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ORIGINAL ARTICLE

Neighborhood-Based Socioeconomic Determinants of Cognitive Impairment in Zambian Children With HIV: A Quantitative Geographic Information Systems Approach

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Background. Place-based inequalities, such as exposure to violence and access to nutritious food and clean water, may contribute to human immunodeficiency virus (HIV)-associated cognitive impairment. In this study, we investigated neighborhood effects on cognition in children and adolescents with HIV in Lusaka, Zambia.

Methods. We conducted a prospective cohort study of 208 children with perinatally acquired HIV (ages 8–17) and 208 HIV-exposed uninfected controls. Participants underwent neuropsychological testing and interviews assessing socioeconomic status. Geographic regions with clusters of participants with HIV and cognitive impairment were identified using quantitative geographic information systems (QGIS) and SaTScan. Associations between location of residence and cognitive function were evaluated in bivariable and multivariable regression models. Mediation analysis was performed to assess direct and indirect effects of location of the residence on cognitive impairment.

Results. Residence in Chawama, one of the poorest neighborhoods in Lusaka, was significantly associated with cognitive impairment in participants with HIV (odds ratio 2.9; $P = .005$) and remained significant in a multivariable regression model controlling for potential confounders. Mediation analysis found that 46% of the cognitive effects of residence in Chawama were explained by higher rates of malnutrition, lower school attendance, and poorer self-reported health.

Conclusions. Place-based socioeconomic inequality contributes to cognitive impairment in Zambian children and adolescents with HIV. Neighborhood effects may be mediated by concentrated poverty, malnutrition, limited access to education and health care, and other yet unknown environmental factors that may be potentially modifiable.

Key words. child health; global health; HIV; infectious diseases; Zambia.

Worldwide more than 1.8 million children are infected with human immunodeficiency virus (HIV), and 20%–50% of these children are cognitively impaired [1, 2]. Cognitive impairment in children with HIV persists despite combined antiretroviral therapy (ART) [3, 4]. Childhood cognitive impairment likely impacts social participation, ART adherence, school performance, and future job participation, making early detection, intervention, and identification of prevention measures crucial [5, 6]. The plurality of childhood HIV infection and cognitive impairment occurs in sub-Saharan Africa [2], although it has been minimally studied in these regions.

Structural factors, such as socioeconomic status (SES), are strong predictors of cognitive outcomes in children with HIV [5, 7–10]. Geographical analysis of these structural factors may reveal place-based inequalities in the distribution of societal resources, exposure to violence, environmental risks, and access to nutritious food and clean water [10–12] which contribute to cognitive impairment—potentially modifiable risk factors. Although geographic information systems (GIS) and spatial analysis have been widely applied to HIV research in Africa [13–16], GIS has not been utilized in the study of HIV-associated cognitive impairment in children and adolescents in the African setting.

The HIV-Associated Neurocognitive Disorders in Zambia (HANDZ) study seeks to understand the cognitive outcomes of children and adolescents with perinatally acquired HIV in

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Lusaka, Zambia. HIV is highly prevalent in Zambia with 12% of individuals aged 15–49 or approximately 960 000 people affected [17, 18], with an estimated 62 000 children currently living with HIV [17]. A previous HANDZ analysis found constituency clustering of neurocysticercosis cases with lack of access to clean water and modern toilet facilities [19]. The aim of this study was to identify place-based socioeconomic inequalities associated with cognitive impairment in Zambian children and adolescents with perinatally acquired HIV.

METHODS

Study Design, Setting, and Participants

HANDZ is a prospective cohort study that explores cognitive and psychiatric outcomes among children and adolescents living with HIV and HIV-exposed, uninfected (HEU) controls in Lusaka Province, Zambia [20]. HANDZ study is based in the Lusaka Province that contains the capital city and is 1 of the 10 Zambian provinces. The Lusaka Province contains 13 socioeconomically diverse constituencies, which are large neighborhoods with single-member representation in the National Assembly of Zambia [21]. Briefly, children and adolescents with perinatally acquired HIV (ages 8–17) were recruited from the Pediatric Center of Excellence (PCOE) in Lusaka, Zambia, a major outpatient pediatric HIV care referral center. Participants with HIV were included if treated with ART for longer than 1 year and excluded if they had a known history of CNS infection [20]. HEU controls were recruited from Lusaka neighborhoods by a community health worker using a stratified sampling method to ensure approximately equal age and sex distribution [20]. The HEU group provided a local normative sample for cognitive tests and served as a comparison group for rates of cognitive impairment.

Data Collection

Each participant completed a demographic questionnaire, standardized interviews, and comprehensive neuropsychological testing. Participants were seen at baseline and subsequently every 3 months, with a median of 2 years of follow-up completed at the time of this analysis.

