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# Risk of cerebrovascular disease among 13 457 five-year survivors of childhood cancer: A population-based cohort study

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## Abstract

Survivors of childhood cancer treated with cranial irradiation are at risk of cerebrovascular disease (CVD), but the risks beyond age 50 are unknown. In all, 13457 survivors of childhood cancer included in the population-based British Childhood Cancer Survivor Study cohort were linked to Hospital Episode Statistics data for England. Risk of CVD related hospitalisation was quantified by standardised hospitalisation ratios (SHRs), absolute excess risks and cumulative incidence. Overall, 315 (2.3%) survivors had been hospitalised at least once for CVD with a 4-fold risk compared to that expected (95% confidence interval [CI]: 3.7-4.3). Survivors of a central nervous system (CNS) tumour and leukaemia treated with cranial irradiation were at greatest risk of CVD (SHR = 15.6, 95% CI: 14.0-17.4; SHR = 5.4; 95% CI: 4.5-6.5, respectively). Beyond age 60, on average, 3.1% of CNS tumour survivors treated with cranial irradiation were hospitalised annually for CVD (0.4% general population). Cumulative incidence of CVD increased from 16.0% at age 50 to 26.0% at age 65 (general population: 1.4-4.2%). In conclusion, among CNS tumour survivors treated

**Abbreviations:** AER, absolute excess risk; BCCSS, British Childhood Cancer Survivor Study; CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; CVD, cerebrovascular disease; HES, hospital episode statistics; ICD, International Classification of Diseases; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NHS, National Health Service; RER, relative excess risk; RR, relative risk; SHR, standardised hospitalisation ratio.

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with cranial irradiation, the risk of CVD continues to increase substantially beyond age 50 up to at least age 65. Such survivors should be: counselled regarding this risk; regularly monitored for hypertension, dyslipidaemia and diabetes; advised on lifestyle risk behaviours. Future research should include the recall for counselling and brain MRI to identify subgroups that could benefit from pharmacological or surgical intervention and establishment of a case-control study to comprehensively determine risk-factors for CVD.

#### KEYWORDS

cancer survivorship, cohort, epidemiology, late effects

## 1 | BACKGROUND

Survival after childhood cancer has markedly improved over the last few decades with overall 5-year survival in the United Kingdom now exceeding 80%.<sup>1</sup> Although the number of long-term survivors continues to increase, many subgroups of survivors are at risk of developing adverse health conditions many years after treatment.<sup>2,3</sup> Circulatory conditions, including cerebrovascular disease (CVD), are the leading cause of death among ageing survivors.<sup>4</sup> Studies specifically investigating CVD in survivors have reported substantively increased risks among survivors previously treated with cranial radiotherapy, but only up to age 50.<sup>5-12</sup> Beyond age 50, the risk of developing CVD in the general population doubles every 10 years,<sup>13</sup> but it is uncertain how the risk among survivors of childhood cancer, particularly those treated with cranial radiotherapy, develops with increasing age. If the relative risk (RR) remains elevated into ages at which the risk of developing CVD in the general population starts to increase substantially, then a considerable number of survivors could be affected. To our knowledge, this is the first large-scale study to quantify the risks of CVD up to age 65 according to whether survivors were treated with cranial radiotherapy or not.

The principal aim of our study was to determine the long-term risks of hospitalisations due to CVD among 5-year survivors of childhood cancer—particularly among those treated with cranial radiotherapy—through electronic linkage of the British Childhood Cancer Survivor Study (BCCSS) with the national hospital episode statistics (HES) database.

## 2 | METHODS

### 2.1 | British Childhood Cancer Survivor Study

The BCCSS is a population-based cohort of 17 980 individuals diagnosed with a childhood cancer between 1940 and 1991 inclusive, before age 15 years, in Great Britain and who survived for at least 5 years from diagnosis.<sup>14</sup> The cohort was identified through the population-based National Registry of Childhood Tumours.

### What's New?

Many sub-groups of childhood-cancer survivors have an increased risk of developing adverse health conditions later in life. In our study, the authors found that patients who were treated with cranial irradiation in childhood face a substantially greater risk of cerebrovascular disease after age 50. By age 65, as many as 26% of these patients will have been hospitalised for a cerebrovascular event. These survivors should therefore be counselled regarding lifestyle behaviours to reduce this risk. They should also be regularly monitored for hypertension, dyslipidaemia and diabetes.

### 2.2 | Hospital episode statistics

HES are a centralised data warehouse maintained by National Health Service (NHS) Digital containing records of inpatient, outpatient and accident and emergency admissions to NHS hospitals within England.<sup>15</sup> Records in HES are classified into hospital episodes which relate to a period of care for a patient under a single consultant. Variables recorded in HES include: an episode start and end date, a primary diagnosis code and 19 additional subsidiary diagnosis codes which may relate to the primary diagnosis or to other coexisting conditions.<sup>16</sup> Diagnosis codes are classified using the International Classification of Diseases 10th revision (ICD-10). The BCCSS cohort was electronically linked by a third party (Northgate Solutions) to the inpatient HES database covering inpatients episodes from 1 April 1997 to 31 December 2012 using NHS number, date of birth, postcode and sex. Survivors who had died before 1 April 1997 (N = 2378) or who were Scottish or Welsh residents (N = 2101) were excluded.

### 2.3 | Definition of CVD

The primary and 19 subsidiary diagnosis code fields for each inpatient HES record were used to identify CVD related hospitalisations

(ICD-10:I60-68). If an individual had multiple CVDs, then only the first occurrence was considered except for analyses relating to the mean cumulative count. Survivors with any hospitalisation recorded as “sequelae of CVD” (ICD-10:I69), but no prior CVD recorded in HES were excluded (N = 44); as such survivors most likely have had a prior CVD before the HES database was available for linkage.

