American Journal of Epidemiology

Vol. 187, No. 5
DOI: 10.1093/aje/kwx322
Advance Access publication: September 27, 2017

Original Contribution

Socioeconomic Status and Childhood Cancer Incidence: A Population-Based Multilevel Analysis

Rebecca D. Kehm*, Logan G. Spector, Jenny N. Poynter, David M. Vock, and Theresa L. Osypuk

* Correspondence to Dr. Rebecca D. Kehm, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, West Bank Office Building, 1300 S Second Street, Minneapolis, MN 55455 (e-mail: kehmx003@umn.edu).

Initially submitted June 14, 2017; accepted for publication September 18, 2017.

The etiology of childhood cancers remains largely unknown, especially regarding environmental and behavioral risk factors. Unpacking the association between socioeconomic status (SES) and incidence may offer insight into such etiology. We tested associations between SES and childhood cancer incidence in a population-based case-cohort study (source cohort: Minnesota birth registry, 1989–2014). Cases, ages 0–14 years, were linked from the Minnesota Cancer Surveillance System to birth records through probabilistic record linkage. Controls were 4:1 frequency matched on birth year (2,947 cases and 11,907 controls). We tested associations of individual-level (maternal education) and neighborhood-level (census tract composite index) SES using logistic mixed models. In crude models, maternal education was positively associated with incidence of acute lymphoblastic leukemia (odds ratio (OR) = 1.10, 95% confidence interval (CI): 1.02, 1.19), central nervous system tumors (OR = 1.12, 95% CI: 1.04, 1.21), and neuroblastoma (OR = 1.15, 95% CI: 1.02, 1.30). Adjustment for established risk factors—including race/ethnicity, maternal age, and birth weight—substantially attenuated these positive associations. Similar patterns were observed for neighborhood-level SES. Conversely, higher maternal education was inversely associated with hepatoblastoma incidence (adjusted OR = 0.70, 95% CI: 0.51, 0.98). Overall, beyond the social patterning of established demographic and pregnancy-related exposures, SES is not strongly associated with childhood cancer incidence.

childhood cancer incidence; multilevel methods; socioeconomic status

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS, central nervous system; OR, odds ratio; SES, socioeconomic status.

Socioeconomic status (SES) is consistently linked to a range of health outcomes in children and adults including many adulthood cancers (1–3). SES may also be associated with childhood cancer incidence, operating through various mechanisms at both the individual and area levels. Individual-level SES may influence incidence through mediators such as parental occupational exposures, dietary patterns, infectious agents, family reproductive decisions (such as maternal age and family size), and birth outcomes such as birth weight (4, 5). SES may also operate as a mediator of other preceding demographic social determinants of health including foreign birthplace or race/ethnicity (4, 6). For example, a recent study reported lower risk of several cancers among Hispanic children of foreign-born mothers compared with US-born mothers (6). Area-level SES may independently influence risk through mediators such as environmental pollutants and toxins, infectious agents, and social norms regarding lifestyle behaviors (7, 8). Therefore, in-depth knowledge of the association between SES and childhood cancer risk may provide etiologic insight into the role of environmental and behavioral exposures, particularly given that exogenous causes of childhood cancer are not well understood.

Empirical evidence of an association between SES and childhood cancer incidence remains limited and inconclusive. While ecological findings from international and within-country small-area studies suggest a positive association between higher SES and incidence of some childhood cancers (7, 9–12), individual-level studies largely report null associations (13–18). However, there are several limitations to previous work conducted at the individual level. First, studies have predominantly focused on childhood leukemia due to its higher incidence and suspected infectious etiology (19–21). Given that different cancers likely have different etiologies (22), it is important to investigate

associations of SES with other nonleukemic cancers. Second, a case-control study design is commonly used to test associations between SES and incidence due to the rarity of childhood cancers. Because controls in studies requiring active participation tend to be higher SES than the source population of interest (23), participation-based case-control studies can produce biased estimators. Third, established risk factors associated with SES, such as birth weight and maternal age (4), have not been consistently controlled for across studies. This hinders cross-study comparisons and potentially obscures underlying mechanisms contributing to a SES association. Finally, to our knowledge, no study has used multilevel methods to test for independent associations of SES at the individual and small-area levels. Without a multilevel approach, it is possible that SES at one level is merely a proxy for SES at another level, thus masking etiology. In this study, we address these limitations by leveraging registry data in a population-based case-cohort study. We assessed SES at both the individual and neighborhood levels, and we accounted for established demographic and pregnancy-related risk factors that may confound or mediate associations between SES and childhood cancer incidence.

METHODS

Study population

We ascertained cases, diagnosed at ages 0–14 years, from the Minnesota Cancer Surveillance System, which is estimated to have 99.7% cancer case completeness and 96.5% overall data accuracy (24). We restricted our sample to cases born between 1989 (when residential addresses were first recorded on birth certificates) and 2014, with a linked Minnesota birth record (86%). Records were linked based on first and last name, date of birth, and social security number (when available) through probabilistic record linkage using LinkPlus software (25, 26). We then implemented a case-cohort study design in which we randomly sampled 4 controls per case, frequency matched on birth year, from the Minnesota birth registry without regard to case status (27). To rule out children with higher-penetrance genetic syndromes (28, 29), we excluded 20 cases and 5 controls with Down syndrome recorded on the birth record and 11 cases with multiple primary tumors, resulting in a final analytical sample of 2,947 cases and 11,907 controls ($n = 14{,}854$). This study was approved by the institutional review board at the University of Minnesota.

Outcome

We assessed incidence of combined (all cancer diagnoses) and individual types of childhood cancer. We evaluated the major types of childhood cancer based on the *International Classification of Childhood Cancer, Third Edition*, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia, lymphomas, combined central nervous system (CNS) tumors, neuroblastoma, retinoblastoma, Wilms tumor, hepatoblastoma, and rhabdomyosarcoma (30). Bone sarcomas and germ-cell tumors were not assessed individually because these cancers are most common in adolescents (22).