Measurements

Comprehensive neuropsychological testing was performed using a combination of the National Institutes of Health Toolbox—Cognition Battery and standard pencil-and-paper neuropsychological tests on a quarterly and annual basis, respectively [20]. Cognitive impairment was defined using a Global Deficit Score (GDS) approach [20]. Domain-specific deficit scores were calculated based on standard deviations below the mean performance of the control population, then domain-specific deficit scores were averaged to create the GDS. By convention, cognitive impairment was defined as a GDS score of greater than or equal to 0.5 [22]. SES was measured using an adaptation of the UNICEF Multiple Indicator Cluster Survey (MICS4) [23]. Individual SES variables of prespecified importance (maternal education, electricity, access to running water, presence of a flush toilet, food security, income, and possession index) were combined to form an SES index (SESI) ranging from 0 to 12. Negative life events (eg, hospitalization, exposure to violence or abuse, and illness or death of a family member) were measured using an instrument designed for the HANDZ study, the Negative Life Event Questionnaire (NLEQ), and summed into a Negative Life Event Index [20]. The components of the SES Index and Negative Life Event Index are listed in Supplementary Table 1.

Geographic Analysis

Each participant's location of residence was approximated using Google Maps and OpenStreetMap. Estimated latitude/longitude coordinates and shapefiles of the Lusaka constituencies were overlayed in maps generated by quantitative GIS (QGIS) software (version 3.2.0) [24]. The geospatial relationship of prespecified socioeconomic factors was visualized. Distance between PCOE and the participants' residence was calculated using the HubDistance tool in QGIS. To ensure the confidentiality and privacy of participants in the HANDZ study, participant points were enlarged, and constructed maps were zoomed out to view the entire city of Lusaka without specific landmarks.

Statistical Methods

Geographic clustering analysis was performed with a spatial statistics software, SaTScan (version 9.6; https://www.satscan.org) using a Bernoulli model [25]. Maximum spatial cluster sizes were set at less than 50% of the population at risk within a circular window, default SaTScan parameters. Likelihood ratios were calculated for each cluster. Cluster analysis was not performed on the HEU sample, as these participants were recruited from specific constituencies, thus clustering detected in HEU participants could be an artifact of the location of recruitment.

Additional statistical analyses were conducted using Stata 16.1 (College Station, TX). Chi-squared tests evaluated differences in dichotomous variables, *t*-test statistics for normally distributed continuous variables, and Kruskal-Wallis ranks for non-normally distributed continuous or ordinal variables. Constituencies identified as having clusters of participants with cognitive impairment using SaTScan with a significance of <=0.2 were evaluated with bivariable and multivariable logistic regression models. Two separate logistic regression models were fit; in the first, we adjusted for other SES variables and parental education in order to estimate the total causal effect of neighborhood of residence. In the second, we adjusted for confounding variables as well as all measured potential mediating variables in order to estimate the "direct" effect of neighborhood of residence. Using Dagitty (V. 3.0, http://www.dagitty.net), directed acyclic graphs (DAGs) were used to generate a causal model and select which variables to include in multivariable models (see Figure 1; Supplementary Table 2) [26, 27]. Mediation analysis using the "ldecomp" package in Stata was used to evaluate direct and indirect effects of neighborhood of residence on cognitive impairment [28]. Neighborhood of residence was used as the primary exposure variable, with each potential mediating variable chosen based on the DAG. *P*-values of <= .05 were considered significant in regression models.

Ethics Statement

This study was approved by the institutional review boards of the University of Zambia (reference #004-08-17), the University of Rochester (protocol #00068985), and the National Health Research Authority of Zambia. Verbal and written parental permission were obtained from the parents of all participants who participated. Verbal and written assent was obtained from all participants aged 12 years and older.

RESULTS

Demographic and Socioeconomic Trends

Demographic and socioeconomic indicators of HANDZ participants with HIV are described in Table 1. The median age of participants with HIV was 12, and there were roughly equal numbers of males and females. Participants with HIV were more likely to have cognitive impairment than HEU controls (34% vs 19%, $P = .001$). Statistically significant risk factors for cognitive impairment among participants with HIV in the bivariable analysis included self-reported poor health, low SESI, lack of access to indoor toilets, and running water. In addition, cognitively impaired participants with HIV were more likely to have growth stunting (52% vs 22%, $P < .001$) and to not attend school (14% vs 4%, $P = .01$). Although not statistically significant, among cognitively impaired participants with HIV, fewer had electricity in their home (74% vs 81%), and a greater number had a history of malnutrition (33% vs 29%) or severe malnutrition (26% vs 18%). Aerial distance to PCOE was not statistically different between cognitively impaired or unimpaired participants with HIV.

