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Socio-economic outcomes among long-term childhood acute lymphoblastic leukaemia survivors enrolled between 1971 and 1998 in EORTC CLG studies: Results of the 58LAE study

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Abstract

Objective: The objective of this study is to evaluate the socio-economic outcomes of survivors of childhood acute lymphoblastic leukaemia (ALL).

Methods: Childhood ALL adult survivors, enrolled in EORTC trials between 1971 and 1998 in France and Belgium, were invited to fill out a questionnaire with information about their socio-economic situation (living with a partner, having a university degree, having a job, working part time and history of having a paid job). The outcomes were compared with two matched control populations.

Results: Among 1418 eligible patients, 507 (35.8%) participated, including 39 (8%) and 61 (12%) patients who received a haematopoietic stem cell transplantation (HSCT) and a cranial radiotherapy (CRT), respectively. The median time to follow-up was 20 years, and median age was 25 years. Survivors showed a socio-economic level at least as good as controls. HCST and CRT were associated with a higher probability of not obtaining a bachelor degree (respectively OR = 3.49, 95% CI: 1.46–8.35 and OR = 2.31, 95% CI: 1.04–5.15), HSCT was associated with unemployment (OR = 2.89, 95% CI: 1.09–7.65) and having a relapse was associated with a higher probability of not having a partner (OR = 1.88, 95% CI: 1.01–3.51) adjusting for confounders.

Conclusion: Childhood ALL survivors showed a high level of socio-economic participation. HCST and CRT were associated with poorer functioning.

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KEYWORDS
childhood ALL, educational achievement, employment, long-term cancer survivors, marital status, socio-economic status

1 | INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy and accounts for around 30% of all childhood cancers (Smith et al., 2010). Over the last 50 years, there have been considerable improvements in the survival of childhood ALL patients following the progress in supportive care, the refinement of risk-based stratification and the use of intensive treatments, including haematopoietic stern cell transplantation (HSCT) and cranial radiotherapy (CRT) for specific subgroups. The 5-year overall survival probabilities progressively raised from 20% in 1970 to 90% with post-millennial therapy in westernised countries members of the Children's Oncology Group (COG) (Hunger & Mullighan, 2015). In this context, major challenges for paediatric oncologists evolved and currently include the management of late adverse events, the de-escalation of treatments and, more recently, the implementation of long-term follow-up programmes and the improvement of the long-term quality of life and the socio-economic functioning of the survivors. The long-term socio-economic outcomes after childhood ALL can be affected by persisting adverse effects, present in up to half of the survivors (Essig et al., 2014), neurocognitive impairment (especially for survivors who received CRT; Krull, Zhang, & Santucci, 2013), second cancer (Schmiegelow et al., 2013) and psychological problems (Massimo et al., 2005). Increasing awareness is emerging in some paediatric cancer follow-up cohorts (Gurney et al., 2009; Kirchhoff et al., 2011; Nathan et al., 2018) with studies which reported more unemployment, less academic achievement and a lower rate of relationship for cancer survivors compared to control groups. But literature remain still controversial, and certain authors described 'no negative impact' of ALL on long-term socio-economic outcome (Essig et al., 2014). In addition, it seems difficult to clearly identify the risk factors associated with a poorer socio-economic level after a childhood ALL as CRT or HSCT, and relapse, young age at diagnosis or female gender still argued despite meta-analysis (Lund et al., 2011). The conduct of studies evaluating long-term outcomes is methodologically a challenge and it may explain why the available data is inconsistent. Indeed, a small sample size (Holmqvist et al., 2010) can bias results a bit or a short follow-up time (Berbis et al., 2016; Pui et al., 2003) may distort the assessment of the career development not yet achieved. The inclusion of several childhood cancers in one cohort (Dumas et al., 2016; Mader et al., 2017; Wengenroth et al., 2014) (e.g., brain cancer and leukaemia) and the heterogeneity of treatments (Jacola et al., 2016) do not allow a robust conclusion by subgroup. Finally, the use of siblings as controls (Mody et al., 2008) is debated because illness could impact the whole family (Yang et al., 2016) in contrast to a general population control group.

The objectives of this study were to evaluate the socio-economic outcomes of adult survivors of childhood ALL, to investigate the effect of patient's characteristics and treatment modalities on the socio-economic outcomes and to describe the perception of the impact of cancer on work and education. This study is part of the larger EORTC 58LAE (Late Adverse Effect) study.

2 | PATIENTS AND METHODS

2.1 | Patient population and treatment protocol

All childhood ALL and lymphoblastic lymphoma (LBL) patients eligible to be treated between 1971 and 1998 in the BFM-based EORTC studies 58741, 58831/2 and 58881 conducted in Belgium and France (see Figure S1 and Table S1), younger than 18 years of age at diagnosis, alive and at least 18 years of age at the time of the follow-up were eligible for this socio-economic evaluation (Figure 1).

2.2 | Data collection

Between September 2011 and August 2017, eligible survivors were invited to fill out the 'Questionnaire on long-term outcome after leukemia', derived from the 'Life Situation Questionnaire' of the EORTC Lymphoma group (Van der Kaaij et al., 2012) and including information about the socio-economic situation of the survivors and their perception of the impact of the disease on their work and education. Additionally, treating institutions provided medical updates based on cancer registry data or medical records. Patients were considered as 'lost to follow-up' in case patient could not be reached (after at least two attempts to contact a patient). They were considered as 'refusing to take part' in case they stated their refusal by mail or by phone.

