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Association of Neighborhood Socioeconomic Status With Risk of Infection and Sepsis

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Background. Prior studies suggest disparities in sepsis risk and outcomes based on place of residence. We sought to examine the association between neighborhood socioeconomic status (nSES) and hospitalization for infection and sepsis.

Methods. We conducted a prospective cohort study using data from 30 239 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. nSES was defined using a score derived from census data and classified into quartiles. Infection and sepsis hospitalizations were identified over the period 2003–2012. We fit Cox proportional hazards models, reporting hazard ratios (HRs) with 95% confidence intervals (CIs) and examining mediation by participant characteristics.

Results. Over a median follow-up of 6.5 years, there were 3054 hospitalizations for serious infection. Infection incidence was lower for participants in the highest nSES quartile compared with the lowest quartile (11.7 vs 15.6 per 1000 person-years). After adjustment for demographics, comorbidities, and functional status, infection hazards were also lower for the highest quartile (HR, 0.84 [95% CI, .73–.97]), with a linear trend ($P = .011$). However, there was no association between nSES and sepsis at presentation among those hospitalized with infection. Physical weakness, income, and diabetes had modest mediating effects on the association of nSES with infection.

Conclusions. Our study shows that differential infection risk may explain nSES disparities in sepsis incidence, as higher nSES is associated with lower infection hospitalization rates, but there is no association with sepsis among those hospitalized. Mediation analysis showed that nSES may influence infection hospitalization risk at least partially through physical weakness, individual income, and comorbid diabetes.

Keywords. sepsis; risk factor; mediation; socioeconomic status.

Sepsis is life-threatening organ dysfunction resulting from a dysregulated host response to infection. Sepsis places an immense burden on the US healthcare system, resulting in 1.5 million hospitalizations and 850 000 emergency department visits annually [1, 2]. While numerous studies have addressed the acute care of sepsis patients, relatively little is known about long-term risk factors for infection and sepsis-related organ dysfunction [3]. However, prior efforts have noted geographic and racial differences in sepsis mortality, as well as differences in sepsis hospitalization by insurance type [4–7].

Place of residence is an important predictor of health, above and beyond the effects of individual lifestyle factors and genetics [8–13]. Neighborhood socioeconomic status (nSES) may be associated with hospitalization for infection and sepsis through several potential mechanisms. For instance, individuals in low-nSES areas may delay seeking appropriate ambulatory care for infections, resulting in an increased risk of hospitalization. Increased levels of chronic, low-grade inflammation could also lead individuals living in low-SES neighborhoods to experience more severe infections. This is supported by studies examining the associations of inflammatory biomarkers with sepsis risk [14, 15]. Factors related to low-nSES residence, such as increased psychosocial stress, environmental exposures, and limited access to preventive care, may then create a proinflammatory state that facilitates the development of severe infection or sepsis-related organ dysfunction.

Despite a wealth of studies examining the relationship between neighborhood socioeconomic characteristics and health outcomes, there is a paucity of data pertaining to infection and sepsis. Hence, we sought to examine the associations of nSES with risk of future hospitalization for infection and sepsis using a national cohort of community-dwelling adults in the United States.

METHODS

Study Design

We performed a retrospective study using data prospectively collected as part of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. REGARDS is one of the largest ongoing national cohorts in the United States, comprised of 30 239 white and black community-dwelling adults aged ≥45 years; the study design, objectives, and sampling

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strategy have been previously described in detail [16]. In brief, the study oversampled black individuals and those living in the southeastern United States, with the overall cohort being 45% male, 42% black, and 69% aged >60 years.

The REGARDS study enrolled participants between 2003 and 2007, obtaining baseline data for each participant using phone interview and an in-person evaluation. REGARDS contacted study participants at 6-month intervals by telephone, identifying the date, location, and attributed reason for all hospitalizations. The REGARDS-Sepsis ancillary study collected additional data on hospitalization for infection. The REGARDS study was approved by the institutional review boards of participating institutions, and all participants provided verbal consent before the telephone interview and written informed consent before the in-home study visit.

