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Quality of life of adolescent and adult survivors of childhood cancer in Europe—A systematic review

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Abstract

Advances in diagnostics and treatment of childhood cancer during the past few decades have substantially increased survival, resulting in a growing population of survivors of childhood cancer. Somatic and mental late effects of the cancer and the treatment may impact the quality of life (QoL). Previous reviews of QoL in survivors of childhood cancer have shown contradictory findings across studies and the majority of studies included have been based on data from North America and may not be directly comparable to a European setting. The aim of our study was to critically evaluate and summarise the latest evidence on the QoL of childhood cancer survivors in Europe and to identify survivors at particular risk. The eligible studies were published between 2008 and 2022, conducted in Europe and included participants who had survived at least 5 years after diagnosis of a childhood cancer. The main outcome of interest was QoL of survivors which was measured with validated qualitative and quantitative QoL questionnaires. A systematic literature search conducted in PubMed, EMBASE, PsycINFO and CINALH resulted in inclusion of 36 articles with a total of 14 342 survivors of childhood cancer. The majority of included studies found that childhood cancer survivors reported poorer QoL than comparisons. Female gender, treatment with haematopoietic stem cell transplantation and a brain tumour diagnosis were associated with lower QoL. With a growing population of childhood cancer survivors with many years ahead of them, targeted interventions and optimal follow-up care are important to improve the QoL of survivors.

KEYWORDS
childhood cancer survivors, quality of life, systematic review

What's new?

While decades of diagnostic and treatment advances have resulted in a steadily growing population of childhood cancer survivors, somatic and mental late effects of both the cancer and the treatment may impact survivors' long-term quality of life. This systematic review found that childhood cancer survivors report worse quality of life than comparison groups, although the score

Abbreviations: AXIS, appraisal tool for cross-sectional studies; CNS, central nervous system; HSCT, haematopoietic stem cell transplantation; MCS, mental component summary; PCS, physical component summary; QoL, quality of life; SF-36, 36-item Short Form Survey.

differences were small to moderate. Survivors of brain tumours, female survivors and survivors treated with haematopoietic stem cell transplantation were at particular risk. Targeted interventions and optimal follow-up care are important to improve the quality of life of childhood cancer survivors.

1 | INTRODUCTION

In Europe, approximately 15 000 children aged 0 to 14 years and 20 000 adolescents and young adults aged 15 to 24 years are diagnosed with cancer each year.[1] As a result of more effective treatment, the 5-year survival after childhood cancer has increased markedly over the past few decades and exceeds 80% in most European countries.[2,3] This substantial improvement in survival has resulted in a steadily growing population of childhood cancer survivors, who are, however, at increased risk of a wide range of somatic and psychiatric disorders, adverse mental late effects such as fatigue, neurocognitive sequelae (eg, impairments in memory), anxiety, depression, sleep disturbances and long-term socioeconomic consequences, such as lower educational attainment and unemployment.[4-12] These late effects may have a negative impact on the quality of life (QoL) of survivors.[13] For the sake of simplicity, the population of survivors who were diagnosed with cancer before the age of 21 will henceforth be referred to as childhood cancer survivors.

Previous reviews of studies of QoL in survivors of childhood cancer have shown that overall survivors are similar to comparisons with regard to physical, psychological and social domains of QoL but that subgroups of survivors have impaired QoL. Older age at diagnosis, longer time since diagnosis, female gender, being a survivor of a central nervous system (CNS) tumour or bone cancer, treatment with radiation therapy and certain socioeconomic factors such as lower educational attainment have been found to reduce QoL.[14-17] Lack of comparability among studies in these reviews obviates firm conclusions as populations were highly diverse. The study populations consisted, for example, of both children and adults, survivors and patients with current cancer and used both proxy and self-reported outcomes. Further, most of the studies in the previous reviews were of North American samples, and the results may not be generalizable to a European setting because of cultural differences and variations in healthcare systems. Therefore, we have focused on increasing comparability among studies by harmonising the population, which therefore only includes adolescent and adult survivors of childhood cancer in Europe.

The aim of this review is to critically appraise and summarise evidence from studies on the QoL of survivors of childhood cancer in Europe published since the latest relevant review.[17] A further aim is to identify factors related to poor QoL and survivors who are at particular risk.

2 | MATERIALS AND METHODS

The PRISMA guidelines were used for this systematic review.[18] The research strategy and eligibility criteria were determined, and then relevant articles were identified and selected through a systematic literature search of four databases, PubMed, EMBASE, PsycINFO and CINALH, on 27 January 2020. The search in PubMed was updated on 15 December 2022. Potentially eligible articles were identified by combining five components in the search: cancer, survivorship, childhood, QoL and questionnaire. The PubMed search strategy is presented in Table S1. To find further studies, the reference lists of included articles were examined, and the latest citations were checked in the Scopus database.

2.1 | Study selection and eligibility criteria

As relevant studies published up to February 2008 were included in a previous systematic review,[17] articles published between March 2008 and December 2022 were eligible for inclusion. Inclusion was limited to articles in English based on European data. The outcomes of interest were the QoL of survivors and factors correlated with lower and higher scores of QoL. Studies were included if a validated quantitative or qualitative QoL instrument was applied. Studies were included regardless of the chosen comparison group which could be internal, healthy controls or standard populations. Studies of survivors of all childhood cancers diagnosed before the age of 21 years were eligible. This criterion was changed from 20 years during study selection to ensure inclusion of additional relevant articles. Studies of QoL in survivors under 15 years of age have often had proxy respondents rather than self-reports of QoL by survivors, which may emphasise physical rather than psychological problems. Therefore, we set the minimum age for evaluation of QoL at 15 years. As the QoL of newly diagnosed individuals still undergoing treatment may differ from that of individuals who have been cured, we included only studies of children who had survived for at least 5 years after the initial diagnosis to exclude acute effects of diagnosis and treatment. Intervention studies, reviews and studies conducted to validate or describe QoL questionnaires were excluded.

The screening and selection process was performed using the software Covidence. Two independent researchers (PAL, CP) assessed each article from its title and abstract and then extracted and screened full-text articles according to the eligibility criteria. Discrepancies between the two researchers were discussed and resolved by agreement. The data extracted (PAL, CP) from the articles included the first author's name, year of publication, country, study design, cancer type, sample size, age at diagnosis and evaluation, follow-up since diagnosis, period of diagnosis, comparison group(s), questionnaires used, factors related to QoL and main QoL outcomes. All data extracted from articles is presented in Table 1. Excel was used to organise and compare studies. As included studies used different QoL

TABLE 1 Characteristics of included articles.