2.3 | Ethics

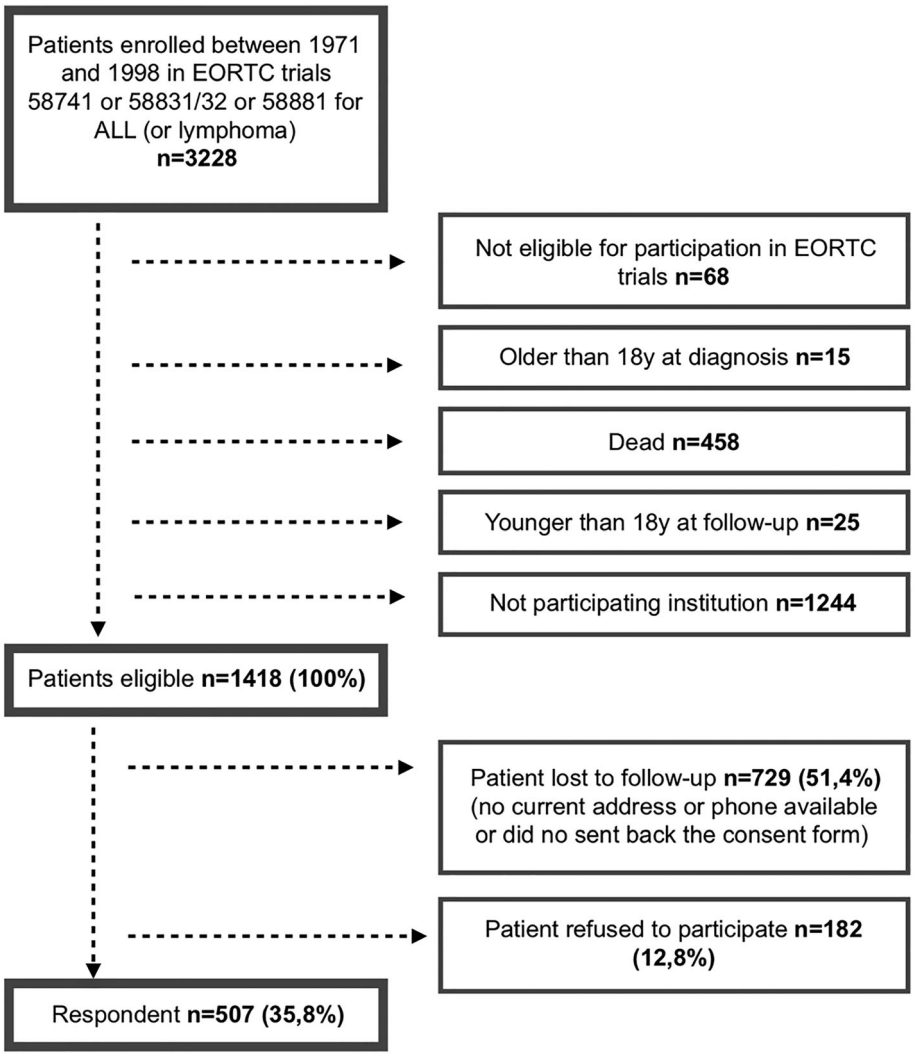
At the time of the enrolment in studies 58741, 58831/2 and 58881, informed consent was sought according to local practice of each participating centre and in accordance with the Declaration of Helsinki. The 58LAE study was approved by the Ethical Committees of the participating institutions and informed consent was obtained from all patients, in accordance with the applicable national legislation.

2.4 | Control groups

2.4.1 | European Union Labour Force Survey (LFS) controls

The LFS was used as the first source of general population controls. The LFS is a major source of information for European statistics about

FIGURE 1 Flow chart



the labour market. It is conducted by the national statistical institutes all over Europe and is centrally processed by Eurostat (2019), the statistical office of the European Union. It provides detailed information on topics including employment and education. The sampling is designed in order to ensure representativeness for the overall population. The data is collected based on individual interviews (see https://ec.europa.eu/eurostat for details). Specific items used in this study are listed in the Supporting Information. Individual participant LFS data from the countries and the period of time corresponding to the LSQ survey was made available by Eurostat for this project. Each survivor was matched by age, sex, country and exact year of survey with 93 LFS controls. This was the maximum number of controls with the desired values of matching factors that was available for all survivors. In case more than 93 matched LFS controls were available, those included in the analyses were randomly selected. Only survivors aged more than 20 years were compared to the LFS controls because LFS provided information about age in five-year intervals (e.g., 20–25). In order to ensure a comparable socio-economic status between cancer survivors and controls, a second sample was obtained that, in addition to the factors previously used for matching, was also matched by the level of education.

2.4.2 | Panel controls

Two control samples were obtained, one matched and one not matched by the level of education. In the first step, for each survivor a population control was sampled with the same age category (18–19, 20–21, ..., 38–39, 40–44, 45–52 years), province and level of urbanisation (urban vs. rural area). The level of urbanisation was based on the postal codes of residential addresses. The controls were sampled from a panel of 110,000 individuals in Belgium and 390,000 individuals in France, registered in the database of SurveyEngine, a company specialised in the conduct of surveys (https://surveyengine.com). In case more than one panel member matched a cancer survivor, one panel member was randomly selected to be invited to participate in the study. Between April 2019 and February 2020, the controls were provided with a computer- and mobile-device-based survey through an anonymous link, so that the General Data Protection Regulation was guaranteed. The questionnaire they filled in ('Global questionnaire for general population') was identical to the one completed by the survivors (except for questions related to ALL). One to one matched controls could be identified for 503 survivors. These 503 controls constituted the sample of controls matched by age

category, province and level of urbanisation but not the level of education.

