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SURVIVORSHIP: RESEARCH ARTICLE

Mental health and health-related quality of life in preschool-aged childhood cancer survivors. Results of the prospective cohort study ikidS-OEVA

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Abstract

Objectives: Long-term survivors of childhood cancer are at increased risk for sequelae such as poor mental health (MH) or impaired health-related quality of life (HrQoL). We aimed to evaluate early adverse effects on MH and HrQoL in young childhood cancer survivors (YCCS) before school entry.

Methods: In a nationwide prospective cohort study, children with cancer other than brain tumors diagnosed at preschool age and completed cancer treatments were identified from the German Childhood Cancer Registry. The comparison group was children of the same age without a cancer diagnosis who participated in the prospective population-based health survey ikidS. MH problems and HrQoL were assessed by parental versions of the Strengths and Difficulties Questionnaire (SDQ) and the questionnaire for health-related quality of life in children (KINDL), respectively. Associations between cancer and MH as well as HrQoL were analyzed by multivariable linear regression.

Results: Of 382 YCCS contacted, 145 were enrolled (mean age 6.6 years) and 124 analyzed. Compared to children without a cancer diagnosis (3683 contacted, 2003

Abbreviations: CHC, chronic health condition; CI, confidence interval; GCCR, German Childhood Cancer Registry; HrQoL, health-related quality of life; ikidS, "I am starting school" (German: ich komme in die Schule); IQR, interquartile range; KiGGS, German Health Interview and Examination Survey for Children and Adolescents (German: Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland); KINDL, questionnaire for health-related quality of life in children (German: KINDerfragebogen für Lebensqualität); MH, mental health; OEVA, Oncological Disease at Preschool Age (German: Onkologische Erkrankung im Vorschulalter, excluding brain tumors); PHE, preschool health examination; SDQ, Strengths and Difficulties Questionnaire; SHCN, special health care need; YCCS, young childhood cancer survivors.

enrolled, 1422 analyzed), YCCS had more MH problems (13% vs. 3%) and slightly worse HrQoL (median 78.7 vs. 80.2 points). In the adjusted analysis, YCCS had higher SDQ scores (2.2 points, 95% confidence interval [CI] 1.3, 3.0) and lower KINDL scores (−2.4 points, 95% CI −3.7, −1.1) compared to children without cancer diagnosis.

Conclusion: Already at preschool age, YCCS may be at increased risk of MH problems and impaired HrQoL. This could have impacts on subsequent school performance and educational attainment. Follow-up health care for YCCS may include early screening for MH problems and reasons for HrQoL deficits.

KEYWORDS
child health study, childhood cancer, early childhood, health-related quality of life, mental health, survivorship

1 | INTRODUCTION

In Germany, about 2200 children and adolescents at ages 0–17 years are diagnosed with cancer each year. However, the prognosis of childhood cancer has improved substantially over the last decades, with survival exceeding 80% nowadays.[1] Because of improving survival and lack of preventive measures to prevent cancer disease, the number of childhood cancer survivors is growing steadily. In the past, especially survival and somatic late effects have been of interest in the care of childhood cancer survivors. Mental health (MH) and health-related quality of life (HrQoL) have only been emphasized more recently. Because of the severity of their disease and potential long-term sequelae, childhood cancer survivors need special attention regarding their further development. It has been shown that long-term survivors of childhood cancer are at increased risk for sequelae like poor MH or impaired HrQoL.[2–7] The World Health Organization defines MH as "a state of well-being, in which an individual realizes his or her own abilities, can cope with normal stresses of life, can work productively, and is able to make a contribution to his or her community."[8] HrQoL is a multidimensional construct, including physical, psychological, and social dimensions, especially the individual's subjective perception is of interest.[9]

MH conditions are particular risk factors for poor school performance and educational attainment.[10] Thus, children with chronic physical health conditions may be screened for additional MH problems prior to school entry to prevent long-lasting negative effects on educational outcomes. However, only a small number of studies have investigated MH and HrQoL in young childhood cancer survivors (YCCS) during the transition phase between kindergarten and primary school.