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
Survivors of various cancers														
19	Tremolada, 2016	Italy	All cancers (CNS tumours)	205	<18	15-25	N/A	Healthy students	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Cancer survivors reported significantly better scores on the subscales RP (86.78 vs 80.89; $P = .02$), RE (75.47 vs 58.43; $P = .0001$), MH (71.59 vs 65.77; $P = .001$), SF (76.27 vs 71.45; $P = .004$), VT (63.35 vs 55.44; $P = .0001$) and BP (87.90 vs 79.53; $P = .0001$) than the comparison group.	Treated with HSCT, haematologic cancer, older age at evaluation and female gender	14
20	Tremolada, 2015	Italy	All cancers (CNS tumours)	213	<18	15-25	N/A	Population norms	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Childhood cancer survivors scored particularly low on the domains GH ($M = 75.14$, SD 19.83), VT ($M = 62.57$, SD 16.52) and MH ($M = 70.72$, SD 17.32). A high percentage of survivors scored below the 25th percentile, considerably below the Italian norm.	Higher patient satisfaction	7
21	van Erp, 2022	Netherlands	Hematologic cancers, CNS tumours and solid tumours	151	<18	18-30	N/A	General population	5 years postdiagnosis	PedsQL Self-reported	Institution-based	Compared to the general population, survivors scored lower on the physical (80.2 vs 87.1; $P < .001$), social (82.1 vs 87.2; $P = .001$) and school/work (76.8 vs 82.3; $P < .001$) scales.	Need for support	18
22	van Erp, 2021	Netherlands	All cancers	2301	<18	>18	1963-2001	Population norms	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Male and female CCS scored significantly worse than the male and female general population on PCS, MCS, PF, SF, VT and GH.	Gender, relationship status, education, older age at diagnosis time since treatment, relapse status, type of cancer and type of treatment.	16
23	van Erp, 2021	Netherlands	Hematologic cancers, CNS tumours and solid tumours	151	<18	18-30	N/A	Population norms	5 years postdiagnosis	PedsQL Self-reported	Institution-based	Survivors scored significantly lower than the reference group on total PedsQL-YA (77.7 vs 83.9; $P = .008$).	Socialising, body and health, sibling concerns, life challenges and relationship concerns.	18

(Continues)

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
24	van Gorp, 2021	Netherlands	All cancers	1766	<18	>18	1963-2001	General population	10 years postdiagnosis	TAAQOL Self-reported.	Institution-based	The odds of impairment for both sexes were higher in CCSs in cognitive functioning, gross and fine motor functioning, vitality, pain and sleep compared to the reference group. In addition, Female CCSs had higher odds of impairment in daily activities and sexuality than female references, but had less often increased aggressive emotions than female references.	Older age at evaluation, CNS tumours, retinoblastoma and bone tumours and radiotherapy.	20
25	Penson, 2022	Netherlands	All cancers	1695	<18	>18	1963-2001	1. Internal comparison by CF 2. General population	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Survivors with CF scored significantly lower on all HRQoL domains ($P < .001$) compared to survivors without CF. Largest differences were seen on the domains RP, RE and VT. Additionally, survivors with CF reported worse HRQoL than the general population on all domains ($P < .001$).	—	16
26	Bagur, 2015	France	All cancers (leukaemia)	130	<15	>18	1987-1992	Internal comparison by psychiatric disorder	5 years postdiagnosis	SF-36 Self-reported	Population-based	Survivors' mean score of global QoL was 76.4 ± 14.5. Lower scores correlated significantly with the presence of suicidal risk (62.3 vs 78.4; $P < .001$), anxiety (69.0 vs 81.6; $P < .001$), mood disorder (65.3 vs 81.6; $P < .001$) and psychotic disorder (64.8 vs 77.4, $P = .01$).	Anxiety, mood disorder, suicidal risk and psychotic disorder	18
27	Gianinazzi, 2014	Switzerland	Leukaemia, lymphoma, CNS tumours, malignant solid tumours, Langerhans cell histiocytosis	319	<16	>18	1990-2009	Internal comparison by information needs	5 years postdiagnosis	SF-12 Self-reported	Population-based	Survivors wanting more information on illness ($M_{diff} = -3.40$; $P = .02$), treatment ($M_{diff} = -3.16$; $P = .03$) and late effects ($M_{diff} = -4.94$; $P = .006$) scored significantly lower MCS.	Information needs	19

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
28	Halvorsen, 2018	Norway	All cancers	91	<21	18-29	1991-2007	University students	5 years postdiagnosis	PedsQL™ 4.0 Self-reported	Population-based	No significant difference in total PedsQL was found between survivors and university students (77.41 vs 80.32; $P = .144$). However, survivors scored significantly lower on physical health (78.28 vs 83.74; $P = .035$). Female survivors scored significantly lower on physical functioning/health (73.91 vs 78.95; $P = .024$) than female controls. Survivors scoring above the cut-off for distress had significantly lower total PedsQL (61.81 vs 68.38; $P = .03$) and physical functioning (61.68 vs 71.42; $P = .017$) than controls scoring above the cut-off.	Older age at evaluation, female gender, lower educational achievement and poor economic status	14
29	Maurice-Stam, 2009	Netherlands	Leukaemia, lymphoma, solid tumour and brain tumour	353	<18	18-30	N/A	Internal comparison by medical and survivor characteristics	5 years postdiagnosis	RAND-36 Self-reported	Institution-based	Survivors with psychosocial, cognitive and neurological late effects (MCS: −0.11; $P < .05$ and PCS: −0.15; $P < .05$) and current health complaints (MCS: −0.12; $P < .05$ and PCS: −0.28; $P < .05$) reported worse health-related QoL. 'Interpretative control' affected PSC negatively (−0.13; $P < .05$), while 'predictive control' affected MCS (0.25; $P < .05$) and PCS (0.18; $P < .05$) positively. 'Passive coping' was associated negatively with MCS (−0.29; $P < .05$) and PCS (−0.17; $P < .05$), as was 'sharing emotions' with MCS (−0.17; $P < .05$). In contrast, 'active coping' had a positive effect on MCS (0.21; $P < .05$).	Older age at diagnosis, treated with chemotherapy, brain tumour, longer time since treatment, relapse, psychosocial, cognitive and neurological late effects and coping styles	18

(Continues)

