Is the risk of childhood leukaemia associated with socioeconomic measures in Denmark? A nationwide register-based case-control study

Erdmann, Friederike; Hvidtfeldt, Ulla Arthur; Feychting, Maria; Sørensen, Mette; Raaschou-Nielsen, Ole

Published in:
International Journal of Cancer

DOI:
10.1002/ijc.33402

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Erdmann, F., Hvidtfeldt, U. A., Feychting, M., Sørensen, M., & Raaschou-Nielsen, O. (2021). Is the risk of childhood leukaemia associated with socioeconomic measures in Denmark? A nationwide register-based case-control study. *International Journal of Cancer*, *148*(9), 2227-2240. https://doi.org/10.1002/ijc.33402

Received: 1 October 2020 | Revised: 28 October 2020 | Accepted: 9 November 2020

DOI: 10.1002/ijc.33402

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Is the risk of childhood leukaemia associated with socioeconomic measures in Denmark? A nationwide register-based case-control study

Friederike Erdmann[1] | Ulla Arthur Hvidtfeldt[2] | Maria Feychting[3] | Mette Sørensen[2,4] | Ole Raaschou-Nielsen[2,5]

[1]Division of Childhood Cancer Epidemiology, Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[2]Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark

[3]Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[4]Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark

[5]Department of Environmental Science, Aarhus University, Roskilde, Denmark

Correspondence
Friederike Erdmann, Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Obere Zahlbacher Str. 69, 55131 Mainz, Germany.
Email: friederike.erdmann@uni-mainz.de

Funding information
Børnecancerfonden, Grant/Award Number: 2017-2018

Abstract

The aetiology of childhood leukaemia is poorly understood. Knowledge about differences in risk by socioeconomic status (SES) may enhance etiologic insights. We conducted a nationwide register-based case-control study to evaluate socioeconomic differences in the risk of childhood leukaemia in Denmark and to access whether associations varied by different measures of SES, time point of assessment, leukaemia type and age at diagnosis. We identified all cases of leukaemia in children aged 0 to 19 years, born and diagnosed between 1980 and 2013 from the Danish Cancer Registry (N = 1336) and sampled four individually matched controls per case (N = 5330). We used conditional logistic regression models for analysis. Medium and high level of parental education was associated with a higher risk of acute myeloid leukaemia (AML) in the offspring, mainly driven by children diagnosed at ages 0 to 4 years [odds ratio (OR) for high maternal education = 3.07; 95% confidence interval (CI): 1.44-6.55]. We also observed a modestly increased risk for lymphoid leukaemia (LL) in association with higher level of parental education, but only in children diagnosed at ages 5 to 19 years. Higher parental income was associated with an increased risk of LL but not AML among children aged 5 to 19 years at diagnosis (OR for high maternal income = 2.78; 95% CI: 1.32-5.89). Results for neighbourhood SES measures indicated null associations. Bias or under-ascertainment of cases among families with low income or basic education are unlikely to explain the observed socioeconomic differences. Future research addressing explicitly the underlying mechanisms of our results may help to enhance etiologic insights of the disease.

KEYWORDS

childhood cancer, childhood leukaemia, Denmark, lymphoid leukaemia, myeloid leukaemia, register-based study, socioeconomic factors, socioeconomic status

List of Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; ICCC, International Classification of Childhood Cancer; LL, lymphoid leukaemia; ELF-MF, extremely low-frequency electromagnetic fields; OR, odds ratio; SES, socioeconomic status.

1 | INTRODUCTION

Leukaemia is the most frequent cancer diagnosis in children worldwide,[1] accounting for about one quarter of all cancers diagnosed in 0- to 19-year-olds in Europe and other high-income countries.[1] Lymphoblastic leukaemia (LL) is the most common type of childhood leukaemia and represents more than 75% of all cases, followed by acute myeloid leukaemia (AML) which accounts for about 15% to 18% of all leukaemia cases in 0- to 19-year-olds.[1]

Although a growing body of research has addressed a broad range of potential risk factors including pregnancy-related factors,[2-4] exposure to infections,[3-6] environmental pollutants,[7,8] parental lifestyle[9-13] and occupational exposures,[14,15] the aetiology of childhood leukaemia is still poorly understood.[16,17] For acute lymphoblastic leukaemia (ALL) specifically, there is a suggestion that B-cell precursor ALL may be the result of a rare abnormal reaction to common infections, possibly in connection with lack of immunological training during infancy,[18] but the evidence remains inconclusive. To date, only a few chromosomal and genetic conditions,[16] exposure to high-dose ionising radiation,[19,20] high or low birth weight[2,16] and advanced maternal age[16] have been confirmed as risk factors for childhood leukaemia. However, these factors only explain a small proportion of all cases[17] and the underpinning leukaemogenic mechanisms remain unclear. Early age at diagnosis indicates that childhood leukaemia might originate in utero and that factors prior to birth or early-life exposures may be important determinants.[18,21]

Although socioeconomic status (SES) is not an aetiological risk factor for disease occurrence per se, it may be associated with the risk of childhood leukaemia through the social patterning of aetiological factors such as pregnancy-related factors or environmental and occupational exposures.[22,23] Research findings on the association between SES and childhood leukaemia risk are heterogeneous across studies, with higher SES being associated with higher risk, null associations reported and rarely also inverse associations being found.[24-35] However, particularly earlier studies suffered largely from methodological limitations including nonparticipation,[27] self-reported SES information, small sample size, single or few SES measures used or evaluation of only a single point in time[27] and cross-study comparison is hampered by large differences in design, SES measures used[24-34] and population under study.[24-35] More recent investigations took more often advantage of high-quality cancer registry data with linkage to other administrative data sets[24,26-32,34] and hereby minimised potential for bias. However, also recent studies rarely distinguished between different SES measures acting at different points in time.[24-26,28,30-34]

In this nationwide population-based register study, we evaluated the association between SES and risk of childhood leukaemia in Denmark. The population register infrastructure with high-quality health and socioeconomic data in Denmark constitute an ideal and unique setting to overcome limitations of previous studies. We aimed to assess whether associations varied with different measures of SES, with different points in time, with leukaemia type and with age at diagnosis. Furthermore, we aimed to examine whether demographic and pregnancy-related factors mediated associations with measures of SES.

What's new?

The aetiology of childhood leukaemia is still poorly understood. In this nationwide register-based case-control study, the authors found that higher level of parental education was associated with higher risk of childhood leukaemia in Denmark, particularly acute myeloid leukaemia. Higher parental income was also associated with an increased risk of lymphoid leukaemia, but only among children aged 5-19 years. Bias or under-ascertainment of cases among families with low income or basic education are unlikely to explain the observed socioeconomic differences. Identifying differences in the risk of childhood leukaemia by socioeconomic group may help to generate new etiologic hypotheses, which are urgently needed for developing prevention strategies.

2 | MATERIAL AND METHODS

We conducted a nationwide matched case-control study based on Danish registry data. The Danish Civil Registration System with its unique personal identification numbers (Centrale Person Register (CPR)-number) used in all national registries in Denmark enabled accurate linkage of individual information across registries.[36] Moreover, the unique CPR-numbers allowed linkage to first-degree relatives. Data linkage between registries provided the basis for our study.

