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Early mortality in children with cancer in Denmark and Sweden: The role of social background in a setting with universal healthcare

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Abstract

Socioeconomic differences in overall survival from childhood cancer have been shown previously, but the underlying mechanisms remain unclear. We aimed to investigate if social inequalities were seen already for early mortality in settings with universal healthcare. From national registers, all children diagnosed with cancer at ages 0–19 years, during 1991–2014, in Sweden and Denmark, were identified, and information on parental social characteristics was collected. We estimated odds ratios (OR) and 95% confidence intervals (CI) of early mortality (death within 90 days after cancer diagnosis) by parental education, income, employment, cohabitation, and country of birth using logistic regression. For children with acute lymphoblastic leukaemia (ALL), clinical characteristics were obtained. Among 13,926 included children, 355 (2.5%) died within 90 days after diagnosis. Indications of higher early mortality

Giorgio Tettamanti and Line Kenborg contributed equally to this work.

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were seen among the disadvantaged groups, with the most pronounced associations observed for maternal education ($OR_{adj\_Low\_vs\_High}$ 1.65 [95% CI 1.22–2.23]) and income ($OR_{adj\_Q1(lowest)\_vs\_Q4(highest)}$ 1.77 [1.25–2.49]). We found attenuated or null associations between social characteristics and later mortality (deaths occurring 1–5 years after cancer diagnosis). In children with ALL, the associations between social factors and early mortality remained unchanged when adjusting for potential mediation by clinical characteristics. In conclusion, this population-based cohort study indicated differences in early mortality after childhood cancer by social background, also in countries with universal healthcare. Social differences occurring this early in the disease course requires further investigation, also regarding the timing of diagnosis.

KEYWORDS
childhood cancer, cohort, early mortality, register-based study, socioeconomic factors

What's new?

In high-income countries in Europe, childhood cancer survival is suspected of being linked to socioeconomic status, despite mandates for equal access to healthcare. Little is known, however, about the impact of socioeconomic differences on early mortality in settings with universal healthcare. This study analyzed mortality following childhood cancer diagnosis in Sweden and Denmark. Early mortality was associated with socioeconomic status, wherein socially disadvantaged groups were at increased risk of death within three months of diagnosis. This was most clearly seen for maternal income and education. The relevance of socioeconomic differences on timing of childhood cancer diagnosis and survival warrants further investigation.

1 | INTRODUCTION

Remarkable advances in diagnostics and treatment of childhood cancers have led to substantial improvements in survival[1,2]; the overall 5-year survival probability in Europe is now 81%[3] and even higher among children diagnosed in Sweden and Denmark.[3–5] The use of standardized treatment protocols with better risk grouping, clinical trial participation, improved supportive care, and cross-national collaborations among paediatric oncologists are examples of reasons underlying this development.[1,2,6]

Socioeconomic differences in overall survival from childhood cancer have previously been described, also for high income countries in Europe, where equal access to healthcare is presumed.[7,8] British researchers observed that differences in survival from acute lymphoblastic leukaemia (ALL) by socioeconomic status emerged at the time when treatment management required parental/child adherence, that is from start of oral treatment in the outpatient setting, hypothesizing that socioeconomic differences in treatment adherence may explain their findings.[9] However, studies from Sweden and Denmark have shown survival differences by parental education or family characteristics already within the first year after diagnosis.[10,11] A recent study from the US investigated the role of area-based social measures in relation to early mortality in childhood cancer, and observed that children living in disadvantaged counties had a higher risk of dying during the first month after a haematological malignancy, compared to children living in more affluent areas.[12] If there are social differences in mortality this early after the cancer being diagnosed, these differences are unlikely to be related to treatment adherence, but more likely to have other underlying explanations, which may be related to the timeliness of diagnosis, disease severity or treatment initiation. However, in contrast to the United States, access to cancer care services is assumed to be universal in the Nordic countries, and therefore it is of importance to assess whether similar associations are found in this setting. We hypothesize that social background could be associated with early mortality also in the Nordic countries, and that this is related to other underlying mechanisms than pure income barriers to treatment.

Using a population- and register-based cohort study including all children diagnosed with cancer in Denmark and Sweden, we aimed to determine whether social background was associated with early mortality in childhood cancer. We also sought to assess whether potential associations differed from corresponding associations for later mortality. Moreover, we examined the role of clinical characteristics for the associations between social background and early mortality, among children with ALL.

2 | MATERIALS AND METHODS

2.1 | Setting

Denmark and Sweden have a civil registration system with nationwide administrative registers and a unique personal identification number that enables individual linkage of information. Moreover, Denmark

and Sweden have similar healthcare systems, paid through taxes and with universal access, as well as longstanding largely standardized diagnostic procedures and treatment protocols,[6,13] which made it appropriate to combine data from the two populations into one comprehensive register-based cohort study.