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
30	Michel, 2009	UK	All cancers	112	<16	18-45	N/A	Population norms	5 years postdiagnosis	SF-12 Self-reported	Institution-based	Compared to US norms, survivors reported comparable PCS ($P = .827$) and MCS ($P = .664$). Survivors who reported lower MCS rated supportive care as more important ($r = -0.27$; $P = .005$) and survivors who reported lower PCS rated clinical care as more important ($r = -.20$; $P = .042$).	Supportive and clinical care and female gender	16
31	Rueegg, 2013	Switzerland	Leukaemia, lymphoma, CNS tumours, malignant solid tumours and Langerhans cell histiocytosis	1.593	<16	>16	1976-2005	Siblings	5 years postdiagnosis	SF-36 Self-reported	Population-based	Compared to siblings, survivors reported significantly lower PF (49.0 vs 52.9; $P < .001$), RP (49.5 vs 50.4; $P = .003$), GH (53.5 vs 56.6; $P < .001$) and PCS (52.0 vs 54.6; $P < .001$). Survivors scored higher than siblings on MCS (52.2 vs 50.0; $P = .017$).	Treated with surgery, CNS irradiation and HSCT, retinoblastoma, CNS tumour, bone tumour and soft tissue tumour, physical late effects, older age at evaluation and female gender	20
32	Seitz, 2011	Germany	All cancers	820	15-18	>18	N/A	General population	5 years postdiagnosis	Questions on Life Satisfaction FLZ^M Self-reported	Population-based	Compared to the general population, survivors were significantly less satisfied with their general life (53.6 vs 66.7; $P < .001$) and health-related life (69.9 vs 87.9; $P < .001$). Dimensions affected were 'friends/acquaintances', 'health', 'housing/living conditions', 'partner relationship/sexuality', 'physical condition/fitness', 'ability to relax/stay on a keel', 'energy/zest for life', 'vision and hearing', 'freedom from anxiety' and 'freedom from aches and pain' ($P \leq .001$).	Solid tumour, longer time since treatment, depression, anxiety, posttraumatic growth, somatic late effects, unemployment, relationship status and higher educational achievement	17

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
33	Sundberg, 2010	Sweden	All cancers	246	<18	>18	1985-1999	General population	5 years postdiagnosis	SEIQoL-DW and SF-36 Self-reported	Institution-based	Compared to the general population, survivors scored significantly lower on the subscale RP (81.6 vs 87.5; $P < .01$). Most frequently reported influences on QoL were 'family life', 'relation to other people', 'work, career' and 'interests, leisure activities' - same areas as reported by the comparison group.	–	17
34	Thouvenin-Doulet, 2018	France	All cancers (leukaemia)	972	<18	>18	1948-1992	General population	5 years postdiagnosis	SF-36 Self-reported	Institution- and population-based	Compared to the general population, significantly lower scores were found on each of the eight dimensions of the SF-36 ($P < .001$).	Psychological disorders, locomotor late effects, growth insufficiency, older age at evaluation and higher standardised fecundity ratio	19
35	van Dijk, 2008	The Netherlands	All cancers	60	<16	16-40	N/A	Population norms	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Compared to Dutch norms, survivors experienced lower QoL on the subscales GH (52.7 vs 78.2; $P < .001$), PF (87.3 vs 93.1; $P < .01$), SF (48.1 vs 87.8; $P < .001$), BP (47.5 vs 80.9; $P < .001$), VT (52.2 vs 70.7; $P < .001$) and MH (62.3 vs 78.7; $P < .001$).	–	16
36	Tremolada, 2022	Italy	All cancers (CNS tumours)	205	<18	15-25	N/A	Healthy peers	5 years postdiagnosis	Ladder of Life Self-reported	Institution-based	Compared to healthy peers no differences were found regarding perception of current and future QoL. CCSs reported worse QoL in the 5 years before current time than healthy peers ($P < .001$).	Age at diagnosis, years off treatment and HSCT.	15
Survivors of haematological cancers														
37	Benadiba, 2015	France	ALL	316	<18	>18	1980-2009	1. Population norms 2. Internal comparison by treatment modality	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Compared to French population norms, survivors scored significantly lower on MCS (45.2 vs 47.9; $P < .001$), SF (80.5 vs 84.6; $P = .003$), RE (72.9 vs 87.5; $P < .001$) and PF (93.2 vs 95.1; $P = .046$).	Treated with chemotherapy	17

(Continues)

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
38	Berbis, 2013	France	ALL and AML	492	<18	>18	1980-2009	1. Population norms 2. Internal comparison by treatment modality	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Compared to French population norms, survivors scored significantly lower on PF, SF, RP, RE, GH and MCS ($P < .05$).	Treated with HSCT	16
39	Visentin, 2016	France	Acute leukaemia treated with HSCT	99	<18	>18	1997-2012 (treated)	1. Internal comparison by HSCT donor type 2. Population norms	5 years postdiagnosis	SF-36 Self-reported	Institution-based	Compared to French population norms, survivors scored significantly lower on PF ($P < .001$), SF ($P < .001$), RP ($P < .001$), RE ($P < .001$), VT ($P < .01$), BP ($P < .05$), GH ($P < .001$), PCS ($P < .001$) and MCS ($P < .01$). Survivors treated with HSCT from a sibling donor (PCS = 52.1, MSC = 47.3), an unrelated volunteer donor (PCS 50.4, MCS 47.3) or an unrelated umbilical cord donor (PCS = 50.3, MCS = 43.3) reported similar QoL (PCS $P = .72$, MCS $P = .28$).	—	14
40	Chantziara, 2022	France and Belgium	ALL	186	<18	>18	1971-1998	General population	12 years postdiagnosis	SF-12 Self-reported	Institution-based	ALL survivors scored higher than population controls on VT (81.27 vs 77.34; $P = .002$), SF (79.52 vs 70.49; $P = .0002$), RE (78.28 vs 68.84; $P = .003$) and MCS (47.31 vs 43.41; $P = .0001$).	—	17
41	Sleurs, 2021	France and Belgium	ALL	186	<18	>18	1971-1998	Internal comparison by medical and survivor characteristics	12 years postdiagnosis	SF-12 Self-reported	Institution-based	Survivors with a relapse or second cancer reported significantly worse MCS ($P = .01$). Survivors of a high-risk cancer ($P = .01$) and irradiated survivors ($P = -.001$) scored significantly worse on PCS.	—	14
42	Corella Aznar, 2019	Spain	ALL and AML	54	<14	>18	1995-2006	Population norms	10 years postdiagnosis	SF-36 Self-reported	Institution-based	Survivors' perception of QoL was good, with an average score above the Spanish average. Survivors of high-risk tumours (83.2 vs 89.5; $P < .05$), female survivors (81.8 vs 89.9; $P < .05$) and survivors with severe comorbidity (80.4 vs 88.7; $P < .05$) reported poorer overall QoL.	High-risk tumours, higher treatment intensity, female gender, physical late-effects and number and severity of late effects	17