Socioeconomic differences between constituencies are summarized for participants with HIV in Table 2. Noted constituencies with low median SESI were Chawama and Kabwata. In Chawama, Katuba, and Lusaka Central, more than half of participants with HIV were GDS impaired. Additionally, constituency size and census population data are also shown

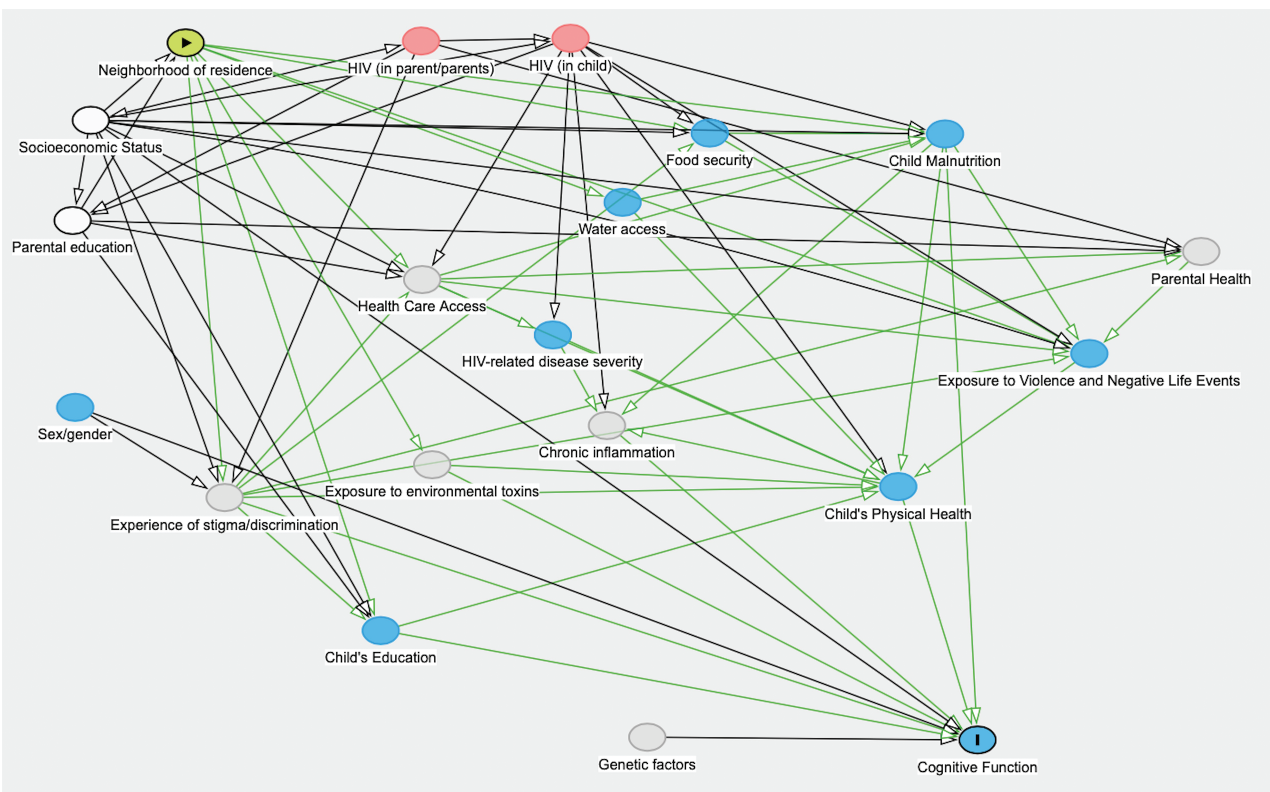

Figure 1. A directed acyclic graph (DAG) model of how socioeconomic status (SES) and neighborhood of residence influence cognitive impairment in Zambian children with HIV. This model implies that total effect of neighborhood of residence on cognition may be estimated by controlling for other SES variables and parental education. Testable implications of this model are that effects may be mediated through malnutrition, access to education, and exposure to violence and other negative life events.

Table 1. Demographics and Socioeconomic Indicators of Participants With HIV: Impaired vs Unimpaired

