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ORIGINAL ARTICLE

Birthweight and all-cause mortality after childhood and adolescent leukemia: a cohort of children with leukemia from Denmark, Norway, Sweden, and Washington State

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ABSTRACT

Background: High birthweight may predispose children to acute lymphoid leukemia, whereas low birthweight is associated with childhood morbidity and mortality. Low and high birthweight have been inconsistently associated with mortality in children with leukemia.

Material and methods: In a cohort of childhood and adolescent leukemia (0–19 years) patients from registries in Denmark, Norway, Sweden, and Washington State in the United States (1967–2015), five-year all-cause mortality was assessed by birthweight and other measures of fetal growth using the cumulative incidence function and Cox regression with adjustment for sex, diagnosis year, country, the presence of Down's syndrome or other malformations, and type of leukemia.

Results: Among 7148 children and adolescents with leukemia (55% male), 4.6% were low (<2500 g) and 19% were high (≥4000 g) birthweight. Compared with average weight, hazard ratios (HRs) of death associated with low birthweight varied by age at leukemia diagnosis: 1.5 (95% confidence interval (CI): 0.7, 3.2) for patients 0–1 year old, 1.6 (95% CI: 1.0, 2.6) for >1–2 years old; 1.0 (95% CI: 0.6, 1.5) for 3–8 years old; 1.0 (95% CI: 0.6, 1.8) for 9–13 years old; and 1.2 (95% CI: 0.7, 2.1) for 14–19 years old, and were similar for size for gestational age and Ponderal index. In analyses restricted to children born full term (37–41 weeks of gestation), results were only slightly attenuated but risk was markedly increased for infants aged ≤1 year (HR for low birthweight = 3.2, 95% CI: 1.2, 8.8).

Conclusion: This cohort study does not suggest that low birthweight or SGA is associated with increased five-year all-cause mortality risk among children with any type of childhood leukemia or acute lymphoblastic leukemia, specifically, beyond infancy.

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Introduction

Acute leukemia constitutes approximately 30% of all childhood and adolescent malignancies in Europe and the United States (US) [1], with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) accounting for 80% and 20% of cases, respectively [1]. Leukemia prognosis has improved due to treatment advances in recent decades, with approximately 80% five-year overall survival in industrialized countries [2], but with higher survival for ALL than for AML [3].

High birthweight has been associated with up to 50% increased risk for leukemia compared with average weight in several registry-based case-control studies [4–6], but evidence for a potential influence of birthweight on cancer-related or all-cause mortality after diagnosis among those with childhood leukemia is lacking. Some [7–9], but not all [10], studies from the 1960s to 1980s that examined birth characteristics and subsequent cancer or cancer-specific mortality in the US and Great Britain, suggest that high or low birthweight children have increased risk of cancer-related mortality after diagnosis compared with normal birthweight children. A more recent registry-based cohort study from Korea also reported a 14% increased relative risk of cancer-related mortality associated with both low and high birthweight in all births during 1995–2006 [11]. These studies were, however, limited by small numbers.

The aim of this study was to examine whether low or high birthweight was associated with all-cause mortality in a cohort of children and adolescents with leukemia from Denmark, Norway, Sweden, and Washington State in the US.

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Supplemental data for this article can be accessed here.

We further investigated associations with size for gestational age and Ponderal index.

Material and methods

Setting

This cohort study was based on a collaboration between Denmark, Norway, Sweden, and Washington State, US, using linked data from population-based registries. In the Nordic countries, all inhabitants are assigned a unique identifier, which allows for unambiguous linkage between registries [12–14]. In Washington State, health registry data linkages have been conducted routinely for many years using a sequential process based on identifiers contained within each registry [15], and more recently using the Link Plus probabilistic record linkage program (Centers for Disease Control and Prevention National Program of Cancer Registries).

Data sources

The cancer registries of the Nordic countries were established in 1943 (Denmark), 1953 (Norway), and 1958 (Sweden), based on mandatory reporting of all incident tumors across health care providers, including date of diagnosis and tumor histology [16–18]. The cancer registries in Washington State were established in 1974 (western Washington, containing the majority of residents) and 1994 (statewide) with mandatory reporting and active surveillance. These also contain information on cancer diagnosis date and tumor histology. The Scandinavian medical birth registries were founded in 1973 (Denmark and Sweden), and 1967 (Norway). Electronic records of births since the 1960s are available in Washington State. All birth registries are based on mandatory reporting of all births [14,19,20]. The medical birth registries and Washington birth records include information on maternal, perinatal, and delivery characteristics. Population registries in the Scandinavian countries track migration and vital status of the entire population with virtually no loss to follow-up [12–14]. We linked the data to population registries in the Scandinavian countries for retrieval of information on vital status during follow-up. Mortality information for cases in Washington State was obtained from the cancer registries, which conduct active follow-up to ascertain mortality *via* linkage to state and national death certificate databases.

Study design and populations

We identified all children with leukemia (only ALL in Sweden [21]) diagnosed between birth and 19 years of age by extracting diagnostic codes from the cancer registries. Because birthweight was our primary exposure, the cohort was restricted to patients born in-country/state with information available in the birth registries.