Measures of SES

Individual-level SES. We used maternal education to measure individual-level SES. The validity of using maternal education as a measure of childhood SES has been demonstrated previously (31, 32), and it is commonly used as a reliable measure of SES in US birth registry studies (33). Between 1989 and 2010, maternal education was recorded on birth certificates as years of schooling, ranging from 0 to 17. Beginning in 2011, education was recorded as highest degree earned, ranging from 8th grade or less to doctorate/professional degree. We grouped education into 4 categories to ensure sufficient sample size and consistency across years: <12 years of schooling or less than high-school diploma; 12 years of schooling or high-school diploma; 13–15 years of schooling or some college or associate degree; or ≥16 years of schooling or bachelor degree or higher. After confirming linearity (Web Figure 1, available at https://academic.oup.com/aje), we modeled education ordinally.

Neighborhood-level SES. Residential addresses were abstracted from birth records and geocoded to census tracts using normalized 2010 geographic boundaries (34), which allows for cross-decade comparisons. Normalization was performed by Geolytics and available via the Neighborhood Change Database (35). We created a composite SES index derived from the first component score from a nationwide principal-components analysis (36) of 5 tract-level US Census variables: % poverty, % on welfare or public assistance, % aged ≥16 years unemployed, % female-headed households with children, and % aged ≥25 years with less than a high-school education (37, 38). A separate principal-components analysis was performed for each decade (1980–2010) using decennial census data for 1980–2000 and, for 2010, American Community Survey data from 2005–2009. We assigned values based on year of birth and linearly interpolated SES scores for intercensal years. High internal consistency was observed for each decade of data (Cronbach's α range = 0.89–0.92) (38), and indices were highly correlated across decades (Pearson $\rho = 0.81$–0.93). We confirmed linearity (Web Figure 1) and standardized index scores so that a 1-unit change equated to 1 standard deviation (range = −7.3–1.5); higher values indicate higher neighborhood SES.

Statistical analysis

We compared demographic, socioeconomic, and pregnancy-related characteristics of cases and controls using Pearson's χ^2 test for categorical measures and the 2-sample t test for continuous measures. To untangle associations of SES and childhood cancer incidence (combined and by individual type), we tested logistic mixed models with a random intercept for clustering within census tracts. Intraclass correlations estimated from unimputed bivariate logistic mixed models revealed minimal tract-level clustering across cancer subtypes (intraclass correlation < 0.08), except rhabdomyosarcoma (intraclass correlation = 0.29), although intraclass correlations for rare outcomes may be unreliable (39). We tested 2 sets of models, one specifying maternal education as the primary predictor ("A" models), the other specifying neighborhood SES as the primary predictor ("B" models). Model 1 tested bivariate associations between SES and childhood cancer incidence. Model 2 tested these

associations, adjusting for maternal race/ethnicity (non-Hispanic white vs. other). Model 3 further adjusted for maternal age (years) (4, 40), live-birth order (first-born vs. higher) (4, 41), birth year (4), and sex (4). Model 4 further adjusted for birth weight (grams; values <350 grams considered implausible and recoded to missing) (4, 42) and gestational age (weeks; values <20 or >45 weeks considered implausible and recoded to missing) (4, 43). Finally, model 5 tested the independent association of SES at each level of exposure by simultaneously fitting models with both maternal education and neighborhood SES, along with all other previously specified covariates.

To further characterize the utility of covariate adjustment in studies of childhood cancer etiology, we tested additional models probing associations between SES and established demographic and pregnancy-related risk factors. First, for cancers in which covariate adjustment attenuated SES associations, we tested trivariate models of SES predicting cancer incidence, adjusting for each covariate, previously specified in model 4, one at a time. We then calculated the percentage change in SES-cancer estimates between bivariate (model 1) and trivariate models (% change = $(\beta_{bivar} - \beta_{trivar})/\beta_{bivar}$). Second, to assess the utility of adjusting for SES in prediction models, we compared associations between cancer incidence and previously established risk factors including race/ethnicity, maternal age, birth weight, gestational age, and birth order estimated from models fully adjusting for all covariates including SES, to estimates from models adjusting for all covariates except SES.

Complete data were available for 95% of our sample, and the proportion of missing data was <3% for any given variable (Table 1). Nevertheless, we used multiple imputation by chained equations to impute missing data for all variables (44). Statistical significance was tested using 2-sided hypothesis tests ($P < 0.05$). Multiple imputation and analyses were performed using Stata, version 14.2 (StataCorp LP, College Station, Texas) (45).

RESULTS

Descriptive characteristics of cases and controls are compared in Table 1. Cases were more likely to be male, have higher birth weight, and exhibit slightly shorter gestation compared with controls. Mothers of cases were older, had higher education levels, and were more likely to be non-Hispanic white than controls. Cases had higher neighborhood SES than controls. Descriptive characteristics by cancer type are available in the supplemental materials (Web Table 1). Variable correlations are available in the supplemental materials (Web Table 2); the 2 SES measures displayed moderate correlation (Spearman $\rho = 0.35$).