2.1 | Study population

We included all cases of first leukaemias in children aged 0 to 19 years, born and diagnosed between June 01, 1980 and December 31, 2013 from the Danish Cancer Registry, a nationwide register of all cancers diagnosed in Denmark with excellent quality and high completeness (95%-98%).[37,38] For each case, four random controls, individually matched by sex and date of birth, were sampled from the entire childhood population using the Central Population Register. Cases and controls had to be living in Denmark at date of birth and controls had to be alive and cancer free at time of diagnosis of the corresponding case to be eligible as control. We excluded 28 cases and 5 controls with Down syndrome (information obtained from the National Patient Registry), resulting in a final sample of 1336 cases and 5330 controls.

Leukaemia diagnoses were classified according to the International Classification of Childhood Cancer (ICCC) first version (ie, the Birch and Marsden Classification)[39] until 2003 and ICCC third version[40] thereafter) and leukaemia types grouped as follows: lymphoid leukaemia (ICCC1 group Ia+b; ICCC3 group Ia) and acute myeloid leukaemia (ICCC1 group Ic; ICCC3 group Ib).

2.2 | Measures of SES

SES is an established multidimensional construct in health research.[22,41] It refers to both material and social resources and assets as well as the individual's rank or status within a social hierarchy of a society.[22] SES as a term is used to refer to differences between individuals or groups in the asset of resources. It is determined in various ways, including both measures at the individual and area level. Different socioeconomic factors might impact health at different phases across the life course and through different causal pathways.[41]

We evaluated both individual and neighbourhood-based SES measures at different time-windows: during pregnancy and during childhood (measured 1 year before diagnosis). As indicators for the child's individual level SES, we used maternal and paternal highest attained education and annual disposable income. We obtained annual information on maternal and paternal highest education and disposable income from the Danish education[42] and income registers[43] administered by Statistics Denmark. We grouped parental highest education into basic (primary and lower secondary education, ≤9 years), medium (upper secondary including vocational upper secondary education, 10-12 years) and high (>12 years) education, following the International Standard Classification of Education. Disposable income refers to the annual individual income after tax, interest and alimony payments and was categorised into five groups based on the sex-specific and calendar year-specific income distribution (quintiles) of the entire Danish population.

We operationalised three neighbourhood SES measures based on the distribution of educational achievements, disposable income and profession among inhabitants of a given parish as described previously.[44] Parish is the smallest geographical unit at which socioeconomic information is available in Denmark. In 2013, parishes (N = 2160) differed in size from 0.12 to 126.2 km^2 (mean area = 19.9 km^2) and in population from 26 to 42 251 inhabitants (median = 1037 inhabitants). We defined the neighbourhood SES measures as follows: proportion of inhabitants aged 30 to 60 years in a given parish with (a) basic education as the highest attained educational level, (b) low disposable income level (defined as family disposable income among the lowest quartile of the income distribution of the entire Danish population) and (c) manual profession (defined as unskilled or semi-skilled profession). Since individuals at ages 30 to 60 years determine strongest the societal socioeconomic resources and assets of the respective neighbourhood, we focussed only on this population group. We obtained parish codes from the Danish Geodata Agency and socioeconomic data aggregated to the parish level by calendar year from Statistics Denmark and calculated quintiles of the respective SES measure proportion distribution across all parishes in Denmark in a given calendar year, weighted by the number of 30- to 60-year-old inhabitants living in a respective parish. The level of SES was assigned according to the quintiles. Level 1 indicates highest level of SES, as it reflects the lowest proportions of inhabitations with basic education, low disposable income or manual profession in a parish, whereas level 5 stands for the lowest level of SES. We traced residential addresses of the children during childhood and their mothers during pregnancy via the Central Population Register, identified the corresponding parish and assigned each child the socioeconomic level according to the respective parish at the relevant point in time.

All socioeconomic information was applied to the time windows 'during pregnancy' and 'before diagnosis' (defined as 1 year before date of diagnosis/index date). In the scenario, that 1 year before diagnosis was before 'during pregnancy', the SES measures corresponded to the situation 'during pregnancy'.

2.3 | Demographic and pregnancy-related characteristics

We used information on parental age at birth of the child from the Central Population Register. We calculated the number of full and half siblings, defined as having either the same (biological or adoptive) mother or father, stillborn children excluded, assessed 1 year before the cancer diagnosis or reference date in controls via the Danish Fertility Database.[45] Data on birthweight, birth order and caesarean section were obtained from the Medical Birth Register, which contains mandatory, continuously updated reports on all births in Denmark.[45] Birth order was defined by counting all live-births of the same mother.

2.4 | Statistical analysis

We calculated Spearman's rank correlation coefficients (r_s) between the different individual and neighbourhood-level SES measures and between the two time points of assessment.

We fitted conditional logistic regression models to assess the association of SES with the risk of childhood leukaemia at the time of pregnancy and 1 year before diagnosis. We conducted separate analyses by SES measure, histological leukaemia type and age at diagnosis (0-4 and 5-19 years). The analyses accounted for sex, age at diagnosis and calendar time by keeping the individual matching. We further adjusted for maternal or paternal age at child's birth, respectively, to account for potential confounding. Results were expressed as odds ratios (ORs) with two-sided 95% confidence intervals (CIs).

As the neighbourhood SES measures were only available for the years from 1986 onwards, those analyses were restricted to children born in 1986 or later.

We repeated analyses for our main findings with further adjustment for birthweight, number of siblings, birth order (two last-mentioned variables as proxies for exposure to infections), delivery by caesarean section and both maternal and paternal ages to explore whether associations with SES were mediated by the social patterning of those risk factors. Of note, we considered maternal and paternal age as both potential confounder as well as mediator for this analysis.

All statistical analyses were performed using STATA, version 14.2.[46]

3 | RESULTS

Of the 1336 children with leukaemia, 1054 (78.9%) were diagnosed with LL and 201 (15.1%) with AML. Most of the cases were diagnosed at ages 1 to 4 years (Table 1). Controls and cases showed some expected differences in the distribution of maternal and paternal age and birthweight. The distribution of individual and neighbourhood-level socioeconomic measures is given in Tables 1, S1 and S2. The proportion of missing

TABLE 1 Characteristics of the study population, cases of leukaemia[a] in children aged 0 to 19 years at diagnosis, born and diagnosed between 1980 and 2013 in Denmark and matched controls

	Controls N = 5330 %	All leukaemias N = 1336 %	Lymphoid leukaemia N = 1054 %	Acute myeloid leukaemia N = 201 %
Sex				
Boy	55.9	55.9	57.7	46.3
Girl	44.1	44.1	42.3	53.7
Age at diagnosis/index date				
<1	5.7	5.8	2.2	18.4
1–4	51.0	51.0	55.5	34.8
5–9	22.9	22.8	24.4	18.4
10-14	11.9	11.9	11.4	13.9
15-19	8.5	8.5	6.6	14.4
Year of birth				
1980-1989	35.1	35.0	34.8	39.8
1990-1999	36.1	36.1	36.5	32.8
2000-2009	26.7	26.7	26.5	25.4
2010-2013	2.2	2.3	2.2	2.0
Year of diagnosis/ index date				
1980-1989	13.7	13.7	13.9	14.4
1990-1999	29.1	29.1	30.6	25.9
2000-2009	40.7	40.7	39.1	46.3
2010-2013	16.4	16.5	16.5	13.4
Maternal age at child's birth (years)				
<25	21.6	20.1	19.3	24.9
25-29	38.8	38.0	37.9	36.3
30–34	28.0	27.5	27.7	24.9
35-39	10.0	12.7	13.4	13.9[b]
≥40	1.6	1.7	1.8	
Paternal age at child's birth (years)				
<25	10.3	8.8	8.3	11.5
25–29	31.3	30.7	30.0	34.0
30–34	33.6	32.0	33.3	25.5
35-39	17.1	18.9	18.2	22.0
40-45	5.6	6.5	7.0	4.5
≥45	2.1	3.1	3.2	2.5
Birth weight (g)				
<2500	4.9	4.3	3.8	7.6
2500-3999	77.4	76.4	77.3	71.2
≥4000	17.6	19.3	18.9	21.2
Number of siblings[c]				
0	21.0	21.6	22.1	18.9
1	43.5	42.7	42.5	43.8