We therefore initiated the study "I am starting school - Oncological Disease at Preschool Age" (German: "**i**ch **k**omme **i**n **d**ie **S**chule – **O**nkologische **E**rkrankungen im **V**orschul**a**lter" [ikidS-OEVA]) to evaluate early adverse effects of early childhood cancer on MH and HrQoL in preschool age.

2 | METHODS

2.1 | Study design and participants

The present study is based on the registry-based ikidS-OEVA and the population-based ikidS ("I am starting school"; German: "ich komme in die Schule") cohorts. ikidS-OEVA was a nationwide prospective cohort study in Germany from June 2016 to July 2017. Eligible patients were identified in the German Childhood Cancer Registry (GCCR). Children were included if they (i) were 5 or 6 years of age (i.e., potential candidates for school enrollment), (ii) had been diagnosed with childhood cancer in the past, and (iii) had fully completed cancer treatment at a German childhood cancer care center. The research protocol was approved by the local ethics committee of the Medical Association of Rhineland-Palatinate and the working group "Long-Term Outcomes" of the German Society for Pediatric Oncology. The latter restricted this study to survivors without brain tumors for ethical reasons.

The comparison group consisted of children of the same age without prior childhood cancer diagnosis, who participated in the population-based prospective cohort study ikidS. This study was conducted in the city of Mainz and the more rural district of Mainz-Bingen (Federal state Rhineland-Palatinate, Germany). Methodological aspects as well as descriptions of the target population and cohort have been reported elsewhere.[11] Children were eligible if they (i) were formally registered for school entry in 2015 in one of the 79 regional primary schools, and (ii) had attended their mandatory preschool health examination (PHE) between September 2014 and July 2015. The study was additionally approved by the regional supervisory school authority and the state representative for data protection in Rhineland-Palatinate.

For the present study, solely children of both cohorts expected to be enrolled in primary school were included. Written informed consent was obtained from the legal guardians for all participants in both cohort studies.

2.2 | Procedures and data collection

In both cohort studies, data were collected prior to school entry in a similar manner using the same standardized instruments and items. In ikidS-OEVA, study-specific paper–pencil questionnaires were sent via the GCCR either (i) to the treatment centers to be delivered to the parents of participants during a follow-up visit, or (ii) directly to the families' addresses. In ikidS, some data were collected at the PHE and provided by the Department of Public Health of the County Government Mainz-Bingen. The remaining data were obtained by study-specific parental questionnaires sent to the families' addresses. Questionnaires covered general health conditions and MH, HrQoL, presence of a chronic health condition (CHC), need for and use of special health care, family structure and burden, sleep behavior, leisure time activities, nutritional habits, environmental conditions, migration background, and socio-economic status. Instruments and items were based on the German Health Interview and Examination Survey for Children and Adolescents (German: Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland) (KiGGS).[12,13] Cancer-related data (age at diagnosis, type of cancer) were obtained from the GCCR.

2.3 | Assessment of mental health problems

MH problems were assessed by a German parental version of the Strengths and Difficulties Questionnaire (SDQ).[14] The SDQ covers five MH domains with five items each: emotional problems, conduct problems, hyperactivity/inattention, peer problems, and prosocial behavior. The 20 items of the four problem subscales were summed up into one total difficulty score, if at least 12 items were filled in. In the case of missing values, the filled items were extrapolated to the missing items. Hence, the total difficulty score ranged from 0 to 40, with higher scores indicating poorer MH. Age-specific German reference values were used to classify children as borderline (14–16 points) or abnormal (>16 points).[15,16]

2.4 | Assessment of health-related quality of life

HrQoL was assessed by the age-specific parental version of the questionnaire for health-related quality of life in children (KINDL) (German: "Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern und Jugendlichen"). The KINDL was designed for use in clinical as well as healthy populations and covers six dimensions of HrQoL, with four items each: physical well-being, emotional well-being, self-esteem, family, friends, and school/kindergarten. The subscales of these six dimensions can be combined to a total score ranging from 24 to 120 points, if at least 70% of the items are nonmissing. In the case of missing values, the filled items were extrapolated to the missing items. Scores were normalized to a range from 0 to 100, with higher scores indicating better HrQoL.[17,18]