2.2 | Study population

We identified all incident cases of first cancers (including also non-malignant central nervous system [CNS] tumours) diagnosed in children aged 0–19 in the period 1991–2014 from the Danish and Swedish national cancer registers.[14] Registration of all cancers diagnosed within the two countries is mandatory and does not depend on given treatment. We categorized cancer diagnoses according to the International Classification of Childhood Cancer (ICCC),[15] into leukaemia (group I: ALL [group Ia] and acute myeloid leukaemia [AML, group Ib] separately), lymphomas (group II), CNS tumours (group III) and other non-CNS solid tumours (all other malignant tumours). We excluded children who were not resident in the country at the time of diagnosis or emigrated within 1 year after diagnosis, children for which no biological parents could be identified, and children with the cancer pre-disposing syndromes Down syndrome, neurofibromatosis, and tuberous sclerosis (Figure 1).

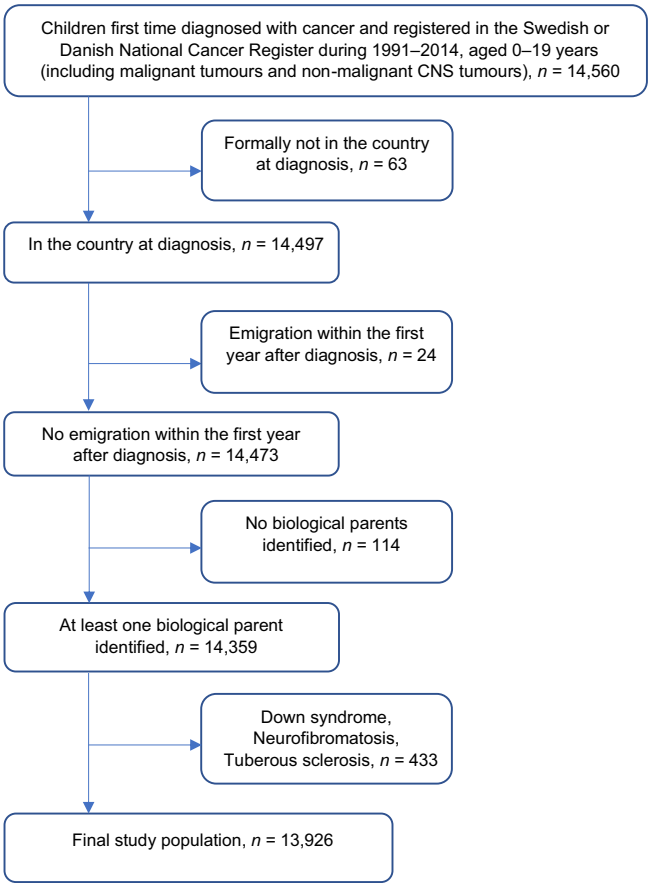

FIGURE 1 Flow chart of inclusion and exclusion criteria for the study population.

2.3 | Outcome

Early mortality, our primary outcome, was defined as death from any cause within the first 90 days after the cancer diagnosis. Information on the date of death was obtained from the national causes of death registers, whereas the date of diagnosis was obtained from the national cancer registers. Date of diagnosis is defined as the date of the first examination/test underlying the diagnosis (Sweden),[16] and as the "admission date for the first contact during which the diagnosis was confirmed" (Denmark).[17] In the Danish Cancer Registry, the exact date of diagnosis is available from 2004 onwards, before that only month of diagnosis was recorded.[14] For the main analyses, the date of diagnosis for Danish children diagnosed prior to 2004 were set to the 15th of the month. For comparison with earlier studies, we also assessed mortality within the first 30 days after diagnosis as a secondary analysis including only children for which the exact date of diagnosis was available ($n = 11,178$; 80.3%).

To investigate if potential associations with early mortality differ from associations with later mortality, we included the outcome later mortality (defined as deaths occurring 1–5 years, 366–1825 days, after cancer diagnosis). To have a clear distinction between early and later mortality, deaths occurring 91–365 days after the diagnosis were not our main outcome. For transparency, these deaths were analysed separately as a secondary analysis.

2.4 | Parental social characteristics

We retrieved information about parental social characteristics for biological parents the year closest available before the child's diagnosis. The information was retrieved from the Danish social registries (Education registers, The Income Statistics Register, The Integrated Database for Labour Market Research and Danish Civil Registration System),[18–20] and the Swedish Longitudinal integrated database for health insurance and labour market studies and Total Population Register.[21,22] The social characteristics included parental education (lower secondary or less, upper secondary, postsecondary), employment (employed, unemployed [including outside of workforce]), country of birth (Nordic [Denmark, Sweden, Finland, Iceland, Norway], non-Nordic), cohabitation (single, cohabiting/married), and income (quartiles). Parental income was defined as each parent's individual disposable income, categorized in quartiles based on the sex- and calendar year specific income distribution of the entire population in Denmark and Sweden, respectively.

2.5 | Clinical characteristics

For children diagnosed with ALL ($n = 2590$), we obtained clinical information from the Nordic Society of Paediatric Haematology and Oncology (NOPHO) database on immunophenotype (B-precursor, T-cell), genotype (HeH/*ETV6-RUNX1*: "favourable genotype" [high hyperdiploidy-HeH or *ETV6-RUNX1*], other; available from

1992 and onwards), and white blood cell count at diagnosis (<10, 10–50, >50 [$\times 10^9$/L]). Valid linkage was done for 2380 children (91.9%) after exclusion of 35 children with mature B-cell and bilinage ALL. For children dying after a diagnosis of ALL, we obtained information regarding in what phase the death occurred (during induction, in remission, after relapse, after a second malignant neoplasm).