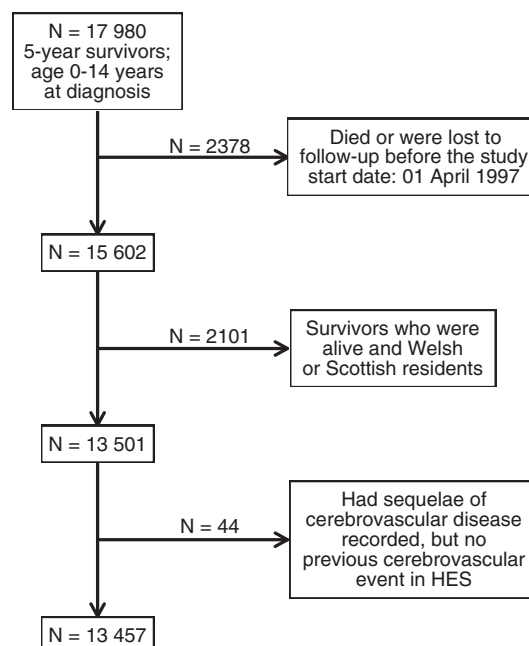
## 2.4 | Radiotherapy ascertainment

Information on initial radiotherapy treatment in the form of yes/no has previously been abstracted from medical records for 74% of all survivors in the cohort available for analyses. We assumed that any survivor with a tumour site “brain” or “meninges” and who had been treated with radiotherapy had been exposed to cranial irradiation. Any leukaemia survivor treated with radiotherapy before 1991 was assumed to have received prophylactic cranial irradiation unless information in the medical record unequivocally stated that no radiotherapy was given. Survivors who had received radiotherapy for a tumour other than a central nervous system (CNS) tumour or leukaemia that was within the neck or head region were considered as having received “head and neck” radiotherapy. For survivors of any other tumour site—regardless of whether they were treated with radiotherapy or not—we assumed that they had not been exposed to cranial irradiation or radiation to the head and neck. Separate analyses were conducted for CNS tumour, leukaemia and head and neck tumour survivors treated with radiotherapy as these were assumed a priori to be at high risk. Analyses for Hodgkin lymphoma survivors treated with radiotherapy were not conducted as it was not possible to accurately determine the site of the radiation.

## 2.5 | Statistical methods

Survivors entered the period at risk at 1 April 1997 and exited at the earliest occurrence of: death, loss-to follow-up, hospitalisation for CVD, or 31 December 2012 (study end date). CVD-related hospitalisation rates for the general population were derived from the entire (anonymised) HES dataset by dividing the number of individuals with a hospitalisation by the mid-year general population estimates for each age (1-year bands), sex and calendar-year (1-year bands).<sup>17</sup> The accumulated person-years within each age, sex and calendar year stratum in the survivor cohort were multiplied by the corresponding general population rates to obtain the expected number of CVD hospitalisations. The risks of hospitalisation due to CVD were quantified by standardised hospitalisation ratios (SHRs) and absolute excess risks (AERs). The SHR was defined as the number of observed divided by the number of expected CVD hospitalisations. The AER was defined as the number of observed CVD hospitalisations minus the number of expected CVD hospitalisations divided by the number of person-years at risk and then multiplied by 10 000. The AER may be interpreted as the number of additional hospitalisations per year per 10 000 survivors attributable to the original childhood cancer diagnosis or its treatment. SHRs and AERs were stratified by the following

factors: sex, type of childhood cancer,<sup>18</sup> age at childhood cancer diagnosis (0-3/4-7/9-11/12-14 years), period of cancer diagnosis (<1970/1970-74/1975-79/1980-84/1985-91), attained age (<20/20-29/30-39/40-49/50-59/≥60 years) and cranial radiotherapy (yes/no). To investigate the simultaneous effect of potential risk factors of CVD, a multivariable Poisson regression model with the log of the expected number of CVD hospitalisations as the offset was used to estimate the RRs.<sup>19</sup> RRs can be interpreted as the ratio of the SHRs adjusted for potential confounders. A similar multivariable Poisson regression model but with the offset being the  $\ln(\text{person-years})$  and the link function:  $\ln(\mu_j - d_j^*)$ , where  $\mu_j$  is the observed and  $d_j^*$  the expected number of CVDs for stratum  $j$  of a relevant factor, was fitted to estimate relative excess risks (RERs).<sup>20</sup> RERs can be interpreted as the ratio of the AERs adjusted for potential confounders. Negative binomial regression was used instead of Poisson regression when the model fit showed signs of overdispersion. A likelihood-ratio test was used to test for linear trend of a factor by comparing the deviance of a model including the factor variable of interest, which was coded using consecutive nonnegative integer values (eg, 0/1/2/3), to the deviance of a model without the factor variable of interest. The cumulative incidence of the first occurrence of being hospitalised for CVD was calculated taking into account the competing risk of death.<sup>21</sup> In addition, the mean cumulative count (MCC) of being hospitalised for a CVD including for any recurrent CVDs was calculated.<sup>22</sup> The MCC can be interpreted as the average number of CVD hospitalisations per survivor. Statistical significance was taken at the 5% level (two-sided test). All statistical analyses were conducted in Stata statistical software version 16 except for the MCC which was conducted in R.



**FIGURE 1** Flow diagram showing exclusions for the cohort of British Childhood Cancer Survivor Study linked with HES

### 3 | RESULTS

#### 3.1 | Cohort characteristics

Of the 17 980 childhood cancer survivors in the cohort, 13 457 (74.8%) were eligible for linkage with HES (Figure 1). The total follow-up

was 200 146 person-years with a median follow-up time of 15.8 years. Overall, 315 (2.3%) survivors had been hospitalised at least once for CVD with 20% (N = 63) of all survivors hospitalised at least twice. CVD was most common after a CNS tumour (N = 186; 59%), leukaemia (N = 57; 18%) and Hodgkin lymphoma (N = 17; 5%) (Table 1).