In Table 2, we present associations between maternal education and childhood cancer incidence. In crude model 1A, a 1-step increase in maternal education (e.g., from high-school graduate to some college) was associated with an 8% increase in risk of combined childhood cancers (odds ratio (OR) = 1.08, 95% confidence interval (CI): 1.04, 1.13). Unadjusted positive associations with higher maternal education were also observed for ALL (OR = 1.10, 95% CI: 1.02, 1.19), lymphomas (OR = 1.11, 95% CI: 0.99, 1.25), CNS tumors (OR = 1.12, 95% CI: 1.04, 1.21), neuroblastoma (OR = 1.15, 95% CI: 1.02, 1.30), and

Table 1. Characteristics of Cases and Controls, Registry-Based Case-Cohort Study (Total Sample = 14,854), Linked Minnesota Birth and Cancer Records, 1989–2014

Variable	Control (n = 11,907)		Case (n = 2,947)		P Value[a]	Missing, %
	%	Mean (SD)	%	Mean (SD)		
Birth characteristics						
Birth year		1999 (6.54)		1999 (6.52)	0.87	0.0
Female	49.2		44.3		<0.001	0.0
Birth weight, grams		3,403 (585.08)		3,437 (607.57)	0.01	0.1
Gestational age, weeks		38.9 (2.04)		38.8 (2.17)	0.01	2.2
First-born	38.7		39.8		0.27	0.5
Maternal characteristics						
Age at delivery, years		28.1 (5.79)		28.5 (5.66)	<0.01	0.5
Non-Hispanic white	81.4		85.0		<0.001	0.6
Education					<0.01	2.4
Below high-school diploma	10.9		9.0			
High-school diploma	29.6		28.0			
Some college	26.8		27.9			
Bachelor's degree or beyond	32.7		35.1			
Neighborhood SES[b]		−0.02 (1.02)		0.06 (0.92)	<0.001	0.0

Abbreviations: SD, standard deviation; SES, socioeconomic status.

[a] P values compare characteristics of cases and controls estimated from Pearson's χ^2 test for categorical measures and the 2-sample t test for continuous measures using a 2-sided hypothesis test.

[b] Higher values indicate higher neighborhood SES.

Table 2. Associations Between Maternal Education and Childhood Cancer Incidence, Registry-Based Case-Cohort Study (Total Sample = 14,854; Controls = 11,907), Linked Minnesota Birth and Cancer Records, 1989–2014

Model	All Childhood Cancers Combined (n = 2,947)			Acute Lymphoblastic Leukemia (n = 673)			Acute Myeloid Leukemia (n = 112)[a]			Lymphomas (n = 311)			CNS Tumors (n = 662)		
	OR	95% CI	*P* Value[b]	OR	95% CI	*P* Value[b]	OR	95% CI	*P* Value[b]	OR	95% CI	*P* Value[b]	OR	95% CI	*P* Value[b]
1A[c]	1.08	1.04, 1.13	<0.001	1.10	1.02, 1.19	0.02	1.03	0.86, 1.25	0.73	1.11	0.99, 1.25	0.07	1.12	1.04, 1.21	0.01
2A[d]	1.06	1.01, 1.10	0.01	1.08	1.00, 1.18	0.05	1.06	0.87, 1.29	0.55	1.11	0.98, 1.25	0.10	1.06	0.97, 1.15	0.18
3A[e]	1.03	0.98, 1.08	0.18	1.07	0.97, 1.17	0.17	0.98	0.79, 1.22	0.85	1.12	0.98, 1.28	0.10	1.06	0.96, 1.16	0.24
4A[f]	1.03	0.98, 1.08	0.26	1.05	0.96, 1.16	0.27	0.96	0.78, 1.20	0.75	1.12	0.98, 1.28	0.10	1.05	0.96, 1.16	0.29
5A[g]	1.02	0.97, 1.07	0.36	1.05	0.95, 1.15	0.36	0.95	0.76, 1.19	0.66	1.10	0.96, 1.26	0.18	1.04	0.95, 1.15	0.42
	Neuroblastoma (n = 267)			Retinoblastoma (n = 80)			Wilms Tumor (n = 198)[b]			Hepatoblastoma (n = 50)			Rhabdomyosarcoma (n = 79)		
	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]
1A[c]	1.15	1.02, 1.30	0.03	1.15	0.91, 1.44	0.23	1.15	1.00, 1.32	0.06	0.72	0.54, 0.94	0.02	0.91	0.73, 1.14	0.41
2A[d]	1.13	0.99, 1.29	0.06	1.21	0.96, 1.53	0.11	1.08	0.93, 1.25	0.32	0.74	0.55, 0.98	0.04	0.85	0.67, 1.08	0.19
3A[e]	1.07	0.93, 1.24	0.33	1.28	0.97, 1.68	0.08	1.04	0.87, 1.23	0.69	0.66	0.48, 0.90	0.01	0.79	0.61, 1.02	0.08
4A[f]	1.07	0.93, 1.24	0.34	1.27	0.97, 1.68	0.09	1.02	0.86, 1.20	0.85	0.69	0.50, 0.96	0.03	0.78	0.60, 1.01	0.06
5A[g]	1.09	0.94, 1.26	0.28	1.25	0.94, 1.65	0.12	1.02	0.86, 1.21	0.83	0.70	0.51, 0.98	0.04	0.77	0.59, 1.00	0.05

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio; SES, socioeconomic status.

[a] Random intercepts dropped from models 1A–3A due to nonconvergence from zero-value intraclass correlations.

[b] *P* values estimated from a logistic mixed model with a random intercept for census tract clustering using a 2-sided hypothesis test.

[c] Model 1A: bivariate.

[d] Model 2A adjusted for maternal race/ethnicity.

[e] Model 3A adjusted for maternal race/ethnicity, maternal age, birth order, birth year, and sex.

[f] Model 4A adjusted for maternal race/ethnicity, maternal age, birth order, birth year, sex, birth weight, and gestational age.

[g] Model 5A adjusted for maternal race/ethnicity, maternal age, birth order, birth year, sex, birth weight, gestational age, and neighborhood SES.