2.5 | Identification of children with special health care needs

Children with CHC other than cancer were identified by the Children with Special Health Care Needs (CSHCN) screener. The screener identifies chronically ill children irrespective of a specific diagnosis. It contains 14 items for the following five domains: (1) need or use of prescription medication; (2) above average use or need of medical, MH, or educational services; (3) functional limitations compared with others of same age; (4) use or need of specialized therapies (physical, occupational, or speech therapy); and (5) treatment or counseling for emotional, behavioral, or developmental problems. Special health care needs (SHCN) due to a CHC are present, if (i) at least one of the five aspects is confirmed, (ii) the respective consequence is due to any kind of CHC, and (iii) the CHC has lasted or is expected to last for at least 12 months.[19]

2.6 | Statistical analysis

In the descriptive analysis, sociodemographic and clinical characteristics of children included in the ikidS-OEVA study were compared to all eligible patients registered in the GCCR to evaluate representativeness of the sample. The distribution of SDQ scores, KINDL scores, SHCN, and potential confounders was compared between children with and without cancer diagnosis. Characteristics were described by appropriate statistical parameters (e.g., absolute or relative frequencies for categorical variables, median and interquartile range [IQR] for non-normally distributed variables).

Potential confounders were selected separately for MH problems and HrQoL and were included based on literature and statistical associations with cancer diagnosis and the respective dependent variable. Two confounder sets for each dependent variable were formed. The first confounder set included child- and family-related variables. The second confounder set included additional lifestyle-related variables. Both sets are presented in Table S1.

In order to estimate the effects of a childhood cancer diagnosis on the outcomes, the independent variable was categorized into three mutually exclusive groups: (1) YCCS, (2) children without cancer diagnosis but with SHCN, and (3) children with neither cancer diagnosis nor SHCN (i.e., reference group). Associations with MH and HrQoL were analyzed by linear regression models adjusted for potential confounders (see above). For each outcome (MH and HrQoL), we computed three regression models: (1) unadjusted, (2) adjusted for confounder set 1, and (3) adjusted for confounder set 2.

In each regression model, children with missing data in the respective dependent variable were excluded. Missing values in the independent and confounder variables were imputed 10 times using multivariate imputations by chained equations with 100 iterations (R package *mice*[20]). Pooled model results were reported as mean differences in the dependent variable including standard error (SE), 95% confidence interval (CI), and *p*-value between the respective group and the

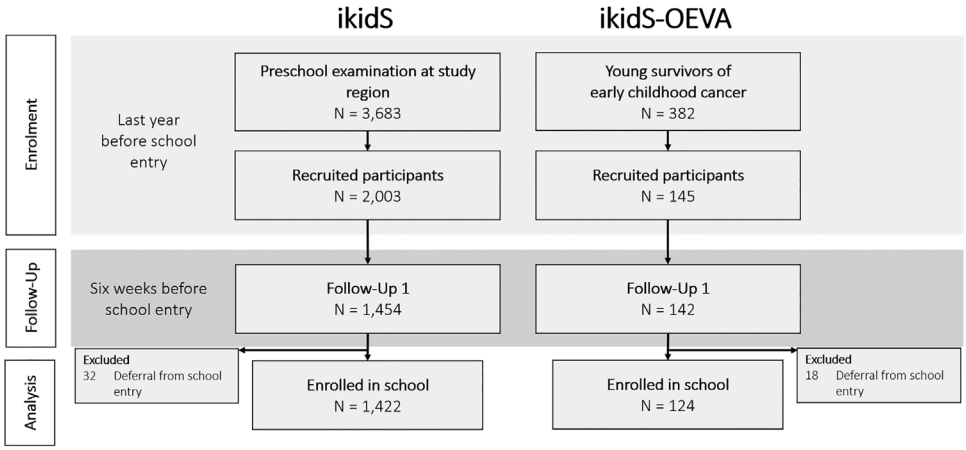

FIGURE 1 Flowchart for the participants of the German ikidS and ikidS-OEVA studies (study follow-up in 2015 and 2016). ikidS, I am starting school (German: ich komme in die Schule); OEVA, oncological disease at preschool age (German: Onkologische Erkrankung im Vorschulalter)

reference group. All statistical analysis was performed using the software R (version 3.6.0).