TABLE 1 (Continued)

	Controls N = 5330 %	All leukaemias N = 1336 %	Lymphoid leukaemia N = 1054 %	Acute myeloid leukaemia N = 201 %
2	23.0	23.4	22.3	28.4
≥3	12.4	12.4	13.1	9.0
Birth order				
First	45.9	46.1	46.5	43.7
Second	36.4	36.0	35.9	38.2
Third+	17.7	17.9	17.7	18.1
Caesarean section				
No	88.6	88.3	88.5	87.1
Yes	11.4	11.7	11.5	12.9
SES measures (before diagnosis)				
Maternal education[d]				
Basic	22.2	19.6	20.0	17.3
Medium	45.0	47.6	46.4	49.8
High	32.8	32.8	33.6	33.0
Paternal education[d]				
Basic	19.9	18.4	18.6	16.0
Medium	52.6	55.0	54.3	55.2
High	27.5	26.6	27.1	28.9
Maternal income[e]				
1 (low)	6.3	5.9	5.6	7.0
2	10.0	10.0	9.8	10.5
3	22.7	20.5	20.9	18.0
4	32.0	35.5	35.1	37.0
5 (high)	29.1	28.1	28.7	27.5
Paternal income[e]				
1 (low)	8.8	8.5	7.9	9.4
2	13.9	12.0	11.8	14.2
3	24.3	25.2	24.8	28.4
4	28.2	27.6	29.0	19.8
5 (high)	24.8	26.6	26.5	27.9
Neighbourhood basic education[f]				
5 (low SES)	19.6	20.2	19.4	22.2
4	21.3	21.2	21.2	18.3
3	19.7	20.4	20.7	20.9
2	20.4	20.5	21.2	19.0
1 (high SES)	19.0	17.8	17.6	19.6
Neighbourhood low income[b]				
5 (low SES)	19.5	19.3	18.8	19.6
4	20.3	19.9	20.5	20.3
3	20.2	18.6	17.4	22.2
2	20.0	22.8	23.4	20.9
1 (high SES)	20.1	19.4	20.0	17.0
Neighbourhood manual profession[h]				
5 (low SES)	20.4	21.7	20.2	26.1
4	20.7	21.1	20.8	23.5

(Continues)

TABLE 1 (Continued)

	Controls N = 5330 %	All leukaemias N = 1336 %	Lymphoid leukaemia N = 1054 %	Acute myeloid leukaemia N = 201 %
3	20.4	20.9	22.7	14.4
2	19.7	18.1	18.1	17.0
1 (high SES)	18.8	18.2	18.2	19.0

Note: Missing information: maternal age: 0.03%; paternal age: 0.80%; birth weight: 0.95%; birth order: 0.41%; maternal education before diagnosis: 2.0%; paternal education before diagnosis: 3.2%; maternal income before diagnosis: 0.7%; paternal income before diagnosis: 1.7%; neighbourhood basic education, neighbourhood low income and neighbourhood manual profession: 2.2%; remaining characteristics have complete information.

[a]Classified by the International Classification of Childhood Cancer (ICCC), up to 2003 by Birch & Marsden (first edition) and from 2003 onwards by ICCC third version. Grouped as follows: lymphoid leukaemia (ICCC1 group Ia+b; ICCC3 group Ia) and acute myeloid leukaemia (ICCC1 group Ic; ICCC3 group Ib).

[b]Information for the age categories 35 to 39 and ≥40 years combined.

[c]Number of full and half siblings (defined as having the same mother or father) assed 1 year before diagnosis. In the scenario, that 1 year before diagnosis was before 'during pregnancy', the number of siblings corresponds to the situation during pregnancy.

[d]Categorised according to highest attained level [basic (primary and lower secondary education, ≤9 years in Denmark); medium (upper secondary including vocational upper secondary education, 10-12 years); high (>12 years)].

[e]Refers to the annual individual income after tax, interest and alimony payments, categorised based on income quintiles of the entire Danish population by calendar year and sex.

[f]Based on the proportions of inhabitants aged 30 to 60 years with basic highest attained educational level in a given parish. Levels of SES are consecutively numbered. Includes only children born and diagnosed between 1986 and 2013.

[g]Based on the proportions of inhabitants aged 30 to 60 years with low disposable income (defined as family disposable income among the lowest quartile of the income distribution of the entire Danish population) in a given parish. Levels of SES are consecutively numbered. Includes only children born and diagnosed between 1986 and 2013.

[h]Based on the proportions of inhabitants aged 30 to 60 years with manual profession (defined as unskilled or semi-skilled profession) in a given parish. Levels of SES are consecutively numbered. Includes only children born and diagnosed between 1986 and 2013. Includes only children born and diagnosed between 1986 and 2013.

information was overall very low and differed by SES measure and time point of assessment between 0.2% and 3.6% (Tables S1 and S2).

The correlations between the different SES measures are presented in Tables S3 and S4. Level of education at the two time windows under study was strongly correlated for both mothers and fathers, whereas level of income was only moderately correlated. Individual and neighbourhood SES measures were overall weakly correlated (Table S4).

3.1 | Individual SES measures

Table 2 shows that higher maternal and paternal level of education was associated with a higher risk of AML in the offspring, with the effect size being similar for the two time windows under study and ORs ranging between 1.5 and 1.8. Analyses by age at diagnosis (Table 3) revealed that mainly the children diagnosed at ages 0 to 4 years drove those associations for parental education; maternal medium or high educational level was associated with a 3-fold increased risk of AML (OR high maternal education during pregnancy = 3.07; 95% CI: 1.44-6.55), whereas no increase in risk was seen among the 5- to 19-year-olds. Associations with paternal education were similarly stronger in children diagnosed at ages 0 to 4 years (OR high paternal education during pregnancy = 2.10; 95% CI: 1.05-4.20), but ORs were still modestly elevated in children diagnosed at older ages. The age-specific analyses showed further that maternal and paternal medium or high educational level were also associated with a modest increased risk for LL but only among children diagnosed at 5 to 19 years of age (OR medium paternal education during pregnancy = 1.46; 95% CI: 1.09-1.94). Overall, risk patterns and effect estimates for maternal and paternal education were similar for the two time windows under study.

Analyses of parental disposable income revealed an increased risk of LL for children aged 5 to 19 years at diagnosis of parents with higher income than the lowest level (Table 3). The association was most distinct for maternal income at time before diagnosis (OR high maternal income = 2.78; 95% CI: 1.32-5.89). A similar risk patterns was neither evident for children diagnosed with LL at younger age nor for children with AML diagnosed at any age. We observed a tendency of low maternal income being associated with a higher risk of AML in children diagnosed at 5 to 19 years of age, but CIs were wide (Table 3).

Overall, associations found for parental education or level of income did not show a linear social gradient but ORs were similarly elevated across higher categories in comparison to the lowest SES level.