Table 3. Associations Between Maternal Education and Childhood Cancer Incidence Estimated From Bivariate and Trivariate Models, Registry-Based Case-Cohort Study (Total Sample = 14,854; Controls = 11,907), Linked Minnesota Birth and Cancer Records, 1989–2014

Model	All Childhood Cancers Combined (n = 2,947)				Acute Lymphoblastic Leukemia (n = 673)				Lymphomas (n = 311)			
	OR	95% CI	*P* Value[a]	%[b]	OR	95% CI	*P* Value[a]	%[b]	OR	95% CI	*P* Value[a]	%[b]
Bivariate[c]	1.08	1.04, 1.13	<0.001		1.10	1.02, 1.19	0.02		1.11	0.99, 1.25	0.07	
Trivariate, adjusting for												
Race/ethnicity[d]	1.06	1.01, 1.10	0.01	30	1.08	1.00, 1.18	0.05	15	1.11	0.98, 1.25	0.10	6
Maternal age	1.06	1.02, 1.11	0.01	20	1.08	0.99, 1.18	0.08	18	1.09	0.96, 1.24	0.19	20
Birth weight	1.07	1.03, 1.12	<0.01	6	1.09	1.00, 1.18	0.04	12	1.11	0.99, 1.24	0.08	5
Gestational age	1.08	1.04, 1.13	<0.001	−1	1.10	1.02, 1.19	0.02	0	1.11	0.99, 1.25	0.07	1
First-born	1.08	1.04, 1.13	<0.001	0	1.10	1.02, 1.19	0.02	0	1.11	0.99, 1.25	0.06	−1
Sex	1.08	1.04, 1.13	<0.001	−1	1.10	1.02, 1.19	0.02	−1	1.11	0.99, 1.25	0.06	−1
Birth year	1.08	1.04, 1.13	<0.001	−1	1.10	1.02, 1.19	0.02	−1	1.13	1.01, 1.27	0.04	−13
	CNS Tumors (n = 662)				Neuroblastoma (n = 267)				Wilms Tumor (n = 198)[e]			
	OR	95% CI	*P* Value[a]	%[b]	OR	95% CI	*P* Value[a]	%[b]	OR	95% CI	*P* Value[a]	%[b]
Bivariate[c]	1.12	1.04, 1.21	0.01		1.15	1.02, 1.30	0.03		1.15	1.00, 1.32	0.06	
Trivariate, adjusting for												
Race/ethnicity[d]	1.06	0.97, 1.15	0.18	50	1.13	0.99, 1.29	0.06	12	1.08	0.93, 1.25	0.32	46
Maternal age	1.13	1.03, 1.23	0.01	−5	1.15	1.00, 1.32	0.05	−2	1.14	0.97, 1.33	0.12	8
Birth weight	1.11	1.03, 1.20	0.01	8	1.15	1.02, 1.30	0.03	−2	1.13	0.98, 1.30	0.10	13
Gestational age	1.12	1.03, 1.21	0.01	0	1.15	1.02, 1.30	0.03	−2	1.15	1.00, 1.33	0.06	−1
First-born	1.12	1.03, 1.21	0.01	1	1.15	1.01, 1.30	0.03	1	1.15	0.99, 1.32	0.06	1
Sex	1.12	1.04, 1.21	0.01	0	1.15	1.02, 1.30	0.03	−1	1.15	1.00, 1.32	0.06	0
Birth year	1.13	1.04, 1.22	<0.01	−4	1.12	0.99, 1.27	0.08	19	1.13	0.98, 1.31	0.08	9

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio.

[a] *P* values estimated from a logistic mixed model with a random intercept for census tract clustering using a 2-sided hypothesis test.

[b] Compared the β coefficients for maternal education predicting cancer incidence estimated from bivariate and trivariate models (i.e., $\beta_{bivar} - \beta_{trivar}/\beta_{bivar}$).

[c] Equal to model 1A in Table 2.

[d] Equal to model 2A in Table 2.

[e] Random intercepts dropped from models 1A–3A due to nonconvergence from zero-value intraclass correlations.

Wilms tumor (OR = 1.15, 95% CI: 1.00, 1.32). After adjusting for race/ethnicity (model 2A) and pregnancy-related risk factors (models 3A and 4A), these associations were attenuated towards the null. Adjustment for neighborhood SES (model 5A) did not further alter estimates. An elevated odds ratio was also observed for maternal education predicting retinoblastoma incidence, although confidence intervals were wide (e.g., model 5A, OR = 1.25, 95% CI: 0.94, 1.65).

Conversely, we found an inverse association between higher SES and hepatoblastoma incidence. In crude model 1A, a 1-step increase in maternal education was associated with a 28% reduced risk of hepatoblastoma (OR = 0.72, 95% CI: 0.54, 0.94). This association was robust to comprehensive covariate adjustment (model 5A OR = 0.70, 95% CI: 0.51, 0.98). An inverse, although less pronounced, association was also observed between higher maternal education and rhabdomyosarcoma incidence (model 5A OR = 0.77, 95% CI: 0.59, 1.00).

For cancers in which the SES association was substantially attenuated by covariate control (combined, ALL, lymphomas, CNS tumors, neuroblastoma, Wilms tumor), we further investigated which of the established risk factors accounted for associations (Table 3). Adjustment for race/ethnicity reduced the estimated association between maternal education and cancer incidence by more than 10% for combined and individual childhood cancers except lymphomas (6%); the largest reductions were observed for combined childhood cancers (30%), Wilms tumor (46%), and CNS tumors (50%). Adjustment for maternal age reduced the maternal education association by >10% for combined childhood cancers (20%), ALL (18%), and lymphomas (20%); adjustment for birth weight reduced the association by >10% for ALL (12%) and Wilms tumor (13%); and adjustment for birth year reduced the association by >10% for neuroblastoma (19%). Individual adjustment for gestational age, birth order, and sex did not substantively alter maternal education associations.

