer Interaction Rank: Q1 Scopus - Software Rank: Q1 IF: 5,0

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