To take into account the peak in incidence of LL between the ages of 2 and 5 years, we conducted additional subanalyses specifically addressing children with LL of this age group. Results were overall similar to those for children with LL diagnosed at ages 0 to 4 years, with the exception of ORs for paternal higher income during pregnancy being slightly elevated (data not shown).

The relationships of maternal and paternal educational level and income in association with childhood leukaemia were further analysed in models adjusting for birthweight, number of siblings, birth order, delivery by caesarean section and both maternal and paternal ages. As

TABLE 2 Association[a] between maternal and paternal highest attained education[b] and maternal and paternal disposable income[c] and risk of leukaemia in children aged 0 to 19 years at diagnosis, by leukaemia type[d] and time of assessment

		All leukaemias		Lymphoid leukaemia		Acute myeloid leukaemia	
		N cases	OR (95% CI)	N cases	OR (95% CI)	N cases	OR (95% CI)
Maternal education							
During pregnancy	*Basic*	289	1.0	233	1.0	37	1.0
	Medium	631	1.16 (0.98-1.36)	487	1.09 (0.91-1.31)	100	1.56 (1.00-2.45)
	High	386	1.09 (0.91-1.32)	314	1.04 (0.85-1.29)	58	1.70 (1.01-2.86)
Before diagnosis	*Basic*	257	1.0	207	1.0	34	1.0
	Medium	624	1.19 (1.01-1.41)	481	1.13 (0.94-1.37)	98	1.45 (0.92-2.30)
	High	429	1.11 (0.92-1.33)	348	1.07 (0.87-1.32)	65	1.54 (0.93-2.56)
Paternal education							
During pregnancy	*Basic*	247	1.0	199	1.0	31	1.0
	Medium	731	1.15 (0.98–1.36)	575	1.09 (0.90-1.30)	108	1.59 (1.01-2.50)
	High	311	1.05 (0.87-1.28)	248	0.99 (0.80-1.24)	53	1.84 (1.10-3.09)
Before diagnosis	*Basic*	238	1.0	191	1.0	31	1.0
	Medium	712	1.12 (0.95-1.32)	557	1.06 (0.88-1.28)	107	1.50 (0.95-2.37)
	High	345	1.02 (0.84-1.23)	278	0.98 (0.79-1.21)	56	1.67 (1.01-2.78)
Maternal income							
During pregnancy	*1 (low)*	125	1.0	94	1.0	22	1.0
	2	179	1.04 (0.80-1.34)	145	1.19 (0.88-1.59)	26	0.65 (0.34-1.24)
	3	336	1.01 (0.80-1.28)	259	1.04 (0.79-1.35)	45	0.68 (0.38-1.23)
	4	429	1.00 (0.79-1.25)	341	1.05 (0.81-1.36)	66	0.75 (0.43-1.30)
	5 (high)	260	0.83 (0.65-1.07)	212	0.89 (0.67-1.19)	40	0.70 (0.38-1.30)
Before diagnosis	*1 (low)*	78	1.0	58	1.0	14	1.0
	2	133	1.08 (0.79-1.48)	102	1.11 (0.77-1.58)	21	0.91 (0.42-1.95)
	3	272	0.96 (0.72-1.27)	219	1.03 (0.75-1.42)	36	0.66 (0.32-1.32)
	4	470	1.17 (0.89-1.53)	367	1.20 (0.88-1.64)	74	1.07 (0.56-2.04)
	5 (high)	372	0.99 (0.75-1.30)	300	1.06 (0.77-1.46)	55	0.83 (0.42-1.65)
Paternal income							
During pregnancy	*1 (low)*	122	1.0	89	1.0	24	1.0
	2	202	1.20 (0.94-1.54)	158	1.30 (0.98-1.73)	32	0.88 (0.48-1.63)
	3	350	1.09 (0.87-1.37)	280	1.20 (0.92-1.56)	52	0.82 (0.47-1.42)
	4	382	1.21 (0.96-1.52)	315	1.36 (1.05-1.77)	40	0.67 (0.38-1.20)
	5 (high)	259	1.11 (0.87-1.42)	198	1.18 (0.89-1.57)	50	1.11 (0.63-1.96)
Before diagnosis	*1 (low)*	112	1.0	82	1.0	19	1.0
	2	158	0.93 (0.71-1.21)	123	0.98 (0.72-1.33)	28	0.86 (0.44-1.68)
	3	331	1.09 (0.86-1.39)	258	1.12 (0.85-1.47)	56	1.14 (0.62-2.09)
	4	362	1.02 (0.80-1.29)	301	1.12 (0.85–1.47)	39	0.67 (0.36-1.25)
	5 (high)	349	1.09 (0.86-1.39)	275	1.17 (0.88-1.54)	55	1.06 (0.58-1.96)

[a]Conditional logistic regression analyses [odds ratio (and 95% confidence interval)] adjusted for maternal or paternal age at child's birth, respectively, modelled by age categories (<25, 25-34, 35-39, ≥40/40-44, ≥ 45 years for paternal). Accounted for sex, age at diagnosis and calendar time by design.
[b]Categorised according to the highest attained level [basic (primary and lower secondary education, ≤9 years in Denmark); medium (upper secondary including vocational upper secondary education, 10-12 years); high (>12 years)].
[c]Refers to the annual individual income after tax, interest and alimony payments, categorised by income quintiles of the entire Danish population by calendar year and sex.
[d]Classified by the International Classification of Childhood Cancer (ICCC), up to 2003 by Birch and Marsden (first edition) and from 2003 onwards by ICCC third version. Grouped as follows: lymphoid leukaemia (ICCC1 group Ia+b; ICCC3 group Ia) and acute myeloid leukaemia (ICCC1 group Ic; ICCC3 group Ib).

TABLE 3 Association[a] between maternal and paternal highest attained education[b] and maternal and paternal disposable income[c] and risk of leukaemia in children, by leukaemia type[d], time of assessment and age strata