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
43	Essig, 2012	Switzerland	ALL	457	<16	>16	1976-2003	1. Population norms 2. Internal comparison by relapse status	5 years postdiagnosis	SF-36 Self-reported	Population-based	Compared to population norms, survivors reported higher scores for PF, BP, VT and MH. In a comparison of relapsed and nonrelapsed survivors, relapsed survivors scored significantly lower GH (51.6 vs 55.8; $P = .005$).	Relapse	20
44	Gunn, 2013	Finland	ALL	52	<16	>25	1970-1995	1. Controls recruited from occupational health services 2. Population norms 3. Internal comparison by treatment modality	10 years postdiagnosis	RAND-36 Self-reported	Institution-based	Compared to controls, ALL survivors scored significantly lower on PF (91.5 vs 97.8; $P = .007$), RE (81.4 vs 92.9; $P = .013$), MH (75.4 vs 81.3; $P = .01$) and GH (72.6 vs 81.3; $P = .007$). Compared to population norms, survivors scored significantly lower PF (91.5 vs 95.3; $P = .041$) and RP (83.8 vs 90.6; $P = .045$). In a comparison of treatment modalities, survivors who received more gonadotoxic treatment scored significantly lower on MH ($P = .029$) and VT ($P < .001$).	Older age at diagnosis, treated with chemotherapy or radiation, more intensive treatment and higher educational achievement	18
45	Harila, 2010	Finland	ALL	74	<16	>17	1971-1994 (treated)	1. Population norms 2. General population	10 years postdiagnosis	RAND-36 Self-reported	Institution-based	In comparison with Finnish population norms, survivors scored significantly better on PF (94 vs 90; $P < .01$), RE (91 vs 81; $P < .001$), VT (75 vs 65; $P < .001$), MH (80 vs 74; $P < .01$), GH (75 vs 68; $P < .05$) and SF (91 vs 83; $P < .001$). Compared to healthy young controls, survivors scored significantly better on RE (91 vs 82; $P < .05$), VT (75 vs 68; $P < .01$) and MH (80 vs 75; $P < .05$).	Longer time since diagnosis, relapse, high-grade late effects and female gender	19

(Continues)

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
46	Kanellopoulos, 2013	Norway	ALL and lymphomas	285	<18	>18	1970-2002	General population	7 years postdiagnosis	SF-36 Self-reported	Institution-based	Compared to the general Norwegian population, survivors had significantly worse PF (90.1 vs 94.0; $P < .001$), RP (75.0 vs 87.4; $P < .001$), BP (72.2 vs 79.0; $P < .001$), GH (64.1 vs 80.1; $P < .001$), VT (51.1 vs 60.1; $P < .001$), SF (82.6 vs 89.0; $P < .001$), MH (74.4 vs 79.1; $P < .001$), PCS (48.8 vs 52.9; $P < .001$) and MCS (49.1 vs 50.6; $P = .032$).	Psychological conditions, chronic pain, obesity and regular use of medication	20
47	Sundberg, 2013	Sweden	ALL and lymphoblastic lymphoma	70	<16	>18	1985-1999 (treated)	Internal comparison by treatment modality	5 years postdiagnosis	SEI QoL-DW and SF-36 Self-reported	Institution- and population-based	The overall SEI QoL score was significantly lower in the HSCT survivor group than in the non-HSCT survivor group (4.9 vs 5.5; $P < .01$). Significant difference found in proportion of statements categorised as 'bodily impairment and dysfunction' (56% HSCT, 16% non-HSCT; $P < .01$) and in the mean rating score, indicating severity, of statements categorised as 'limitations in activity and participation (2.3 HSCT vs 4.4 non-HSCT; $P < .05$)	Treated with HSCT and unemployed	15
48	Aili, 2021	Sweden	ALL	227	<15	>18	1985-1997	1. Siblings 2. Population norms	14 years postdiagnosis	SF-36 Self-reported	Population-based	Compared to siblings, survivors rated their GH ($P = .01$) and RE significantly lower ($P = .023$). Compared to population norms, ALL survivors scored lower on SF and RE	Social support and self-efficacy.	19
Survivors of brain tumours														
49	Gunn, 2016	Finland	Ependymoma and medulloblastoma	19	<16	>16	N/A	General population	5 years postdiagnosis	15D instrument Self-reported	Population-based	Compared to controls, the total 15D score was significantly lower for survivors (0.90 vs 0.94; $P = .008$). Survivors scored significantly lower in the following dimensions: mobility ($P = .009$), vision ($P < .001$), hearing ($P < .001$), eating ($P < .001$), speech ($P < .001$), usual activities ($P < .001$), mental function	Medulloblastoma	12

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
												($P = .01$) and sexual activity ($P = .008$). No differences were found for breathing, or vitality. excretion, distress, discomfort and symptoms and depression. Survivors scored significantly higher on sleeping ($P = 0.033$).		
50	Kristiansen, 2019	Sweden	Low-grade astrocytoma in posterior fossa	14	<18	>21	1995-2011	Population norms	5 years postdiagnosis	RAND-36 Self-reported	Institution-based	Compared to Swedish population norms, survivors scored lower on VT (63.46 vs 70.8; $P = .054$), but not significantly different.	—	12
51	Scholtes, 2019	Germany	Brain tumour in the posterior fossa	270	<15	25-45	1980-2002	1. General population 2. Internal comparison by WHO grades	5 years postdiagnosis	EORTC QLQ-C30 Self-reported	Population-based	Compared to the general population, survivors of grades I-II BTS reported significantly lower role ($P = .013$), emotional ($P = .048$) and cognitive functioning ($P < .001$) and survivors of grades III-IV BTS reported significantly worse physical ($P < .001$), role ($P < .05$), emotional ($P < .05$), cognitive ($P < .001$) and social functioning ($P < .001$) and total QoL ($P < .05$). Survivors of grades III-IV BTS reported significantly worse results for physical ($P < .001$), role ($P = .005$), cognitive ($P = .001$ and social functioning ($P < .001$) than grades I-II BTS.	High-risk tumour, sensitivity disorder, dyspnoea, higher educational achievement and living at home or in the assistive facility	19
52	Ljungman, 2022	Finland	Brain tumours	60	N/A	>16	1970-2008	General population	5 years postdiagnosis	RAND-36 Self-reported	Institution-based	Female survivors reported significantly lower PF ($P < .001$) than controls. Men scored lower PF ($P < .01$), GH ($P < .05$), VT ($P < .01$), SF ($P < .05$) and RE ($P < .05$).	Female gender, older age at diagnosis, severity of late effects, work and education status and depression.	11

(Continues)

TABLE 1 (Continued)

Ref. no.	First author, publication year	Country	Cancer type (exception)	Sample size	Age at diagnosis (years)	Age at evaluation (years)	Period of diagnosis	Comparison group	Minimum follow-up	Instrument and informant	Population- or institution-based	Main outcomes	Significant characteristics	Quality assessment (points)
Survivors of other cancers														
53	Nies, 2017	Netherlands	Differentiated thyroid carcinoma	67	<18	>18	1970-2013	Peers approached by survivors	5 years postdiagnosis	SF-36 and THYCA-QoL Self-reported	Population-based	Compared to controls, survivors had significantly lower scores on PF (95 vs 100; $P = .031$), RP (100 vs 100; $P = .021$) and PCS (53 vs 57; $P = .024$).	Unemployed	19
54	Vaarwerk, 2019	UK and Netherlands	Head-and-neck rhabdomyosarcoma	31	<18	>18	1990-2010	Population norms	6 years postdiagnosis	PedsQL™ 4.0 Self-reported	Institution-based	In general, HRQoL of survivors did not differ significantly from reference values, except for school/work, which was significantly lower in the Dutch survivor cohort (72.5 vs 82.57; $P = .007$).	Burden score	13

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BP, bodily pain; BTS, brain tumour survivors; CNS, central nervous system; GH, general health perception; HSCT, haematopoietic stem cell transplantation; MCS, mental component score; MH, mental health; PCS, physical component score; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical problems; SD, SD; SF, social functioning; UK, United Kingdom; US, United States; VT, vitality; CF, Chronic fatigue.

questionnaires and different types of comparison groups, it was not feasible to conduct a meta-analysis on all of the included papers.