Follow-up

Patient follow-up was accrued from date of leukemia diagnosis for a maximum of five years (after which risk of disease-related mortality is markedly reduced) to death, emigration, loss to follow-up, or censoring on 31 December 2015 in Denmark and Norway, 18 June 2013 in Sweden, and 29 January 2016 in Washington State, whichever came first.

Analytic variables

Type of leukemia was classified as lymphoid, myeloid or other based on *International Classification of Disease Oncology* (ICD-O) third revision codes or *Systematized Nomenclature of Medicine* morphology codes in the cancer registries. Data from Sweden only included ALL cases from an existing cohort [21]. Demographic characteristics included the child's sex, age at diagnosis, and calendar year of diagnosis to account for treatment protocol changes in 1984, 1988, 1993, 2004, and 2008, as leukemia treatment has been standardized since 1984 in Scandinavia and follows guidelines published by the Nordic Society of Pediatric Hematology and Oncology and to some extent international landmark advances in treatment [22,23].

Perinatal characteristics included birthweight as a continuous variable and categorized as <2500 g (low birthweight), 2500–3999 (average birthweight), ≥ 4000 g (large birthweight), gestational age (23–36, 37–41, 42–44 weeks), infant length (<50, 50–52, 53, 54–62 cm; data not available in Washington State), and the presence of Down's syndrome or other malformations (both separately as yes/no).

For the Scandinavian countries, size-for-gestational-age *Z*-scores were calculated using a Nordic reference [24], to determine the expected birthweight and standard deviation. In the Washington State population, the expected birthweight and standard deviation came from a US reference population [25]. Size for gestational age was classified as small (SGA): <2 standard deviations (SD) below mean birthweight for gestational age; large (LGA): >2 SD above mean birthweight for gestational age; and appropriate for gestational age (AGA): within 2 SD of mean birthweight.

We also calculated Ponderal index for leukemia patients from the Scandinavian countries only (birth length not available from Washington State) as the child's birthweight divided by cubed birth length (categorized as <24, 24–<30, ≥ 30).

Statistical analysis

We used proportions for categorical variables and medians with interquartile range for continuous variables to summarize descriptive characteristics of children with leukemia overall and by country.

Based on numbers of patients, deaths and person-years of follow-up we computed cumulative incidence estimates of death as the complements of the Kaplan–Meier estimators with a follow-up period of five years by baseline characteristics using time since leukemia diagnosis as the underlying

time scale. We examined the possible non-linear relationship between age at diagnosis, birthweight, birth length, gestational age, size for gestational age, and Ponderal index as continuous variables in a Cox regression model with calendar time (in days) as the underlying time scale. Five-year mortality was non-parametrically modeled with restricted cubic splines that included 5 knots. [26]. All models were adjusted for sex, country, year of diagnosis, the presence of Down's syndrome or other congenital malformations, and type of leukemia defined as lymphoid, myeloid or other.

The relative mortality risk associated with categories of birthweight as the primary exposure was examined in a Cox proportional hazards regression model with calendar time (in days) as the underlying time scale. Because age at leukemia diagnosis exhibited a U-shaped association with five-year mortality, separate Cox regression models were used for children aged 0–1, >1–2, 3–8, 9–13 and 14–19 years to examine associations with five-year all-cause mortality risk. The proportionality assumption for the age-stratified models was examined by computing log-log plots and was deemed

Table 1. Characteristics of 7148 children and adolescents with leukemia from Denmark, Norway, Sweden, and Washington State, 1967–2015.