We then evaluated associations between neighborhood SES and childhood cancer incidence (Table 4). In crude models (model 1B), higher neighborhood SES was positively associated with incidence of combined childhood cancers (OR = 1.09, 95% CI: 1.04, 1.14), ALL (OR = 1.10, 95% CI: 1.01,

Table 4. Associations Between Neighborhood Socioeconomic Status and Childhood Cancer Incidence, Registry-Based Case-Cohort Study (Total Sample = 14,854; Controls = 11,907), Linked Minnesota Birth and Cancer Records, 1989–2014

Model	All Childhood Cancers Combined (n = 2,947)			Acute Lymphoblastic Leukemia (n = 673)			Acute Myeloid Leukemia (n = 112)			Lymphomas (n = 311)			CNS Tumors (n = 662)		
	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]
1B[b]	1.09	1.04, 1.14	<0.001	1.10	1.01, 1.20	0.03	1.07	0.88, 1.30	0.52	1.14	1.01, 1.30	0.04	1.18	1.08, 1.29	<0.001
2B[c]	1.05	1.00, 1.11	0.04	1.08	0.99, 1.19	0.10	1.12	0.91, 1.39	0.30	1.15	1.00, 1.31	0.05	1.09	0.99, 1.20	0.09
3B[d]	1.04	0.99, 1.09	0.12	1.07	0.97, 1.17	0.18	1.08	0.87, 1.33	0.50	1.14	0.99, 1.32	0.06	1.09	0.98, 1.20	0.10
4B[e]	1.04	0.99, 1.09	0.16	1.06	0.97, 1.17	0.22	1.07	0.86, 1.33	0.54	1.15	1.00, 1.32	0.06	1.09	0.98, 1.20	0.11
5B[f]	1.03	0.98, 1.09	0.21	1.05	0.96, 1.16	0.29	1.08	0.87, 1.34	0.49	1.13	0.98, 1.30	0.10	1.08	0.97, 1.19	0.15
	Neuroblastoma (n = 267)			Retinoblastoma (n = 80)			Wilms Tumor (n = 198)			Hepatoblastoma (n = 50)			Rhabdomyosarcoma (n = 79)		
	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]
1B[b]	1.01	0.89, 1.15	0.82	1.07	0.85, 1.36	0.55	1.13	0.96, 1.32	0.14	0.83	0.66, 1.03	0.09	1.14	0.87, 1.50	0.34
2B[c]	0.97	0.84, 1.11	0.67	1.16	0.90, 1.50	0.25	1.01	0.85, 1.20	0.90	0.86	0.67, 1.11	0.24	1.06	0.79, 1.42	0.71
3B[d]	0.95	0.82, 1.09	0.45	1.17	0.90, 1.51	0.24	0.99	0.83, 1.18	0.92	0.84	0.65, 1.09	0.19	1.04	0.77, 1.41	0.80
4B[e]	0.95	0.82, 1.09	0.43	1.16	0.90, 1.51	0.25	0.98	0.83, 1.17	0.85	0.88	0.68, 1.14	0.33	1.03	0.76, 1.40	0.83
5B[f]	0.93	0.81, 1.08	0.35	1.13	0.87, 1.46	0.37	0.98	0.82, 1.17	0.83	0.92	0.70, 1.20	0.52	1.08	0.79, 1.48	0.63

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio.

[a] *P* values estimated from a logistic mixed model with a random intercept for census tract clustering using a 2-sided hypothesis test.

[b] Model 1B: bivariate.

[c] Model 2B adjusted for maternal race/ethnicity.

[d] Model 3B adjusted for maternal race/ethnicity, maternal age, birth order, birth year, and sex.

[e] Model 4B adjusted for maternal race/ethnicity, maternal age, birth order, birth year, sex, birth weight, and gestational age.

[f] Model 5B adjusted for maternal race/ethnicity, maternal age, birth order, birth year, sex, birth weight, gestational age, and maternal education.

Table 5. Associations Between Established Risk Factors and Combined Childhood Cancer Incidence, Crude and Adjusted for Socioeconomic Status (Total Sample = 14,854; Controls = 11,907), Registry-Based Case-Cohort Study, Linked Minnesota Birth and Cancer Records, 1989–2014

Variable	Adjusted for Demographic and Birth Covariates (SES Excluded From Model)[a]			Adjusted for Demographic, Birth, and SES Covariates (SES Included in Model)[b]		
	OR	95% CI	*P* Value[c]	OR	95% CI	*P* Value[c]
Race/ethnicity, NH white vs. other	1.23	1.09, 1.38	<0.01	1.17	1.03, 1.33	0.02
Maternal age, per 5-year increase	1.05	1.01, 1.09	0.01	1.04	0.99, 1.08	0.11
Birth weight, per 500-gram increase	1.11	1.06, 1.16	<0.001	1.10	1.06, 1.16	<0.001
Gestational age, per 1-week increase	0.94	0.92, 0.97	<0.001	0.94	0.92, 0.97	<0.001
First-born, first-born vs. other	1.11	1.02, 1.22	0.02	1.10	1.01, 1.21	0.04

Abbreviations: CI, confidence interval; NH, non-Hispanic; OR, odds ratio; SES, socioeconomic status.

[a] Adjusted for maternal race/ethnicity, maternal age, birth order, birth year, sex, birth weight, and gestational age.

[b] Adjusted for maternal race/ethnicity, maternal age, birth order, birth year, sex, birth weight, gestational age, maternal education, and neighborhood SES.

[c] *P* values estimated from a logistic mixed model with a random intercept for census tract clustering using a 2-sided hypothesis test.

1.20), lymphomas (OR = 1.14, 95% CI: 1.01, 1.30), and CNS tumors (OR = 1.18, 95% CI: 1.08, 1.29). Neighborhood SES was no longer associated with incidence of combined or individual cancers in models adjusting for race/ethnicity and pregnancy-related risk factors (models 3B and 4B) or in models further adjusting for maternal education (model 5B). Among cancers in which the SES association was altered by covariate control (combined, ALL, lymphomas, CNS tumors), adjustment for race/ethnicity reduced the estimated association between neighborhood SES and cancer incidence by >10% for combined childhood cancers (39%), ALL (18%), and CNS tumors (49%); adjustment for maternal age reduced the association by >10% for combined childhood cancers (14%), ALL (15%), and lymphomas (12%); and adjustment for birth weight reduced the association for ALL by 10% (Web Table 3).