The sample of controls matched additionally by the level of education was created as follows. Using the 503 controls, 348 survivors could be matched one to one by region (Flanders vs. Wallonia vs. Brussels, vs. France), level of urbanisation, sex and level of education (no secondary school diploma vs. secondary school diploma and no university degree vs. university degree) with the population controls. In case several of the 503 controls matched one survivor, one control was randomly selected to be used in the analysis. Controls matched one to one by region, level of urbanisation, sex and the level of education were then sampled for the remaining cancer survivors.

2.5 | Statistical analysis

For all estimated parameters, point estimates and two-sided 95% confidence intervals are presented. All tests were performed at a two-sided significance level of 0.05. The analysis was performed in SAS, version 9.4. The confidence intervals for proportions were estimated using the exact method of Clopper and Pearson (1934). The difference between proportions was tested using the chi-square test.

Logistic regression was used to investigate the associations between CRT (yes vs. no), HSCT (yes vs. no), relapse status (yes vs. no), age at diagnosis (<6 vs. 6–9 vs. 10–17 years) and NCI risk group at diagnosis (high risk vs. standard risk) and socio-economic outcomes adjusting for confounders. For CRT and HSCT, the models were adjusted for the other treatment (yes vs. no), sex, age at diagnosis (<6 vs. 6–9 vs. 10–17 years), relapse status/type (CNS relapse vs. other relapse without CNS relapses vs. no relapse), country (France vs. Belgium) and age at follow-up. For relapse, the models were adjusted for sex, age at diagnosis, country and age at follow-up. For age at diagnosis and risk group at diagnosis, the models were adjusted for protocol, sex, country and age at follow-up. To allow for non-linear effects, age at follow-up was modelled using restricted cubic splines with four knots located at the 5th, 25th, 75th and 95th percentiles (Harrell, 2001). The inference was based on the Wald tests and confidence intervals.

3 | RESULTS

3.1 | Study population

Among 1418 eligible survivors, more than a third ($N = 507$) provided information about socio-economic outcomes and were included in the analysis (Figure 1).

Females were overrepresented among the study participants. Patients lost to follow-up, those who refused to participate and respondents were comparable in terms of treatment protocol, age at diagnosis, white blood cells at diagnosis, NCI risk group, CNS involvement and early relapse rate (see Table S2).

The median age at socio-economic follow-up was 25 years (range 18–53). The median time between the diagnosis and the current study was 20 years (range 13–42). Among study participants, 149 (29%) were high risk at diagnosis according to the NCI classification (Table 1). CRT was used in 61 (12%) patients (37 in first line treatment), and 39 (8%) patients received stem cell transplantation (nine in first line treatment).

The sample of LFS controls included 42,036 subjects matched one to one by age, sex, country and year of survey with the survivors (each survivor was matched with 93 LFS controls with the same values for all matching factors). The response rate for panel controls was 25%. We identified 503 panel controls individually matched with cancer survivors by age, province, level of urbanisation and sex. Due to concerns about data quality (large number of missing values and inconsistent answers), 12 panel controls were excluded from the analysis. The final sample used in the analysis included 491 survivors and 491 matched one to one panel controls. Data for 480 panel controls matched one to one by region, level of urbanisation, sex and the level of education were available for a sensitivity analysis correcting for this indicator of the socio-economic status. Characteristics of patients and controls are available in Tables S3 and S4.

3.2 | Socio-economic outcomes among childhood ALL survivors compared to population controls

Among childhood ALL survivors, 38% were married or lived with a partner, 52% had a bachelor degree (or equivalent or higher) and 64% worked at the time of the follow-up (Table 2). Among those working, 79% worked full time. More than 70% of survivors had ever had a paid job. Survivors were similar to both LFS and panel controls in terms of having a partner and full-time employment among those working and had a higher level of education and a much higher employment rate compared to LFS controls (Table 3). In the analysis matched by the level of education, we did not observe any differences in the socio-economic endpoints between survivors and LFS or panel controls (see Tables S5 and S6). Ever having a paid job was not compared between survivors and panel controls due to the large number of missing data for panel controls.

3.3 | Associations between treatment exposures and patient's characteristics and socio-economic outcomes

Both HSCT and CRT were significantly associated with a higher probability of not obtaining a bachelor degree (OR = 3.49, 95% CI: 1.46–8.35 for HCST and OR = 2.31, 95% CI: 1.04–5.15 for CRT, respectively), and HSCT was associated with not having a job (OR = 2.89, 95% CI: 1.09–7.65), adjusting for possible confounders (Figure 2). We found no evidence of associations between treatment exposures and having a partner. The associations between age at diagnosis and NCI risk group at diagnosis and the socio-economic outcomes were not