	Denmark 1973–2013		Norway 1967–2015		Sweden 1973–2011		Washington State 1974–2014		All	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Overall	1724	100	1871	100	2043	100	1510	100	7148	100
Type of leukemia										
Myeloid	300	17.4	361	19.3	–	–	278	18.4	939	13.1
Lymphoid	1355	78.6	1369	73.2	2043	100	922	61.1	5689	79.6
Other	69	4.0	141	7.5	–	–	310	20.5	520	7.3
Diagnosis year										
1967–1983	166	9.6	449	24.1	283	13.9	74	4.9	972	13.6
1984–1987	147	8.5	163	8.7	212	10.4	78	5.2	600	8.4
1988–1992	213	12.4	188	10.0	291	14.2	136	9.0	828	11.6
1993–2003	547	31.7	511	27.3	760	37.2	495	32.8	2313	32.4
2004–2007	247	14.3	188	10.0	239	11.7	225	14.9	899	12.6
2008–2015	404	23.4	372	19.9	258	12.6	502	33.2	1536	21.5
Sex										
Male	953	55.3	1017	54.4	1131	55.4	823	54.5	3924	54.9
Female	771	44.7	854	45.6	912	44.6	687	45.5	3224	45.1
Age group at diagnosis										
0–12 months	98	5.7	79	3.9	117	6.3	101	6.7	395	5.5
1–2	413	23.9	517	25.3	454	24.3	333	22.1	1717	24.1
3–8	765	44.4	977	47.8	788	42.1	642	42.5	3172	44.4
9–13	231	13.4	285	13.9	256	13.7	203	13.4	975	13.6
14–19	217	12.6	185	9.1	256	13.7	231	15.3	889	12.4
Median age at diagnosis (interquartile range)	4	(2;9)	4	(2;9)	4	(2;8)	4	(2;10)	4	(2;9)
Birthweight, g										
<2500	75	4.4	69	3.7	86	4.2	99	6.6	329	4.6
2500–3999	1330	77.1	1376	73.5	1540	75.4	1181	78.2	5427	75.9
≥4000	310	18.0	425	22.7	409	20.0	222	14.7	1366	19.1
Missing	9	0.5	1	0.1	8	0.4	8	0.5	26	0.4
Median birthweight, g (interquartile range)	3500 (3100; 3850)		3600 (3220; 3950)		3570 (3210; 3900)		3486 (3118; 3827)		3530 (3160; 3890)	
Gestational age, weeks										
23–36	88	5.1	112	6.0	120	5.9	142	9.4	462	6.5
37–41	1293	75.0	1437	76.8	1717	84.0	1008	66.8	5455	76.3
42–44	117	6.8	204	10.9	197	9.6	111	7.4	629	8.8
Missing	226	13.1	118	6.3	9	0.4	249	16.5	602	8.4
Size for gestational age										
Small	65	3.8	71	3.8	62	3.0	159	10.5	357	5.0
Appropriate	1379	80.0	1622	86.7	1831	89.6	1077	71.3	5909	82.7
Large	50	2.9	82	4.4	81	4.0	175	11.6	388	5.4
Missing	230	13.3	96	5.1	69	3.4	99	6.6	494	6.9
Birth length, cm										
<50	248	14.4	568	30.4	609	29.8	–	–	1425	19.9
50–52	769	44.6	937	50.1	1046	51.2	–	–	2752	38.5
53	254	14.7	182	9.7	207	10.1	–	–	643	9.0
54–62	429	24.9	137	7.3	166	8.1	–	–	732	10.2
Missing	24	1.4	47	2.5	15	0.7	1510	100	1596	22.3
Ponderal index, kg/m^3										
<24	620	36.0	130	6.9	158	7.7	–	–	908	12.7
24–30	1043	60.5	1349	72.1	1548	75.8	–	–	3940	55.1
≥30	37	2.1	345	18.4	319	15.6	–	–	701	9.8
Missing	24	1.4	47	2.5	18	0.9	1510	100	1599	22.4
Down's syndrome	45	2.6	64	3.4	47	2.3	24	1.6	180	2.5
Other malformations	46	2.7	55	2.9	8	0.4	18	1.2	127	1.8

Gestational age available from 1978 in Denmark.
Birth length not available for Washington State.
Diagnosis year group defined according to NOPHO guideline changes in 1984, 1988, 1993, 2004, and 2008.

acceptable. Further adjustment for gestational age did not essentially change results, and thus these results are not presented.

We then tested for heterogeneity of associations, separately, with country and diagnosis year (1967–1987, 1988–2003, and 2004–2015) using the chi-square statistic. Results did not differ between country or diagnosis year (all $p > .05$; data not shown).

As secondary exposures, we examined mortality risk associated with size for gestational age and Ponderal index similarly to analyses of birthweight.

In sensitivity analyses, we repeated all models restricted to children born full term and then, separately, restricted to ALL patients and those without Down's syndrome or other malformations. We computed models by index year calendar periods (1967–1987, 1988–2003, 2004–2015). Finally, we repeated analyses with country as a stratum variable in a stratified Cox model. Results were similar using this approach compared to results from the main analysis and are not presented (data not shown).

All analyses were conducted using SAS version 9.4® (SAS Institute Inc., Cary, NC, USA).

Results

Descriptive characteristics

Analyses included 7148 children and adolescents with leukemia diagnosed between birth and 19 years of age from Denmark ($n = 1724$), Norway ($n = 1871$), Sweden ($n = 2043$), and Washington State ($n = 1510$) in the period 1967 through 2015 (Table 1). Most patients were diagnosed with lymphoid leukemia (80%). There were slightly more boys (55%), and median age at diagnosis was four years (interquartile range: 2; 9). Three quarters (76%) of the cases weighed 2500–3999 g at birth and 76% of all cases were born at term (defined as 37–41 weeks of gestation). Five percent of cases were SGA and 5.4% were LGA; 2.5% of all leukemia cases were recorded with Down's syndrome and 1.8% had other malformations.

Five-year all-cause mortality risk by sex, age at diagnosis and birthweight

Crude five-year all-cause mortality risk was 23.2% for the overall cohort of leukemia children included during 1967–2015, similar for males (23.7%) and females (22.5%), and higher for children diagnosed in their first live year than in older children (Table 2). Five-year all-cause mortality was 26.9% in low birthweight cases (<2500 g) and 24.2% in normal weight cases (2500–3999 g), and higher for those with myeloid than lymphoid leukemia (44.0% vs. 18.4%).

Five-year all-cause mortality risk by birthweight

Spline regression analyses (Figure 1) showed that age at diagnosis exhibited a U-shaped association with mortality with the lowest mortality at ages 2–3 years. Birthweight exhibited a slightly U-shaped or partly near linear association with the lowest mortality risk around 3600 g.