As illustrated in Table 5, associations between established demographic and pregnancy-related risk factors and combined childhood cancer incidence were not considerably altered by adjustment for maternal education and neighborhood SES. Associations for individual types of childhood cancer are provided in the supplemental materials (Web Table 4).

DISCUSSION

To our knowledge, this is the first study to employ multilevel methods to examine associations between SES and childhood cancer incidence. We tested associations in a population-based sample using a registry-based case-cohort study design, thus minimizing multiple potential sources of bias. Through our analysis, we generated several findings. First, we found that higher SES at both levels (maternal education and census tract composite index) was consistently positively associated with incidence of many childhood cancers in crude models. Second, these positive associations were accounted for by established demographic and pregnancy-related risk factors. Third, associations between established risk factors and childhood cancer incidence were robust to adjustment for SES. Fourth, higher individual-level SES was associated with lower incidence of hepatoblastoma, even after comprehensive control of other risk factors.

Higher SES, whether operationalized as maternal education at the individual-level or as an area-level index, was associated with higher risk of the most common childhood cancers (combined, ALL, lymphomas, and CNS tumors), with a similar pattern emerging for both SES measures. However, associations between higher SES and incidence of combined or specific childhood cancers were markedly weakened after accounting for established demographic and pregnancy-related risk factors. This suggests that crude associations of SES at either level primarily capture established risk factors not specified in the model. In particular, non-Hispanic white race/ethnicity accounted for a substantial portion of positive associations of higher SES, especially for combined childhood cancers, CNS tumors, and Wilms tumor. Older maternal age and higher birth weight also explained some of the positive SES association, although to varying degrees across cancer types.

Investigation of associations between established risk factors, such as race/ethnicity and birth weight, and childhood cancer incidence revealed that these associations were robust to adjustment for SES, further suggesting that SES is not strongly associated with incidence of most childhood cancers beyond the social patterning of known exposures. Therefore, adjustment for proximal demographic and pregnancy-related risk factors is likely sufficient in analyses of childhood cancer etiology. This is reassuring, especially given the lack of socioeconomic data in medical records and cancer registries (46). However, it remains important to note that SES is a common prior cause of some of these more proximal risk factors including birth weight and maternal age.

We did identify an inverse association between higher maternal education and hepatoblastoma incidence that was independent of established risk factors. Although little is known about the etiology of hepatoblastoma, some studies have identified parental tobacco use as a potential risk factor (47), which may explain a social patterning of incidence. Due to insufficient smoking data in our study, we look to future

studies to explore this potential mechanism. We note that a similarly designed study using pooled data from 5 US state registries found no evidence of an inverse association between higher maternal education and risk of hepatic tumors (13). Therefore, additional research is needed to replicate our finding and to explore potential effect modifiers that may explain cross-place differences.

Limitations

This study has several limitations. First, there are limitations to our SES measures. Because the measures were limited to a single exposure window at birth, although this is a common approach for operationalizing childhood SES, we cannot draw conclusions about SES later in childhood. Yet neighborhood SES at birth was strongly correlated with SES at diagnosis among cases (Pearson $\rho = 0.72$), suggesting temporal stability, which has been reported previously (48, 49). Beside education, we could not account for other dimensions of individual-level SES, such as household income or occupation, in our primary analysis. In a secondary analysis of combined childhood cancers, we assessed paternal involvement, based on paternal information present versus missing on the birth certificate, as an alternative measure of SES (13, 50, 51), and this produced similar patterns of association as those with our measure of maternal education (Web Table 5). We also did not consider area-level factors such as racial segregation or geographic variation in our primary analysis. We did conduct a secondary analysis of combined childhood cancers stratified by rural/urban status, which revealed comparable SES associations by rural/urban status (Web Table 6).

Further, the use of a composite index to operationalize neighborhood SES may mask any differential effects of the various dimensions of SES included in the index and may violate the consistency assumption (52). We note that the 5 index variables were strongly correlated (Web Table 7), and we performed a sensitivity analysis testing associations between each of the 5 neighborhood SES variables and combined childhood cancer incidence, which revealed comparable associations across measures (Web Table 8). We also note that linear interpolation of intercensal years may introduce measurement error, especially for years at the midpoint between censuses (53). We performed a sensitivity analysis comparing associations between combined childhood cancer incidence and interpolated versus non-interpolated (assigned based on census closest to birth year) measures of neighborhood SES among our entire sample, as well as among a subset of our sample restricted to births occurring within 2 years of a census ($n = 10{,}762$). Estimates were comparable across measures and samples (Web Table 9).

Another study limitation is the potential for bias resulting from conditioning on intermediates (54), such as birth weight and gestational age in models 4 and 5. To address this, we compared estimates across several models of increasing covariate control. Our study was also limited by sample size due to the rarity of childhood cancers. This prevented us from testing more homogeneous cancer subgroups or stratifying by age in primary analyses. We assessed subtypes of lymphomas (Web Table 10) and CNS tumors (Web Table 11) in a secondary analysis, which revealed some variability in SES associations across subgroups. We also performed a secondary analysis of combined childhood cancer incidence stratified by age at diagnosis, which demonstrated similar neighborhood SES associations across age groups (Web Table 12). This somewhat mitigates concern that neighborhood SES may be better measured for children diagnosed at younger ages, given that neighborhood SES is derived from the address at birth. The positive crude association between maternal education and combined childhood cancer incidence diminished with increasing age, although adjusted maternal education associations were comparable across age groups.

Given the high proportion of non-Hispanic whites in our sample (81%), we were unable to stratify by race/ethnicity in our primary analysis, and results may be less generalizable to more racially diverse populations. We did conduct a secondary analysis stratified by race/ethnicity for combined childhood cancers, which indicated that positive SES associations may be driven by non-Hispanic white children (Web Table 13); however, analyses were underpowered for racial minority groups. Prior ecological studies have reported differential associations between SES and childhood cancer incidence across racial/ethnic groups (7, 55), and thus future studies should continue to explore race/ethnicity as a potential effect modifier.