TABLE 1 Characteristics of childhood ALL/LBL survivors

	HSCT		CRT		
	No ($N = 468$)	Yes ($N = 39$)	No ($N = 446$)	Yes ($N = 61$)	Total ($N = 507$)
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
EORTC study					
58741	25 (5.3)	0 (0.0)	0 (0.0)	25 (41.0)	25 (4.9)
58831/2	100 (21.3)	9 (23.1)	89 (20.0)	20 (32.8)	109 (21.5)
58881	343 (73.3)	30 (76.9)	357 (80.0)	16 (26.2)	373 (73.6)
Sex					
Male	208 (44.4)	22 (56.4)	203 (45.5)	27 (44.3)	230 (45.4)
Female	260 (55.6)	17 (43.6)	243 (54.5)	34 (55.7)	277 (54.6)
Age at diagnosis, years					
<6	307 (65.6)	25 (64.1)	296 (66.4)	36 (59.0)	332 (65.5)
6–9	95 (20.3)	10 (25.6)	91 (20.4)	14 (23.0)	105 (20.7)
10–17	66 (14.1)	4 (10.3)	59 (13.2)	11 (18.0)	70 (13.8)
NCI risk group					
Standard risk	340 (72.6)	18 (46.2)	317 (71.1)	41 (67.2)	358 (70.6)
High risk	128 (27.4)	21 (53.8)	129 (28.9)	20 (32.8)	149 (29.4)
Disease ($N = 506$)					
ALL	460 (98.5)	38 (97.4)	439 (98.4)	59 (98.3)	498 (98.4)
LBL	7 (1.5)	1 (2.6)	7 (1.6)	1 (1.7)	8 (1.6)
CRT					
No	412 (88.0)	34 (87.2)	446 (100.0)	0 (0.0)	446 (88.0)
Yes	56 (12.0)	5 (12.8)	0 (0.0)	61 (100.0)	61 (12.0)
HSCT					
No	468 (100)	0 (0.0)	412 (92.4)	56 (91.8)	468 (92.3)
Yes	0 (0.0)	39 (100)	34 (7.6)	5 (8.2)	39 (7.7)
Relapse status/type					
No relapse	430 (91.9)	10 (25.6)	402 (90.1)	38 (62.3)	440 (86.8)
Non-CNS relapse	27 (5.8)	19 (48.7)	36 (8.1)	10 (16.4)	46 (9.1)
CNS relapse	11 (2.3)	10 (25.6)	8 (1.8)	13 (21.3)	21 (4.1)
Age at follow-up, years					
18–24	225 (48.1)	16 (41.0)	232 (52.0)	9 (14.8)	241 (47.5)
25–34	198 (42.3)	22 (56.4)	198 (44.4)	22 (36.1)	220 (43.4)
35 or older	45 (9.6)	1 (2.6)	16 (3.6)	30 (49.2)	46 (9.1)

Abbreviations: ALL, acute lymphoblastic leukaemia; CNS, central nervous system; CRT, cranial radiotherapy; HSCT, haematopoietic stem cell transplantation; LBL, lymphoblastic lymphoma; NCI, National Cancer Institute.

statistically significant (see Tables S7 and S8). Having a relapse was associated with a higher probability of not having a partner (OR = 1.88, 95% CI: 1.01–3.51, see Table S9).

3.4 | Perception of the impact cancer on work and education

Among survivors who were at school at diagnosis, 60% had the feeling that ALL or its treatment had impact on their education and 22% retook 1 year at school due to ALL or its treatment (Table 4). Interestingly, 21% of survivors reported they had more education ambitions due to ALL or its treatment. Among survivors who had ever had a paid job, 23% felt that ALL or its treatment had impact on their work and 2% were unable to work due to ALL or its treatment.

4 | DISCUSSION

Overall, childhood ALL and LBL survivors showed socio-economic outcomes comparable to the general population controls. The level of education in our sample of patients appeared much higher than

TABLE 2 Socio-economic outcomes of childhood ALL/LBL survivors by treatment exposures

	HSCT		CRT		
	No ($N = 468$)	Yes ($N = 39$)	No ($N = 446$)	Yes ($N = 61$)	Total ($N = 507$)
Endpoint	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Being married or living with a partner ($N = 503$)					
No	283 (61.0)	29 (74.4)	279 (63.1)	33 (54.1)	312 (62.0)
Yes	181 (39.0)	10 (25.6)	163 (36.9)	28 (45.9)	191 (38.0)
Level of education ($N = 499$)					
No secondary school diploma	18 (3.9)	2 (5.1)	12 (2.7)	8 (13.6)	20 (4.0)
Secondary school diploma, no bachelor degree	196 (42.6)	24 (61.5)	188 (42.7)	32 (54.2)	220 (44.1)
Bachelor degree/or equivalent or higher	246 (53.5)	13 (33.3)	240 (54.5)	19 (32.2)	259 (51.9)
Currently working ($N = 503$)					
No	162 (34.9)	19 (48.7)	166 (37.5)	15 (25.0)	181 (36.0)
Yes	302 (65.1)	20 (51.3)	277 (62.5)	45 (75.0)	322 (64.0)
Employment time among working ($N = 320$)					
Part time	60 (19.9)	6 (31.6)	55 (20.0)	11 (24.4)	66 (20.6)
Full time	241 (80.1)	13 (68.4)	220 (80.0)	34 (75.6)	254 (79.4)
Ever having a paid job ($N = 501$)					
No	127 (27.5)	11 (28.2)	132 (29.9)	6 (10.2)	138 (27.5)
Yes	335 (72.5)	28 (71.8)	310 (70.1)	53 (89.8)	363 (72.5)

Abbreviations: CRT, cranial radiotherapy; HSCT, haematopoietic stem cell transplantation.

expected based on data from the EU-LFS, a major source of information for European statistics. This observation can possibly be explained by an over-representation of patients with a high socio-economic status among study participants. Adjusting for differences in the level of education, marital status, employment status, working time and history of having a paid job were similar between survivors and population controls. Although 60% of survivors who were at school at diagnosis felt that leukaemia or its treatment had impact on their education, only 4% reported they were unable to finish education due to leukaemia or its treatment. Only 3% of those working at the time of the study felt lack of correspondence between their work and qualifications due to leukaemia. However, HSCT and CRT were associated with poorer socio-economic outcomes and having a relapse was associated with a higher probability of not having a partner.