2.2 | Quality assessment

As all the studies included were cross-sectional in design, the Appraisal Tool for Cross-sectional Studies (AXIS) was used to assess their quality.[55] The 20-item tool allows measurement of methodological quality according to the following criteria: clarity of aims and reference population, appropriateness of study design and sample frame, justification of the sample size, process of selecting participants, measures taken to include nonresponders and potential response bias, appropriate measurement of risk factors and outcome variables, elaboration of methods and statistical approach, adequate description of results, including internal consistency, justified discussion and conclusion, discussion of limitations and statement of ethical approval, participant consent and any conflict of interest. The items were scored 'yes' or 'no' (PAL).[55] To the knowledge of the authors no manual or instruction regarding division in relation to the degree of quality exists. The AXIS domains most frequently found to reduce the methodological quality were lack of justification for sample size, lack of information about nonresponders, a low response rate (raising concern about nonresponse bias) and internally inconsistent results.

3 | RESULTS

The literature search resulted in 2629 articles published between 1 March 2008 and 19 October 2022. Duplicates were excluded, and articles were screened for eligibility, resulting in inclusion of 36 articles (Figure 1). Most of the articles excluded were non-European studies, conference reports, studies of adult cancer or studies of children undergoing cancer treatment. The characteristics of the included studies are summarised in Table 1, and the QoL instruments used in the studies are presented in Table 2. The assessment of study quality is shown in Table S2.

The included articles provided data on a total of 14 342 survivors of childhood cancer. Three articles were based on data from a French cohort of survivors of leukaemia,[37-39] two articles were from studies in northern Italy,[19,20] two articles were based on data from a Belgian and French cohort of survivors of hematologic cancers[40,41] and five articles used data from the Dutch LATER registry,[21-25] with overlapping populations. All articles were screened for overlapping populations. Survivors of various cancers were included in 18 studies.[19-36] Twelve studies were of survivors of haematological cancers,[37-48] four of brain tumour survivors[49-52] and two of survivors of other cancers, that is, differentiated thyroid carcinoma[53] and head-and-neck rhabdomyosarcoma.[54] The period of diagnosis ranged from 1948 to 2013, but in most studies, it was between 1970 and 2010. Of the 36 studies, 20 were conducted in Western European populations,[21-27,29,31,32,34,35,37-41,43,51,53] 11 were conducted in Northern Europe,[28,30,33,44-50,52] four in Southern

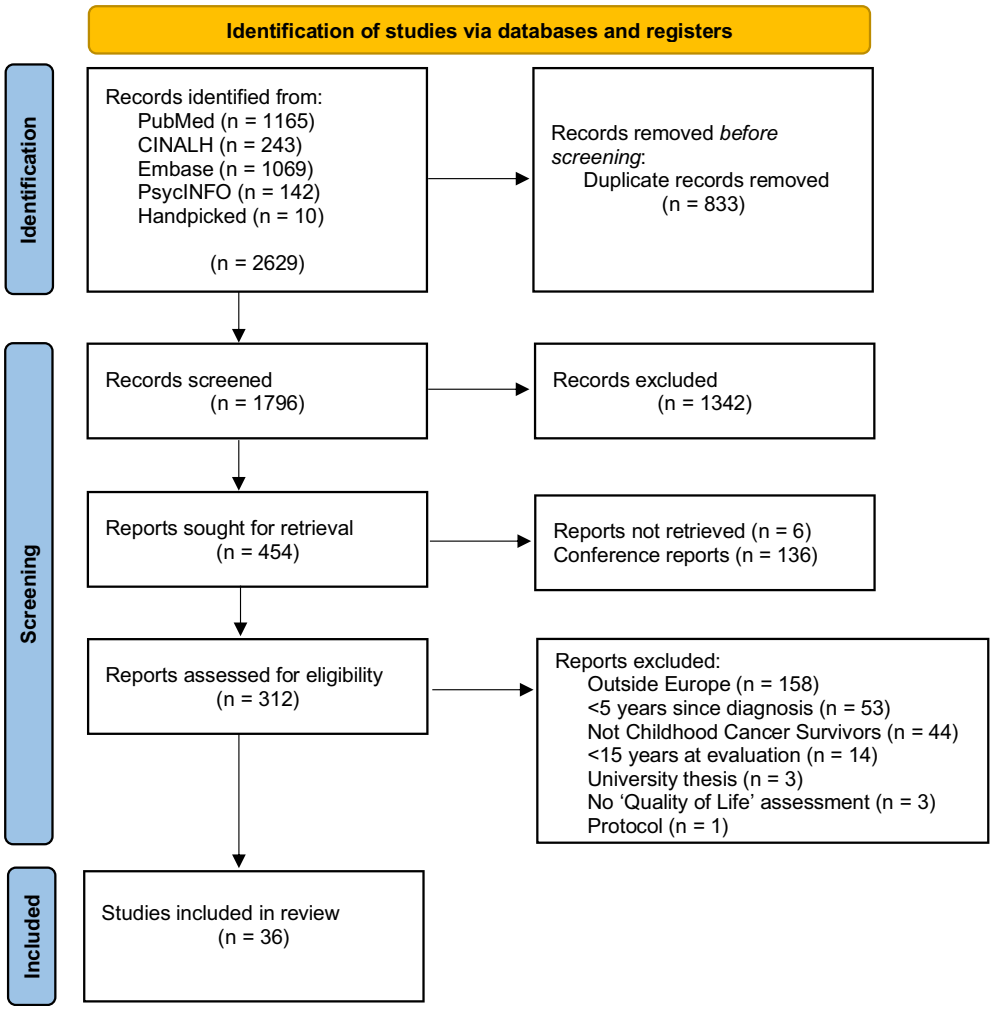

FIGURE 1 Flow chart of study selection process. [Color figure can be viewed at wileyonlinelibrary.com]

Europe[19,20,36,42] and one in both a western and a northern European population.[54] QoL was measured as the primary outcome in 30 studies and as the secondary outcome in the six other studies. The primary outcomes of these studies were psychiatric disorders,[26] information needs,[27] long-term complications,[50] patient satisfaction,[20] psychosocial well-being[54] and support needs.[21]

3.1 | Quality of life

In most studies, the 36-item Short Form Survey (SF-36) or RAND-36 questionnaire was used to assess the QoL of survivors and comparisons (Table 2). Both consist of 36 questions that can be summarised in eight scales: physical functioning (PF), role limitation due to physical health (RP), bodily pain (BP), general health perception (GH), energy and vitality (VT), social functioning (SF), role limitation due to emotional problems (RE) and mental health (MH). The scores on each scale range from 0 to 100, with 100 indicating the highest rating of QoL. The eight scales can be further aggregated into a 'physical component summary' (PCS) and a 'mental component summary' (MCS).[67,68] The other less frequently used questionnaires also included different aspects of QoL ranging from physical challenges to psychosocial problems.