Finally, there is the potential for disease misclassification bias if children born in Minnesota subsequently moved out of state and developed cancer. However, given the rarity of childhood cancers and low out-migration rate among Minnesota youth (56), this is not a major threat to validity. There is also the potential for selection bias if cases without a matching birth record were in fact born in Minnesota, and thus part of the source cohort. This may have occurred because of inconsistent (e.g., name changes) or missing data. We found that unmatched cases resided in lower-SES neighborhoods at the time of diagnosis than did matched cases, which may reflect differences in data quality according to SES (33). However, it may also reflect higher residential mobility among lower-SES cases (48), and thus a higher in-migration rate to Minnesota during childhood. Our 86% record-linkage rate is comparable to prior registry-based studies of childhood cancer (57–59).

Conclusion

Results from this study suggest that SES is not strongly associated with childhood cancer incidence beyond the social patterning of established demographic and pregnancy-related risk factors such as race/ethnicity, maternal age, and birth weight. It is reassuring that these socially patterned risk factors of childhood cancer incidence are already known and well-described in the literature. However, given that these exposures account for only a small portion of the total disease burden (4), more work is needed to better understand childhood cancer etiology. Unfortunately, while it is important to continue monitoring socioeconomic differences in risk to ensure health equity, our findings suggest that continued investigation of SES associations may not generate new etiological insight into childhood cancer incidence, at least for the more common cancers.

ACKNOWLEDGMENTS

Author affiliations: University of Minnesota School of Public Health, Division of Epidemiology and Community

Health, Minneapolis, Minnesota (Rebecca D. Kehm, Theresa L. Osypuk); University of Minnesota, Division of Epidemiology and Clinical Research, Department of Pediatrics, Minneapolis, Minnesota (Logan G. Spector, Jenny N. Poynter); and University of Minnesota School of Public Health, Division of Biostatistics, Minneapolis, Minnesota (David M. Vock).

This work was supported by the National Institutes of Health Translational Pediatric Cancer Epidemiology Training Grant (T32CA099936).

We thank the Minnesota Cancer Surveillance System and the Minnesota Center for Health Statistics at the Minnesota Department of Health for their support with data acquisition.

Conflict of interest: none declared.

REFERENCES

1. Starfield B, Riley AW, Witt WP, et al. Social class gradients in health during adolescence. *J Epidemiol Community Health*. 2002;56(5):354–361.
2. Starfield B, Robertson J, Riley AW. Social class gradients and health in childhood. *Ambul Pediatr*. 2002;2(4):238–246.
3. Sommer I, Griebler U, Mahlknecht P, et al. Socioeconomic inequalities in non-communicable diseases and their risk factors: an overview of systematic reviews. *BMC Public Health*. 2015;15:914.
4. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. *Pediatr Clin North Am*. 2015; 62(1):11–25.
5. Blumenshine P, Egerter S, Barclay CJ, et al. Socioeconomic disparities in adverse birth outcomes: a systematic review. *Am J Prev Med*. 2010;39(3):263–272.
6. Heck JE, Park AS, Contreras ZA, et al. Risk of childhood cancer by maternal birthplace: a test of the Hispanic paradox. *JAMA Pediatr*. 2016;170(6):585–592.
7. Pan IJ, Daniels JL, Zhu K. Poverty and childhood cancer incidence in the United States. *Cancer Causes Control*. 2010; 21(7):1139–1145.
8. Ash M, Fetter TR. Who lives on the wrong side of the environmental tracks? Evidence from the EPA's risk-screening environmental indicators model. *Soc Sci Q*. 2004;85(2):441–462.
9. Kamihara J, Ma C, Fuentes Alabi SL, et al. Socioeconomic status and global variations in the incidence of neuroblastoma: call for support of population-based cancer registries in low-middle-income countries. *Pediatr Blood Cancer*. 2017;64(2): 321–323.
10. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull*. 1996;52(4): 682–703.
11. Parkin D, Kramarova E, Draper G, et al. *International Incidence of Childhood Cancer, Volume II*. Lyon, France: IARC Scientific Publications; 1998.
12. Alston RD, Rowan S, Eden TO, et al. Cancer incidence patterns by region and socioeconomic deprivation in teenagers and young adults in England. *Br J Cancer*. 2007;96(11): 1760–1766.
13. 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(1):136–142.
14. Adam M, Kuehni CE, Spoerri A, et al. Socioeconomic status and childhood leukemia incidence in Switzerland. *Front Oncol*. 2015;5:139.
15. 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(7):736–743.
16. Raaschou-Nielsen O, Obel J, Dalton S, et al. Socioeconomic status and risk of childhood leukaemia in Denmark. *Scand J Public Health*. 2004;32(4):279–286.
17. Dockerty JD, Draper G, Vincent T, et al. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol*. 2001;30(6):1428–1437.
18. Keegan TJ, Bunch KJ, Vincent TJ, et al. Case-control study of paternal occupation and social class with risk of childhood central nervous system tumours in great Britain, 1962–2006. *Br J Cancer*. 2013;108(9):1907–1914.
19. Poole C, Greenland S, Luetters C, et al. Socioeconomic status and childhood leukaemia: a review. *Int J Epidemiol*. 2006; 35(2):370–384.
20. Adam M, Rebholz CE, Egger M, et al. Childhood leukaemia and socioeconomic status: what is the evidence? *Radiat Prot Dosimetry*. 2008;132(2):246–254.
21. McNally RJ, Eden TO. An infectious aetiology for childhood acute leukaemia: a review of the evidence. *Br J Haematol*. 2004;127(3):243–263.
22. Ries LAG, Smith MA, Gurney J, et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Bethesda, MD: National Cancer Institute, SEER Program; 1999. (NIH Pub. No. 99-4649). https://seer.cancer.gov/archive/publications/childhood/. Accessed November 22, 2016.
23. Puumala SE, Spector LG, Robison LL, et al. Comparability and representativeness of control groups in a case-control study of infant leukemia: a report from the children's oncology group. *Am J Epidemiol*. 2009;170(3):379–387.
24. Minnesota Cancer Surveillance System. *Cancer in Minnesota, 1988–2009*. St. Paul, MN: Minnesota Department of Health; 2012.
25. Jaro MA. Probabilistic linkage of large public health data files. *Stat Med*. 1995;14(5–7):491–498.
26. Division of Cancer Prevention and Control. Registry Plus, a suite of publicly available software programs for collecting and processing cancer registry data. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2015. https://www.cdc.gov/cancer/npcr/tools/registryplus/index.htm. Accessed November 22, 2016.
27. Rothman KJ, Greenland S, Lash TL. Case-control studies. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:111–127.
28. Maloney KW, Taub JW, Ravindranath Y, et al. Down syndrome preleukemia and leukemia. *Pediatr Clin North Am*. 2015;62(1):121–137.
29. Cybulski C, Nazarali S, Narod SA. Multiple primary cancers as a guide to heritability. *Int J Cancer*. 2014;135(8):1756–1763.
30. Steliarova-Foucher E, Stiller C, Lacour B, et al. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103(7):1457–1467.
31. Hauser RM. Measuring socioeconomic status in studies of child development. *Child Dev*. 1994;65(6):1541–1545.
32. Zill N. Parental schooling and children's health. *Public Health Rep*. 1996;111(1):34–43.
33. Northam S, Knapp TR. The reliability and validity of birth certificates. *J Obstet Gynecol Neonatal Nurs*. 2006;35(1):3–12.
34. Goldberg, DW, Kohler, B, Kosary, C. The Texas A&M, North American Association of Central Cancer Registries, National Cancer Institute Geocoding Service. https://www.naaccr.org/gis-resources/. Accessed November 22, 2016.