**TABLE 1** Observed and expected numbers of any cerebrovascular hospitalisations, standardised hospitalisation ratios and absolute excess risks for all childhood cancer survivors combined

				Any cerebrovascular hospitalisation	
		No	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)
Overall		13 457	315/78.9	4.0 (3.7,4.3)	11.8 (10.6,13.1)
Sex	Male	7347	183/47.7	3.8 (3.3,4.4)	12.4 (10.2,15.1)
	Female	6110	132/31.1	4.2 (3.6,5.0)	11.0 (8.8,13.8)
	<i>P</i> <sub>heterogeneity</sub>			.382	.426
Type of childhood cancer <sup>b</sup>	CNS tumour	2885	186/19.6	9.5 (8.2,10.9)	40.7 (34.7,47.8)
	Leukaemia	3544	57/12.2	4.7 (3.6,6.0)	8.4 (6.0,11.7)
	Hodgkin's lymphoma	961	17/7.0	2.4 (1.5,3.9)	7.0 (3.1,15.7)
	Soft tissue sarcoma	691	12/6.7	1.9 (1.0,3.7)	4.1 (1.0,16.3)
	Non-Hodgkin lymphoma	922	9/4.7	1.8 (1.0,3.2)	3.9 (1.1,13.7)
	Wilms tumour	605	9/5.9	1.6 (0.7,3.8)	2.0 (0.2,21.3)
	Others	1198	8/8.4	1.5 (0.8,2.9)	1.7 (0.3,11.4)
	bone sarcoma	508	6/4.2	1.4 (0.6,3.2)	2.4 (0.2,33.1)
	neuroblastoma	1169	5/3.1	1.0 (0.5,1.9)	0.0
	NH-retinoblastoma	549	4/4.2	1.0 (0.4,2.6)	0.0
	H-retinoblastoma	425	2/3.0	0.7 (0.2,2.7)	0.0
	<i>P</i> <sub>heterogeneity</sub>			<.001	<.001
Age at diagnosis (y)	0-3	5322	78/25.0	3.1 (2.5,3.9)	6.6 (4.8,9.2)
	4-8	3301	92/16.2	5.7 (4.6,7.0)	15.4 (12.0,19.8)
	9-11	2549	83/16.9	4.9 (4.0,6.1)	17.7 (13.5,23.2)
	12-14	2285	62/20.7	3.0 (2.3,3.8)	12.2 (8.4,17.8)
	<i>P</i> <sub>trend</sub>			.827	.001
Decade of diagnosis	<1970	2484	102/38.8	2.6 (2.2,3.2)	17.7 (12.9,24.2)
	1970-1974	1640	47/9.9	4.8 (3.6,6.3)	15.4 (10.7,22.1)
	1975-1979	2148	53/9.0	5.9 (4.5,7.7)	13.6 (9.9,18.9)
	1980-1984	2599	69/7.7	8.9 (7.1,11.3)	15.7 (12.0,20.5)
	1985-1991	4586	44/13.5	3.3 (2.4,4.4)	4.4 (2.9,6.8)
	<i>P</i> <sub>trend</sub>			<.001	<.001
Attained age (y)	<20	164	18/8.7	2.1 (1.3,3.3)	3.2 (1.3,7.9)
	20-29	2584	57/7.0	8.2 (6.3,10.6)	8.0 (5.9,10.7)
	30-39	4615	89/14.3	6.2 (5.0,7.6)	12.4 (9.7,15.9)
	40-49	3804	72/20.1	3.6 (2.8,4.5)	16.0 (11.6,22.0)
	50-59	1601	56/19.0	3.0 (2.3,3.8)	28.8 (19.4,42.8)
	60+	689	23/9.9	2.3 (1.6,3.5)	45.0 (22.0,92.0)
	<i>P</i> <sub>trend</sub>			.014	<.001

Abbreviations: AER, absolute excess risk; CI, confidence interval; O/E, observed/expected; SHR, standardised hospitalisation ratio.

<sup>a</sup>AERs per 10 000 person-years.

<sup>b</sup>Childhood cancer types as defined by the International Childhood Cancer Classification, version 3.

**TABLE 2** Observed and expected numbers of a cerebrovascular related hospitalisation, standardised hospitalisation ratios, and absolute excess risks among central nervous system (CNS) tumour survivors