Variable	Impaired (n = 70)	Unimpaired (n = 136)	*P*-Value
Mean age (+/– SD)	11.9 +/– 2.2	12.4 +/– 2.4	.140*
Female (f/m)	51% (36/34)	41% (56/80)	.161**
Nadir $CD4^+$ count, n = 188	547	598	.313*
Mean viral load, mean copies per mL+/– SD, n = 180	6896 +/– 18439	2124 +/– 10 053	.026*
History of WHO Stage 4, n = 194	66% (37/29)	41% (53/75)	.052**
% ART non-adherent in last year % (yes/no), n = 201	3% (2/67)	8% (11/121)	.226**
History of malaria, % (yes/no)	60% (42/28)	64% (87/49)	.649**
History of TB, % (yes/no)	39% (27/43)	31% (42/94)	.279**
No. of known hospitalizations, mean +/– SD	1.4 +/– 1.2	1.7 +/– 1.9	.192*
Stunted % (yes/no), n = 204	52% (36/33)	22% (30/105)	<.001**
Aerial distance to PCOE (in km) n = 201 mean +/– SD	9.0 +/– 7.4	8.5 +/– 7.3	.667*
Median Socioeconomic Status Index, n = 191	5	6	<.001***
Low Socioeconomic Status Index (Socioeconomic Status Index <= 2), n = 191	20% (13/51)	9% (12/115)	.036**
Self-reported poor health (yes/no), n = 204	17% (12/57)	7% (9/126)	.027**
Running water (yes/no)	33% (23/47)	54% (74/62)	.003**
Flush toilet (yes/no)	24% (17/53)	46% (62/74)	.003**
Electricity (with/without)	74% (52/18)	81% (110/26)	.274**
Malnutrition (yes/no)	33% (23/47)	29% (40/96)	.611**
Severe malnutrition (yes/no)	26% (18/52)	18% (25/111)	.220**
Mean negative life events, n = 199	1.76	1.52	.647***
Negative life events >=4 (yes/no) n = 199	15% (10/57)	9% (12/120)	.237**
Not in school	14% (10/60)	4% (6/130)	.012**

Abbreviations: WHO, World Health Organization; ART, antiretroviral therapy; TB, tuberculosis; PCOE, Pediatric Center of Excellence, Lusaka, Zambia.
*Two-sample *t*-test.
**Fisher's exact.
***Kruskal-Wallis.

[29, 30]. In Chawama, Kanyama, Katuba, and Munali, more than 28% of participants with HIV reported severe malnutrition.

Geographic Analysis

Given that several constituencies had low numbers of participants with HIV (see Table 2), we performed a geographic clustering analysis independent of administrative boundaries to identify clusters of cognitive impairment and socioeconomic disparity. Clustering analysis demonstrated a grouping of cognitively impaired participants with HIV in regions that overlap with the Chawama and Kanyama constituencies (see Figure 2). The prevalence of cognitive impairment among participants with HIV in this 76 km^2 area was 52.2%, compared with 34% over the entire geographic area (observed/expected ratio of 1.50; relative risk 2.03; *P* = .128). Similar geographic clustering was observed with the socioeconomic variables: lack of access to running water, greater than or equal to 4 negative life events, severe malnutrition, and low school attendance (see Figure 3; Supplementary Figures 1 and 2). These clusters qualitatively overlapped with the Chawama constituency. There was no geographically significant increased prevalence of malaria or tuberculosis infection history (not shown). Tabulated results of the clustering analyses are displayed in Supplementary Table 3.

Regression Model and Mediation Analysis Results

Given that the cluster of cognitively impaired participants with HIV predominantly overlapped Chawama and Kanyama, these 2 constituencies were further examined in bivariable and multivariable regression models. Bivariable analysis revealed that residence in Chawama was significantly associated with cognitive impairment in participants with HIV (odds ratio [OR] 2.9; 95% confidence interval [CI], 1.4-6.2; *P* = .005). In participants with HIV, residence in Chawama remained significantly associated with cognitive impairment in a multivariable regression model controlling for SES and parental education (adjusted OR 3.2; 95% CI, 1.3-8.1; *P* = .01); and in a second model controlling for age, sex, SES, negative life events, malnutrition, growth stunting, and self-reported poor health (adjusted OR 2.7; 95% CI, 1.1-6.6; *P* = .04). Residence in Chawama was associated with having a $CD4^+$ nadir of <=200 (OR 3.9; 95% CI, 1.3–11.0; *P* = .01) but was not associated with other HIV-specific disease measures such as WHO stage, mean viral load, or non-adherence with ART in the last year. Mediation analysis suggested that the effect of residence in Chawama was partially mediated through malnutrition, poor health, and lack of school attendance, but that these effects accounted for only 46% of the total effect. Residence in Kanyama was not significantly associated with cognitive impairment among participants with HIV (OR 1.2; 95% CI, 0.6–2.6; *P* = .6).