Most previous studies reported a worse socio-economic status for cancer survivors compared to peers, but they considered all paediatric cancers (Mader et al., 2017; Wengenroth et al., 2014) including brain tumours (Dumas et al., 2016). Comparable or even better outcomes of leukaemia survivors were reported by the French cohort study 'LEA' (Berbis et al., 2016) regarding employment and by Zynda et al. (2012) regarding education. Apart from the possibility of selection bias, the improved socio-economic outcome could be explained by some resilience (Cho et al., 2016). Indeed, in our study, more than 20% of survivors reported having more educational ambitions due to leukaemia or its treatment. The high level of socio-economic participation can also be explained by the social welfare system in France and Belgium, which aims to reduce inequalities through social reintegration and special education programs for most vulnerable people. This could also explain the differences between results of survivorship evaluations conducted in Europe and the United States (de Boer et al., 2006) added with the fact that CRT has been used in ALL first line treatment longer in United States than in Europe (Vilmer & Suciu, 2000). Mody et al. (2008) reported, in a large multicentre North American long-term follow-up study, a lower rate of marriage and university degree in childhood ALL survivors compared to siblings.

Our study confirms the negative impact of CRT on educational achievement of survivors, as already described (Harila-Saari et al., 2007). The likely explanation of this result is the occurrence of neurocognitive sequelae (Krull, Brinkman, & Li, 2013). We previously evaluated the long-term outcomes of the randomised question comparing *No CRT* versus *CRT* in medium/high-risk ALL patients included in study 58832 and reported cognitive disturbance in 18.8% of the patients in the *No CRT* arm versus 42.1% in the *CRT* arm (Piette et al., 2020).

HSCT was associated with a higher probability of not obtaining a bachelor degree and not having a job. Due to its recent use and limited indications, the impact of HSCT on the long-term socio-economic outcomes and quality of life has not been thoroughly studied to date. Two studies, with small sample size, reported a negative impact of HSCT on physical functioning, but not on social functioning (Freycon et al., 2014; Sundberg et al., 2013). The largest cohort of childhood ALL survivors who received HSCT ('LEA') reported poorer socio-economic outcomes as compared to the French reference population (Bernard et al., 2014; Visentin et al., 2016). The social impact of HSCT

TABLE 3 Comparison of socio-economic outcomes between childhood ALL/LBL survivors and LFS controls and panel controls

	Survivors		LFS controls			Survivors		Panel controls		
Endpoint	***N***	**% (95% CI)**	***N***	**% (95% CI)**	***P* value[a]**	***N***	**% (95% CI)**	***N***	**% (95% CI)**	***P* value[a]**
Being married or living with a partner	449[b]		42,036[b]		0.16	487[b]		489[b]		0.15
No	262	58.4 (53.6–63.0)	23,138	55.0 (54.6–55.5)		300	61.6 (57.1–65.9)	279	57.1 (52.5–61.5)	
Yes	187	41.6 (37.0–46.4)	18,898	45.0 (44.5–45.4)		187	38.4 (34.1–42.9)	210	42.9 (38.5–47.5)	
Level of education	446[b]		42,036[b]		<0.001	483[b]		483[b]		<0.001
No secondary school diploma	18	4.0 (2.4–6.3)	7116	16.9 (16.6–17.3)		19	3.9 (2.4–6.1)	1	0.2 (0.0–1.1)	
Secondary school diploma, no bachelor degree	189	42.4 (37.7–47.1)	19,921	47.4 (46.9–47.9)		212	43.9 (39.4–48.4)	152	31.5 (27.3–35.8)	
Bachelor degree/or equivalent or higher	239	53.6 (48.8–58.3)	14,999	35.7 (35.2–36.1)		252	52.2 (47.6–56.7)	330	68.3 (64.0–72.5)	
Currently working	450[b]		42,036[b]		0.007	487[b]		491[b]		0.98
No	137	30.4 (26.2–34.9)	15,362	36.5 (36.1–37.0)		177	36.3 (32.1–40.8)	178	36.3 (32.0–40.7)	
Yes	313	69.6 (65.1–73.8)	26,674	63.5 (63.0–63.9)		310	63.7 (59.2–67.9)	313	63.7 (59.3–68.0)	
Employment time among working	311[b]		26,674[b]		0.79	308[b]		300[b]		0.44
Part time	61	19.6 (15.3–24.5)	5391	20.2 (19.7–20.7)		63	20.5 (16.1–25.4)	54	18.0 (13.8–22.8)	
Full time	250	80.4 (75.5–84.7)	21,283	79.8 (79.3–80.3)		245	79.5 (74.6–83.9)	246	82.0 (77.2–86.2)	
Ever having a paid job	448[b]		42,036[b]		0.81					
No	95	21.2 (17.5–25.3)	9114	21.7 (21.3–22.1)						
Yes	353	78.8 (74.7–82.5)	32,922	78.3 (77.9–78.7)						

Abbreviations: CI, confidence interval; LFS, Labour Force Survey.

[a]*P* value from the chi-square test.

[b]Number of subjects with available information. Study participants younger than 20 years of age were excluded from LFS comparison (see Section 2.5 for motivation).