		Lymphoid leukaemia		Acute myeloid leukaemia	
		0-4 years[e] OR (95% CI)	5-19 years[e] OR (95% CI)	0-4 years[e] OR (95% CI)	5-19 years[e] OR (95% CI)
Maternal education					
During pregnancy	*Basic*	1.0	1.0	1.0	1.0
	Medium	0.97 (0.76-1.23)	1.29 (0.97-1.71)	2.88 (1.45-5.73)	0.85 (0.46-1.59)
	High	1.00 (0.76-1.31)	1.10 (0.79-1.52)	3.07 (1.44-6.55)	0.88 (0.40-1.92)
Before diagnosis	*Basic*	1.0	1.0	1.0	1.0
	Medium	1.00 (0.78-1.25)	1.42 (1.05-1.92)	2.75 (1.38-5.47)	0.73 (0.38-1.39)
	High	0.99 (0.76-1.30)	1.22 (0.88-1.70)	3.07 (1.46-6.46)	0.69 (0.32-1.46)
Paternal education					
During pregnancy	*Basic*	1.0	1.0	1.0	1.0
	Medium	0.88 (0.70-1.12)	1.46 (1.09-1.94)	2.00 (1.06-3.77)	1.27 (0.65-2.48)
	High	0.83 (0.63-1.10)	1.30 (0.92-1.84)	2.10 (1.05-4.20)	1.58 (0.70-3.57)
Before diagnosis	*Basic*	1.0	1.0	1.0	1.0
	Medium	0.86 (0.68-1.10)	1.45 (1.08-1.94)	2.02 (1.07-3.80)	1.12 (0.57-2.18)
	High	0.85 (0.65-1.12)	1.22 (0.87-1.71)	1.94 (0.98-3.85)	1.41 (0.64-3.08)
Maternal income					
During pregnancy	*1 (low)*	1.0	1.0	1.0	1.0
	2	1.10 (0.76-1.59)	1.37 (0.84-2.22)	0.98 (0.38-2.52)	0.43 (0.17-1.11)
	3	0.87 (0.62-1.22)	1.40 (0.90-2.16)	0.90 (0.37-2.20)	0.51 (0.23-1.16)
	4	0.90 (0.64-1.26)	1.35 (0.88-2.06)	0.90 (0.37-2.16)	0.64 (0.30-1.34)
	5 (high)	0.76 (0.52-1.10)	1.16 (0.74-1.83)	1.06 (0.41-2.75)	0.47 (0.21-1.06)
Before diagnosis	*1 (low)*	1.0	1.0	1.0	1.0
	2	0.95 (0.64-1.43)	2.05 (0.88-4.78)	0.96 (0.38-2.43)	0.80 (0.20-3.20)
	3	0.80 (0.55-1.15)	2.51 (1.16-5.41)	0.57 (0.23-1.42)	0.65 (0.21-2.09)
	4	0.96 (0.67-1.36)	2.82 (1.33-5.98)	1.19 (0.53-2.67)	0.84 (0.28-2.53)
	5 (high)	0.74 (0.50-1.07)	2.78 (1.32-5.89)	1.13 (0.46-2.76)	0.57 (0.19-1.77)
Paternal income					
During pregnancy	*1 (low)*	1.0	1.0	1.0	1.0
	2	1.16 (0.81-1.68)	1.50 (0.94-2.40)	0.81 (0.35-1.88)	1.13 (0.44-2.91)
	3	0.97 (0.69-1.36)	1.60 (1.04-2.45)	0.88 (0.42-1.85)	0.81 (0.35-1.87)
	4	1.07 (0.76-1.50)	1.87 (1.23-2.85)	0.68 (0.31-1.47)	0.73 (0.30-1.77)
	5 (high)	1.00 (0.70-1.43)	1.47 (0.94-2.32)	1.16 (0.54-2.48)	1.17 (0.48-2.81)
Before diagnosis	*1 (low)*	1.0	1.0	1.0	1.0
	2	0.93 (0.63-1.36)	1.08 (0.64-1.84)	0.96 (0.40-2.32)	0.81 (0.28-2.30)
	3	1.01 (0.71-1.42)	1.38 (0.86-2.20)	1.09 (0.49-2.41)	1.32 (0.51-3.40)
	4	0.97 (0.69-1.37)	1.41 (0.89-2.23)	0.79 (0.34-1.80)	0.58 (0.22-1.49)
	5 (high)	0.99 (0.69-1.41)	1.49 (0.95-2.35)	1.42 (0.62-3.27)	0.83 (0.33-2.09)

[a]Conditional logistic regression analyses [odds ratio (and 95% confidence interval)] adjusted for maternal or paternal age at child's birth, respectively, modelled by age categories (<25, 25-34, 35-39, ≥40/40-44, ≥45 years for paternal). Accounted for sex, age at diagnosis and calendar time by design.
[b]Categorised according to the highest attained level [basic (primary and lower secondary education, ≤9 years in Denmark); medium (upper secondary including vocational upper secondary education, 10-12 years); high (>12 years)].
[c]Refers to the annual individual income after tax, interest and alimony payments, categorised by income quintiles of the entire Danish population by calendar year and sex.
[d]Classified by the International Classification of Childhood Cancer (ICCC), up to 2003 by Birch and Marsden (first edition) and from 2003 onwards by ICCC third version. Grouped as follows: lymphoid leukaemia (ICCC1 group Ia+b; ICCC3 group Ia) and acute myeloid leukaemia (ICCC1 group Ic; ICCC3 group Ib).
[e]years of age at diagnosis or index date, respectively.

TABLE 4 Selected associations[a] between maternal and paternal highest attained education[b] and maternal and paternal disposable income[c] and risk of leukaemia in children, adjusted for demographic and pregnancy-related risk factors

		Lymphoid leukaemia5-19 years[d] OR (95% CI)	Acute myeloid leukaemia0-4 years[d] OR (95% CI)
Maternal education			
During pregnancy	*Basic*	1.0	1.0
	Medium	1.27 (0.95-1.71)	3.68 (1.74-7.74)
	High	1.12 (0.79-1.58)	4.16 (1.82-9.52)
Before diagnosis	*Basic*	1.0	1.0
	Medium	1.43 (1.04-1.95)	3.58 (1.69-7.57)
	High	1.28 (0.90-1.80)	4.25 (1.87-9.64)
Paternal education			
During pregnancy	*Basic*	1.0	1.0
	Medium	1.48 (1.10-1.99)	2.46 (1.25-4.83)
	High	1.29 (0.90-1.85)	2.84 (1.33-6.08)
Before diagnosis	*Basic*	1.0	1.0
	Medium	1.47 (1.09-1.99)	2.49 (1.26-4.91)
	High	1.20 (0.84-1.76)	2.60 (1.22-5.52)
Maternal income			
During pregnancy	*1 (low)*	1.0	
	2	1.48 (0.89-2.45)	
	3	1.56 (0.98-2.47)	
	4	1.55 (0.99-2.42)	
	5 (high)	1.32 (0.82-2.13)	
Before diagnosis	*1 (low)*	1.0	
	2	1.95 (0.83-4.59)	
	3	2.54 (1.17-5.50)	
	4	2.80 (1.32-5.94)	
	5 (high)	2.81 (1.32-5.97)	
Paternal income			
During pregnancy	*1 (low)*	1.0	
	2	1.59 (0.99-2.56)	
	3	1.67 (1.08-2.58)	
	4	1.95 (1.27-2.98)	
	5 (high)	1.53 (0.96-2.44)	
Before diagnosis	*1 (low)*	1.0	
	2	1.22 (0.70-2.10)	
	3	1.53 (0.94-2.50)	
	4	1.58 (0.98-2.55)	
	5 (high)	1.65 (1.02-2.65)	

[a]Conditional logistic regression analyses [odds ratio (and 95% confidence interval)] adjusted for maternal and paternal age at child's birth, modelled by age categories (<25, 25-34, 35-39, ≥40/40-44, ≥ 45 years for paternal), birthweight, number of siblings, birth order and delivery by caesarean section. Accounted for sex, age at diagnosis and calendar time by design.

[b]Categorised according to the highest attained level [basic (primary and lower secondary education, ≤9 years in Denmark); medium (upper secondary including vocational upper secondary education, 10-12 years); high (>12 years)].

[c]Refers to the annual individual income after tax, interest and alimony payments, categorised by income quintiles of the entire Danish population by calendar year and sex.

[d]years of age at diagnosis or index date, respectively.