The hazard ratios for death associated with birthweight <2500 g was 1.1 (95% confidence interval (CI): 0.9, 1.4) and 1.0 (95% CI: 0.9, 1.2) for those ≥4000 g (Table 3). Hazard ratios for low birthweight and death depended on age at leukemia diagnosis: 1.5 (95% CI: 0.7, 3.2) for patients 0–1 year old, 1.6 (95% CI: 1.0, 2.6) for >1–2 years; 1.0 (95% CI: 0.6, 1.5) for 3–8 years; 1.0 (0.6, 1.8) for 9–13 years; and 1.2 (95% CI: 0.7, 2.1) for 14–19 years. Hazard ratios for those born ≥4000 g by age at diagnosis approached unity (Table 4).

Table 2. Cumulative proportion of deaths in 7148 children and adolescents with leukemia from Denmark, Norway, Sweden, and Washington State, 1967–2015.

	Five-year all-cause mortality risk, % (95% CI)
Overall	23.2 (22.6, 23.8)
Sex	
Male	23.7 (22.9, 24.5)
Female	22.5 (21.6, 23.3)
Age group at diagnosis	
0–12 months	49.0 (46.1, 52.0)
1–2 years	20.0 (18.9, 21.2)
3–8 years	18.1 (17.3, 18.9)
9–13 years	25.0 (23.4, 26.7)
14–19 years	34.1 (32.2, 36.0)
Birthweight, g	
<2500	26.9 (21.5, 33.2)
2500–3999	24.2 (22.9, 25.6)
≥4000	19.4 (17.0, 22.2)
Gestational age, weeks	
23–36	25.3 (22.9, 27.8)
37–41	22.4 (21.8, 23.1)
42–44	22.9 (21.1, 24.9)
Size for gestational age	
Small	26.9 (24.2, 29.9)
Appropriate	22.4 (21.7, 23.0)
Large	22.0 (19.6, 24.7)
Birth length, cm	
<50	25.2 (23.9, 26.6)
50–52	23.8 (22.8, 24.7)
53	23.0 (21.2, 25.0)
54–62	21.4 (19.7, 23.2)
Ponderal index, kg/m^3	
<24	26.0 (24.3, 27.7)
24–30	23.6 (22.9, 24.4)
≥30	21.4 (19.7, 23.2)
Down's syndrome	
No	22.9 (22.3, 23.5)
Yes	33.0 (29.1, 37.3)
Other malformations	
No	23.1 (22.5, 23.7)
Yes	24.5 (20.3, 29.4)
Leukemia subtype	
Myeloid	45.05 (43.1, 47.0)
Lymphiod	19.0 (18.4, 19.7)
Other	31.9 (29.0, 34.9)
Year of diagnosis	
1967–1983	43.1 (41.4, 45.0)
1984–1987	26.9 (24.9, 29.0)
1988–1992	25.9 (24.2, 27.6)
1993–2003	20.0 (19.0, 20.9)
2004–2007	13.8 (12.6, 15.2)
2008–2015	15.3 (14.1, 16.6)

Diagnosis year group defined according to NOPHO guideline changes in 1984, 1988, 1993, 2004, and 2008.