In the 31 studies in which survivors were compared to a comparison group survivors scored worse than healthy controls,[21,24,25,28,32-34,44,46,49,51-53] population norms[20,22,23,35,37-39,48,54] or siblings[31,48] on a QoL summary score or subdomain in 23 studies. Three studies found no significant differences in perceived QoL[30,36,50] and five studies found that survivors rated QoL or subscales higher than a comparison group.[19,40,42,43,45] Of the 23 studies that found a lower QoL in survivors, 12 were based on survivors of various cancers,[20-25,28,31-35] six on survivors of haematological cancers,[37-39,44,46,48] three on brain tumour survivors,[49,51,52] one on survivors of differentiated thyroid carcinoma[53] and one on survivors of head-and-neck rhabdomyosarcoma.[54] The five studies that found a higher QoL in survivors were based mainly on survivors of haematological cancers.[19,40,42,43,45] One of the three studies that found no difference in QoL was based on brain tumour survivors,[50] while the other two were based on survivors of various cancers.[30,36]

Of the 23 studies that found a lower QoL in survivors, 22 found this outcome in at least one physical subdomain,[20-25,28,31-35,37-39,44,46,48,49,51-53] while 17 found the outcome in at least one mental subdomain.[20-23,25,32,34,35,37-39,44,46,48,51,52,54]

The physical subdomains found mainly to be correlated with worse QoL were PF,[22,25,28,31,32,34,35,37-39,44,46,49,51-53] GH[20,22,25,31,32,34,35,38,39,44,46,48,52] and RP (problems at work or in other

TABLE 2 Instruments used to assess the quality of life in studies of childhood cancer survivors.

Instrument (ref.)	No. of studies in which used	Domains covered
SF-36[56]	18	Physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality and general health perceptions
RAND-36[57]	5	Physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, energy/fatigue and general health perceptions
SF-12[58]	4	Physical component score and mental component score
PedsQL 4.0[59]	4	Physical, emotional, social, school/work and psychosocial health
SEIQoL-DW[60]	2	The most important aspects of life for the individual survivor, individual rating of aspects and rating of the importance of the aspects against each other
15D instrument[61]	1	Breathing, mental function, speech, vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity and depression
EORTC QLQ-C30[62]	1	Functional scales (physical, role, cognitive, emotional and social), symptom scales (fatigue, pain and nausea and vomiting) and a global health and quality of life scale
FLZM[63]	1	*General*: friends/acquaintances, leisure time/hobbies, health, income/financial security, occupation/work, housing/living conditions, family life/children and partner relationship/sexuality *Health*: physical condition/fitness, ability to relax/stay on an even keel, energy/zest for life, mobility, vision and hearing, freedom from anxiety, freedom from aches and pains and independence from help/care
THYCA-QoL[64]	1	Voice and throat problems, temperature problems, pain and cramps, weight changes, headache and attention problems, restlessness, agitation and anxiety and sexual interest
TAAQOL[65]	1	Gross motor functioning, fine motor functioning, cognitive functioning, sleep, pain, social functioning, daily activities, sexuality, vitality, positive emotions, depressive emotions and aggressive emotions
Ladder of Life[66]	1	Quality of life 5 years before disease, quality of Life of current life and quality of life 5 years after diagnosis

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; PedsQL™ 4.0, Paediatric Quality of Life Inventory 4.0; SEIQoL-DW, Schedule for the Evaluation of Individual Quality of Life—Direct Weighting; SF, simple form; THYCA-QoL, disease-specific health-related quality of life questionnaire for thyroid cancer survivors; TAAQOL, TNO-AZL Questionnaire for Adult Health-Related Quality of Life.

regular daily activities due to physical health).[25,31,33,34,38,39,44,46,53] Fewer studies found that the subdomain BP was coherent with worse QoL.[25,32,34,35,39,46] The size of the effect varied by subscale but was generally small, such as in a Swiss study of 1593 survivors of various childhood cancers, who reported poorer PF (mean, 49.0 vs 52.9, $P < .001$), RP (mean, 49.5 vs 50.4, $P = .003$) and GH (mean, 53.5 vs 56.6, $P < .001$) than siblings.[31] A study in Norway of 285 survivors of childhood acute lymphoblastic leukaemia and lymphoma found medium-sized differences when comparing scores in survivors with that of the general population on PF (mean, 90.1 vs 94.0, $P < .001$), BP (mean, 72.2 vs 79.0, $P < .001$), RP (mean, 75.0 vs 87.4, $P < .001$) and GH (mean, 64.1 vs 80.1, $P < .001$).[46]

The main mental subdomains found to be coherent with worse QoL were SF[22,25,32,34,35,37-39,46,48,51,52] and MH,[20,25,32,34,35,44,46,49,51] but several studies also found that VT[20,22,25,32,34,35,39,46,52] and RE[25,34,37-39,44,48,52] were connected with lower QoL. The effect sizes in the studies that found a significantly lower score for mental subdomains in survivors compared to the population norm or a comparison group were small to medium. A study in Norway of 285 survivors of childhood acute lymphoblastic leukaemia and lymphoma found lower scores in survivors than in the general population for MH (mean, 74.4 vs 79.1, $P < .001$), SF (mean, 82.6 vs 89.0, $P < .001$) and VT (mean, 51.1 vs 60.1; $P < .001$).[46] The largest differences in effect sizes were seen in a Dutch study of 60 survivors of childhood cancer, in which lower scores were found for VT (mean, 52.2 vs 70.7; $P < .001$), MH (mean, 62.3 vs 78.7; $P < .001$) and SF (mean, 48.1 vs 87.8; $P < .001$).[35]

In the five studies that reported comparably better QoL[19,40,42,43,45] among survivors of childhood cancer, both physical and mental scores of QoL were higher, but better MH and better VT were the subdomains most often reported.[19,40,43,45] Effect sizes varied, but were generally small. In an Italian study of 205 survivors of various cancers other than CNS tumours, survivors reported significantly better scores than healthy students on all four mental subdomains on the SF-36 questionnaire ($mean_{MH}$, 71.59 vs 65.77, $P = .001$; $mean_{VT}$, 63.35 vs 55.44, $P = .0001$; $mean_{SF}$, 76.27 vs 71.45, $P = .004$; and $mean_{RE}$, 75.47 vs 58.43, $P = .0001$) and on two of the four physical subdomains ($mean_{BP}$, 87.90 vs 79.53, $P = .00013$; $mean_{RE}$, 86.78 vs 80.89, $P = .02$).[19] A Swiss study[43] of 457 long-term survivors of relapsed childhood acute lymphoblastic leukaemia reported higher scores in survivors in all four physical subdomains: PF (mean, 52.0), BP (mean, 57.1), RP (mean, 51.0) and GH (mean, 54.0) compared to the German population norm of 50.0. They also found higher scores in survivors for two of the mental subdomains: MH (mean, 54.0) and VT (mean 57.0) compared to population norms (mean 50.0).

