

**Title:** Neighborhood-level social determinants of health and late mortality among survivors of childhood cancer

**CCSS Working Groups:** Biostatistics/Epidemiology; Cancer Control and Intervention

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## Background

Social and built environment factors are important predictors of cancer-related outcomes. Among long-term survivors of childhood cancer, living in neighborhoods with greater socioeconomic disadvantage/deprivation has been associated with worse outcomes, including poor quality of life<sup>1</sup>, obesity<sup>2</sup>, and frailty<sup>3</sup>. In previous work among 3,407 adult survivors of childhood cancer in the St. Jude Lifetime Cohort (SJLIFE), Ehrhardt *et al.*<sup>4</sup> reported survivors living in neighborhoods characterized by the most socioeconomic deprivation (Area Deprivation Index<sup>5-7</sup> or ADI in 81-100 percentile) had a nearly 9-fold (95% CI: 2.0-37.6) and 16-fold (95% CI: 2.1-123.7) higher overall and health-related mortality rate, respectively, than the least (ADI, 1-10 percentile), adjusting for demographics, individual-level socioeconomic status, treatment, and modifiable chronic health conditions (CHCs). Interestingly, Ehrhardt *et al.*<sup>4</sup> observed the adjusted associations between the rate of death and high neighborhood-level socioeconomic deprivation were considerably larger in magnitude than any other modeled risk factor, including radiotherapy dose and CHC burden.

Disparities in disease incidence and premature mortality have been linked to emerging, and more granular metrics of neighborhood-level social determinants of health (SDoH) in the general population<sup>8-14</sup>. Census tract-level variations in the Social Vulnerability Index<sup>15,16</sup> (SVI), a measure of neighborhood-level deprivation reflecting four domains (socioeconomic status; household characteristics; racial/ethnic minority status; housing type and transportation) and originally developed by the Centers for Disease Control and Prevention (CDC) to identify communities vulnerable to catastrophic events, has been linked to disparities in disability and mortality<sup>8-10</sup>. In comparison to ADI, which only provides information about overall socioeconomic deprivation and most heavily weights poverty, income, and education, SVI supports the study of four thematic domains of deprivation to facilitate the identification of under-resourced communities<sup>17,18</sup>. Furthermore, unlike ADI, Minority Health SVI (MHSVI) considers county-level health care infrastructure and medically vulnerability status<sup>15,16,18,19</sup>. Disparities in cancer-related outcomes associated with other metrics of neighborhood-level SDoH including persistent poverty<sup>11,12</sup>, i.e., counties with at least 20% of residents living below the poverty level since 1980<sup>20</sup>, and mortgage lending or redlining bias<sup>13,14</sup>, i.e., mortgage discrimination on the basis of

property location, have been reported. Compared to ADI and SVI, these latter metrics reflect distinct, complex, and historical aspects of neighborhood-level structural inequity. For example, persistent poverty counties frequently coincide with rural areas with limited healthcare access<sup>21</sup>, while redlining has resulted in the systematic residential segregation of Black and minoritized populations in the US<sup>22</sup> with important consequences in access to quality healthcare<sup>23,24</sup>.

These emerging neighborhood-level SDoH metrics have not been investigated in the context of late mortality among survivors of childhood cancer. While cancer treatment is associated with increased risk for premature mortality and other late effects, the progression of these late effects may be intensified among cancer survivors living in neighborhoods with limited community resources and social support. Identifying specific neighborhood-level SDoH and their impact on mortality will help clinicians and policymakers create targeted interventions to prevent worsening health outcomes for childhood cancer survivors. Therefore, building on previous work by Ehrhardt *et al.*<sup>4</sup> in SJLIFE, we propose to conduct comprehensive studies of late mortality and these emerging neighborhood-level metrics of structural inequity and deprivation in the larger multi-institutional Childhood Cancer Survivor Study, including more survivors (N>25,000) with longer study follow-up. This proposal also builds upon research described in the approved CCSS concept proposal 20-07 (Howell *et al.*, manuscript in progress), utilizing newly available geocoded data among survivors and siblings participating in CCSS with addresses provided at study recruitment and last follow-up linked to geospatial data. We further propose to evaluate the joint relationship between neighborhood-level SDoH and individual-level socioeconomic factors on late mortality.