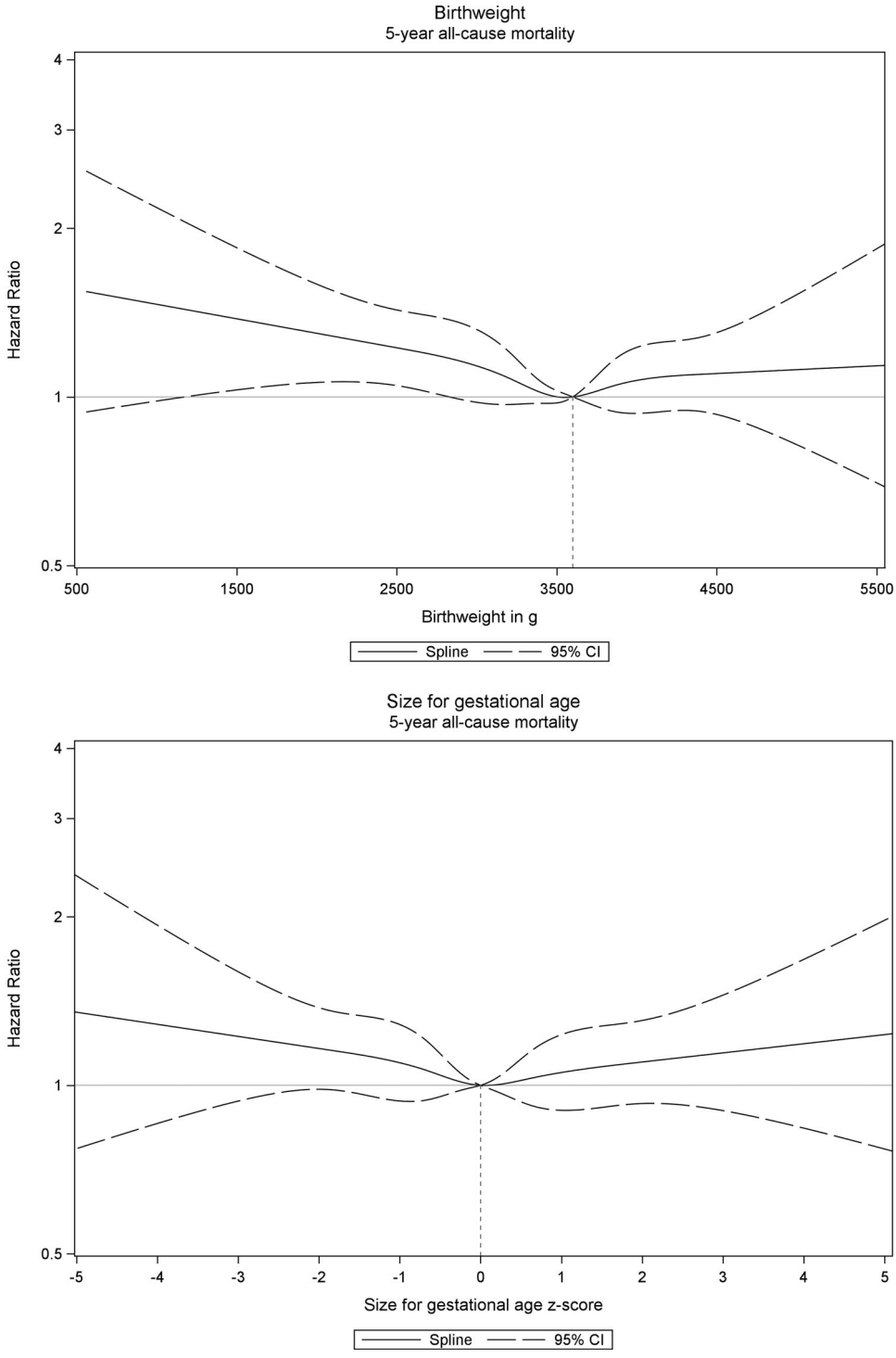

Figure 1. Illustration of restricted cubic spline models for the association of age at diagnosis, birthweight, size for gestational age, and Ponderal index with five-year all-cause mortality risk in 7148 children and adolescents with leukemia from Denmark, Norway, Sweden, and Washington State, 1967–2015.