DISCUSSION

In this prospective cohort study, we investigated the effects of place-based inequality on cognition in children and adolescents with HIV in Lusaka, Zambia. We identified a geographic

Table 2. Demographic, SES, and HIV Characteristics by Lusaka Constituency for HANDZ Participants With HIV

	Chawama	Chilanga	Chongwe	Kabwata	Kanyama	Katuba	Lusaka Central	Mandevu	Matero	Munali
n, observations	37	20	6	27	40	3	7	32	13	19
Mean age +/− SD	10.7 +/− 2.6	11.1 +/− 2.4	10.4 +/− 1.8	11.3 +/− 2.5	12.2 +/− 2.3	11.3 +/− 2.3	12 +/− 2	12.6 +/− 2.1	11.9 +/− 2.3	11.9 +/− 2.2
Median SES Index	5	3.5	8	8	6	5	7	6	8	7
Running water %, yes/no	22%, 8/28	40%, 8/12	80%, 4/1	26%, 20/7	35%, 14/26	33%, 1/2	86%, 6/1	44%, 14/18	85%, 11/2	58%, 11/8
Severe malnutrition %, yes/no	35%, 13/24	15%, 3/17	0%, 0/6	4%, 1/26	28%, 11/29	33%, 1/2	14%, 1/6	19%, 6/26	8%, 1/12	32%, 6/13
Mean negative life events	2.2	1.4	2.3	1.6	1.6	2.3	2.1	1.1	1	1.2
Not in school %, yes/no	20%, 6/24	13%, 2/13	0%, 0/5	5%, 1/19	12%, 3/23	0%, 0/2	0%, 0/5	5%, 1/20	0%, 0/10	0%, 0/16
History of WHO Stage 4 %, yes/no	53%, 19/17	39%, 7/11	17%, 1/5	54%, 14/12	51%, 20/19	100%, 1/0	29%, 2/5	45%, 14/17	31%, 4/9	47%, 9/10
Stunted %, yes/no	35%, 12/22	30%, 6/14	0%, 0/6	33%, 9/18	33%, 13/27	25%, 1/3	0%, 0/4	10/22	42%, 5/7	37%, 7/12
Distance to PCOE, km[a]	4.8	22.5	22.5	4.1	7.8	16.2	5.8	7.6	7.9	6.4
GDS impaired %, yes/no	55.9%, 19/15	47.4%, 9/10	16.7%, 1/5	22.2%, 6/21	37.5%, 15/25	66.7%, 2/1	57.1%, 4/3	25%, 8/24	15.4%, 2/11	21.1%, 4/15
Area (square km)[a]	55	1336	2537	46	98	1722	110	54	40	52
Total population, 2000 Census [26]	139 998	56 673	100 281	89 556	170 803	56 628	99 431	219 285	189 480	176 150
Total population, 2010 Census [27]	187 565	107 051	192 303	174 338	364 655	79 306	117 097	358 788	282 734	261 975
Calculated population density 2000, people/km^2	2545	42	40	1947	1743	33	904	4061	4737	3388
Calculated population density 2010, people/km^2	3410	80	76	3790	3721	46	1065	6644	7068	5038

Abbreviations: HANDZ, HIV-Associated Neurocognitive Disorders in Zambia; WHO, World Health Organization; GDS, global deficit scale; PCOE, Pediatric Center of Excellence, Lusaka, Zambia; SES, socioeconomic status. QGIS, quantitative geographic information systems.
[a]Computed in QGIS.

region, centered on the Lusaka constituency Chawama, where socioeconomic disparities including the lack of running water, higher exposure to negative life events, severe malnutrition, and lower school attendance overlapped with regions of participants with HIV who were cognitively impaired. Residence in Chawama was significantly associated with cognitive impairment in participants with HIV. Notably, when we controlled for Chawama-specific socioeconomic disparity, Chawama residency remained a significant contributor to cognitive impairment suggesting other, unrecorded environmental drivers. Mediation analysis revealed that about half of the residency effect of Chawama might be explained by higher rates of malnutrition, decreased school attendance, and self-reported poorer health of participants with HIV. Our data also suggest that the geographic drivers of cognitive impairment in Chawama may be specific to HIV infection, given that cognitively impaired HEU controls were not clustered in the Chawama constituency.

Neighborhood SES is foundational for childhood cognitive, social, and cultural development [11]. Social-interactive mechanisms including increased social disorder, less social cohesion, lack of safety, and structure of the family environment likely mediate this effect [11, 31–36]. Recent studies of Alzheimer's disease and adult-onset mild cognitive impairment have highlighted the importance of environmental influences on cognition including the size and density of buildings, access to community centers and green spaces, proximity to hospitals, and the level of pollution [37, 38]. In individuals with HIV, social comorbidities such as poverty, lack of access to education, and exposure to trauma likely contribute to cognitive impairment [39, 40]. Additionally, chronic exposure to low-resource environments and trauma may diminish neurocognitive reserves worsening HIV-associated cognitive impairment [41]. Our results generally aligned with these previous studies with several indicators of low SES associated with cognitive impairment in our cohort as a whole (see Table 1), examples including lack of school attendance and lack of access to running water. An exception is the number of negative life events, a summary statistic of exposure to trauma and violence in our cohort, which was not associated with cognitive impairment in bivariable analysis (see Table 1). Additionally, despite high numbers of negative life events geographically clustering in Chawama (Figure 3), this variable was not a significant contributor in the mediation analysis. In a previous analysis of the HANDZ cohort by Molinaro et al [42], we know that negative life events are associated with depression, but in this study, the direct effect of negative life events on cognition was small and not statistically significant.