TABLE 3 Quality of life-related characteristics.

Characteristics	References	No. of times a characteristic was significant			No. of studies in which characteristic was studied
		Overall QoL	Subscales of QoL	Total	
1. *Medical characteristics*					
Age at diagnosis	19,22-24,29-31,35,36,41,42,44,46,49,52,53	1	3	4	16
Type of cancer	19,22-24,29,31,32,34,46,49	2	5	7	10
Tumour risk	41,42,51,53	1	2	3	4
Type of treatment	19,22-24,28,29,31,32,36-39,41,42,44-47	2	10	12	18
Treatment intensity	30,42,44,46,53	0	2	2	5
Duration of treatment	29,32	2	0	2	2
Relapse	22-24,29,31,41,43-46	1	4	5	10
Time since diagnosis	19,22,23,31,32,36,44-46,53	0	3	3	10
2. *Physical and psychological characteristics*					
Physical complications	23,29,31,32,34,42,46,51,53	5	3	8	9
Psychological complication	23,26,29,32,34,46,52	6	1	7	7
Psychosexual functioning	35	0	0	0	1
No. and severity of complication	42,45,52,54	2	2	4	4
Regular use of medication	46	1	0	1	1
3. *Sociodemographic characteristics*					
Age at evaluation	19,22,24,28-31,34,46,47,53	2	3	5	11
Gender	19,22-24,28-32,36,41,42,45-47,52,53	2	7	9	17
Education	22,23,28,32,44,46,51-53	2	4	6	9
Employment	32,44,47,52,53	2	2	4	5
Relationship status	22,32,44,46,53	1	1	2	5
Having children	34,44	1	0	1	2
Living situation	51	0	1	1	1
Economic status	23,28	1	0	1	2
Developmental milestones	29	0	0	0	1
Social support	23,29,48	2	0	2	3
Risk behaviour	29	0	0	0	1
Information needs	21,23,27,30	0	3	3	4
Coping	29	1	0	1	1
Patient satisfaction	20	0	1	1	1

3.2 | Quality of life-related characteristics

The characteristics correlated with QoL were examined in 32 studies. We categorised the findings as cancer and treatment, physical and mental and sociodemographic characteristics. Studies in which characteristics were significant can be found in Table 3.

3.2.1 | Cancer and treatment characteristics

Survivors' age at diagnosis was not correlated with QoL in most studies.[19,23,24,30,31,35,36,41,42,46,49,53] In four studies, however, older age at diagnosis was associated with lower QoL.[22,29,44,52] Survivors treated with haematopoietic stem cell transplantation (HSCT) reported poorer physical health than non-HSCT-treated survivors in the seven studies that investigated this.[19,22,31,36,38,42,47] Treatment with radiation,[22,24,31,41,42,44] chemotherapy[29,37,44] or surgery[31] also negatively influenced subdomains of QoL, while other studies found no correlation with treatment.[23,28,32,39,45,46] In seven of 10 studies that evaluated the relevance of cancer type, significant associations were found. Survivors of medulloblastoma reported less VT than survivors of ependymoma,[49] survivors of brain tumours had lower QoL than survivors of haematological cancers,[22,24,29] survivors of solid tumours reported lower life satisfaction than survivors of brain tumours and haematological cancers,[32] and survivors of CNS tumours, retinoblastoma, bone tumours and soft tissue tumours had lower PCS than survivors of other cancers.[31] In a different study, survivors of haematological cancers treated with HSCT reported poorer physical

functioning than survivors of other cancers.[19] Treatment intensity,[30,46,53] time since diagnosis,[19,23,31,32,44,46,53] tumour stage[53] and relapse status[23,24,31,44,46] did not affect QoL in most studies, but some found that intensive treatment was related to worse mental scores,[42,44] that longer time since diagnosis resulted in greater VT and MH[45] and that a higher tumour stage was associated with poorer QoL.[41,42,51] Conflicting results were found with regard to relapse status. In four studies, lower GH,[43] worse PCS[22] and QoL[29,36] were reported by survivors who had experienced a relapse than by those who had not. In another study, however, better MH and VT were found in survivors who had had a relapse.[45] Longer duration of treatment was found to be significantly associated with poorer QoL in three studies.[22,29,32]

3.2.2 | Physical and mental characteristics

Physical conditions such as obesity, chronic pain, thyroid alterations, sensitivity disorders and insufficient growth were found to affect QoL negatively.[23,29,31,32,34,42,46,51] Poorer QoL was also found among survivors with anxiety and depression,[26,32,46,52] suicidal thoughts,[26] psychotic disorders,[26] a chronic somatic condition,[46] life challenges[23] and fatigue.[46] No association with QoL was found with addictive disorders,[26] eating disorders[26] or psychosexual problems.[35] Survivors who experienced posttraumatic growth—a positive psychological change after a highly challenging life circumstance—reported higher QoL.[32,69] Having had several severe late effects (graded according to the Common Terminology Criteria for Adverse Events, a system for grading acute and late effects of cancer treatment) correlated with worse QoL in three studies[42,52,54] but with better VT and MH in another study.[45]

3.2.3 | Sociodemographic characteristics

Age at evaluation was not correlated with reported QoL in most studies[23,29,30,46,47,53]; however, older age at evaluation was negatively associated with SF,[19] MCS[31] and overall QoL in two studies.[28,34] In a third study, survivors aged 18-25 were at higher risk of impaired PCS than survivors aged 46-55.[22] Female survivors reported worse QoL in seven studies[19,22,24,28,30,42,52] and better QoL in two[31,45]; gender was not associated with QoL in other studies.[23,29,32,36,41,46,47,53] Higher educational achievement[22,28,32,44,51,52] and being employed[32,47,52,53] were generally correlated with better QoL and PF. Family characteristics such as relationship status[44,46,53] and having children[44] were generally not significantly associated with reported QoL, but one study found that unmarried survivors had lower life satisfaction,[32] one found that having a partner decreased the risk of impaired PCS and MCS,[22] and another found that a higher standardised fecundity ratio—the number of children observed to the number that would be expected in the general population—was related to better QoL.[34] Survivors who expressed a need for information about their illness, treatment and late effects,[21,27,30] with interpretive control (seeking information in order to better understand their emotional reactions and the situation in general),[29] those with a passive coping style (survivors who coped with stress by passively allowing themselves to be immersed in the problem),[29] those who shared their emotions,[29] and those with poor economic status[28] had poorer QoL. Predictive control (survivors who were optimistic about the course of their disease) and active coping (survivors with a goal-oriented, calm approach to the situation) were correlated with better QoL,[29] and greater patient satisfaction was associated with more VT.[20]

4 | DISCUSSION

This systematic review of 36 studies of QoL in survivors of childhood cancer published between 2008 and 2022 indicates that survivors of childhood cancer are at risk of reduced QoL. Of the 31 studies including a comparison group, only three found no significant difference in perceived QoL,[30,36,50] five studies found that survivors rated their QoL or subscales higher than a comparison group,[19,40,42,43,45] while 23 studies found that survivors reported lower QoL when compared to control groups or normative data.[20-25,28,31-35,37-39,44,46,48,49,51-54] Effect sizes varied, but were generally small to moderate. In the five studies that reported a higher QoL in survivors, both physical and mental dimensions of QoL were scored higher, whereas in the 23 studies that found a lower QoL in survivors, 22 found that a physical dimension was scored lower and 18 found that a mental dimension was scored lower. A tendency to poorer QoL was found among survivors who had received certain treatments (such as HSCT), survivors of brain tumours, female survivors and survivors experiencing physical and emotional difficulties.