3 | RESULTS

Of 382 eligible YCCS identified and contacted (i.e., study population), 145 participated in ikidS-OEVA, and 124 were eligible for analyses (i.e., analytical sample; Figure 1). There were only small differences between the study population and the analytical sample regarding sex, year of birth, age at diagnosis, and diagnostic group I or II (Table S2). In the analytical sample, mean age at diagnosis was 2.4 years, mean time since treatment completion 3.0 years (SD 1.2 years, range 0.2–6.1 years), and 48% were male. Diagnoses were as follows: 77.4% leukemia/lymphoma, 11.3% neuroblastoma/retinoblastoma/kidney tumor/liver tumor, 8.9% sarcoma, 2.4% germ cell tumor. Treatment modalities were chemotherapy (n = 120, 96.8%), surgery (n = 37, 29.8%), radiotherapy (n = 15, 12.1%), and stem cell transplantation (n = 14, 11.3%). Of 3683 eligible children for the ikidS study, 2003 participated and 1422 datasets were analyzed (Figure 1). Characteristics of children with and without cancer diagnoses are presented in Table 1.

YCCS more often had SHCN than children without cancer diagnosis (35.3% vs. 11.1%). This applied to all five domains: need or use of prescription medication (8.2% vs. 4.3%); use or need of medical, MH, or educational services (22.8% vs. 4.4%); functional limitations (12.3% vs. 2.1%); use or need of specialized therapies (18.2% vs. 4.4%); and treatment or counseling for emotional, behavioral, or developmental problems (17.2% vs. 4.0%).

Furthermore, YCCS had a higher median SDQ score compared to children without cancer diagnosis (8.0 points; IQR 4.0–13.0 vs. 6.0 points; IQR 4.0–9.0). They more often had borderline (7.4% vs. 5.0%) or abnormal scores (13.1% vs. 3.2%). This translates into a mean difference of 2.51 points (95% CI 1.68, 3.34) in the unadjusted analysis. In the adjusted analyses, the mean difference was somewhat reduced to 2.16 points (95% CI 1.34, 2.99) with confounder set 1 and 2.15 points (95% CI 1.32, 2.98) with confounder set 2 (Table 2).

YCCS also had a slightly lower median KINDL score compared to children without cancer diagnosis (78.7 points; IQR 74.0–83.3 vs. 80.2 points; IQR 76.0–84.4). In the unadjusted analysis, the mean difference was −2.77 points (95% CI −4.12, −1.43). In the adjusted analysis, YCCS scored −2.44 points (95% CI −3.7, −1.1; confounder set 1) and −2.39 points (95% CI −3.71, −1.08; confounder set 2) lower compared to the reference group (Table 3).

4 | DISCUSSION

The present study examined MH and HrQoL in YCCS at preschool age based on a nationwide representative sample in Germany. Concerning MH, the prevalence of MH problems in YCCS was higher than in children without cancer diagnosis. In the unadjusted as well as in the adjusted analyses, results were consistent, even though the difference in the adjusted models was less pronounced. The finding of a higher risk for MH problems among survivors of childhood cancer is in line with observations from previous studies.[5,21,22] However, to date there has been no study about short-term survivors of early childhood cancer focusing exclusively on this age group.

The population-based, nationwide BELLA health survey (as part of KiGGS) investigated the MH of children and adolescents in Germany. Summarized prevalences for borderline and abnormal SDQ scores of 10.2% in 3 to 6-year-old children and 19.8% in 7 to 10-year olds were reported.[23] In the present study, YCCS (age range 6–7 years) had a considerably higher prevalence of borderline and abnormal SDQ scores (20.5%), especially in comparison with the population-based ikidS analytical sample (8.2%) of the identical age range. In a British study, Goodman et al. found an association between an increased SDQ score and a higher prevalence of MH disorder. The risk of a clinical MH disorder increased steadily per each SDQ point.[24] In recent literature, increasing prevalence of MH problems in children and adolescents was associated to increasing age.[10,23,25–28] Similarly, the number of individuals