2.6 | Statistical analysis

We assessed the association between each of the parental social characteristics and early mortality by estimating odds ratios (OR) with 95% confidence intervals (CI), using logistic regression models. We fitted univariable and multivariable models, adjusted for sex, age at diagnosis (0, 1–4, 5–9, 10–14, 15–19 years old), year of diagnosis (categorized in 10-year intervals), and country of diagnosis, for each social factor separately. We conducted separate analyses for ALL, AML, lymphomas, CNS-tumours, and non-CNS solid tumours, as well as for country. We chose a logistic regression model instead of a time-to event model because the former is less sensitive to the uncertainty in defining the date of diagnosis; childhood cancer has no clear onset, and practices in setting the date of diagnosis differ between clinics (i.e., sometimes the date of pathology report instead of first examination), and time periods.

The associations between parental social characteristics and later mortality (deaths 366–1825 days after diagnosis) were assessed among children surviving at least 1 year. These analyses were restricted to children diagnosed until 2010 with no emigration within 5 years after diagnosis to ensure full follow-up: in the analyses of earlier deaths, we censored only children that emigrated in the first year.

To evaluate the potential mediating role of clinical characteristics among children with ALL, we first assessed the univariable associations between the social and clinical characteristics using Pearson's chi-squared test. In the next step, clinical characteristics with a statistically significant association to parental social factors (p-value <.05) were included in the regression models of parental social characteristics and early mortality to determine whether they were potentially mediating the associations observed in the main analysis.

In secondary analyses, we evaluated the outcomes early mortality within the first 30 days after diagnosis, and deaths occurring 91–365 days after the diagnosis, by fitting the same regression models as in the main analyses.

Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 16 (StataCorp LP, College Station, TX, USA).

3 | RESULTS

Among the 13,926 children diagnosed with cancer in Denmark and Sweden during 1991–2014, 355 children (2.5%) died within 90 days after diagnosis (Table 1). Figure 2 shows the time trends of early and later mortality. The group of children dying early included a larger proportion of those diagnosed in the first year of life, in the earlier time period (1991–2000), and with AML and CNS-tumours, compared to the full cohort (Table 1).

Children of mothers with lower secondary or less education had a higher risk of early mortality compared to children of mothers with postsecondary education (OR_{adj} 1.65, 95% CI 1.22–2.23). A similar pattern was seen for paternal education although somewhat less pronounced (OR_{adj} 1.35, 95% CI 0.97–1.88), Table 2. Higher risks of early mortality were also seen among children of mothers in the lowest income quartile compared to children with high maternal income (OR_{adj} 1.77, 95% CI 1.25–2.49), whereas such association was not evident for paternal income. Children of unemployed mothers were at higher risk of early mortality, compared to children of employed mothers (OR_{adj} 1.29, 95% CI 1.01–1.64). Moreover, there was a tendency of increased odds of early mortality among children to parents born outside of the Nordic countries (Maternal: OR_{adj} 1.19, 95% CI 0.86–1.63; Paternal: OR_{adj} 1.25, 95% CI 0.92–1.70). In contrast to the results for early mortality, we found weaker or null associations between parental social characteristics and later mortality (deaths 366–1825 days after diagnosis), Table 2. Results were overall similar in Denmark and Sweden; associations for early mortality were seen especially between maternal education and income in both countries (Supplementary Table 1). The impact of paternal education on early mortality was somewhat more pronounced in Denmark than in Sweden.

The stratified analyses for early mortality by cancer types (Table 3) revealed overall similar results as to those seen in the main analysis although confidence intervals were wide. Differences in early mortality by parental education were particularly evident among children with CNS and non-CNS solid tumours. For maternal income, there was a pattern of higher early mortality in the lower income quartiles, particularly pronounced among children with ALL and non-CNS solid tumours (Table 3).

In total, 60/355 children dying early were diagnosed with ALL, and the proportion of early mortality among all children diagnosed with ALL was 2.3% (60/2590). Most of the children dying early from ALL died during the induction phase of the treatment, while children dying later most often died after a relapse (Supplementary Table 2). We examined the associations between parental social factors and clinical characteristics at time of diagnosis among children with ALL (Supplementary Table 3); maternal income was associated with both immunophenotype and genotype (p-value .014 and <.001, respectively), but no clear gradients were seen. Statistically significant associations were also observed between paternal cohabitation and country of birth, and genotype (p-value .016 and .041, respectively), as well as for paternal education level and white blood cell count (p-value .045). To assess the potential mediation from clinical characteristics on the associations with early mortality, we further adjusted for these characteristics in the regression models, but this had no impact on the association between parental social factors and early mortality (Table 4).

TABLE 1 Characteristics of children diagnosed with cancer 1991–2014 in Denmark and Sweden, by early and later mortality.