Outcome Measures

We identified hospital admissions and emergency department visits attributed to serious infection [17]. Trained abstractors reviewed relevant medical records to confirm the presence of infection on initial hospital presentation and its relevance as a reason for admission (Supplementary Appendix 1). Discordances were adjudicated among abstractors, with additional physician review as needed. Initial review of 1349 hospital records indicated excellent interrater agreement for presence of serious infection ($\kappa = 0.92$). For the current analysis, we analyzed events occurring from participant enrollment through 31 December 2012.

In accordance with international consensus definitions, we identified sepsis upon the first infection event using the worst physiologic and laboratory measurements observed during the initial 28 hours [18]. We identified hospitalizations for infection with ≥2 systemic inflammatory response syndrome (SIRS) criteria, including heart rate >90 beats/minute, fever or low body temperature, tachypnea (>20 breaths/minute) or partial pressure of carbon dioxide (pCO_2) <32 mm Hg, and leukocytosis (white blood cells >12 000/µL or <4000 cells/µL or >10% band forms) [19]. We also defined sepsis as infection with ≥2 sepsis-related organ failure assessment (SOFA) score points according to established criteria [19]. Last, we identified infection events with ≥2 "quick" SOFA (qSOFA) criteria, including altered mentation (Glasgow coma score <14 or nonalert per the Alert, Voice, Pain, Unresponsive scale), systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22 breaths/minute [19].

Using clinical data available in patient charts, we also reported infection type and organ dysfunction severity in the form of the SOFA score, length of stay and admission destination among those admitted, in-hospital mortality, and discharge to a nursing, assisted care, or rehabilitation facility.

Primary Exposure and Participant Characteristics

We determined nSES using block group–level data from the 2000 census. The nSES summary score included the following components: (1) median household income; (2) median home value; (3) percentage of households receiving interest, dividend, or rental fees; (4) percentage of adults completing high school or (5) college; and (6) percentage of working individuals in managerial, executive, or professional occupations [8]. For each factor, we calculated Z scores as the offset from the mean divided by the standard deviation, with respect to all block groups in the sample [8]. We calculated the summary score by summing across all 6 standardized components, with lower values corresponding to lower nSES and higher values representing higher nSES. We then grouped composite nSES summary scores into quartiles [8]. Our analyses were limited to those with complete neighborhood characteristic information. Supplementary Figure 1 presents an example nSES score calculation.

Comprehensive data on participant characteristics were obtained at baseline enrollment; detailed variable definitions are provided in Supplementary Table 1. In brief, demographics included age, gender, self-reported annual household income and education, and geographic region. Health behaviors included tobacco and alcohol use [20]. Chronic medical conditions included chronic lung disease, diabetes, hypertension, myocardial infarction, stroke, and body mass index [21]. Baseline biomarkers included serum creatinine and high-sensitivity C-reactive protein (hs-CRP) [22]. Functional status measures included the 12-Item Short-Form Health Survey (SF-12) physical composite score (PCS) and self-reported physical activity/exhaustion [23–25].

Statistical Analysis

We examined differences in nSES score components across nSES quartiles, reporting medians, with 25th and 75th percentiles. We compared demographic, health behaviors, and clinical characteristics across nSES quartiles using Pearson χ^2 tests of association for categorical variables or analysis of variance for continuous variables.

We reported 10-year infection incidence per 1000 person-years with 95% confidence intervals (CIs) across nSES categories. To assess the association of nSES with risk of infection, we fit Cox proportional hazards models, reporting hazard ratios (HRs) and 95% CIs. Models were sequentially adjusted for participant demographics, health behaviors, chronic medical conditions, biomarkers, and measures of functional status. Participants were censored on death, loss to follow-up, or 31 December 2012. The lowest nSES quartile was the reference group. For the full model, we reported adjusted failure curves with all covariates set to reference values. We also performed tests of linear trend over nSES groupings. In sensitivity analyses, we included sepsis subtypes as outcomes in Cox proportional hazards models. The proportional hazards assumption was verified by examining Schoenfeld residuals and testing interactions with the logarithm of time.