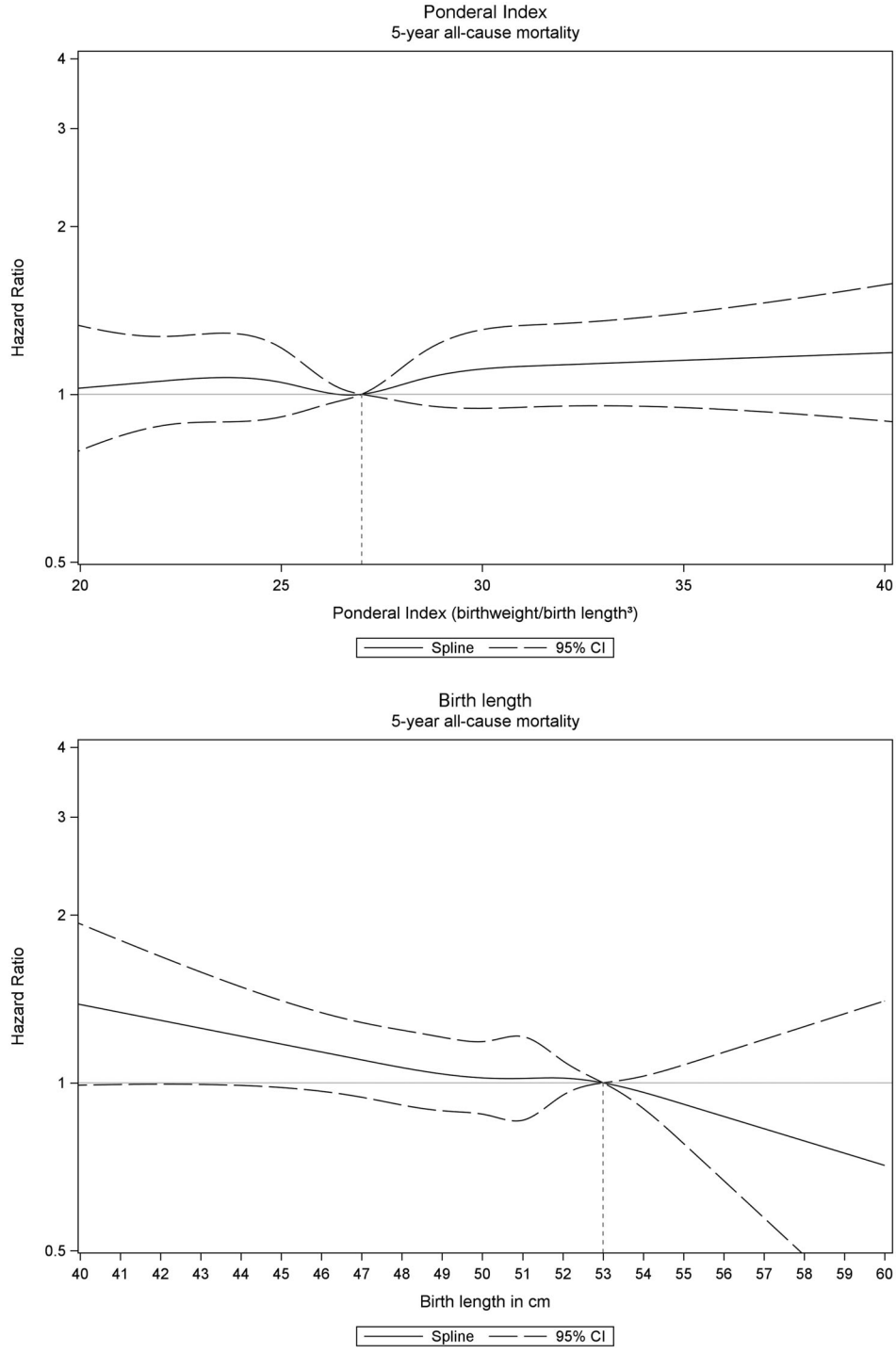

Figure 1. Continued.

Size for gestational age and Ponderal index

Associations with size for gestational age and Ponderal index resembled those for birthweight. Across all age-at-diagnosis groups, hazard ratios were generally increased or 1.0 for SGA children (although CIs included one) as follows: 1.4 (95% CI: 0.8, 2.6) for those aged 0–1 years at diagnosis; 1.7 (95% CI: 1.0, 2.6) for those aged 1–2 years; 0.9 (95% CI: 0.6, 1.3) for those aged 3–8 years at diagnosis; 1.2 (0.7, 2.0) for those aged 9–13 years and 1.0 (95% CI: 0.6, 1.6) in those aged 9–19 years at diagnosis (Supplementary Table S1). Results for Ponderal index, which only included cases from the Nordic countries, were in line with these results for most age groups (Supplementary Table S2).

Sensitivity analyses

In analyses restricted to children born full term (37–41 weeks of gestation), results were only slightly attenuated (Supplementary Table S3) but with a marked increased risk