	Total population		Early mortality (death within 0–90 days after diagnosis)		Later mortality[a] (death within 366–1825 days after diagnosis)	
	n	%	*n*	%	*n*	%
	13,926	**100**	**355**	**2.5**	**1157**	**10.3**
Demographics						
Country						
Denmark	5505	39.5	165	46.5	457	39.5
Sweden	8421	60.5	190	53.5	700	60.5
Sex						
Boys	7578	54.4	177	49.9	667	57.6
Girls	6348	45.6	178	50.1	490	42.4
Age at diagnosis (years)						
0	951	6.8	78	22.0	55	4.8
1–4	3444	24.7	98	27.6	277	23.9
5–9	2451	17.6	44	12.4	224	19.4
10–14	2638	18.9	46	13.0	241	20.8
15–19	4442	31.9	89	25.1	360	31.1
Year of diagnosis						
1991–2000	5612	40.3	179	50.4	627	54.2
2001–2010	5785	41.5	144	40.6	530	45.8
2011–2014	2529	18.2	32	9.0	NA	NA
Cancer type						
Leukaemia	3409	24.5	119	33.5	296	25.6
ALL	*2590*	*18.6*	*60*	*16.9*	*191*	*16.5*
AML	*531*	*3.8*	*46*	*13.0*	*80*	*6.9*
Lymphoma	1858	13.3	39	11.0	70	6.1
CNS-tumours	3383	24.3	117	33.0	308	26.6
Non-CNS solid tumours[b]	5276	37.9	80	22.5	483	41.7
Parental social characteristics						
Maternal education						
Lower secondary or less	2466	18.3	91	26.7	220	19.6
Upper secondary	6611	49.1	157	46.0	570	50.8
Postsecondary	4392	32.6	93	27.3	332	29.6
Paternal education						
Lower secondary or less	2731	20.7	80	23.9	265	23.9
Upper secondary	7014	53.3	183	54.6	573	51.8
Postsecondary	3417	26.0	72	21.5	269	24.3
Maternal income (quartiles)						
Q1 (lowest)	1226	8.9	52	14.9	102	9.0
Q2	2207	16.1	54	15.5	169	14.8
Q3	4500	32.8	127	36.4	367	32.2
Q4 (highest)	5789	42.2	116	33.2	501	44.0
Paternal income (quartiles)						
Q1 (lowest)	1443	10.7	41	12.0	117	10.4
Q2	2369	17.6	66	19.4	220	19.6
Q3	4378	32.6	113	33.1	366	32.6
Q4 (highest)	5252	39.1	121	35.5	420	37.4

(Continues)

TABLE 1 (Continued)

	Total population		Early mortality (death within 0–90 days after diagnosis)		Later mortality[a] (death within 366–1825 days after diagnosis)	
	n	%	*n*	%	*n*	%
	13,926	**100**	**355**	**2.5**	**1157**	**10.3**
Maternal employment						
Unemployed	2903	21.2	94	27.0	253	22.2
Employed	10,802	78.8	254	73.0	885	77.8
Paternal employment						
Unemployed	1790	13.4	50	14.7	154	13.8
Employed	11,583	86.6	290	85.3	966	86.3
Maternal cohabitation[c]						
Cohabiting/married	11,097	82.0	285	82.8	934	83.4
Single	2437	18.0	59	17.2	186	16.6
Paternal cohabitation[c]						
Cohabiting/married	11,131	84.3	279	82.8	944	85.7
Single	2069	15.7	58	17.2	158	14.3
Maternal country of birth						
Nordic country	12,147	87.4	309	87.0	1024	88.7
Non-Nordic country	1746	12.6	46	13.0	131	11.3
Paternal country of birth						
Nordic country	11,915	86.9	296	85.5	996	87.3
Non-Nordic country	1790	13.1	50	14.5	145	12.7

Note: Numbers do not always add up to the total because of missing values. Missing can be due to unknown biological parent or due to missing value. Missing data was less than 6% for all paternal characteristics and less than 4% for all maternal characteristics.
Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CNS, central nervous system.
[a]Including children diagnosed up until 2010 with no emigration within 5 years after diagnosis, $n = 11{,}262$.
[b]Including ICCC groups IV–XII (Neuroblastomas, Retinoblastoma, Renal tumours, Hepatic tumours, Bone tumours, Soft tissue sarcomas, Germ-cell neoplasms, Other malignant epithelial neoplasms and malignant melanomas, Other and unspecified malignant neoplasms).
[c]Cohabitating parents were defined as parents living with a marital or non-marital partner, with the exception that in Sweden only parents living with a marital partner or a non-marital partner that he/she have common children with, were registered as cohabiting.

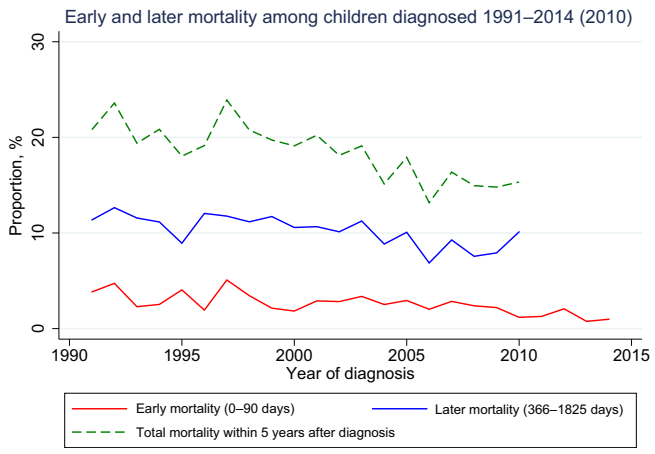

FIGURE 2 Early mortality, later mortality and 5-year mortality among all children diagnosed with cancer 1991–2014 (2010 for 5-year mortality) in Denmark and Sweden, by year of diagnosis.