TABLE 5 Association[a] between measures of neighbourhood socioeconomic status [b] and risk of leukaemia in children aged 0 to 19 years at diagnosis, by leukaemia type[c] and time of assessment

		All leukaemias		Lymphoid leukaemia		Acute myeloid leukaemia	
		N cases	OR (95% CI)	N cases	OR (95% CI)	N cases	OR (95% CI)
Neighbourhood basic education							
During pregnancy	*5 (low SES)*	222	1.0	171	1.0	35	1.0
	4	220	0.96 (0.78-1.19)	182	1.05 (0.83-1.33)	23	0.59 (0.33-1.08)
	3	205	0.92 (0.75-1.14)	157	0.87 (0.68-1.11)	37	1.34 (0.79-2.27)
	2	216	0.91 (0.73-1.12)	179	0.98 (0.77-1.24)	27	0.71 (0.41-1.25)
	1 (high SES)	184	0.81 (0.65-1.01)	142	0.80 (0.62-1.03)	28	0.87 (0.50-1.54)
Before diagnosis	*5 (low SES)*	215	1.0	164	1.0	34	1.0
	4	225	0.97 (0.79-1.20)	179	1.00 (0.79-1.26)	28	0.85 (0.49-1.49)
	3	217	0.99 (0.80-1.23)	175	0.98 (0.77-1.25)	32	1.25 (0.72-2.17)
	2	218	0.96 (0.78-1.19)	179	0.99 (0.78-1.25)	29	1.00 (0.57-1.76)
	1 (high SES)	189	0.88 (0.71-1.10)	149	0.88 (0.68-1.13)	30	1.06 (0.60-1.86)
Neighbourhood low income							
During pregnancy	*5 (low SES)*	270	1.0	214	1.0	36	1.0
	4	193	0.87 (0.71-1.07)	148	0.86 (0.68-1.09)	38	1.08 (0.64-1.84)
	3	194	0.94 (0.76-1.15)	151	0.93 (0.74-1.18)	29	0.90 (0.52-1.56)
	2	216	1.06 (0.86-1.29)	182	1.12 (0.90-1.40)	22	0.79 (0.44-1.42)
	1 (high SES)	174	0.98 (0.79-1.21)	136	0.96 (0.75-1.22)	25	1.03 (0.58-1.83)
Before diagnosis	*5 (low SES)*	205	1.0	159	1.0	30	1.0
	4	212	1.00 (0.80-1.24)	173	1.06 (0.84-1.35)	31	0.86 (0.49-1.52)
	3	198	0.93 (0.75-1.16)	147	0.86 (0.67-1.10)	34	1.20 (0.68-2.13)
	2	243	1.16 (0.94-1.43)	198	1.23 (0.97-1.56)	32	0.97 (0.55-1.71)
	1 (high SES)	206	0.96 (0.78-1.20)	169	1.00 (0.78-1.27)	26	0.81 (0.44-1.49)
Neighbourhood manual profession							
During pregnancy	*5 (low SES)*	216	1.0	168	1.0	35	1.0
	4	191	0.87 (0.70-1.09)	151	0.91 (0.71-1.16)	31	0.84 (0.48-1.46)
	3	202	0.94 (0.76-1.17)	168	1.01 (0.79-1.28)	24	0.70 (0.38-1.28)
	2	232	1.00 (0.81-1.23)	177	0.98 (0.77–1.24)	33	0.90 (0.52–1.56)
	1 (high SES)	206	0.79 (0.64-0.97)	167	0.84 (0.88-1.07)	27	0.61 (0.35-1.08)
Before diagnosis	*5 (low SES)*	231	1.0	171	1.0	40	1.0
	4	224	0.96 (0.78-1.18)	176	1.01 (0.80–1.28)	36	0.95 (0.57-1.59)
	3	222	0.97 (0.79-1.19)	192	1.10 (0.88-1.39)	22	0.63 (0.35-1.13)
	2	193	0.86 (0.69-1.06)	153	0.90 (0.71-1.15)	26	0.77 (0.44-1.35)
	1 (high SES)	194	0.90 (0.72-1.11)	154	0.96 (0.76–1.23)	29	0.82 (0.47–1.42)

[a]Conditional logistic regression analyses [odds ratio (and 95% confidence interval)] adjusted for maternal age at child's birth, modelled by age categories (<25, 25-34, 35-39, ≥40/40-44, ≥45 years for paternal). Accounted for sex, age at diagnosis and calendar time by design.
[b]Based on the proportions of inhabitants aged 30 to 60 years with (a) basic highest attained educational level, (b) low disposable income and (c) manual profession in a given parish. Levels of SES are consecutively numbered; level 1 indicates highest SES, while level 5 stands for lowest SES.
[c]Classified by the International Classification of Childhood Cancer, up to 2003 by Birch and Marsden (first edition) and from 2003 onwards by ICCC-3. Grouped as follows: Lymphoid leukaemia (ICCC1 group Ia+b; ICCC3 group Ia) and acute myeloid leukaemia (ICCC1 group Ic; ICCC3 group Ib).

presented in Table 4, the additional adjustment revealed similar results to those of the main analysis. While effect estimates for associations with LL did not change appreciably, the associations for parental education and AML became stronger when further adjusted. However, CIs were wide.

3.2 | Neighbourhood SES measures

We noted some elevated and some decreased ORs across neighbourhood SES measures quintiles in association with risk of LL and AML, but no systematic risk pattern (Table 5).

4 | DISCUSSION

In this nationwide register-based assessment of socioeconomic differences in the risk of childhood leukaemia in Denmark, we found maternal and paternal higher (high and medium) level of education being associated with a higher risk of AML in the offspring, mainly driven by children diagnosed at ages 0 to 4 years. We also noted a modestly increased risk for LL in children diagnosed at ages 5 to 19 years of parents with medium or high level of education. Higher parental income than the lowest income level was associated with an increased risk of LL among children aged 5 to 19 years at diagnosis. Additional adjustment for birthweight, maternal or paternal age, respectively, number of siblings, birth order and delivery by caesarean section showed results similar to those of our main analysis. Neighbourhood SES measures were not associated with childhood leukaemia. We found little evidence for an association between any SES indicator and LL risk in young children (0-4 years).

The validity of our findings is strengthened by the use of high-quality population-based register data with almost complete coverage, not influenced by self-reported information or nonparticipation and emerging from a country with free access to health care. The registry data enabled analysis of virtually all children with leukaemia and a control group representative for the entire childhood population and without any participation bias.[36-38] Annual socioeconomic information at the parish level and parental highest attained education and disposable income were obtained from Statistics Denmark minimising the risk of information bias. Additional major strengths of our study refer to the evaluation of different SES measures including both individual-level and neighbourhood-level SES measures assessed at two different time points and analysed separately for the two main leukaemia types and by age groups. Previous studies rarely distinguished between different SES measures acting at different time points[24-28,30-34] or different SES measures[24-27,31,32,34] or child's age at diagnosis.[24-27,29,34] With our approach, we tried to disentangle the potential effect of SES during the different stages of development and childhood and to assess differences between individual- and neighbourhood-level SES measures as previously suggested.[35] Given the suggested different risk factors and aetiology for LL and AML, it is crucial to assess also socioeconomic associations separately by leukaemia types. By adjustment for birthweight, number of siblings, birth order, mode of delivery and parental age, we demonstrated that our observed associations with individual SES were not mediated through the social patterning of those risk factors.

A limitation of our study concerns our sample size, albeit unavoidable as it reflects the low incidence of childhood leukaemia and the childhood population size of Denmark. The small sample size of case children particularly for the age group and leukaemia-type specific analyses resulted often in imprecise point estimates and prevented us from further subdividing the analyses by age group and calendar period.

Overall, associations between SES and childhood cancer risk have been most exhaustively studied for leukaemia and specifically ALL as it is the most common cancer in children and due to its suspected infectious aetiology.[18] Most studies have reported evidence of an association between SES indicators and childhood leukaemia risk, but the direction of the association has not been consistent.[25,29-35] Large differences in design and study populations[24-33] challenge direct cross-study comparisons.