Previous reviews have found contradictory findings across studies, but, in general, the survivors' scores on physical, psychological and social domains of QoL were similar to those of comparisons, the greatest difference being in physical well-being.[15,17] Our results are in line with those of previous reviews that the largest difference between survivors and comparisons is in the physical subdomain of QoL. Unlike in previous reviews, most studies in the present review found significantly lower scores on QoL and subdomains for survivors compared to population norms or comparisons, but the differences in scores were small to moderate. While the present review was restricted to studies of QoL in >5-year survivors who were ≥15 years of age at the time of evaluation for QoL, previous reviews also included studies of survivors undergoing treatment and survivors younger than 15 years of age, and in some cases studies with proxy respondents. Further, most of the studies in previous reviews were conducted in North America. In the present review, most studies used the SF-36 questionnaire, facilitating comparison of studies. These factors may explain the differences in findings.

It may be difficult to measure treatment as a predictor of QoL, as survivors often received a combination of treatments, and treatment protocols have changed substantially during the past decades. Survivors treated with radiation, chemotherapy or HSCT reported poorer QoL than survivors treated with other means.[19,29,31,37,38,42,44,47] Radiation, chemotherapy and HSCT have previously been associated with higher risks of adverse health effects, including cardiovascular disease,

endocrinological disturbance, secondary cancers, obesity, fatigue and impaired cognitive function and also with negative impacts on social functioning, educational achievement and employment,[14,70-75] which could be the mechanism by which survivors experience worse QoL. This is supported by several studies included in this review, which showed that QoL was correlated with the physical late effects of the cancer and its treatment and also with mental health problems.[26,29,31,32,34,42,46]

The findings with regard to the impact of certain cancers on QoL were ambiguous, but, as previously observed,[14] survivors of brain tumours and solid tumours tended to report poorer QoL than survivors of haematological cancers.[29,31,32] One study found that the mediating factors between survival from a brain tumour and worse QoL were psychosocial, cognitive and neurological late effects; physical late effects and passive coping were other mediating factors.[29]

Female childhood cancer survivors more often experience reduced QoL.[19,28,30,42] The reasons may include the fact that females tend to discuss problems more openly than men,[76] reflect the findings for the general population[77] or reflect differences in tolerance of therapy.[16]

Although most of the studies in this review found a lower QoL in survivors of childhood cancer than in population norms or comparisons, four studies found a positive effect.[19,42,43,45] Possible explanations include posttraumatic growth after defeating a life-threatening disease, a shift in values and perspectives and acquisition of an increased ability to cope with problems.[76,78] Other proposed explanations are a desire to appear normal and self-deception response bias (an unconscious tendency to deny problems and therefore underreport symptoms and exaggerate positive aspects).[79]

The findings of this review imply that treatment regimens should be continually reassessed, that multidisciplinary care should be part of the follow-up and that further research should be conducted on specific cancers and specific treatments to attenuate potential adverse effects and improve QoL. Future research should also evaluate targeted interventions to prevent and mitigate both health and psychological problems related to the cancer and its treatment, which could positively affect long-term QoL. Actions, when warranted, include less invasive treatments, risk-targeted follow-up to prevent, detect and treat health problems and targeted training programmes to improve daily functioning.

4.1 | Strengths and methodological challenges

A major strength of this comprehensive systematic review is the methodological approach. Four relevant databases were searched for articles, and the reference lists of the studies that were included were reviewed to ensure inclusion of all studies. Another strength is that only studies with self-reported measures of QoL were included. In previous studies, it was found that proxies cite fewer psychological problems and more physical problems than self-reports by survivors.[80] A third strength is that the participants evaluated had survived for at least 5 years, so that the findings are likely to reflect actual long-term complications of the cancer and its treatment and not immediate consequences. A fourth strength of our study is that only European countries were included. It is plausible that differences in health care systems, rehabilitation options and economical aspects of treatment influences the perceived QoL of survivors.

Findings are affected by the limitations of the studies that were included, such as their methodological heterogeneity. Different questionnaires were used to assess QoL, which may limit proper, valid comparison. Another limitation is that, even though recently published studies were included, participants received their diagnoses as early as 1948, and, with changes in treatment protocols over time, survivors may have received different treatments with different late effects. Third, all studies had a cross-sectional design, which does not allow causal inferences or information on specific mechanisms. Forth, the age range of participants and differences in time since diagnosis may result in participants' coping mechanisms, concerns and occurrence of late effects being different. Finally, no studies from Eastern Europe were found in the literature search limiting the generalizability of results to this part of Europe. Other limitations specific to some studies included small samples and low response rates.

5 | CONCLUSION

The findings of this review indicate that survivors of childhood cancer report worse QoL than comparison groups and normative data, although the differences in scores were generally small to moderate. Certain cancers such as brain tumours, treatment with HSCT and late effects appeared to be risk factors for poorer QoL. In addition, female survivors tended to report lower QoL. This systematic review of QoL in European survivors of childhood cancer provides clinicians with important knowledge about possible complications that require attention. Research on the mechanisms underlying poor QoL could help to prevent or alleviate problems, as procedures could be adjusted or changed according to the findings. As more children survive a cancer diagnosis and more challenges are identified, it will be crucial to determine the appropriate care for each child and to target those in greatest need.

AUTHOR CONTRIBUTIONS

Pia Alkærsig Larsen, Jeanette Falck Winther and Camilla Pedersen developed the concept and study design. Pia Alkærsig Larsen and Camilla Pedersen searched the databases and screened articles for their eligibility. Pia Alkærsig Larsen conducted the narrative synthesis and drafted the manuscript with support from Camilla Pedersen. All the authors participated in interpreting the results. All the authors provided critical feedback, revised the manuscript for intellectual content and approved the final version. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used in our study were from published articles identified in electronic databases: PubMed, EMBASE, PsycINFO and CINALH. The literature search was conducted in December 2022. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This article is based only on published peer-reviewed articles.

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