Following sequential analyses of the association between nSES and infection, we examined the relative mediating effect of several factors (individual income, physical weakness, exhaustion, low physical activity, obesity, and diabetes). We fit a Cox proportional hazards model including age, sex, race, education, geographic region, chronic lung disease, hypertension, stroke, myocardial infarction, smoking, alcohol use, hs-CRP, and chronic kidney disease, then added each mediator to the model separately. We reported natural direct (association not through the mediator) and indirect (association through the mediator) effects on the hazard ratio scale, with mediation quantified as the percentage of the total effect mediated on the log hazard scale [26]. Confidence intervals for natural direct and indirect effects were constructed using the delta method. Supplementary Figure 2 presents the conceptual framework for mediation analysis.

Among those with infection, we reported percentages for infection type, sepsis type, intensive care unit admission, SOFA category, in-hospital death, and discharge to a nursing facility, performing χ^2 tests to examine differences by nSES. We also reported median length of stay and examined differences using Kruskal-Wallis tests. In a sensitivity analysis, we fit logistic regression models and compared adjusted odds of sepsis among those with infection.

All analyses were performed using Stata version 13.1 software (StataCorp, College Station, Texas) and SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Among 30 239 participants enrolled over 2003–2007, follow-up was available for 29 683 (98.2%). Geocode and nSES measure data at the block group level were available for 26 604 participants (89.6%). Summary scores varied widely across the cohort, with a median nSES score of –0.92 (25th–75th percentile, –3.90 to 3.08; minimum–maximum, –11.79 to 28.95). The individual components of the nSES score differed substantially across nSES quartiles (Table 1). Participant characteristics differed by nSES quartile, with low-nSES participants being disproportionately black, female, smokers, nonusers of alcohol, from the "Stroke Belt," and having low income and educational attainment (Table 2). Low-nSES participants were also more likely to have comorbidities, abnormal biomarker levels, and reduced functional status.

From 5 February 2003 through 31 December 2012, there were 3054 hospitalizations for serious infection among 2325 individuals. Median follow-up time was 3.7 years for participants experiencing a first infection event and 6.6 years for censored participants. Infection incidence was highest for participants in the lowest nSES quartile and lowest for the highest quartile (Table 3). After adjustment for participant characteristics, infection hazards were 0.84-fold lower for the highest vs lowest quartiles. There was a significant linear trend, but differences in infection hazard were limited to the highest and lowest quartiles, as shown in adjusted failure curves (Figure 1). In analyses of sepsis, we observed similar patterns of incidence and adjusted measures of association for SIRS and SOFA criteria as compared with those for infection (Supplementary Table 2). However, after adjustment, the associations for SOFA criteria were not statistically significant at the .05 level and there was no association for qSOFA.

Of potential mediators, we found that physical weakness, participant income, and comorbid diabetes had modest indirect effects (mediating at least 10% of the association between nSES and infection), suggesting that nSES may impact infection risk through associations with physical health, reported income levels, or risk of diabetes (Table 4).

Among first infections, infection type was similar across nSES quartiles, with respiratory infections being most common (Table 5). In addition, more than half of the participants met ≥2 SIRS criteria, with lower proportions for SOFA and qSOFA criteria. There were no associations between nSES and the likelihood of sepsis at presentation. Median length of stay was longer for participants in the lowest nSES quartile, but measures of event severity did not differ. In a sensitivity analysis using logistic