TABLE 1 Characteristics of YCCS compared to children without cancer diagnosis in the analytical sample

	Children without cancer diagnosis ($n = 1422$)	YCCS ($n = 124$)
Child		
Sex		
Male	726 (51.1)	59 (47.6)
Female	696 (48.9)	65 (52.4)
Age at study follow-up, mean (SD)	6.3 (0.3)	6.6 (0.3)
Migrant background		
Yes	229 (16.9)	16 (13.0)
No	1126 (83.1)	107 (87.0)
Missing, *n*	67	1
Breastfeeding		
Not at all	209 (15.3)	16 (13.0)
Upto 6 months	551 (40.3)	51 (41.5)
More than 6 months	606 (44.4)	56 (45.5)
Missing, *n*	56	1
Family		
SES, mean (SD)	13.9 (3.9)	13.2 (3.7)
Missing, *n*	378	47
Single-parent family		
Yes	108 (7.8)	7 (5.7)
No	1284 (92.2)	116 (94.3)
Missing, *n*	30	1
Smoking in household		
Never	1296 (93.7)	98 (79.7)
Seldom/often	87 (6.3)	25 (20.3)
Missing, *n*	39	1

Note: If not otherwise indicated: *n* (%); % relate to valid values; *n* - missing.
Abbreviations: SD, standard deviation; SES, socio-economic status; YCCS, young childhood cancer survivors.

TABLE 2 Pooled results of unadjusted and adjusted linear regression models on the association between cancer diagnosis and MH problems, measured by the Strengths and Difficulties Questionnaire ($N = 1533$)

	Effect estimate (SE)[a]	95% CI	*p*-Value
Unadjusted			
Special health care needs	3.48 (0.39)	2.72, 4.23	<.001
YCCS	2.51 (0.43)	1.68, 3.34	<.001
Adjusted: Confounder set 1			
Special health care needs	2.90 (0.38)	2.16, 3.64	<.001
YCCS	2.16 (0.42)	1.34, 2.99	<.001
Adjusted: Confounder set 2			
Special health care needs	2.85 (0.37)	2.12, 3.58	<.001
YCCS	2.15 (0.42)	1.32, 2.98	<.001

Note: Reference: no cancer diagnosis, no special health care needs. The data were imputed 10 times using chained equations with 100 iterations and finally pooled.
[a]Dependent variable ranges from 0 to 40, with higher values indicating more MH problems.
Abbreviation: CI, confidence interval; MH, mental health; SE, standard error; YCCS, young childhood cancer survivors.

TABLE 3 Pooled results of unadjusted and adjusted linear regression models on the association between cancer diagnosis and HrQoL, measured by the KINDL questionnaire ($N = 1532$)

	Effect estimate (SE)[a]	95% CI	*p*-Value
Unadjusted			
Special health care needs	−3.24 (0.66)	−4.55, −1.94	<.001
YCCS	−2.77 (0.68)	−4.12, −1.43	<.001
Adjusted: Confounder set 1			
Special health care needs	−2.94 (0.66)	−4.24, −1.64	<.001
YCCS	−2.44 (0.68)	−3.77, −1.10	<.001
Adjusted: Confounder set 2			
Special health care needs	−2.78 (0.66)	−4.08, −1.48	<.001
YCCS	−2.39 (0.67)	−3.71, −1.08	<.001

Note: Reference: no cancer diagnosis, no special health care needs. The data were imputed 10 times using chained equations with 100 iterations and finally pooled.

[a]Dependent variable ranges from 0 to 100, with higher values indicating better HrQoL.

Abbreviation: CI, confidence interval; HrQoL, health-related quality of life; SE, standard error; YCCS, young childhood cancer survivors.

being at risk for MH problems or even showing a manifest MH problem might also further increase over time in YCCS.