35. Geolytics. Neighborhood Change Database Longform Release 2.0. East Brunswick, NJ: Geolytics, Inc.; 2003.
36. Tabachnick BG, Fidell LS. Principal components and factor analysis. Using Multivariate Statistics. Northridge, CA: California State University, Harper Collins College; 1996:635–708.
37. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health*. 2006;83(6):1041–1062.
38. Osypuk TL, Kehm R, Misra DP. Where we used to live: validating retrospective measures of childhood neighborhood context for life course epidemiologic studies. *PLoS One*. 2015; 10(4):e0124635.
39. Pagel C, Prost A, Lewycka S, et al. Intracluster correlation coefficients and coefficients of variation for perinatal outcomes from five cluster-randomised controlled trials in low and middle-income countries: results and methodological implications. *Trials*. 2011;12:151.
40. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology*. 2009; 20(4):475–483.
41. 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(11):2709–2716.
42. Samuelsen SO, Bakketeig LS, Tretli S, et al. Birth weight and childhood cancer. *Epidemiology*. 2009;20(4):484–487.
43. Callan AC, Milne E. Involvement of the IGF system in fetal growth and childhood cancer: an overview of potential mechanisms. *Cancer Causes Control*. 2009;20(10): 1783–1798.
44. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. *J Stat Softw*. 2011; 45(4):1–20.
45. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP; 2015.
46. Krieger N. Socioeconomic data in cancer registries. *Am J Public Health*. 2001;91(1):156–157.
47. Spector LG, Birch J. The epidemiology of hepatoblastoma. *Pediatr Blood Cancer*. 2012;59(5):776–779.
48. Urayama KY, Von Behren J, Reynolds P, et al. Factors associated with residential mobility in children with leukemia: implications for assigning exposures. *Ann Epidemiol*. 2009; 19(11):834–840.
49. Osypuk TL, Slaughter-Acey JC, Kehm RD, et al. Life-course social mobility and reduced risk of adverse birth outcomes. *Am J Prev Med*. 2016;51(6):975–982.
50. Tan H, Wen SW, Walker M, et al. Missing paternal demographics: a novel indicator for identifying high risk population of adverse pregnancy outcomes. *BMC Pregnancy Childbirth*. 2004;4(1):21.
51. Nicolaidis C, Ko CW, Saha S, et al. Racial discrepancies in the association between paternal vs. maternal educational level and risk of low birth weight in Washington State. *BMC Pregnancy Childbirth*. 2004;4(1):10.
52. Rehkopf DH, Glymour MM, Osypuk TL. The consistency assumption for causal inference in social epidemiology: when a rose is not a rose. *Curr Epidemiol Rep*. 2016;3(1):63–71.
53. Weden MM, Peterson CE, Miles JN, et al. Evaluating linearly interpolated intercensal estimates of demographic and socioeconomic characteristics of US counties and census tracts 2001–2009. *Popul Res Policy Rev*. 2015;34(4):541–559.
54. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology*. 2012;23(1):1–9.
55. Wang L, Gomez SL, Yasui Y. Racial and ethnic differences in socioeconomic position and risk of childhood acute lymphoblastic leukemia. *Am J Epidemiol*. 2017;185(12): 1263–1271.
56. Minnesota State Demographic Center. Minnesota on the move: Migration patterns and implications. 2015. https://mn.gov/bms-stat/assets/mn-on-the-move-migration-report-msdc-jan2015.pdf. Accessed November 27, 2016.
57. Puumala SE, Soler JT, Johnson KJ, et al. Birth characteristics and Wilms tumor in Minnesota. *Int J Cancer*. 2008;122(6): 1368–1373.
58. McLaughlin CC, Baptiste MS, Schymura MJ, et al. Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol*. 2006;163(9):818–828.
59. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. *Am J Epidemiol*. 2002;155(7): 603–613.