### **Specific aims**

For the following aims, neighborhood-level structural inequity will be defined by persistent poverty<sup>11,12</sup> and modern redlining bias measures<sup>13,14</sup>. Neighborhood-level deprivation will be defined by the SVI<sup>15,16</sup>. Because each of these neighborhood-level SDoH metrics is theoretically distinct and it is unclear which metric is most predictive of late mortality among survivors, each metric will be evaluated separately. Given the limitations of available geocoding data (e.g., lack of geospatial data resources for older geocodes), our primary analytic strategy is to consider all geocoded addresses reported by each CCSS participant from calendar year 2000 onwards and use the participant geocode reflecting the *greatest* neighborhood-level structural inequity and deprivation in analyses, i.e., assessing exposure to any recent neighborhood-level structural inequity and deprivation. Sensitivity analyses to assess the most chronologically current or oldest available geocode (i.e., the impact of contemporaneous exposure versus earlier childhood/adolescence/young adulthood exposure) will be conducted.

We hypothesize that: (a) survivors who reside in neighborhoods characterized by higher structural inequity and deprivation will have increased late mortality risk; (b) unfavorable individual-level SDoH further increases this risk; and (c) shortage of healthcare resources (typically primary care physicians) will exacerbate the relationship between adverse neighborhood-level SDoH and late mortality. Following these hypotheses, our specific aims are described below:

**Aim 1:** Describe the association between (incident) all-cause and cause-specific late mortality risk and living in neighborhoods characterized by structural inequity and deprivation among survivors.

- Aim 1a: Compare survivors' excess all-cause and cause-specific mortality risks associated with living in neighborhoods characterized by structural inequity and deprivation to CCSS siblings.

**Aim 2:** Assess how individual-level SDoH modifies late mortality risks associated with living in neighborhoods characterized by structural inequity and deprivation among survivors.

**Aim 3:** Evaluate whether poor area-level healthcare accessibility characteristics (i.e., medically underserved areas) exacerbate the relationship between late mortality risk and living in neighborhoods characterized by structural inequity and deprivation among survivors.

## **Analytic framework**

### Study population

All CCSS 5-year survivors and siblings with any geocoded address information as of calendar year 2000 will be included.

### Outcome variables

- Vital status, including date of death and cause of death
  - Causes of death will be organized by major groupings (recurrence; subsequent neoplasm [SN]; cardiovascular; pulmonary; other health cause; external)

### Variables of interest

#### (1) Neighborhood-level geocoded SDoH

Methods for geocoding data reflect methods described in manuscripts in progress by Howell *et al.* and Choi *et al.* In brief, considering our primary analytic strategy, the anticipated median calendar year for CCSS participants' addresses will be ~2010. Addresses have been converted into geographical coordinates or Federal Information Processing System (FIPS) codes corresponding to U.S. census tracts/counties from (2010). These FIPS codes have been linked to various neighborhood-level data characteristics:

- a. Social vulnerability index<sup>15</sup> (SVI) for (2010-2014) and Minority Health SVI<sup>16</sup> (MHSVI) for (2011-2018), covering the 5 SDoH domains outlined in Healthy People 2030<sup>25</sup> including economic stability, education access and quality, healthcare access and quality, neighborhood and built environment, and social and community context.
  - For each census tract, the CDC has generated national SVI/MHSVI percentile ranks for vulnerability ranging from 0 (lowest) to 1 (highest) for all indicators in combination (i.e., overall SVI) and domains; these measures will be quartiled.
- b. Persistent poverty as described in previous cancer mortality work<sup>11,12</sup>, described by the US Department of Agriculture (USDA) Economic Research Service<sup>20</sup> (ERS) as counties with  $\geq 20\%$  of residents experiencing poverty (i.e., income below the federal poverty level) by the decennial censuses in 1980, 1990, and 2000, and by the 2007-2011 American Community Survey.
  - Variable will be dichotomized (persistent poverty vs. not).

- c. Modern redlining index linked by census tract as described in previous cancer mortality work<sup>13,14</sup>, based on Home Mortgage Disclosure Act data (2007-2013).
  - Measures the odds ratio of mortgage application denial on the basis of property location and is categorized by levels of mortgage lending bias (0-0.5 [least], 0.5-1 [low], 1-2 [moderate],  $\geq 2$  [high]).
- d. Medically Underserved Area (MUA), as designated by the Health Resources and Services Administration (HRSA)<sup>26</sup>, will be used to indicate geographic areas with a lack of access to primary care services at the county-level. We will use the Index of Medical Underservice (IMU) score to determine if an area qualifies as MUA (score of 62.0 or below). IMU is comprised of four variables: percentage of the population with incomes below poverty, population-to-primary care physician ratio, infant mortality rate, and percentage of the population aged  $\geq 65$  years. These medical service areas will be reconciled with census tracts and will be evaluated as a modifying/mediating variable.
- e. Area Deprivation Index<sup>5-7</sup> (ADI) will be evaluated as comparison metric of neighborhood-level socioeconomic adversity, as described by Ehrhardt *et al.*<sup>4</sup>