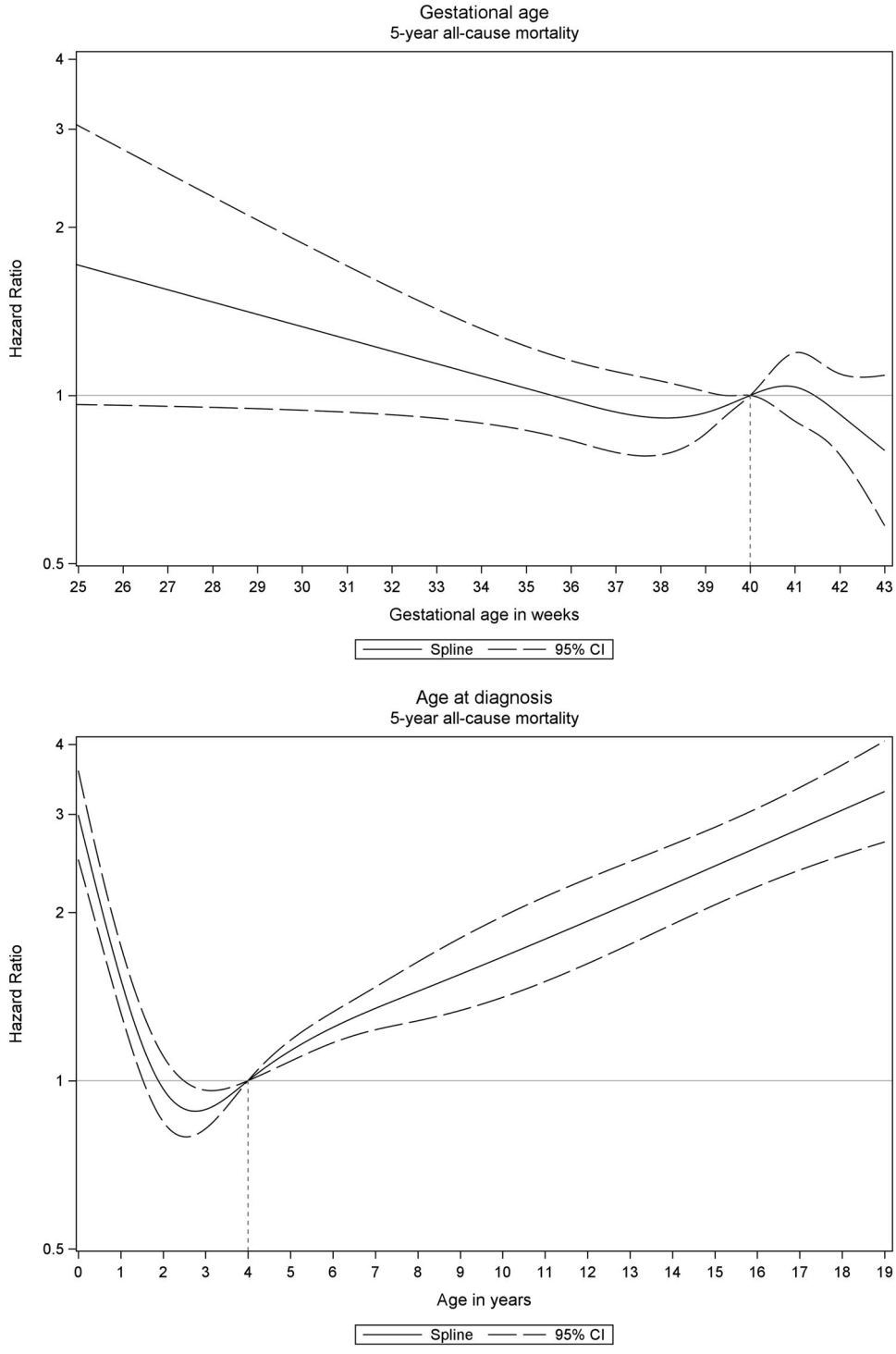

Figure 1. Continued.

for infants aged <1 year, for whom the hazard ratio associated with birthweight <2500 g was 3.2 (95% CI: 1.2, 8.8). In the sensitivity analysis restricted to children with ALL and without the presence of Down's syndrome or malformations, results for birthweight and all-cause mortality were also largely similar to those of the main analysis (Supplementary Table S4). Results by diagnosis year were characterized by small number of deaths, particularly for those with low birthweight (Supplementary Table S5).

Discussion

Data from this large cohort study, comprising leukemia cases from three Nordic countries and Washington State, indicate that low birthweight may be associated with increased five-year all-cause mortality risks after leukemia diagnosis for children who were diagnosed at a young age. SGA and low Ponderal index showed nearly similar associations. However, increased risks were modest, and most CIs included one.

Table 3. Five-year all-cause mortality risk by birthweight categories, size for gestational age, and Ponderal index in 7148 children and adolescents with leukemia from Denmark, Norway, Sweden, and Washington State, 1967–2015.

	5-year mortality			
	Number of deaths	Total years of follow-up	Crude rate (95% CI)	Hazard rate ratio (95% CI)[a]
Birthweight (g)				
<2500	74 (22.5%)	1204	6.1 (4.8, 7.7)	1.1 (0.9, 1.4)
2500–3999	1160 (21.4%)	20,590	5.6 (5.3, 6.0)	1
≥4000	306 (22.4%)	5328	5.7 (5.1, 6.4)	1.0 (0.9, 1.2)
Size for gestational age				
Small	87 (24.4%)	1204	7.2 (5.8, 8.9)	1.2 (0.9, 1.5)
Appropriate	1235 (20.9%)	22,742	5.4 (5.1, 5.7)	1
Large	76 (19.6%)	1424	5.3 (4.2, 6.7)	1.1 (0.9, 1.4)
Ponderal index				
<24	231 (25.4%)	3565	6.5 (5.7, 7.4)	1.1 (0.9, 1.2)
24–30	909 (23.1%)	15,815	5.7 (5.4, 6.1)	1
>30	146 (20.8%)	2892	5.0 (4.3, 5.9)	1.0 (0.8, 1.2)

[a]Adjusted for sex, diagnosis year, country, the presence of Down's syndrome, other malformations, and type of leukemia. Diagnosis year group defined according to NOPHO guideline changes in 1984, 1988, 1993, 2004, and 2008.

Table 4. Five-year all-cause mortality risk by birthweight categories and stratified by age at leukemia diagnosis in 7148 children and adolescents with leukemia from Denmark, Norway, Sweden, and Washington State, 1967–2015.

Age at leukemia diagnosis and child birthweight (g)	5-year mortality			
	Number of deaths	Total years of follow-up	Crude rate (95% CI)	Hazard rate ratio (95% CI)[a]
0–12 months				
<2500	7 (46.7%)	31	22.7 (9.1, 46.7)	1.5 (0.7, 3.2)
2500–3999	148 (47.6%)	815	18.2 (15.4, 21.3)	1
≥4000	30 (44.1%)	200	15.0 (10.1, 21.4)	0.9 (0.6, 1.4)
1–2 years				
<2500	19 (23.8%)	306	6.2 (3.7, 9.7)	1.6 (1.0, 2.6)
2500–3999	247 (18.8%)	5125	4.8 (4.2, 5.5)	1
≥4000	58 (18.4%)	1292	4.5 (3.4, 5.8)	0.9 (0.7, 1.2)
3–8 years				
<2500	21 (15.4%)	527	4.0 (2.5, 6.1)	1.0 (0.6, 1.5)
2500–3999	387 (16.2%)	9650	4.0 (3.6, 4.4)	1
≥4000	123 (19.2%)	2581	4.8 (4.0, 5.7)	1.2 (0.9, 1.4)
9–13 years				
<2500	13 (24.5%)	195	6.7 (3.6, 11.4)	1.0 (0.6, 1.8)
2500–3999	168 (23.0%)	2744	6.1 (5.2, 7.1)	1
≥4000	43 (23.1%)	716	6.0 (4.3, 8.1)	1.0 (0.7, 1.4)
14–19 years				
<2500	14 (31.1%)	145	9.6 (5.3, 16.2)	1.2 (0.7, 2.1)
2500–3999	210 (30.5%)	2255	9.3 (8.1, 10.7)	1
≥4000	52 (33.5%)	539	9.6 (7.2, 12.7)	1.1 (0.8, 1.5)

[a]Adjusted for sex, diagnosis year, country, the presence of Down's syndrome, other malformations, and type of leukemia.