	All CNS tumour survivors				Treated with cranial radiotherapy				No cranial radiotherapy			
	No	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)	O/E	SHR (95% CI)
Overall	2885	186/19.6	9.5 (8.2,11.0)	40.7 (34.7,47.8)	155/9.9	15.6 (14.0,17.4)	73.2 (65.0,82.4)	23/7.8	3.0 (2.2,3.9)	11.3 (7.3,17.5)		
Sex												
Male	1556	109/11.9	9.2 (7.6,11.1)	44.4 (36.0,54.8)	92/6.3	14.5 (11.8,17.8)	77.0 (61.8,95.9)	12/4.4	2.7 (1.5,4.8)	11.1 (4.5,27.2)		
Female	1329	77/7.8	9.9 (7.9,12.4)	36.4 (28.4,46.7)	63/3.6	17.5 (13.7,22.4)	68.3 (52.5,88.7)	11/3.4	3.3 (1.8,5.9)	11.5 (4.9,27.0)		
P <sub>heterogeneity</sub>			.612	.231		.256	.488		.652	.953		
CNS subtype <sup>b</sup>												
Astrocytoma	1482	84/10.7	7.9 (6.3,9.7)	34.3 (26.9,43.8)	67/4.5	14.9 (11.7,18.9)	78.7 (60.9,101.8)	14/5.0	2.8 (1.66,4.73)	10.4 (4.6,23.6)		
Medulloblastoma	380	37/1.9	19.4 (14.0,26.7)	67.7 (48.2,95.0)	37/1.9	19.4 (14.0,26.7)	67.7 (48.2,95.0)	0	–	–		
Ependymoma	224	17/1.6	10.8 (6.7,17.3)	49.9 (29.5,84.2)	15/0.7	20.7 (12.5,34.3)	88.4 (52.0,150.5)	1/0.7	1.4 (0.2,9.8)	3.12 (0.00,3743.36)		
Craniopharyngioma	231	16/1.5	10.8 (6.6,17.6)	46.1 (26.9,79.1)	11/0.8	14.4 (8.0,26.0)	80.1 (42.5,151.2)	3/0.6	5.4 (1.8,16.8)	20.64 (5.16,82.62)		
Others	568	32/4.0	8.1 (5.7,11.5)	34.7 (23.4,51.6)	25/2.0	12.3 (8.3,18.2)	60.3 (39.4,92.4)	5/1.5	3.3 (1.4,7.9)	12.60 (3.58,44.38)		
P <sub>heterogeneity</sub>			.753	.813		.438	.433		.628	.67		
Age at diagnosis (y)												
0-3	641	29/2.9	10.1 (7.1,14.6)	28.9 (19.3,43.3)	23/1.4	17.0 (11.3,25.5)	51.8 (33.6,80.0)	3/1.0	3.0 (1.0,9.4)	7.28 (1.35,39.32)		
4-8	861	56/5.1	11.0 (8.5,14.3)	41.2 (30.9,54.9)	45/2.6	17.3 (12.9,23.2)	68.1 (50.0,92.9)	10/2.0	5.0 (2.7,9.3)	19.79 (9.12,42.92)		
9-11	736	60/5.3	11.3 (8.8,14.6)	53.3 (40.4,70.4)	52/2.7	19.3 (14.7,25.3)	94.6 (71.0,126.0)	6/2.3	2.7 (1.2,5.9)	11.21 (3.10,40.47)		
12-14	647	41/6.3	6.5 (4.8,8.8)	37.6 (26.2,54.1)	35/3.3	10.7 (7.6,14.8)	75.3 (52.2,108.5)	4/2.5	1.6 (0.6,4.2)	4.39 (0.30,64.73)		
P <sub>trend</sub>			.035	.203		.062	.09		.119	.587		
Decade of diagnosis												
<1970	701	64/11.1	5.7 (4.5,7.3)	55.3 (41.1,74.4)	56/5.8	9.7 (7.5,12.6)	96.7 (72.2,129.5)	7/5.0	1.4 (0.7,3.0)	5.24 (0.41,67.72)		
1970-1974	400	26/2.6	9.9 (6.8,14.6)	41.2 (26.9,63.2)	24/1.5	16.2 (10.9,24.2)	68.5 (44.7,105.0)	1/0.9	1.1 (0.2,7.5)	–		
1975-1979	466	32/2.1	15.1 (10.7,21.4)	44.8 (30.9,64.9)	28/1.2	24.1 (16.7,35.0)	72.0 (48.9,105.9)	4/0.9	4.4 (1.6,11.7)	11.03 (3.10,39.28)		
1980-1984	489	41/1.5	27.4 (20.2,37.3)	56.8 (41.3,78.0)	32/0.8	39.4 (27.8,55.6)	81.6 (57.2,116.4)	9/0.6	15.1 (7.8,28.9)	30.39 (15.10,61.19)		
1985-1991	829	23/2.2	10.3 (6.8,15.5)	17.3 (11.0,27.2)	15/0.7	21.2 (12.8,35.2)	37.7 (22.2,64.1)	2/0.3	5.7 (1.4,22.7)	8.23 (1.53,44.27)		
P <sub>trend</sub>			<.001	.001		<.001	.011		<.001	.14		
Attained age (y)												
<20	41	7/1.1	6.1 (2.9,12.7)	14.9 (6.1,36.2)	4/0.4	10.5 (4.0,28.1)	28.4 (9.6,84.0)	1/0.2	6.3 (0.9,44.9)	14.9 (1.5,152.2)		
20-29	390	32/1.2	27.5 (19.4,38.9)	29.6 (20.7,42.4)	24/0.5	48.4 (32.5,72.3)	54.0 (35.9,81.2)	5/0.3	15.8 (6.6,38.06)	16.9 (6.6,43.1)		
30-39	851	54/3.1	17.4 (13.4,22.8)	39.5 (29.8,52.4)	47/1.6	28.5 (21.4,37.9)	66.3 (49.3,89.2)	6/1.1	5.5 (2.5,12.2)	10.9 (4.1,29.0)		
40-49	916	45/5.6	8.1 (6.1,10.9)	44.3 (31.8,61.9)	38/3.1	12.2 (8.9,16.8)	70.0 (49.5,99.0)	6/2.1	2.8 (1.3,6.2)	11.3 (3.2,39.1)		

(Continues)

**TABLE 2** (Continued)

	All CNS tumour survivors				Treated with cranial radiotherapy				No cranial radiotherapy			
	No	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)		O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)	
50-59	472	34/5.7	5.9 (4.2-8.3)	72.4 (48.3-108.5)	31/3.0	10.2 (7.2-14.6)	138.4 (93.7-204.4)		2/2.5	0.8 (0.2-3.2)	–	
60+	215	14/2.9	4.8 (2.9-8.1)	130.5 (67.3-252.8)	11/1.3	8.6 (4.7-15.4)	271.3 (138.9-529.7)		3/1.6	1.9 (0.6-5.9)	30.0 (2.8-324.4)	
<i>P</i> <sub>trend</sub>			<.001	<.001		<.001	<.001			.001	.397	

Abbreviations: AER, absolute excess risk; CI, confidence interval; O/E, observed/expected; SHR, standardised hospitalisation ratio.

<sup>a</sup>AERs per 10 000 person-years.