The societal context is of significance; some countries have large socioeconomic differences in access to and quality of health care services and a relationship with SES is anticipated and not related to true aetiological differences. Research from the Nordic countries, which share similar welfare systems, social structure and a population-based register infrastructure, are most comparable to ours. Recent findings from Norway[29] showed an association of lower family income with a higher risk of LL, while a reverse association was reported for AML and null associations were observed in association with the parent's educational level.[29] Notable, none of these findings from Norway are in line with our observations. Especially the inverse association between family income and LL risk and the null findings for parental education found in the Norwegian study contrast with our observations of a positive association between parental income and LL risk for children diagnosed at ages 5 to 19 years and a strong positive association between parental education and risk of childhood leukaemia with a 2- to 3-fold increased AML risk in young children. Also, results from an earlier study from Denmark analysing leukaemia cases diagnosed between 1976 and 1991 contrasts somewhat with ours. A higher risk of leukaemia for children born in low-income areas was found, but no association in relation to the residential area at the time of diagnosis or individual parental occupational class was observed.[35] Our analyses showed null associations for neighbourhood SES measures at both time points; on the other hand, the neighbourhood SES measures were differently operationalised in the two studies. While Raaschou-Nielsen et al defined neighbourhood SES by the average gross income of inhabitants of a respective municipality,[35] we used population proportions of basic education, low family income and manual profession at the parish level in the present study, which may explain the different findings.

We conducted this study on socioeconomic differences in childhood leukaemia with the overall aim to provide indications about potential causative factors for the disease. We found higher SES at the individual level but not at neighbourhood level to be associated with a higher risk of AML and LL. As also shown by the weak correlation between individual and neighbourhood SES measures, residential neighbourhood SES is not a proxy of personal SES in Denmark. Parental education and income level may be associated with the risk of LL and AML through the social patterning of SES-related mediators, such as environmental or occupational exposures, parental life style, exposure to infections or pregnancy-related factors.[2,16-18] As the adjustment for parental age, number of siblings, birth order, delivery by caesarean section and birth weight showed no appreciable effect on our results, these factors can be eliminated as responsible mediators for our findings. In line with Greaves' 'delayed infection' hypothesis that suggests that B-cell precursor ALL subtypes result from an unregulated immune response from an immature and unchallenged immune system caused by delayed exposure to common infections in

infancy,[5,18] the lower risk of LL seen in children of parents with basic education and low income may be ultimately related to differences in family circumstances and subsequently child's exposure to infections between socioeconomic groups. Direct measurements of exposure to infections and the resulting immune response are almost impossible in epidemiological research, but several proxies have been established including number of siblings assuming lower potential for early infections among children with no siblings and birth order assuming lower potential for infections among firstborn children. As neither the adjustment for birth order nor number of siblings diluted the observed effects, and as we observed these associations only in children diagnosed at 5 to 19 years of age but not in younger aged children in which B-cell precursor ALL most commonly occurs,[18] differences in family circumstances and subsequently child's exposure to infections seems eventually to be an unlikely explanation.

Parental occupational exposure to chemicals as well as unhealthy lifestyle (eg, tobacco smoking) are usually more prevalent in lower SES groups and therefore neither a likely explanation for our observations.

This leaves us with the social patterning of environmental exposures, which might be related to the risk of LL and AML, such as air pollution, radon in the residence and electromagnetic fields from overhead powerlines, as a potential underlying mechanism of our findings. Traffic-related air pollution in general seems not associated with childhood leukaemia in Denmark[47] but the specific air pollutant benzene has been associated with higher risk for childhood AML both in Denmark[7] and elsewhere.[8] To have mediated our results in the observed direction would require that parents of higher SES tend to live at locations with higher benzene concentrations. This is not a likely scenario in Denmark, as benzene is an air toxic emitted from traffic exhaust and fuel evaporation, petrol service stations, the burning of coal and oil and several other sources. Radon concentrations in the residence, however, are generally higher in single-family houses than in apartments, and we expect more parents of high SES to live in single-family houses. A previous study showed that radon in the residence was associated with higher risk for ALL but not acute non-LL in Denmark.[48] The study reported the highest radon-related risk for ALL among the 2- to 4-year-old children, which is not in line with radon being the explanation for our observation of an association between high SES and risk for LL among 5- to 19-year-olds but not among 0- to 4-year-olds. Previous studies have reported an association between exposure to extremely low-frequency electromagnetic fields (ELF-MF) and risk for childhood leukaemia[17,49] and we would expect that lower SES is associated with living near overhead powerlines in Denmark. However, a Danish study found no higher risk of leukaemia for children living closer to powerlines,[50] and another Danish investigation observed little evidence for an association between estimated exposure to ELF-MF and risk of childhood leukaemia for the time period (1987-2003)[51] overlapping the most with that of the present study.

In conclusion, this large nationwide register study with minimal potential for bias found higher parental education being associated with a higher risk of childhood leukaemia, particularly AML, and higher parental income being associated with an increased risk of LL among 5- to 19-year-old children. Under-ascertainment of cases among families with low income or basic education is unlikely to explain our findings, as Denmark is a country with free access to high-quality health care irrespective of SES and has one of the most complete cancer registries worldwide. Future research addressing the underlying mechanisms of these socioeconomic differences in the risk of childhood LL and AML and the observed differences in associations by age at diagnosis may help to enhance etiologic insights of the disease occurrence. The social patterning of environmental or occupational exposures, parental lifestyle, exposure to infections or pregnancy-related factors potentially related to the risk of leukaemia appears not a plausible explanation of our observations.

ACKNOWLEDGEMENTS

The authors are grateful to Andrea Bautz (Danish Cancer Society Research Center, Childhood Cancer Research Group) for her technical support with data preparation. This work was supported by a grant from the Danish Childhood Cancer Foundation (Grant number 2017-2018). The funding sources had no involvement in the content or preparation of the manuscript.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Access to individual-level data is governed by Danish authorities. These include the Danish Data Protection Agency, the Danish Health Data Authority and Statistics Denmark. Each scientific project must be approved before initiation, and approval is granted to a specific Danish research institution. Researchers at Danish research institutions may obtain the relevant approval and access data. International researchers may gain data access if governed by a Danish research institution having the needed approval and data access. All data access requests should be directed to the corresponding author.

ETHICS STATEMENT

No ethics approval and consent was required for this study. This research was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

ORCID

Friederike Erdmann https://orcid.org/0000-0002-9982-3300
Ulla Arthur Hvidtfeldt https://orcid.org/0000-0002-0335-4838
Maria Feychting https://orcid.org/0000-0002-5101-0060
Mette Sørensen https://orcid.org/0000-0002-7302-4789
Ole Raaschou-Nielsen https://orcid.org/0000-0002-1223-0909