Chawama is a densely populated urban community that has experienced significant population growth in the past 2 decades (see Table 2) [29, 30, 43]. Chawama originated as a squatter settlement in the 1950s and lacks planned essential service infrastructure, including central water supply, sanitation service,

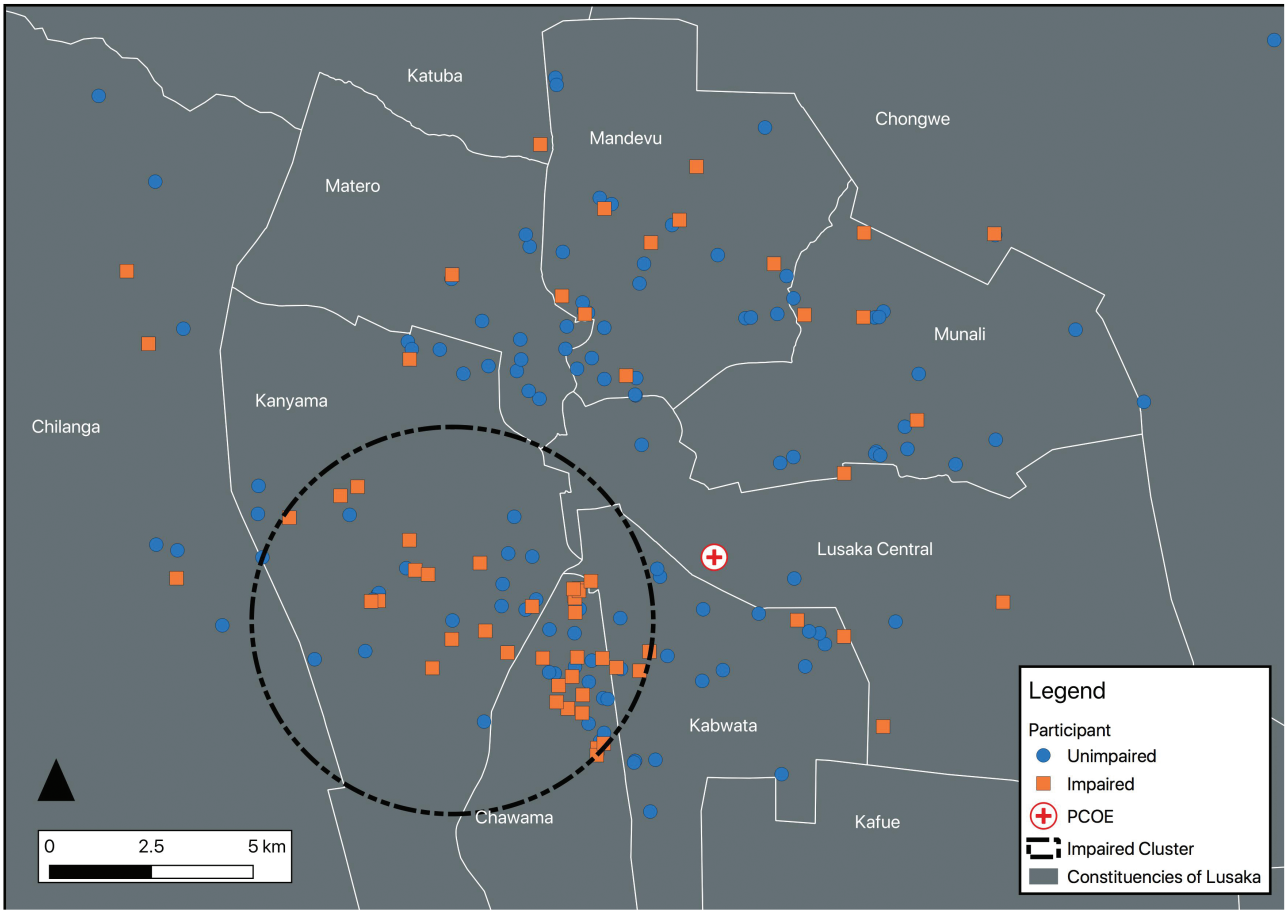

Figure 2. Geographic clustering of cognitively impaired Zambian participants with HIV. This figure shows a 4.92-km-radius cluster of cognitively impaired participants with HIV. The prevalence of cognitive impairment among participants with HIV in this region was 52.2%, compared with the 34% of participants who were cognitively impaired over the entire geographic area. The cluster had an observed/expected ratio of 1.50, a log-likelihood ratio of 6.85, and a *P*-value of .128. Created on December 31, 2020—EPSG:20934 Arc 1950/UTM Zone 34S—Stanford Earthworks, Google Maps, OpenStreetMap, Central Statistical Office of Zambia. The color version of this figure is available in the online edition.