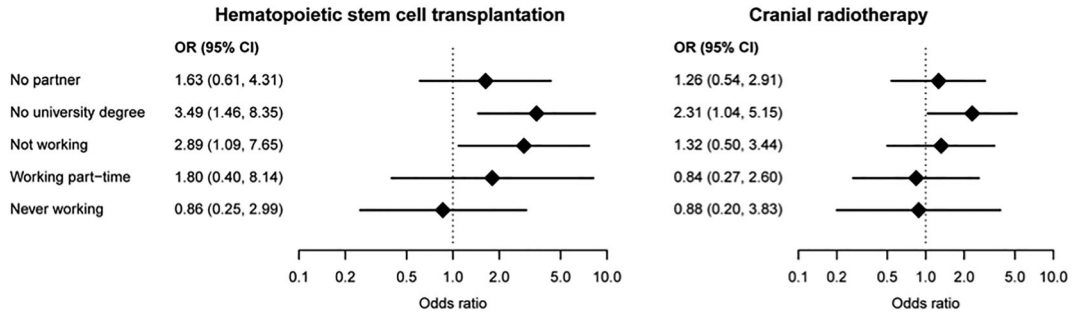


FIGURE 2 Associations between haematopoietic stem cell transplantation, cranial radiotherapy and socio-economic endpoints. Estimated odds ratios (OR) and the 95% confidence interval (CI) from the logistic regression models are provided. For each endpoint, a separate model was fitted including the following covariates: sex, age at diagnosis, country, relapse, age at follow-up, CRT and HSCT. For the endpoint working part time, only survivors currently working were included in the analysis.

TABLE 4 Perception of the impact of cancer on work and education

Survivors who were at school at diagnosis ($N = 331$)		
Impact on education ($N = 329$[a])	***N***	**% (95% CI)**
Feeling that leukaemia or its treatment had impact on education	198	60.2 (54.7–65.5)
More educational ambitions	68	20.7 (16.4–25.5)
Less education ambitions	34	10.3 (7.3–14.1)
Retaking 1 year	71	21.6 (17.3–26.4)
Retaking 2 or more years	18	5.5 (3.3–8.5)
Changing education plans	33	10.0 (7.0–13.8)
Unable to finish education due to leukaemia or its treatment	14	4.3 (2.3–7.0)
Survivors who had ever had a paid job ($N = 363$)		
Impact on work ($N = 354$[a])	***N***	**% (95% CI)**
Feeling that leukaemia or its treatment had impact on work	82	23.2 (18.9–27.9)
More professional ambitions due to leukaemia or its treatment	39	11.0 (8.0–14.8)
Less professional ambitions due to leukaemia or its treatment	8	2.3 (1.0–4.4)
Disabled/unable to work due to leukaemia or its treatment	6	1.7 (0.6–3.7)
Reduced the number of hours worked due to leukaemia or its treatment	6	1.7 (0.6–3.7)
Survivors who had a job at the time of the follow-up ($N = 322$)		
Impact on work ($N = 313$[a])	***N***	**% (95% CI)**
Feeling that work corresponds to qualifications	260	83.1 (78.4–87.1)
Feeling of lack of correspondence between work and qualifications due to leukaemia ($N = 312$[a])	10	3.2 (1.5–5.8)

Abbreviation: CI, confidence interval.
[a]Number of subjects with available information.

can be explained by a break in the academic career (Sodergren et al., 2018), as observed in more than a quarter of the survivors in our study. This can be linked to prolonged hospitalisations and late back-to-school time due to immunodeficiency. Furthermore, survivors with a lower level of education have less access to employment. In addition, HSCT can induce chronic graft-versus-host disease and other physical sequelae that have been shown to decrease social quality of life scores (Ishida et al., 2011).

Concerning relapses, supported by our results, it would seem that experiencing the relapse of leukaemia exposes survivors to a higher risk of celibacy as explained by Howard et al. (2014) who summarised the different psychosocial mechanisms of social and affective isolation lived by cancer survivors.

The main limitation of our study is the possibility of an over-representation of survivors with a high socio-economic status due to possible recruitment bias. However, the respondents and non-respondents showed comparable disease characteristics. The interpretation of socio-economic outcomes of cancer survivors requires data for a reference population, which is typically difficult to collect. In this study, two reference populations were used: one based on LFS, the major source of European statistics about the labour market, and one based on a panel of survey respondents. The response rate of panel controls was only 25%. This could have resulted in a selection bias. Indeed, the level of education of panel controls appeared much higher as compared to LFS controls suggesting a selection bias. In order to deal with the risk of a selection bias, we performed a sensitivity analysis matched by the level of education. However, there may be factors not related to ALL or its treatment other than the matching factors used with a different distribution among ALL survivors and population controls. The drawback of LFS controls is that the LFS data was collected using a different questionnaire than the one filled out by the ALL survivors. However, the fact that the analyses with both control samples provided the same conclusion of similar socio-economic outcomes of ALL survivors and population controls adds credibility to our findings.

This is the largest study in Europe that addressed the socio-economic outcomes of childhood ALL survivors. Besides the large sample size, the study has several other strengths, including the long follow-up time and the use of two individually matched control groups.

In conclusion, childhood ALL survivors in Belgium and France showed socio-economic outcomes comparable to the population controls. HSCT and CRT were associated with poorer socio-economic outcomes. Further refinement of risk-based stratification and de-escalation of treatments at risk of long-term sequelae (e.g., CRT-free treatment or reduced-intensity HSCT conditioning) is warranted (Pui et al., 2009; Sirvent et al., 2011; Sison & Silverman, 2014). Psychosocial and educational support should continue to be easily accessible for childhood ALL survivors.