In secondary analyses, we defined the outcome as early mortality within the first 30 days after diagnosis which occurred in 147 children (1.3%). For these analyses, Danish children diagnosed before 2004 were excluded since their exact date of diagnosis was not available. These analyses showed similar patterns to those of the main analyses, with higher risks of early death especially seen among children of parents with lower education (Supplementary Table 4). We also analysed 686 deaths occurring 91–365 days after the diagnosis among 13,571 included children and observed attenuated associations with parental education compared to the main results of early mortality. However, increased risks of death within this period were observed for children whose fathers had low income or were unemployed, as well as for children of single mothers (Supplementary Table 5).

4 | DISCUSSION

In this unique population-based cohort study including virtually all children diagnosed with childhood cancer in Denmark and Sweden in

TABLE 2 Early and later mortality by parental social characteristics, among children diagnosed with cancer 1991–2014 in Denmark and Sweden, odds ratios (OR) with 95% confidence intervals (CI).

	Early mortality (death within 0–90 days after diagnosis)		Later mortality[a,b] (death within 366–1825 days after diagnosis)	
	Crude	Adjusted[c]	Crude	Adjusted[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal education				
Lower secondary or less	1.77 (1.32–2.38)	1.65 (1.22–2.23)	1.09 (0.91–1.30)	1.02 (0.85–1.23)
Upper secondary	1.12 (0.87–1.46)	1.10 (0.84–1.43)	1.06 (0.92–1.23)	1.04 (0.90–1.20)
Postsecondary	1	1	1	1
Paternal education				
Lower secondary or less	1.40 (1.02–1.94)	1.35 (0.97–1.88)	1.14 (0.95–1.37)	1.09 (0.91–1.31)
Upper secondary	1.24 (0.95–1.64)	1.22 (0.92–1.61)	0.98 (0.84–1.14)	0.97 (0.83–1.13)
Postsecondary	1	1	1	1
Maternal income (quartiles)				
Q1 (lowest)	2.17 (1.55–3.02)	1.77 (1.25–2.49)	1.05 (0.83–1.31)	1.08 (0.86–1.36)
Q2	1.23 (0.89–1.70)	1.03 (0.74–1.44)	0.92 (0.76–1.10)	0.94 (0.78–1.13)
Q3	1.42 (1.10–1.83)	1.28 (0.99–1.65)	0.93 (0.81–1.07)	0.94 (0.81–1.09)
Q4 (highest)	1	1	1	1
Paternal income (quartiles)				
Q1 (lowest)	1.24 (0.87–1.78)	1.10 (0.77–1.58)	1.03 (0.83–1.28)	1.03 (0.83–1.28)
Q2	1.22 (0.90–1.65)	1.04 (0.77–1.42)	1.14 (0.96–1.36)	1.14 (0.96–1.36)
Q3	1.12 (0.87–1.46)	1.03 (0.79–1.34)	1.03 (0.89–1.20)	1.03 (0.89–1.20)
Q4 (highest)	1	1	1	1
Maternal employment				
Unemployed	1.39 (1.09–1.77)	1.29 (1.01–1.64)	1.12 (0.96–1.30)	1.11 (0.95–1.29)
Employed	1	1	1	1
Paternal employment				
Unemployed	1.12 (0.83–1.52)	1.12 (0.82–1.52)	1.05 (0.88–1.26)	1.04 (0.87–1.25)
Employed	1	1	1	1
Maternal cohabitation				
Cohabiting/married	1	1	1	1
Single	0.94 (0.71–1.25)	1.02 (0.77–1.37)	0.92 (0.78–1.09)	0.94 (0.79–1.11)
Paternal cohabitation				
Cohabiting/married	1	1	1	1
Single	1.12 (0.84–1.49)	1.23 (0.92–1.65)	0.92 (0.77–1.10)	0.94 (0.78–1.12)
Maternal country of birth				
Nordic country	1	1	1	1
Non-Nordic country	1.04 (0.76–1.42)	1.19 (0.86–1.63)	1.04 (0.86–1.26)	1.07 (0.88–1.30)
Paternal country of birth				
Nordic country	1	1	1	1
Non-Nordic country	1.13 (0.83–1.53)	1.25 (0.92–1.70)	1.13 (0.94–1.36)	1.16 (0.96–1.39)

Note: Each social factor is included in separate models and not mutually adjusted.

[a]Including children diagnosed up until 2010 with no emigration within 5 years after diagnosis.

[b]Including children surviving at least 366 days.

[c]Adjusted for sex, age at diagnosis, country, and time period of diagnosis.