and waste management; many residents have inadequate household income to finance these services independently [44]. Participants with HIV experiencing severe malnutrition and lack of access to running water clustered in Chawama (see Figure 3), data that were similar to a previous report from our group which identified low rates of flush toilets and running water overlapping with cases of neurocysticercosis in a similar region [19]. We hypothesize that the poor sanitary conditions of Chawama could contribute to the development of malnutrition by increasing exposure to infectious diseases of the gastrointestinal tract, a potentially potent contributor given the immunocompromised population. Other infectious disease vectors, including *Ascaris lumbricoides*, *Giardia duodenalis*, *Schistosoma haematobium*, and *Vibrio cholerae*, have also been reported in Chawama and could be contributing to malnutrition as well [44–46]. Although nutritional and vitamin deficiencies are common comorbidities in HIV-associated cognitive impairment, they have not been causally implicated [47]. Further research of constituency-based disease vector incidence and sanitary conditions is required to explore this hypothesis further.

Environmental pollutants may also play a role in the development of HIV-associated cognitive impairment. Dichlorodiphenyltrichloroethane (DDT), an organic pesticide and known neurotoxin, was applied in Chawama at least 3 times from 2002 to 2012 as part of a pilot study for malaria control [48], corresponding approximately with the perinatal period of the children and adolescents participating in our study. In 2012, significant levels of DDT and its metabolites were found in water and soil samples from Chawama, at much higher concentrations than maximum levels recommended by the World Health Organization. DDT and DDT metabolite exposure has been associated with altered cognitive development in children [49–51], as well as in the development of Alzheimer's disease [52]. Soil pollutants like DDT could be particularly relevant given that geophagy is a known phenomenon in children and