<sup>b</sup>CNS subtype as defined by the International Childhood Cancer Classification, version 3.

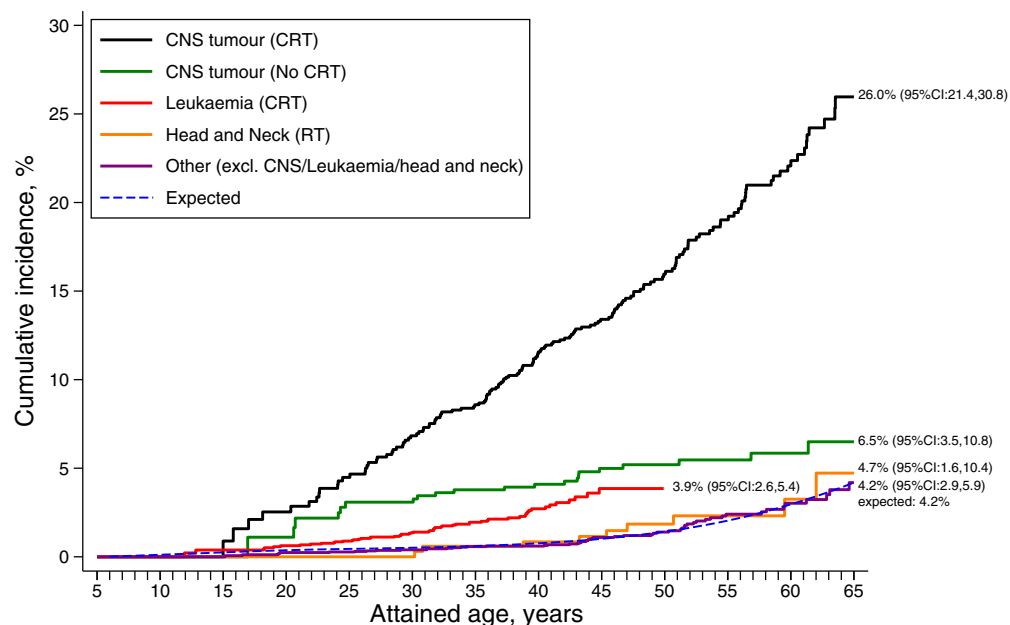
### 3.2 | All survivors

All survivors combined had a 4-fold risk of being hospitalised for CVD compared with expected (95% confidence interval [CI]: 3.7-4.3) (Table 1). Of all types of childhood cancer, survivors of CNS tumours were at the greatest risk of CVD (SHR = 9.5, 95% CI: 8.2-11.0, AER = 40.7); whilst those treated for leukaemia (SHR = 4.7, 95% CI: 3.6-6.1, AER = 8.4), Hodgkin lymphoma (SHR = 2.4, 95% CI: 1.5-3.9, AER = 7.0) and soft tissue sarcoma (SHR = 1.8, 95% CI: 1.0-3.2, AER = 3.9) had significant excess risks but of reduced magnitude. The SHR of developing CVD declined significantly with increasing attained age ( $P_{\text{trend}} = .014$ ), but was still 2.3-fold at ages 60 and older (95% CI: 1.6, 3.5). In contrast, the AER increased significantly with increasing attained age ( $P_{\text{trend}} < .001$ ) from 3 (per 10 000 person-years) among those aged <20 years to 45 among those aged ≥60 years. These trends with attained age were confirmed in multivariable analyses (Table S1).