Inclusion of additional cohorts would increase statistical power to measure these associations.

The strengths of this study include compulsory and complete data from three Nordic countries and one US state [14,16–20]. In contrast to previous studies, we followed patients from leukemia diagnosis instead of birth. There are, however, some limitations. First, we did not have information on leukemia-specific mortality or on treatment characteristics, which may be associated with prognosis [27–30]. We also lacked information on body mass index at diagnosis, and children normalizing their weight may have a different mortality risk than children persistently being small in size. Similarly, the pharmacokinetics of chemotherapy in AML may vary with body weight, with overweight adolescents having greater survival than normal weight adolescents [31].

To capture some of a potential cancer treatment effect, we conducted the analyses with adjustment by years of leukemia treatment protocol changes in 1984, 1988, 1993, 2004, and 2008. Though maternal smoking during pregnancy has been associated with low birthweight and some cancer types, this is generally not the case for childhood leukemia [32]. The 0–1 age group may also include congenital leukemia, which may affect birthweight.

The intrauterine environment may alter susceptibility to disease development during the life course [33–35]. Fetal programming by genetic and environmental insults to cell proliferation and differentiation in the prenatal and early postnatal period has been associated with cardiovascular and metabolic conditions later in life [36]. In fact, low birthweight increases all-cause mortality at least until early adulthood in the general population, whereas children with high birthweight may have a lower mortality risk in the first few years of life compared with children with appropriate birthweight [37–40]. Restricted intrauterine growth is associated with molecular and physiological alterations across organ systems and tissues [41]. Such fetal programming may be associated with reduced resilience and stress tolerance [42]. Low birthweight is associated with increased mortality due

to various diseases such as childhood IgA nephropathy [43], congenital heart disease [44], and hypoplastic left heart syndrome [45]. Thus, elucidating the potential effects and mechanisms of various exposures in the intrauterine environment may provide a further understanding of disease development and course.

Older cohort and twin studies have reported conflicting associations for birthweight and leukemia mortality in the general population and not specifically in a leukemia cohort. For example, two studies from the US including leukemia cases or deaths during the 1940s through 1960 reported no association with birthweight [8,10], whereas a study from the UK reported a positive association between low birthweight and leukemia mortality risk – an association which was more marked among females [9]. In contrast, the more recent Korean registry-based cohort study of all live births during 1995–2006 reported a leukemia-specific mortality rate ratio in the general population through 2006 of 1.14 (95% CI: 0.92, 1.41) for children with birthweight <3000 g and 1.13 (95% CI: 0.94, 1.37) for children ≥ 3500 g, compared to children weighing $3000-3499$ g [11]. As survival for low birthweight infants has increased dramatically since the mid-1900s, we speculate that a higher number of low birthweight babies develop leukemia in more recent years.

This cohort study does not suggest that low birthweight or SGA is associated with increased five-year all-cause mortality risk among children with any type of childhood leukemia or ALL, specifically, beyond infancy.

Ethical approval

The study was approved by the Data Protection Agency in Denmark (Record no. 1-16-02-484-14); the Regional Committee for Medical and Health Research Ethics of South East Norway (Record no. 2016/607); the Regional Ethics Committee, Stockholm, Sweden (Record no. 2012/298-31/1); and the Institutional Review Board of Washington State (Record no. D-082312-H13.03) and the Fred Hutchinson Cancer Research Center (#479) in the USA.

Danish law does not require an ethical approval or an informed consent from patients for studies based on routinely collected registry data.

The study was performed in accordance with the Declaration of Helsinki. The study did not involve any patients since this was a purely registry-based study.

Author contributions

A.G.O., A.E., and H.T.S. conceived the study idea and designed the study. Authors of the respective countries acquired the country-specific data. L.B.C. carried out the analyses. A.G.O. organized the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. A.G.O. and L.B.C. have access to all the data and take responsibility for the data, accuracy of the data analysis, and the conduct of the research. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure statement

The authors report no conflicts of interest.

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Data availability

Data sharing is not allowed according to Danish, Norwegian, Swedish law. Our own approvals to use the data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Interested researchers may apply for Danish data access through the Research Service at the Danish Health Data Authority (e-mail: forskerservice@sundhedsdata.dk; phone: +45 3268 5116). Up-to-date information on data access is available online (http://sundhedsdatastyrelsen.dk/da/forskerservice). Access to data from the Danish Health Data Authority requires approval from the Danish Data Protection Agency (https://www.datatilsynet.dk/english/legislation/). Similar options are available for data from the other countries.

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