REFERENCES

1. Steliarova-Foucher E, Colombet M, Ries L, et al., eds. *International Incidence of Childhood Cancer, Volume III (Electronic Version)*. Lyon, France: International Agency for Research on Cancer; 2017.
2. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. *Int J Cancer*. 2009; 124:2658-2670.
3. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol*. 1999;28:631-639.
4. Von Behren J, Spector LG, Mueller BA, et al. Birth order and risk of childhood cancer: a pooled analysis from five US states. *Int J Cancer*. 2011;128:2709-2716.
5. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer*. 2006;6:193-203.
6. Gilham C, Peto J, Simpson J, et al. Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UKcase-control study. *BMJ*. 2005;330:1294.
7. Raaschou-Nielsen O, Hvidtfeldt UA, Roswall N, Hertel O, Poulsen AH, Sorensen M. Ambient benzene at the residence and risk for subtypes of childhood leukemia, lymphoma and CNS tumor. *Int J Cancer*. 2018;143:1367-1373.
8. Filippini T, Hatch EE, Rothman KJ, et al. Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. *Environ Health Perspect*. 2019;127:46002.
9. Hargreave M, Mørch LS, Andersen KK, Winther JF, Schmiegelow K, Kjaer SK. Maternal use of hormonal contraception and risk of childhood leukaemia: a nationwide, population-based cohort study. *Lancet Oncol*. 2018;19:1307-1314.
10. Orsi L, Rudant J, Ajrouche R, et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. *Cancer Causes Control*. 2015;26:1003-1017.
11. Milne E, Greenop KR, Petridou E, et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the childhood Leukemia International Consortium. *Cancer Causes Control*. 2018;29:539-550.
12. Dessypris N, Karalexi MA, Ntouvelis E, et al. Association of maternal and index child's diet with subsequent leukemia risk: a systematic review and meta analysis. *Cancer Epidemiol*. 2017;47:64-75.
13. Karalexi MA, Dessypris N, Thomopoulos TP, et al. Parental alcohol consumption and risk of leukemia in the offspring: a systematic review and meta-analysis. *Eur J Cancer Prev*. 2017;26:433-441.
14. Spycher BD, Lupatsch JE, Huss A, et al. Parental occupational exposure to benzene and the risk of childhood cancer: a census-based cohort study. *Environ Int*. 2017;108:84-91.
15. Bailey HD, Fritschi L, Infante-Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. *Int J Cancer*. 2014;135:2157-2172.
16. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. *Pediatr Clin North Am*. 2015;62:11-25.
17. Erdmann F, Ghantous A, Schüz J. Environmental agents and childhood cancer. In: Nriagu J, ed. *Encyclopedia of Environmental Health*. 2nd ed. Burlington: Elsevier Science & Technology; 2019:336-347.
18. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer*. 2018;18:471-484.
19. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380:499-505.
20. Little MP, Wakeford R, Borrego D, et al. Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies. *Lancet Haematol*. 2018;5:e346-e358.
21. Greaves M. In utero origins of childhood leukaemia. *Early Hum Dev*. 2005;81:123-129.
22. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health*. 1997;18:341-378.
23. Kachmar AG, Connolly CA, Wolf S, Curley MAQ. Socioeconomic status in pediatric health research: a scoping review. *J Pediatr*. 2019;213: 163-170.
24. Youlden DR, Baade PD, Valery PC, et al. Area-based differentials in childhood cancer incidence in Australia, 1996-2006. *Pediatr Blood Cancer*. 2012;58:390-394.
25. Kroll ME, Stiller CA, Murphy MF, Carpenter LM. Childhood leukaemia and socioeconomic status in England and Wales 1976-2005: evidence of higher incidence in relatively affluent communities persists over time. *Br J Cancer*. 2011;105:1783-1787.
26. Carozza SE, Puumala SE, Chow EJ, et al. Parental educational attainment as an indicator of socioeconomic status and risk of childhood cancers. *Br J Cancer*. 2010;103:136-142.
27. Adam M, Rebholz CE, Egger M, Zwahlen M, Kuehni CE. Childhood leukaemia and socioeconomic status: what is the evidence? *Radiat Prot Dosimetry*. 2008;132:246-254.
28. Adam M, Kuehni CE, Spoerri A, et al. Socioeconomic status and childhood leukemia incidence in Switzerland. *Front Oncol*. 2015;5:139.
29. Del Risco Kollerud R, Blaasaas KG, Claussen B. Poverty and the risk of leukemia and cancer in the central nervous system in children: a cohort study in a high-income country. *Scand J Public Health*. 2015; 43:736-743.
30. Kehm RD, Spector LG, Poynter JN, Vock DM, Osypuk TL. Socioeconomic status and childhood cancer incidence: a population-based multilevel analysis. *Am J Epidemiol*. 2018;187:982-991.
31. Marquant F, Goujon S, Faure L, et al. Risk of childhood cancer and socio-economic disparities: results of the French Nationwide study Geocap 2002-2010. *Paediatr Perinat Epidemiol*. 2016;30: 612-622.
32. Pan IJ, Daniels JL, Zhu K. Poverty and childhood cancer incidence in the United States. *Cancer Causes Control*. 2010;21:1139-1145.
33. Ribeiro KB, Buffler PA, Metayer C. Socioeconomic status and childhood acute lymphocytic leukemia incidence in Sao Paulo, Brazil. *Int J Cancer*. 2008;123:1907-1912.
34. Borugian MJ, Spinelli JJ, Mezei G, Wilkins R, Abanto Z, McBride ML. Childhood leukemia and socioeconomic status in Canada. *Epidemiology*. 2005;16:526-531.
35. Raaschou-Nielsen O, Obel J, Dalton S, Tjønneland A, Hansen J. Socioeconomic status and risk of childhood leukaemia in Denmark. *Scand J Public Health*. 2004;32:279-286.
36. Pedersen CB. The Danish Civil Registration system. *Scand J Public Health*. 2011;39:22-25.
37. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish cancer registry—history, content, quality and use. *Danish Med Bull*. 1997;44: 535-539.
38. Gjerstorff ML. The Danish cancer registry. *Scand J Public Health*. 2011;39:42-45.
39. Birch JM, Mardsen HB. Classification scheme for childhood cancer. *Int J Cancer*. 1987;40:620-624.
40. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. *Cancer*. 2005;103:1457-1467.
41. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health*. 2006;60:7-12.
42. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health*. 2011;39:91-94.
43. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39:103-105.

44. Erdmann F, Hvidtfeldt UA, Sorensen M, Raaschou-Nielsen O. Socioeconomic differences in the risk of childhood central nervous system tumors in Denmark: a nationwide register-based case-control study. *Cancer Causes Control*. 2020;31:915-929.
45. Bliddal M, Broe A, Pottegard A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. *Eur J Epidemiol*. 2018;33:27-36.
46. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP; 2015.
47. Raaschou Nielsen O, Hertel O, Thomsen B, Olsen J. Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol*. 2001; 153:433-443.
48. Raaschou Nielsen O, Andersen CE, Andersen HP, et al. Domestic radon and childhood cancer in Denmark. *Epidemiology*. 2008;19:536-543.
49. Kheifets L, Ahlbom A, Crespi CM, et al. Pooled analysis of recent studies on magnetic fields and childhood leukaemia. *Br J Cancer*. 2010;103:1128-1135.
50. Pedersen C, Raaschou-Nielsen O, Rod NH, et al. Distance from residence to power line and risk of childhood leukemia: a population-based case-control study in Denmark. *Cancer Causes Control*. 2014; 25:171-177.
51. Pedersen C, Johansen C, Schuz J, Olsen JH, Raaschou-Nielsen O. Residential exposure to extremely low-frequency magnetic fields and risk of childhood leukaemia, CNS tumour and lymphoma in Denmark. *Br J Cancer*. 2015;113:1370-1374.

SUPPORTING INFORMATION

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

How to cite this article: Erdmann F, Hvidtfeldt UA, Feychting M, Sørensen M, Raaschou-Nielsen O. Is the risk of childhood leukaemia associated with socioeconomic measures in Denmark? A nationwide register-based case-control study. *Int. J. Cancer*. 2021;148:2227–2240. https://doi.org/10.1002/ijc.33402