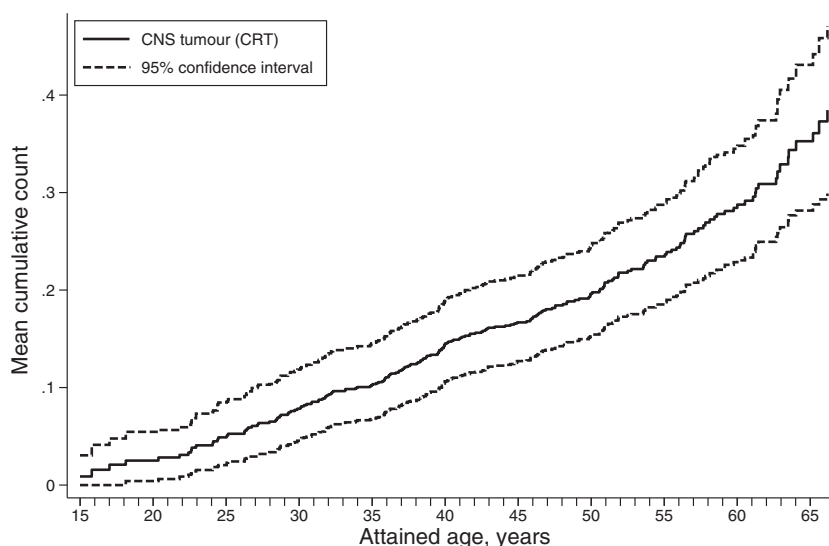
### 3.3 | CNS tumour survivors

CNS tumour survivors treated with cranial irradiation had 15-fold the expected risk of any CVD (95% CI: 14.0-17.4); corresponding to 73 excess hospitalisations per 10 000 person-years (95% CI: 65.0-82.4) (Table 2). The SHR was still more than 8-fold that expected after age 60 (95% CI: 4.7-15.4). The AER increased significantly with attained age reaching 130 for all CNS tumour survivors combined after age 60 and more than 270 for those treated with cranial irradiation. Every year, on average 3.1% ( $\text{rate}_{\text{observed}} = 3.07$  per 100 person-years) of CNS tumour survivors who received cranial irradiation and survived beyond 60 years of age were hospitalised for CVD, whereas only 0.4% ( $\text{rate}_{\text{expected}} = 0.36$  per 100 person-years) was expected. CNS tumour survivors treated without cranial radiotherapy were at 3-fold risk compared with expected (95% CI: 2.2-3.9), but the AER never exceeded 30 at any age. SHRs and AERs did not vary significantly by CNS tumour subtype (all  $P \geq .43$ ). Any significant trends in SHRs and AERs observed by age at diagnosis and decade of treatment were not confirmed in multivariable analyses (Table S2). Among CNS tumour survivors treated with cranial irradiation the cumulative incidence of CVD was 11.6% (95% CI: 8.6-15.0) by age 40, increased to 16.0% (95% CI: 12.7-19.6) by age 50 and reached 26.0% (95% CI: 21.4-30.8) by age 65, whilst only 4.2% was expected by age 65 (Figure 2). At that age the MCC was 0.35 (95% CI: 0.28, 0.43) meaning that by age 65 the average number of CVD hospitalisations per CNS tumour survivor treated with cranial irradiation was 0.35 (Figure 3). For CNS tumour survivors not treated with cranial irradiation the cumulative incidence reached 6.5% (95% CI: 3.5-10.8) by age 65. When evaluating the cumulative incidence by CNS tumour subtype, 29.1% (95% CI: 21.5-37.2) of astrocytoma survivors treated with cranial irradiation had developed CVD by age 65; few medulloblastoma survivors had survived up to age 65, but the cumulative incidence was already 24.5% (95% CI: 17.2-32.5) by age 60 (vs 2.9% expected) (Figure 4).

**FIGURE 2** Cumulative incidence of hospitalisation for a cerebrovascular event by previous cranial radiotherapy (CRT) or not



**FIGURE 3** Mean cumulative count and corresponding 95% confidence intervals of developing cerebrovascular disease among survivors of a CNS tumour treated with cranial radiotherapy as a function of attained age



### 3.4 | Leukaemia survivors

Among leukaemia survivors treated with cranial radiotherapy the SHR was five times that expected (95% CI: 4.5-6.5) (Table 3). In absolute terms, this equated to 10 excess hospitalisations per 10 000 person-years with the AER increasing up to 18 by age 40 years ( $P_{\text{trend}} = .002$ ) (Table 3; Table S3). The cumulative incidence for leukaemia survivors previously treated with cranial irradiation was 3.9% (95% CI: 2.6-5.4) by age 50 years and substantially above that expected (1.4%) (Figure 2).

### 3.5 | Head and neck tumour survivors

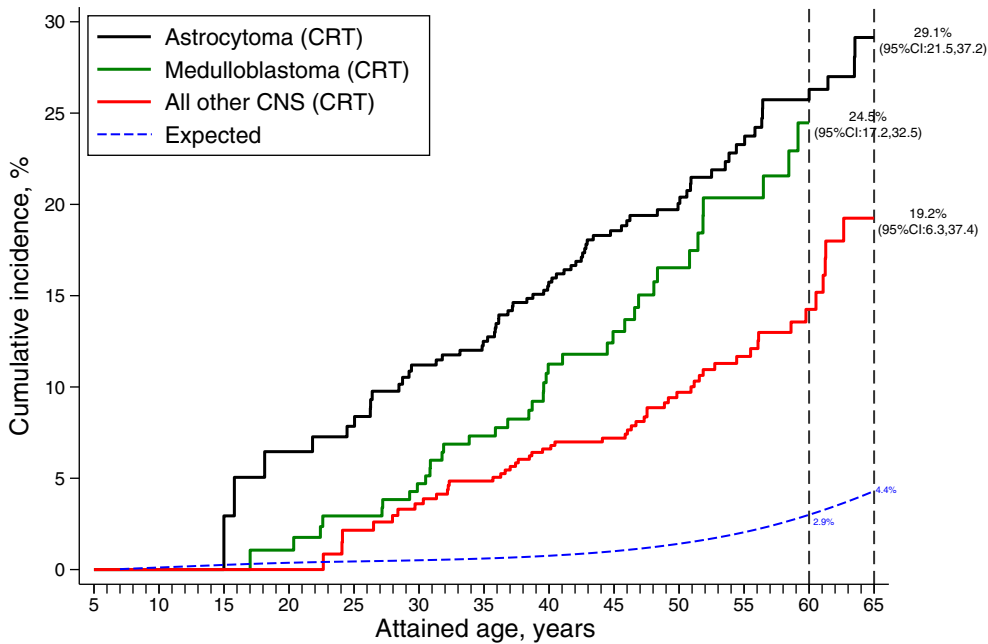
The 736 survivors who were previously diagnosed with a tumour in the head and neck region and treated with radiotherapy (Table S4)

were at 2-fold the expected risk (95% CI: 1.2-4.1; 10 CVD events). The cumulative incidence reached 4.7% (95% CI: 1.6-10.4) for this group by age 65 (Figure 2).

## 4 | DISCUSSION

### 4.1 | Main findings

Evidence is provided—to our knowledge for the first time—that both the absolute risk and the excess number of inpatient hospitalisations for CVD, among survivors of a childhood CNS tumour treated with cranial irradiation, increases substantially beyond age 50 up to at least age 65. By age 65, more than a quarter of such survivors have been hospitalised. Each year lived by such survivors aged over 60 years results in 3% being hospitalised, whilst only 0.4% would be expected.