1991–2014, we found that social background was associated with early mortality. Indications of a pattern with the disadvantaged groups being at highest risk of death within 3 months after cancer diagnosis were seen and the most pronounced associations were observed for maternal education and income. In contrast, we observed attenuated or null associations for later mortality, occurring 1–5 years after

TABLE 3 Early mortality (death within 90 days after diagnosis) among children diagnosed with cancer 1991–2014 in Denmark and Sweden, odds ratios (OR) with 95% confidence intervals (CI), stratified by cancer type.

	ALL, $n = 2590$		AML, $n = 531$		Lymphoma, $n = 1858$		CNS tumours, $n = 3383$		Non-CNS solid tumours,[a] $n = 5276$	
	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]
Maternal education										
Lower secondary or less	11	1.05 (0.48–2.27)	14	1.60 (0.66–3.85)	8	0.96 (0.38–2.39)	33	1.84 (1.10–3.09)	20	2.08 (1.05–4.11)
Upper secondary	28	1.00 (0.55–1.84)	18	0.79 (0.35–1.75)	14	0.62 (0.28–1.38)	49	0.98 (0.62–1.56)	42	1.79 (1.00–3.21)
Postsecondary	18	1	12	1	13	1	32	1	16	1
Paternal education										
Lower secondary or less	9	1.01 (0.41–2.49)	9	0.85 (0.31–2.37)	8	0.73 (0.29–1.86)	36	1.79 (1.05–3.06)	18	1.65 (0.80–3.43)
Upper secondary	38	1.71 (0.86–3.38)	22	1.20 (0.52–2.77)	18	0.69 (0.32–1.47)	50	0.83 (0.51–1.36)	43	1.64 (0.87–3.07)
Postsecondary	11	1	9	1	12	1	26	1	13	1
Maternal income (quartiles)										
Q1 (lowest)	10	2.70 (1.19–6.13)	[c]	1.90 (0.72–5.02)	[c]	1.15 (0.34–3.91)	10	0.90 (0.44–1.86)	19	3.15 (1.65–6.00)
Q2	8	1.12 (0.47–2.67)	[c]	0.91 (0.33–2.52)	[c]	1.10 (0.39–3.09)	21	1.11 (0.64–1.93)	10	0.93 (0.43–2.01)
Q3	23	1.59 (0.84–3.01)	[c]	1.13 (0.52–2.45)	[c]	1.69 (0.78–3.68)	42	1.15 (0.74–1.79)	29	1.48 (0.84–2.60)
Q4 (highest)	17	1	[c]	1	[c]	1	44	1	22	1
Paternal income (quartiles)										
Q1 (lowest)	5	0.70 (0.27–1.86)	6	0.80 (0.29–2.21)	5	1.54 (0.51–4.63)	15	1.37 (0.73–2.56)	6	0.78 (0.31–1.93)
Q2	14	1.08 (0.55–2.10)	9	1.16 (0.48–2.83)	6	1.06 (0.38–2.95)	23	1.22 (0.71–2.10)	14	1.02 (0.52–2.00)
Q3	14	0.64 (0.33–1.25)	13	0.90 (0.41–1.98)	16	1.52 (0.69–3.39)	38	1.13 (0.71–1.80)	30	1.30 (0.75–2.25)
Q4 (highest)	26	1	15	1	11	1	38	1	24	1
Maternal employment										
Unemployed	15	1.13 (0.62–2.07)	12	1.30 (0.63–2.68)	7	0.77 (0.33–1.81)	33	1.40 (0.91–2.13)	23	1.49 (0.91–2.45)
Employed	43	1	32	1	30	1	83	1	57	1
Paternal employment										
Unemployed	5	0.62 (0.24–1.56)	8	1.08 (0.47–2.47)	7	1.48 (0.63–3.46)	14	1.07 (0.60–1.92)	12	1.21 (0.65–2.27)
Employed	54	1	35	1	31	1	99	1	62	1
Maternal cohabitation										
Single	[c]	0.44 (0.16–1.24)	[c]	1.35 (0.61–2.97)	7	1.08 (0.46–2.54)	23	1.32 (0.81–2.14)	11	0.73 (0.38–1.40)
Cohabiting/married	[c]	1	[c]	1	30	1	92	1	66	1
Paternal cohabitation										
Single	[c]	0.68 (0.27–1.73)	[c]	0.88 (0.32–2.42)	6	0.97 (0.39–2.39)	24	1.69 (1.04–2.73)	13	1.13 (0.61–2.09)
Cohabiting/married	[c]	1	[c]	1	32	1	88	1	61	1
Maternal country of birth										

TABLE 3 (Continued)

	ALL, $n = 2590$		AML, $n = 531$		Lymphoma, $n = 1858$		CNS tumours, $n = 3383$		Non-CNS solid tumours,[a] $n = 5276$	
	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]	Deaths, *n*	OR (95% CI)[b]
Nordic country	53	1	39	1	32	1	105	1	67	1
Non-Nordic country	7	1.00 (0.45–2.24)	7	1.01 (0.42–2.44)	7	1.37 (0.59–3.23)	12	1.07 (0.57–2.00)	13	1.64 (0.89–3.03)
Paternal country of birth										
Nordic country	51	1	37	1	31	1	102	1	62	1
Non-Nordic country	8	1.11 (0.52–2.39)	7	1.18 (0.49–2.84)	8	1.67 (0.74–3.77)	13	1.10 (0.60–2.01)	14	1.68 (0.92–3.05)

Note: Each social factor is included in separate models and not mutually adjusted. Numbers don't add up to the total because of missing values.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CNS, central nervous system.