Concerning HrQoL, YCCS had poorer HrQoL than children without cancer diagnosis, observed in both unadjusted and adjusted analyses. This result corresponds with prior research,[3,4] which found a lower HrQoL in childhood cancer survivors compared to the general population or to normative values. In a longitudinal Dutch study, HrQoL in preschool childhood cancer survivors (excluding survivors from central nervous system tumors) was significantly impaired 2 months ($n = 53$) and 1 year after treatment ($n = 38$), but improved over time and had normalized 3 years after the end of treatment ($n = 17$).[29] The latter point of time is comparable with the mean time since the end of treatment in the ikidS-OEVA analytical sample (3.0 years). However, the Dutch study results might be limited by a small sample size and a loss of follow-up during the longitudinal study. Thus, it might be possible that only those survivors with better HrQoL continued study participation (healthy survivor effect).

To further interpret the results regarding MH and HrQoL within the analytical statistics of the present analysis, three subgroups were evaluated. Besides the group of YCCS, the ikidS analytical sample was divided into the following two subgroups with reference to their SHCN: children without cancer diagnosis but with SHCN, and children with neither cancer diagnosis nor SHCN (i.e., reference group). Both, YCCS and children without cancer diagnosis but with SHCN had more MH problems as well as worse HrQoL than children with neither cancer diagnosis nor SHCN. However, for the group with SHCN, a greater difference to the reference group was described than for the YCCS. This result may be due to an inhomogeneity of the SHCN regarding the severity of the underlying diagnoses and CHC.[11] Thus, the group without cancer diagnosis but with SHCN might include children with other CHC with a stronger impact on MH and HrQoL than childhood cancer survivorship.

Overall, more than one-third (35.3%) of the YCCS were identified as having SHCN. This prevalence is considerably higher compared to children without cancer diagnosis (11.1%) and in other population-based studies.[11,30,31] Nevertheless, the prevalence of SHCN was 80% in a study sample solely including children with diagnosis of a CHC (such as asthma, arthritis, dermatitis, epilepsy, cystic fibrosis, diabetes, and cerebral palsy), hence distinctly higher than the prevalence in the ikidS-OEVA analytical sample.[32]

Strengths of the present study include the population-based study design as well as the representativeness of the analytical samples, supporting generalization of the results. Especially, the recruitment of YCCS based on the data from the GCCR allowed identifying and approaching all children with a cancer diagnosis at preschool age in Germany eligible for the study. The questionnaire instruments and items were identical between the ikidS-OEVA and the ikidS study, supporting internal validity. The statistical approach is based on knowledge drawn from previous research. Different sets of potential confounders were used for each dependent variable and were applied stepwise. In the present analysis, missing values were imputed using chained equations.

Several limitations may be mentioned. First, the data assessed within the ikidS-OEVA study are solely based on questionnaires and registry entries; no clinical examinations, hospital reports, or guided interviews were performed additionally. Second, survivors of brain tumors were excluded from the study for ethical reasons as a relevant proportion of this survivor group were expected to suffer from serious MH problems. The present results are therefore not generalizable to this group of childhood cancer survivors. However, the distribution of the remaining cancer diagnoses within the ikidS-OEVA analytical sample is in line with the general distribution of cancer types within the GCCR survivor population.[1] Third, the comparison group came from a regional population-based study conducted in the city of Mainz and the more rural region of Mainz-Bingen. A comparison with the YCCS cases might therefore be biased. However, the ikidS analytical sample is largely comparable with the German population of the same age. There are only small differences in the distribution of sex (male: 51.1% vs.

51.3%), migration background (16.9% vs. 19.3%), and SHCN (11.1% vs. 11.4%) compared to 3 to 6-year-old participants of the nationwide and representative KiGGS baseline study (2003–2006, $n = 3875$).[33]

In conclusion, YCCS are at increased risk of poorer MH and impaired HrQoL not only in the long-term, but already at preschool age. Assuming that poor MH and impaired HrQoL persist or exacerbate over time, this may have a substantial impact on subsequent school performance and educational attainment, which in turn may influence further psychosocial development, participation, and interaction. Accordingly, follow-up health care for YCCS should include early screening for MH problems and other sources of HrQoL deficits.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest. This publication contains data from the medical dissertation of Abigale Robinson.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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