## (2) Individual-level reported SDoH

Similar to recent work evaluating the accumulation of unfavorable individual-level SDoH and premature mortality in the general population<sup>27</sup>, we will use the following 3 dichotomized measures available in CCSS to form a cumulative individual-level SDoH score ranging from 0 to 3, considering responses from CCSS questionnaires:

- a. Educational attainment (high school or less vs. some college or university or above)
- b. Personal income (annual income  $< \$20,000$  vs.  $\geq \$20,000$ )
- c. Health insurance coverage (insured vs. not)

We note that these cumulative individual-level SDoH scores will correspond to the completed CCSS questionnaire that coincides with the start of the at-risk period, i.e., the survey completed on/after calendar year 2000 closest to the date of the relevant geocoded residential address.

### Sociodemographic/clinical variables

- Sex
- Attained age
- Primary cancer diagnosis
- Age at primary cancer diagnosis
- Reported race/ethnicity
- Cancer treatment exposures delivered within 5 years of primary cancer diagnosis
  - Any RT (yes/no)
  - Field-specific RT (yes/no) and dose for each of the 7 major body regions (cranial, neck, chest, abdomen, pelvic, arm, leg)
  - Total body irradiation (yes/no and dose)
  - Chemotherapy
    - Any chemotherapy: yes/no
    - Alkylating agents: yes/no and quantified as cyclophosphamide-equivalent dose<sup>28</sup> (CED)
    - Anthracyclines: yes/no and quantified as doxorubicin-equivalent dose<sup>29</sup> (DED)

- Etoposide (yes/no and dose)
    - Platinum (yes/no and dose)
  - Hematopoietic cell transplantation (yes/no)
- CHCs including SNs (time-varying)
  - CHCs graded using the modified Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grading system<sup>30</sup> where the total number of non-fatal grade  $\geq 3$  CHCs (severe/life-threatening) will be tabulated for each participant

## Statistical analysis

Descriptive statistics will be used to characterize the geospatial features associated with the neighborhoods where survivors and siblings resided at last follow-up. For time-to-event analyses, time at risk will begin at the date of the relevant geocoded residential address (recorded on/after calendar year 2000) and end at either death (event) or censoring (National Death Index query date). All-cause mortality cumulative incidence will be estimated using the Kaplan-Meier method, where log-rank tests will compare mortality curves by categorical neighborhood-level indices of structural inequity and deprivation reflecting the start of the at-risk period. The cumulative incidence of cause-specific mortality (e.g., SNs) accounting for competing risks (other causes of death) will be estimated, where differences by categorical neighborhood-level indices of structural inequity and deprivation will be assessed using Gray's test<sup>31</sup>. Subgroup analyses by treatment cohort/decade and CHC burden will be conducted. Secondary analyses considering subgroups of survivors stratified by CHC burden (e.g., lower vs. higher than median CHC burden) will be conducted to evaluate whether greater high CHC burden modifies the association between neighborhood-level adversity on mortality. These methods will also be applied to compare survivors to siblings. Additionally, we will further contextualize survivors' exposures to neighborhood-level structural inequity and deprivation by comparing all specified SDoH measures for survivors in CCSS to national norms.

Among survivors, multivariable piecewise exponential models will be used to evaluate the association between the mortality rate (overall and cause-specific) and each neighborhood-level SDoH index of interest, including sub-domain/indicator scores (e.g., SVI/MHSVI), considering using the natural logarithm of person-years as an offset. In particular, with respect to SVI/MHSVI, we note that individual SVI and MHSVI indicators will be assessed to elucidate specific social vulnerability factors and their impact on mortality (e.g., poverty rate, crowded housing, physical activity opportunities in the communities). Models will be adjusted for demographics (sex, attained age [time-dependent, cubic splines]), age at childhood cancer diagnosis, cancer treatment decade, and cancer treatments (to be defined in exploratory data analysis). Incremental models will evaluate changes in mortality relative rates for neighborhood-level SDoH factors if adjusted for: (a) unfavorable individual-level SDoH accumulation and (b) as appropriate, time-varying CHC history. Generalized linear mixed models (GLMMs) will be considered if  $>5$  survivors reside in the same census tract/county. These multivariable models will be adapted to compare survivors and siblings, stratified by neighborhood-level SDoH levels. Among survivors, formal interaction tests will be used to evaluate whether neighborhood-level SDoH associations with mortality are modified by individual-level SDoH (with both SDoH variables treated as continuous variables).

We will also further evaluate changes in mortality relative rates associated with neighborhood-level SDoH factors if also adjusted for neighborhood-level healthcare access. To evaluate whether these associations are potentially mediated by neighborhood-level healthcare access, we will conduct mediation analyses using methods previously described by Baron and Kenny<sup>32</sup> and applied in the childhood cancer survivorship literature<sup>33</sup>.