**FIGURE 4** Cumulative incidence of hospitalisation for cerebrovascular disease for specific subtypes of CNS tumours treated with cranial radiotherapy, including astrocytoma, medulloblastoma, and all other CNS tumours

**TABLE 3** Observed and expected numbers of any cerebrovascular related hospitalisation overall among leukaemia survivors, standardised hospitalisation ratios and absolute excess risks

			Any Cerebrovascular hospitalisation				Treated with cranial radiotherapy		
			No	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)	O/E	SHR (95% CI)	AER <sup>a</sup> (95% CI)
Overall		3544	57/12.2	4.7 (3.9,5.6)	8.4 (6.6,10.6)		55/10.2	5.4 (4.47,6.5)	9.5 (7.55,11.95)
Sex	Male	1856	33/6.9	4.8 (3.4,6.7)	9.4 (6.1,14.5)		32/5.8	5.6 (3.9,7.9)	10.7 (7.0,16.3)
	Female	1688	24/5.3	4.5 (3.0,6.8)	7.3 (4.4,12.2)		23/4.4	5.2 (3.4,7.8)	8.2 (5.0,13.7)
	<i>P</i> <sub>heterogeneity</sub>			.866	.454			.793	.437
Age at diagnosis (years)	0-3	1575	28/5.0	5.6 (3.9,8.2)	9.7 (6.2,15.1)		27/4.2	6.5 (4.5,9.5)	10.9 (7.0,17.1)
	4-8	1157	17/3.8	4.5 (2.8,7.2)	7.6 (4.1,13.9)		16/3.3	4.9 (3.0,8.0)	8.1 (4.4,15.0)
	9-11	533	10/2.1	4.8 (2.6,8.9)	10.0 (4.6,21.9)		10/1.7	6.0 (3.2,11.1)	12.1 (5.7,25.4)
	12-14	279	2/1.4	1.5 (0.4,5.8)	1.5 (0.0,126.8)		2/1.1	1.8 (0.4,7.1)	2.4 (0.1,58)
	<i>P</i> <sub>trend</sub>			.071	.308			.103	.376
Decade of diagnosis	<1970	70	0/0.8	—	—		0/0.2	—	—
	1970-1979	1033	24/4.5	5.4 (3.6,8.0)	12.4 (7.6,20.3)		23/4.0	5.75 (3.8,8.7)	13.2 (8.0,21.6)
	1980-1991	2441	33/6.9	4.8 (3.4,6.7)	7.1 (4.6,10.9)		32/6.0	5.34 (3.8,7.5)	8.0 (5.2,12.3)
	<i>P</i> <sub>trend</sub>			.321	.351			.834	.232
Attained age (years)	<20	75	7/3.3	2.1 (1.0,4.5)	3.4 (0.9,13.7)		6/2.6	2.3 (1.0,5.1)	3.9 (0.9,15.9)
	20-29	971	18/2.5	7.3 (4.6,11.6)	6.9 (4.1,11.9)		18/2.3	8.0 (5.0,12.7)	7.7 (4.6,13.1)
	30-39	1571	23/3.7	6.3 (4.2,9.5)	12.3 (7.6,20.0)		23/3.4	6.8 (4.5,10.2)	13.5 (8.4,21.8)
	40+	927	9/2.8	3.2 (1.7,6.1)	14.0 (5.4,36.4)		8/2.0	4.0 (2.0,8.1)	18.0 (7.2,45.1)
	<i>P</i> <sub>trend</sub>			.215	.016			.14	.012

Abbreviations: AER, absolute excess risk; CI, confidence interval; O/E, observed/expected; SHR, standardised hospitalisation ratio.

<sup>a</sup>AERs per 10 000 person-years.

Importantly, we know that the absolute risk of 26% affected by age 65 is an underestimate of the true risk because an independent study of the completeness of ascertainment of cardiovascular disease using HES reported that 71% (95% CI: 62%-79%) of clinically ascertained and confirmed CVD were independently ascertained by HES.<sup>23</sup> In

particular, fatal CVD which occur outside of a hospital setting are unlikely to be captured. To investigate the impact of this particular type of under-ascertainment, we identified such deaths because the cohort is also linked to the national death registry.<sup>24</sup> Including such events resulted in the cumulative incidence of CVD by age

65 increasing by 1% to 27%. There was no evidence that the excess risk varied with age or decade at which cranial irradiation was received.

## 4.2 | Previous studies

Recently, the North-American Childhood Cancer Survivor Study (CCSS)<sup>6</sup> reported risks of self-reported CVD up to age 50 with a cumulative incidence of 19.9% for survivors at high risk. A French study demonstrated that 11.3% of survivors treated with high-dose cranial irradiation with doses exceeding 10 Gray to the major intracranial vessels developed CVD by age 45.<sup>8</sup> A Dutch study including 28 strokes found a cumulative incidence of 10.0% for developing stroke by age 45 among survivors treated with cranial irradiation only.<sup>12</sup> The cumulative incidence figures from these studies are consistent with the 13.4% and 16.0% cumulative incidence at age 45 and 50, respectively, for survivors of a CNS tumour treated with cranial irradiation we report here. However, the current study shows that the cumulative incidence of CVD continues to increase substantially beyond age 50 years up to 26.0% by age 65.

The 4-fold overall increased SHR of CVD among all survivors in our study was similar to that observed in the Scandinavian ALiCCS study<sup>25</sup>; the only other large-scale population-based study investigating long-term risks of CVD hospitalisations. Consistent with our study, the ALiCCS study also demonstrated that the AER of developing CVD increases substantially with attained age, although our study did not report risk estimates by whether survivors had been treated with cranial irradiation.

In our study, CNS tumour survivors treated *without* cranial irradiation were still at excess risk of CVD, although the risks were much lower than among those treated with cranial irradiation. This is consistent with data reported from the CCSS,<sup>5</sup> although the risk when compared with siblings was 13-fold (95% CI: 4.8–34.5) within the CCSS; much higher than the 3-fold increased SHR we report here. Notably, the risks among survivors treated *without* cranial irradiation were mainly high in the first few decades after 5-year survival, but did not appear to increase substantially with increasing attained age.

Several studies among survivors of childhood cancer demonstrated strong dose-response relationships between the cumulative radiation dose to the brain and risk of CVD.<sup>5,8–12</sup> Intracranial vascular damage—including stenosis constricting blood flow and aneurysms—is common after high-dose cranial radiation involving the major cranial blood vessels,<sup>26</sup> although the exact mechanism by which cranial irradiation may increase the risk of CVD is unclear.