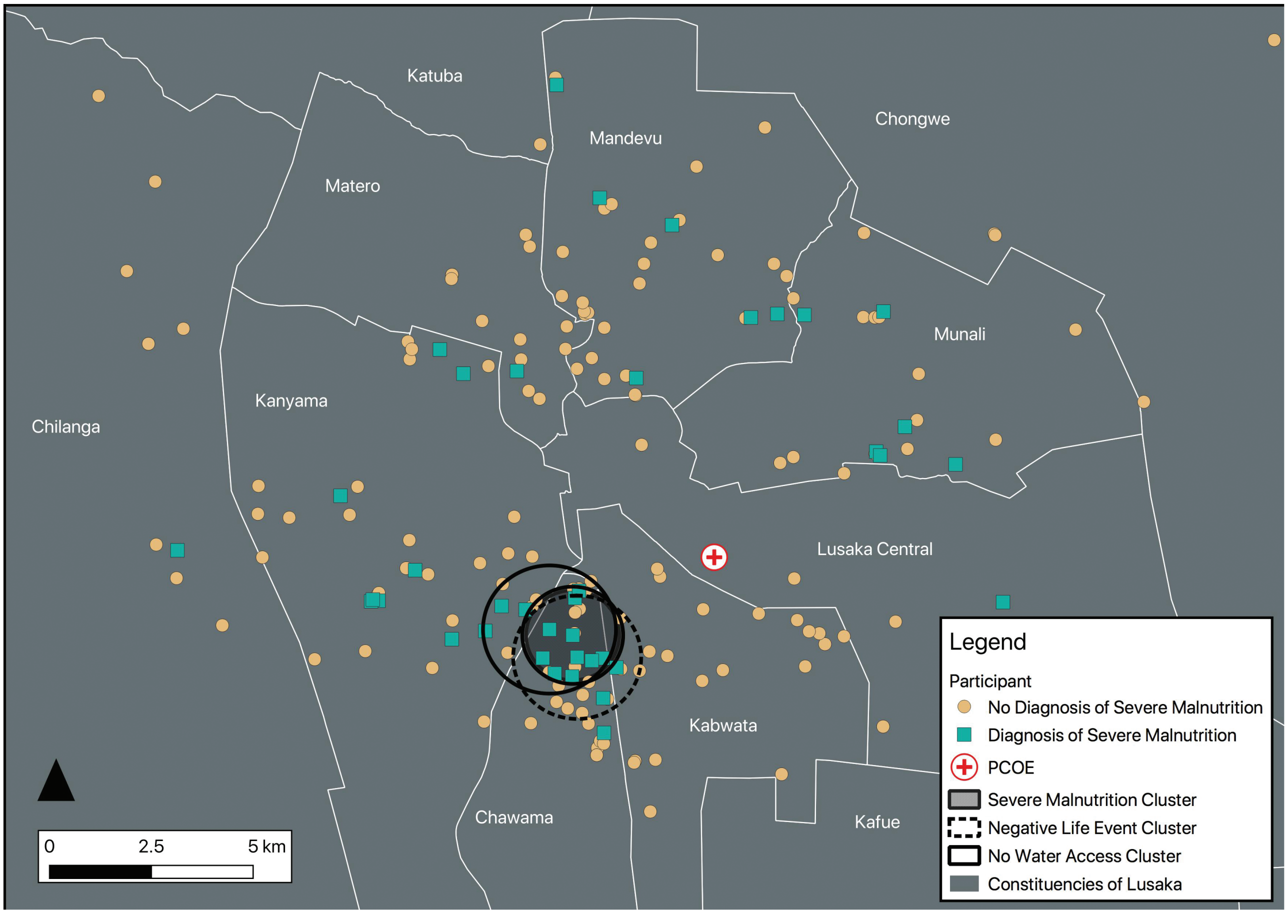

Figure 3. Clusters of severe malnutrition, negative life events, and lack of water access among participants with HIV. This figure shows several sociodemographic indicators clusters in the constituency of Chawama. The 1.14-km-radius severe malnutrition cluster had a case rate of 62.5%, observed/expected ratio of 2.98, a log-likelihood ratio of 7.18, and a *P*-value of .087. The 1.57-km-radius negative life events cluster had a case rate of 46.2%, observed/expected ratio of 4.17, a log-likelihood ratio of 13.03, and a *P*-value of < .001. There were 2 clusters that showed no running water access. Cluster A was a 1.63-km-radius cluster that had a case rate of 10.7%, observed/expected ratio of 0.22, a log-likelihood ratio of 10.4, and a *P*-value of .003. Cluster B was a 1.24-km-radius cluster that had a case rate of 5%, observed/expected ratio of 0.1, a log-likelihood ratio of 10.1, and a *P*-value of .004. Created by A. B. on December 31, 2020, EPSG:20934 Arc 1950/UTM Zone 34S—Stanford Earthworks, Google Maps, OpenStreetMap, Central Statistical Office of Zambia. The color version of this figure is available in the online edition.

pregnant women in Lusaka [46, 53]. Additionally, the Chawama constituency includes industrially zoned areas including factories and cement production quarries which could generate other environmental pollutants [54]. More research into the relationship between HIV-associated cognitive impairment and environmental toxins is necessary.

Strengths of the study include its relatively large sample size and structured acquisition of comprehensive neuropsychological, socioeconomic, and clinicodemographic data of a rarely studied population.

This study also has several limitations. First, household geographic location was manually estimated using OpenStreetMap and Google maps, and although most parts of Lusaka are completely mapped, some areas may have been incompletely or inaccurately annotated. To reduce inaccurate participant mapping, any participant address location that could not be verified by HANDZ staff familiar with Lusaka was excluded. It is also possible that participants could have frequently moved throughout their childhood, confounding our ability to define longitudinal place-based risk; data on the frequency of moving between households were not collected. Second, given that the HANDZ study was not initially designed to look at constituency-based metrics, we did not have sufficient sampling of all constituencies to do comprehensive comparative analyses. Third, the SatScan analysis was limited in that only circular clusters could be detected, and its ability to detect small clusters may be limited [55]. Additionally, simply because we noted geographic clustering in the SatScan analysis does not imply that a biological connection between cases exists. Fourth, several potential key mediators were not measured as part of this study, including measures of healthcare access, stigma/discrimination, toxic exposures, and chronic inflammation. More comprehensive mediation analysis using structural equation models will be utilized in future publications. Fifth, it is possible that participants with HIV receiving their medical care at PCOE in Lusaka are of higher acuity or higher income than the surrounding parts of their neighborhoods given that PCOE is one of the only tertiary care referral centers for pediatric HIV in Lusaka. We believe the latter issue is less likely given that study participants were provided travel stipends to reach their appointments. In addition, within the confines of this study, we were unable to assess the effect of disease control because among the HANDZ participant population, HIV is generally very well controlled. Finally, although we hypothesize that our methods would be similarly useful in identifying high-risk neighborhoods in other locations, it is possible that Lusaka-specific contributions to HIV-associated cognitive impairment would not be applicable in other locations.

CONCLUSIONS

GIS is an important global health tool to understand how place-based socioeconomic determinants affect disease sequelae. In this study, we demonstrated that neighborhood of residence is associated with cognitive impairment in children and adolescents with HIV in Lusaka Province, Zambia. This association appeared to be mediated by malnutrition, poor health, and educational factors, though it is likely that other unmeasured factors also contributed. These risk factors are important from a public health perspective, since they are potentially modifiable. Future interventional studies to improve cognitive outcomes in people living with HIV might target recruitment in neighborhoods at greatest risk for high rates of impairment.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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Potential *conflicts of interest*. There are no relevant conflicts of interest to disclose for any authors related to this work. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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