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CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

According to the EORTC Data Sharing policies, data are available under specific conditions (please refer to https://www.eortc.org/datasharing/).

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REFERENCES

Berbis, J., Reggio, C., & Michel, G. (2016). Employment in French young adult survivors of childhood leukemia: An LEA study (for Leucemies de l'Enfant et de l'Adolescent-childhood and adolescent leukemia). *Journal of Cancer Survivorship*, *10*, 1058–1066. https://doi.org/10.1007/s11764-016-0549-0

Bernard, F., Auquier, P., & Herrmann, I. (2014). Health status of childhood leukemia survivors who received hematopoietic cell transplantation after BU or TBI: An LEA study. *Bone Marrow Transplantation*, *49*, 709–716. https://doi.org/10.1038/bmt.2014.3

Cho, O.-H., Yoo, Y.-S., & Hwang, K.-H. (2016). Impact of ego-resilience and family function on quality of life in childhood leukemia survivors. *Iranian Journal of Public Health*, *45*(11), 1446–1454.

Clopper, C. J., & Pearson, E. S. (1934). The use of confidence of fiducial limits illustrated in the case of the binomial. *Biometrika*, *26*(4), 404–413. https://doi.org/10.1093/biomet/26.4.404

de Boer, A. G. E. M., Verbeek, J. H. A. M., & van Dijk, F. J. H. (2006). Adult survivors of childhood cancer and unemployment: A metaanalysis. *Cancer*, *107*, 1–11. https://doi.org/10.1002/cncr.21974

Dumas, A., Berger, C., & Auquier, P. (2016). Educational and occupational outcomes of childhood cancer survivors 30 years after diagnosis: A French cohort study. *British Journal of Cancer*, *114*, 1060–1068. https://doi.org/10.1038/bjc.2016.62

Essig, S., Li, Q., & Chen, Y. (2014). Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: A report from the Childhood Cancer Survivor Study cohort. *The Lancet Oncology*, *15*, 841–851. https://doi.org/10.1016/S1470-2045(14)70265-7

Eurostat. (2019). Data Explorer. Accessed April 1, 2019. https://ec.europa.eu/eurostat

Freycon, F., Trombert-Paviot, B., & Casagranda, L. (2014). Academic difficulties and occupational outcomes of adult survivors of childhood leukemia who have undergone allogeneic hematopoietic stem cell transplantation and fractionated total body irradiation conditioning. *Pediatric Hematology and Oncology*, *31*, 225–236. https://doi.org/10.3109/08880018.2013.829541

Gurney, J. G., Krull, K. R., & Kadan-Lottick, N. (2009). Social outcomes in the Childhood Cancer Survivor Study cohort. *Journal of Clinical*

Oncology, *27*, 2390–2395. https://doi.org/10.1200/JCO.2008.21.1458

Harila-Saari, A. H., Lähteenmäki, P. M., Pukkala, E., Kyyrönen, P., Lanning, M., & Sankila, R. (2007). Scholastic achievements of childhood leukemia patients: A nationwide, register-based study. *Journal of Clinical Oncology*, *25*, 3518–3524. https://doi.org/10.1200/JCO.2006.09.4987

Harrell, F. (2001). *Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis*. Springer. https://doi.org/10.1007/978-1-4757-3462-1

Holmqvist, A. S., Wiebe, T., Hjorth, L., Lindgren, A., Øra, I., & Moëll, C. (2010). Young age at diagnosis is a risk factor for negative late socioeconomic effects after acute lymphoblastic leukemia in childhood. *Pediatric Blood & Cancer*, *55*, 698–707. https://doi.org/10.1002/pbc.22670

Howard, A. F., Tan de Bibiana, J., & Smillie, K. (2014). Trajectories of social isolation in adult survivors of childhood cancer. *Journal of Cancer Survivorship*, *8*, 80–93. https://doi.org/10.1007/s11764-013-0321-7

Hunger, S. P., & Mullighan, C. G. (2015). Acute lymphoblastic leukemia in children. *The New England Journal of Medicine*, *373*, 1541–1552. https://doi.org/10.1056/NEJMra1400972

Ishida, Y., Honda, M., & Kamibeppu, K. (2011). Social outcomes and quality of life of childhood cancer survivors in Japan: A cross-sectional study on marriage, education, employment and health-related QOL (SF-36). *International Journal of Hematology*, *93*, 633–644. https://doi.org/10.1007/s12185-011-0843-6

Jacola, L. M., Edelstein, K., & Liu, W. (2016). Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: A report from the Childhood Cancer Survivor Study. *Lancet Psychiatry*, *3*, 965–972. https://doi.org/10.1016/S2215-0366(16)30283-8

Kirchhoff, A. C., Krull, K. R., & Ness, K. K. (2011). Occupational outcomes of adult childhood cancer survivors: A report from the childhood cancer survivor study. *Cancer*, *117*, 3033–3044. https://doi.org/10.1002/cncr.25867

Krull, K. R., Brinkman, T. M., & Li, C. (2013). Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St Jude lifetime cohort study. *Journal of Clinical Oncology*, *31*, 4407–4415. https://doi.org/10.1200/JCO.2012.48.2315

Krull, K. R., Zhang, N., & Santucci, A. (2013). Long-term decline in intelligence among adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiation. *Blood*, *122*, 550–553. https://doi.org/10.1182/blood-2013-03-487744

Lund, L. W., Schmiegelow, K., Rechnitzer, C., & Johansen, C. (2011). A systematic review of studies on psychosocial late effects of childhood cancer: Structures of society and methodological pitfalls may challenge the conclusions. *Pediatric Blood & Cancer*, *56*, 532–543. https://doi.org/10.1002/pbc.22883

Mader, L., Michel, G., & Roser, K. (2017). Unemployment following childhood cancer. *Deutsches Ärzteblatt International*, *114*, 805–812. https://doi.org/10.3238/arztebl.2017.0805

Massimo, L., Zarri, D., & Caprino, D. (2005). Psychosocial aspects of survivors of childhood cancer or leukemia. *Minerva Pediatrica*, *57*(6), 389–397.