## Example tables/figures

**Table 1:** Major characteristics of CCSS survivors and siblings

Characteristics	Survivors		Siblings	
	N	% or median (IQR)	N	% or median (IQR)
Age at cancer diagnosis, years (median [IQR])				
Treatment decade				
1970-1979				
1980-1989				
1990-1999				
Type of cancer diagnosis				
Leukemia				
Hodgkin lymphoma				
Central nervous system tumor				
Non-Hodgkin lymphoma				
Sarcoma				
Other				
Treated with any radiotherapy				
Treated with any chemotherapy				
Age at evaluation, year (median [IQR])				
Sex				
Male				
Female				
Race and ethnicity				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Other				
Educational attainment				
≤High school diploma/GED				
Some college/university or graduate degree				
Personal income, annual in US dollars				
<\$20,000				
≥\$20,000				
Health insurance				
No insurance				
Public/private insurance				
Reported ≥1 prior severe/life-threatening CHC				
Neighborhood with high vulnerability: 3 <sup>rd</sup> /4 <sup>th</sup> SVI/MHSVI quartiles				
Overall				
Socioeconomic				
Household composition				
Minority status/language				
Housing/transportation				
Health care infrastructure/ access				
Medical vulnerability				
Neighborhood with persistent poverty				
Neighborhood with moderate/high lending bias				
Neighborhood overlapping MUAs				
Vital status: Died				
Cause of death				
Recurrence				
SN				
Cardiovascular				
Other health cause				
External				

**Table 2:** Adjusted overall mortality rate associations with SVI categories

- Repeat for persistent poverty and redlining bias index
- Repeat for cause-specific mortality (SN, cardiovascular)

Social vulnerability index	Multivariable model, adjusted for demographics, cancer/treatment features		Adjusted for unfavorable individual-level SDoH accumulation score		Adjusted for CHCs (time-varying)	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Overall score <sup>c</sup>						
Q1	Ref.					
Q2						
Q3						
Q4						
Domain-specific score						
Socioeconomic <sup>c</sup>						
Q1	Ref.					
Q2						
Q3						
Q4						
Household composition <sup>c</sup>						
Q1	Ref.					
Q2						
Q3						
Q4						
Minority status/language						
Q1	Ref.					
Q2						
Q3						
Q4						
Housing/transportation						
Q1	Ref.					
Q2						
Q3						
Q4						
Healthcare infrastructure/access						
Q1	Ref.					
Q2						
Q3						
Q4						
Medical vulnerability						
Q1	Ref.					
Q2						
Q3						
Q4						

**Table 3: Mortality among survivors by neighborhood- and individual-level SDoH**

Neighborhood-level SDoH and mortality	Unfavorable individual-level SDoH accumulation (adjusted change in rate, 95% CI)				Interaction P
	0 SDoH	1 SDoH	2 SDoH	3 SDoH	
SVI index					
Overall mortality					
SN cause death					
CV cause death					
Persistent poverty					
Overall mortality					
SN cause death					
CV cause death					
Redlining index					
Overall mortality					
SN cause death					
CV cause death					

Estimates reflect the change in the adjusted mortality rate per increase in neighborhood-level SDoH (treated as a continuous variable, e.g., SVI quartile; binary persistent poverty; increasing redlining index category).

**Figure 1:** Cumulative incidence of overall and cause-specific mortality (SN; cardiovascular; other health cause) among CCSS survivors and siblings by SVI categories

**Figure 2:** Cumulative incidence of overall and cause-specific mortality (SN; cardiovascular; other health cause) among CCSS survivors and siblings by persistent poverty categories

**Figure 3:** Cumulative incidence of overall and cause-specific mortality (SN; cardiovascular; other health cause) among CCSS survivors and siblings by redlining bias categories

**Figure 4:** Adjusted mortality relative rates comparing CCSS survivors to siblings, stratified by neighborhood-level SDoH

- Forest plots with RRs, 95% CI by SVI category
- Forest plots with RRs, 95% CI by persistent poverty category
- Forest plots with RRs, 95% CI by redlining bias category

**Figure 5:** Mortality rates by SVI/persistent poverty/redlining bias categories and individual-level SDoH at last follow-up

- x-axis: SVI percentile, 0-100 (separately for overall and domains), or persistent poverty/redlining bias categories
- y-axis: Mortality rate per 1,000 person-years (separately for overall and SN-/CV-cause mortality)
- Show subgroups by individual-level SDoH score (e.g., 0, 1, 2, 3 unfavorable individual-level SDoH characteristics)

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