[a]Including ICCC groups IV-XII (Neuroblastomas, Retinoblastoma, Renal tumours, Hepatic tumours, Bone tumours, Soft tissue sarcomas, Germ-cell neoplasms, Other malignant epithelial neoplasms and malignant melanomas, Other and unspecified malignant neoplasms).

[b]Adjusted for sex, age at diagnosis, country, and time period of diagnosis.

[c]Less than 5 deaths in at least one category.

diagnosis. Assessed only among children with ALL, clinical characteristics did not explain the associations between social background and early mortality.

Our findings of a higher early mortality among the disadvantaged groups are in line with the results from a US study, where several measures of social disadvantage were shown to be associated with early deaths from haematological malignancies and CNS-tumours in crude analyses.[12] However, in multivariable analyses, the only analysed indicator of social disadvantage was neighbourhood income among children with haematological malignancies, and the higher risk of early death among children in disadvantaged income areas remained.[12] We have not identified any studies from countries with universal healthcare investigating the association between social factors and early childhood cancer mortality. However, socioeconomic differences in overall mortality from childhood cancer has been observed also in such countries,[7,8] for example Finland, Switzerland and the United Kingdom.[9,23,24] It has been hypothesized that the differences could be explained by lower adherence to complex treatment protocols among socially disadvantaged children, supported by results from a British study that observed survival differences in ALL when the treatment moved to outpatient care.[9] However, a recent Danish study including 173 children with ALL, showed no differences in adherence to maintenance therapy between families of different socioeconomic position, but a difference in doctor's compliance to protocol recommendations measured by prescribed drug doses.[25] Both family adherence and doctor's compliance would have an impact on survival later in the disease course, while our findings indicate that the survival differences are mainly evident in the period closest to the diagnosis. However, the underlying mechanisms might differ between settings and cancer types, and our cancer type specific analyses do not allow firm conclusions.

To assess whether the early differences in mortality by social background, could be explained by differences in more specific features of the disease, we assessed the associations between social and clinical characteristics in children with ALL. Although there were some statistically significant findings, there were no clear patterns and inclusion of these clinical characteristics in the regression models of early mortality did not appreciably change effect estimates. Two previous studies assessed the association between socioeconomic status or parental education, and white blood cell count among children with leukaemia, and observed no associations,[26,27] although children of single parents were more likely to have a higher white blood cell count.[27]

The first symptoms of childhood cancer are often few and unspecific,[28] and an increased utilization of primary care has been documented already several months before the diagnosis.[29] The increase in use of primary care seems to be modified by social background with somewhat higher rates of additional contacts among disadvantaged groups.[29] This may suggest that disadvantaged families experience more difficulties in the trajectory to a cancer diagnosis which may result in a later defined date of diagnosis, although such conclusions are speculative, and its impact on prognosis and early mortality is unclear.

We included several measures of social background in this study since they might have different associations with cancer survival.[30]

TABLE 4 Early mortality (death within 90 days after diagnosis) among children diagnosed with ALL 1991–2014 in Denmark and Sweden and included in the NOPHO database,[a] odds ratios (OR) with 95% confidence intervals (CI).

	Deaths, *n*	OR (95% CI)[b]	OR (95% CI),[b] additionally adjusted for immunophenotype	OR (95% CI),[b] additionally adjusted for genotype	OR (95% CI),[b] additionally adjusted for white blood cell count
Paternal education					
Lower secondary or less	5	0.75 (0.25–2.27)	NA	NA	0.78 (0.26–2.37)
Upper secondary	34	1.93 (0.91–4.07)	NA	NA	2.05 (0.97–4.34)
Postsecondary	9	1	NA	NA	1
Maternal income (quartiles)					
Q1 (lowest)	7	2.52 (0.96–6.57)	2.65 (1.00–7.05)	2.52 (0.81–7.84)	NA
Q2	7	1.24 (0.48–3.21)	1.34 (0.51–3.51)	1.38 (0.48–4.00)	NA
Q3	19	1.67 (0.81–3.43)	1.81 (0.87–3.79)	1.91 (0.83–4.39)	NA
Q4 (highest)	13	1	1	1	NA
Paternal cohabitation					
Single	[c]	0.75 (0.26–2.11)	NA	0.75 (0.23–2.47)	NA
Cohabiting/married	[c]	1	NA	1	NA
Paternal country of birth					
Nordic country	43	1	NA	1	NA
Non-Nordic country	5	0.82 (0.32–2.11)	NA	0.66 (0.20–2.18)	NA

Note: Each social factor is included in separate models and not mutually adjusted. Numbers don't add up to the total because of missing values.
Abbreviations: ALL, acute lymphoblastic leukaemia; NA, not applicable; NOPHO, Nordic Society of Paediatric Haematology and Oncology.
[a]Information is obtained for 2380/2590 children identified in the NOPHO database for whom the date of diagnosis differed by less than 31 days compared to the national cancer registers. Children with mature B-cell and bi-linage ALL are excluded (n = 35).
[b]Adjusted for sex, age at diagnosis, country, and time period of diagnosis.
[c]Less than 5 deaths in at least one category.