Mody, R., Li, S., & Dover, D. C. (2008). Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: A report from the Childhood Cancer Survivor Study. *Blood*, *111*, 5515–5523. https://doi.org/10.1182/blood-2007-10-117150

Nathan, P. C., Henderson, T. O., Kirchhoff, A. C., Park, E. R., & Yabroff, K. R. (2018). Financial hardship and the economic effect of childhood cancer survivorship. *JCO*, *36*, 2198–2205. https://doi.org/10.1200/JCO.2017.76.4431

Piette, C., Suciu, S., & Bertrand, Y. (2020). Long-term outcome evaluation of medium/high risk acute lymphoblastic leukaemia children treated with or without cranial radiotherapy in the EORTC 58832 randomized study. *British Journal of Haematology*, *189*, 351–362. https://doi.org/10.1111/bjh.16337

Pui, C.-H., Campana, D., & Pei, D. (2009). Treating childhood acute lymphoblastic leukemia without cranial irradiation. *The New England Journal of Medicine*, *360*, 2730–2741. https://doi.org/10.1056/NEJMoa0900386

Pui, C.-H., Cheng, C., & Leung, W. (2003). Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. *The New England Journal of Medicine*, *349*, 640–649. https://doi.org/10.1056/NEJMoa035091

Schmiegelow, K., Levinsen, M. F., & Attarbaschi, A. (2013). Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology*, *31*, 2469–2476. https://doi.org/10.1200/JCO.2012.47.0500

Sirvent, N., Suciu, S., Rialland, X., Millot, F., Benoit, Y., Plantaz, D., Ferster, A., Robert, A., Lutz, P., Nelken, B., Plouvier, E., Norton, L., Bertrand, Y., & Otten, J. (2011). Prognostic significance of the initial cerebro-spinal fluid (CSF) involvement of children with acute lymphoblastic leukaemia (ALL) treated without cranial irradiation: Results of European Organization for Research and Treatment of Cancer (EORTC) Children Leukemia Group study 58881. *European Journal of Cancer*, *47*, 239–247. https://doi.org/10.1016/j.ejca.2010.10.019

Sison, E. A. R., & Silverman, L. B. (2014). CNS prophylaxis in pediatric acute lymphoblastic leukemia. *Hematology. American Society of Hematology. Education Program*, *2014*, 198–201. https://doi.org/10.1182/asheducation-2014.1.198

Smith, M. A., Seibel, N. L., & Altekruse, S. F. (2010). Outcomes for children and adolescents with cancer: Challenges for the twenty-first century. *Journal of Clinical Oncology*, *28*, 2625–2634. https://doi.org/10.1200/JCO.2009.27.0421

Sodergren, S. C., Husson, O., & Rohde, G. E. (2018). A life put on pause: An exploration of the health-related quality of life issues relevant to adolescents and young adults with cancer. *Journal of Adolescent and Young Adult Oncology*, *7*, 453–464. https://doi.org/10.1089/jayao.2017.0110

Sundberg, K. K., Wettergren, L., Frisk, P., & Arvidson, J. (2013). Self-reported quality of life in long-term survivors of childhood lymphoblastic malignancy treated with hematopoietic stem cell transplantation versus conventional therapy. *Pediatric Blood & Cancer*, *60*, 1382–1387. https://doi.org/10.1002/pbc.24519

Van der Kaaij, M. A. E., Heutte, N., & Meijnders, P. (2012). Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: A European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Étude des Lymphomes de l'Adulte Cohort Study. *Journal of Clinical Oncology*, *30*, 291–299. https://doi.org/10.1200/JCO.2011.37.1989

Vilmer, E., & Suciu, S. (2000). Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report. *Leukemia*, *14*, 2257–2266. https://doi.org/10.1038/sj.leu.2401960

Visentin, S., Auquier, P., & Bertrand, Y. (2016). The impact of donor type on long-term health status and quality of life after allogeneic hematopoietic stem cell transplantation for childhood acute leukemia: A Leucémie de l'Enfant et de L'Adolescent Study. *Biology of Blood and Marrow Transplantation*, *22*, 2003–2010. https://doi.org/10.1016/j.bbmt.2016.08.004

Wengenroth, L., Rueegg, C. S., & Michel, G. (2014). Life partnerships in childhood cancer survivors, their siblings, and the general population.

Pediatric Blood & Cancer, *61*, 538–545. https://doi.org/10.1002/pbc.24821

Yang, H.-C., Mu, P.-F., Sheng, C.-C., Chen, Y.-W., & Hung, G. Y. (2016). A systematic review of the experiences of siblings of children with cancer. *Cancer Nursing*, *39*, E12–E21. https://doi.org/10.1097/NCC.0000000000000258

Zynda, A., Reinmuth, S., Pfitzer, C., Hohmann, C., Keil, T., & Borgmann-Staudt, A. (2012). Childhood leukemia and its impact on graduation and having children: Results from a national survey. *Leukemia & Lymphoma*, *53*, 2419–2422. https://doi.org/10.3109/10428194.2012.688965

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