Children's Oncology Group survivorship guidelines<sup>27</sup> from the USA indicate that survivors treated with cranial radiotherapy with doses exceeding 18 Gray should be considered for brain magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA) as clinically indicated. Current childhood cancer survivorship guidelines from the United Kingdom do not make reference to surveillance for CVD.<sup>28</sup> In the general population, silent CVD is 10 times more prevalent than symptomatic stroke<sup>29</sup> and it is conceivable that the

prevalence of silent CVD would be even greater in the survivor population. In a study<sup>30</sup> among 132 paediatric patients treated with brain radiotherapy 41.6% showed microbleeds or cavernomas after a mean follow-up of only 11 years—which is a remarkably large percentage considering the young age of these patients. In studies among individuals from the general population the risk of developing a symptomatic, mainly ischaemic, stroke after a silent brain infarct was 1.5- to 3.3-fold.<sup>31</sup>

## 4.3 | Implications for clinical practice

As reported in a recent review,<sup>32</sup> there is suggestive evidence that conditions which predispose to CVD such as hypertension, dyslipidaemia and diabetes are more common<sup>33,34</sup> and tend to develop at younger ages among childhood cancer survivors as compared with siblings or the general population.<sup>35–37</sup> Therefore, to avoid the potential for underdiagnosis, it would be prudent that survivors who received cranial irradiation are regularly monitored for such conditions. The review<sup>32</sup> also identified suggestive evidence of lifestyle factors being important in terms of reducing the risk of cardiovascular conditions among survivors, in particular exercise<sup>38</sup> and diet.<sup>33</sup> Smoking and alcohol consumption are risk factors for stroke in the general population.<sup>39,40</sup> Therefore, regular counselling in follow-up clinics in relation to exercise, diet, smoking and alcohol would be prudent from a precautionary perspective. However, most previous work relates to cardiac disease and there is a need for detailed aetiological studies concerning CVD.

## 4.4 | Implications for further research

A question raised by such a large absolute risk (26% affected by age 65) is whether some form of screening (eg, MRA) to detect abnormalities whilst asymptomatic would be beneficial to survivors. However, this immediately begs the question—if abnormalities are found, is there a suitable intervention to prevent or reduce the risk of symptomatic CVD developing? At present, we do not know the answer to this question and in particular we do not have an understanding of the developmental processes leading to CVD. A first step should probably involve investigating intracranial vasculature abnormalities present in those at greatest excess risk—survivors of CNS tumours which were cranially irradiated and aged over 50, or possibly younger. The recall of this national high-risk group for counselling and a brain MRI (with MRA) to characterise the nature and extent of intracranial vasculature abnormalities needs serious consideration. The motivation for such an undertaking is to determine whether a subgroup can be identified for whom pharmacological or surgical intervention could bring preventive/risk reduction benefit. For example, there is recent evidence that suggests that surgical revascularisation in *moya-moya* substantially reduces the risk of further stroke.<sup>41–45</sup> To fully understand the aetiology of CVD after cancer when young, we propose to undertake a large population-based nationwide case-control study to

determine the role of cumulative dose of radiation to the intracranial vasculature, cumulative dose of individual cytotoxics, surgery for cancer, genotypic factors, age, gender, ethnicity, co-morbidities and potentially modifiable risk factors including smoking, alcohol, waist-to-hip ratio, diet and physical activity. We have previously published on the substantial risk of CVD among survivors of teenage and young adult cancer which revealed that by age 60 9%, 6% and 5% of CNS tumour, head and neck cancer and leukaemia survivors, respectively, had been hospitalised with CVD whereas 2% were expected.<sup>46</sup> The case-control study would be nested within the entire national population-based childhood, teenage and young adult cohort combined.

#### 4.5 | Study limitations

A limitation of this cohort study concerns the limited information available relating to cumulative exposure of the intracranial vasculature to radiation as a result of radiotherapy, but we plan to address this in the planned case-control study. Additionally, as a result of the level of ascertainment of events specified as haemorrhagic or infarction differing between observed and expected, we could not investigate excess risks for these different types of events because of the potential for bias in the SHR and AERs. It should also be acknowledged that the risks presented here relate to survivors treated three or more decades ago and that the risks might not be translatable to survivors treated more recently. Current radiation regimes, techniques, modalities and volumes have changed with more conformal techniques minimising non-target tissue radiation exposure, hence the risks presented here may be an overestimate of the risk of CVD for patients treated more recently with cranial radiotherapy.

#### 4.6 | Conclusions

Among CNS tumour survivors treated with cranial irradiation, the risk of developing CVD increases substantially between age 40 and 65 years. Clinically, such survivors should be: counselled with regards to the substantially increased risk; regularly monitored for hypertension, dyslipidaemia and diabetes; and advised on the potential benefits of exercise, healthy diet, smoking cessation and drinking within guidelines. Future research among such survivors should include: the recall for counselling and brain MRI (including MRA) of those aged 50 years—or possibly younger—to identify subgroups that could potentially benefit from pharmacological or surgical intervention; and establishment of a large-scale case-control study to determine the aetiology of CVD for future prevention or intervention.

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#### CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

#### ETHICS STATEMENT

Our study was approved by the National Research Ethics Committee (10/H1102/86). The Confidentiality Advisory Group consented to processing identified data without individual patient consent (ECC 2-02 (f)/2011).

#### DATA AVAILABILITY STATEMENT

Individual patient data are not publicly available due to potential identification of individuals. Access to other anonymised aggregated data may be granted under conditions agreed with the relevant legal and research ethics committees and with appropriate data sharing agreements and permissions from external data providers in place. All outputs are subject to the codes of practice for official statistics. The corresponding author should be contacted to for enquiries relating to potential data access.

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#### SUPPORTING INFORMATION

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

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