We included individual level information of both biological parents, while area-based measures of disadvantage have been used previously.[12] When area-based measures are used as a proxies for individual measures, it might misclassify individuals leading to underestimation of potential associations.[31] However, the social context of the neighbourhood may in itself affect health,[31] and potentially early mortality in childhood cancer, which is an aspect that remains to be investigated in the Nordic context.

The infrastructure in Denmark and Sweden with long-standing high-quality national population- and health registers, provides an ideal setting for investigating socioeconomic differences in relation to the risk of early childhood cancer mortality. Information on parental social characteristics was gathered before the cancer diagnosis and did not depend on study participation and self-reporting. Moreover, registration in the national cancer registers is mandatory and independent on both treatment and survival, meaning we were likely to capture virtually all cases. We observed that 2.5% of the children diagnosed with cancer died within 3 months after diagnosis, and 1.3% within the very first month after diagnosis. These proportions are comparable to estimates of deaths within the first month after diagnosis from other population-based registers in high-income countries,[12,32,33] although direct comparisons are challenging because of differences in the definition of date of diagnosis.[32] Due to the difficulty of setting a date of diagnosis in diseases with no clear onset, and the potential differences and temporal changes in practice at clinics and registry offices, we focused on early deaths occurring within 90 days after diagnosis, instead of 1 month.[12] This is also the reason why we chose to use a logistic regression model instead of a time-to-event approach. Most of the early deaths occurred within one and a half month after diagnosis, and the 3 months cut point for early deaths is unlikely to be sensitive to the uncertainties in determining date of diagnosis.

A few other limitations with the current study should be mentioned. First, statistical power is limited in some analyses. Early deaths in childhood cancer are rare and even though we included nationwide information from two countries over 24-years, the cancer type specific analyses included few cases and chance cannot be ruled out as an explanation for some associations. Second, we only excluded children with the most common types of cancer predisposing syndromes (Down syndrome, neurofibromatosis, and tuberous sclerosis) from the study. However, since other cancer predisposing syndromes are very rare, they are unlikely to have any impact on the associations between parental social characteristics and early mortality. Last, we only had information regarding clinical characteristics among children with ALL. Inclusion of further clinical information, such as tumour stage, for other cancer types would be beneficial for understanding the underlying mechanisms of social differences in early mortality.

5 | CONCLUSION

This population-based study combining data from Denmark and Sweden indicated that there were differences in early mortality in childhood cancer by social background, also within these Nordic countries with universal and free cancer care. Social differences occurring early in the disease course, rather than later, require further investigation and indicate that attention should also be given to the timing of diagnosis.

AUTHOR CONTRIBUTIONS

Hanna Mogensen: Conceptualization; Methodology; Data curation; Investigation; Formal analysis; Visualization; Writing—original draft; Writing—review & editing; Validation; Project administration. **Friederike Erdmann**: Conceptualization; Methodology; Data curation; Supervision; Writing—review & editing. **Luzius Mader**: Methodology; Writing—review & editing. **Gitte Vrelits Sørensen**: Data curation; Methodology; Writing—review & editing. **Mats Talbäck**: Data curation; Software; Writing—review & editing. **Thomas Tjørnelund Nielsen**: Data curation; Software; Writing—review & editing. **Henrik Hasle**: Data curation; Methodology; Supervision; Writing—review & editing. **Mats Heyman**: Data curation; Methodology; Supervision; Writing—review & editing. **Jeanette Falck Winther**: Data curation; Methodology; Resources; Supervision; Writing—review & editing. **Maria Feychting**: Data curation; Methodology; Resources; Supervision; Writing—review & editing. **Giorgio Tettamanti**: Conceptualization; Methodology; Data curation; Software; Formal analysis; Supervision; Writing—review & editing; Validation; Funding acquisition; Project administration. **Line Kenborg**: Conceptualization; Methodology; Data curation; Supervision; Writing—review & editing; Validation; Funding acquisition; Project administration. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the information of this manuscript were accessed remotely on a secure platform at Statistics Denmark. Pseudonymized individual-level data were obtained from national registry holders after ethical approval (where applicable) and secrecy assessment. Individual-level sensitive data can only be made available for researchers who fulfil legal requirements. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This project has been approved by Statistics Denmark and the Ethical review board in Stockholm (2011/634-31/4, 2014/417-32, 2016/27-32, 2016/716-32, 2017/1827-32, 2018/1257-32). The research was carried out in compliance with the requirements of the General Data Protection Regulation (GDPR). The project is listed in a local archive (2019-DCRC-0034) at the Danish Cancer Institute, which provides an accurate, updated overview of ongoing projects and of ongoing research projects involving personal data under the GDPR.

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SUPPORTING INFORMATION

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

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