Table 1. Census Block Group Socioeconomic Measures

	nSES Quartile, Median (25th–75th Percentile)			
Block Group nSES Measure	Q1 [Lowest] nSES Score (–11.79 to –3.90) (n = 6651)	Q2 nSES Score (–3.89 to –0.93) (n = 6654)	Q3 nSES Score (–0.92 to 3.08) (n = 6648)	Q4 [Highest] nSES Score (3.09–28.95) (n = 6651)
Median household income, $	21 955 (17 298–26 445)	31 855 (27 283–36 645)	42 022 (36 259–48 261)	62 143 (51 759–75 509)
Median home value, $	49 300 (39 400–59 900)	69 500 (58 100–83 200)	94 600 (81 300–116 200)	162 800 (129 400–224 400)
Households with interest, dividend, or rental income, %	10.1 (6.3–14.3)	19.3 (14.2–24.4)	30.1 (23.1–37.7)	50.3 (40.8–59.9)
Adult residents completed high school, %	61.2 (55.2–66.4)	73.9 (69.4–78.4)	83.7 (79.5–87.3)	93.0 (89.8–95.9)
Adult residents completed college, %	10.3 (7.2–13.5)	18.0 (14.5–21.9)	28.5 (23.9–33.7)	49.4 (40.7–59.5)
Employed residents with executive, managerial, or professional occupations, %	15.7 (11.7–20.1)	23.1 (19.3–27.2)	31.6 (27.4–36.4)	47.7 (41.1–55.7)

Total of 26 604 Reasons for Geographic and Racial Differences in Stroke (REGARDS) participants. Block group–level measures obtained from economic census data.
Abbreviation: nSES, neighborhood socioeconomic status.

Table 2. Characteristics of Participants by Neighborhood Socioeconomic Status Score

	nSES Quartile				
Participant Characteristic	Q1 [Lowest] nSES Score (–11.79 to –3.90) (n = 6651)	Q2 nSES Score (–3.89 to –0.93) (n = 6654)	Q3 nSES Score (–0.92 to 3.08) (n = 6648)	Q4 [Highest] nSES Score (3.09–28.95) (n = 6651)	*P* Value[a]
Demographics					
Age, y, mean (SD)	64.8 (9.5)	64.8 (9.4)	64.9 (9.4)	65.2 (9.4)	.09
Race, %					<.001
Black	71.3	47.3	33.8	15.7	
White	28.7	52.7	66.2	84.4	
Gender, %					<.001
Male	38.6	43.1	46.8	51.4	
Female	61.4	56.9	53.2	48.6	
Education, %					<.001
Less than high school	25.5	14.7	7.4	2.5	
High school graduate or more	74.6	85.3	92.6	97.6	
Missing, No. (%)	10 (0.2)	4 (0.1)	5 (0.1)	4 (0.1)	
Income, %					<.001
<$20 000	34.6	20.8	11.7	5.0	
≥$20 000	51.8	66.8	76.7	83.2	
Not reported	13.6	12.4	11.6	11.9	
Geographic region, %					<.001
Non–Stroke Belt/Buckle	35.2	39.1	49.4	57.3	
Stroke Belt	40.8	38.3	32.7	25.8	
Stroke Buckle	24.0	22.6	17.9	16.9	
Health behaviors					
Tobacco use, %					<.001
Current	19.5	16.2	13.2	8.8	
Past	36.7	40.0	41.7	43.1	
Never	43.8	43.7	45.1	48.1	
Missing, No. (%)	32 (0.5)	29 (0.4)	20 (0.3)	25 (0.4)	
Alcohol use, %					<.001
Heavy	2.6	3.4	4.2	6.0	
Moderate	21.6	27.3	35.3	49.4	
None	75.8	69.4	60.5	44.6	
Missing, No. (%)	129 (1.9)	143 (2.2)	127 (1.9)	110 (1.7)	
Chronic medical conditions, %					
Chronic lung disease	9.3	9.5	9.1	9.3	.89
Diabetes	33.5	28.1	21.9	16.2	<.001
Hypertension	68.8	62.8	57.2	48.4	<.001
Myocardial infarction	13.9	13.3	12.1	10.9	<.001
Stroke	9.0	7.1	5.8	4.1	<.001
BMI category, %					<.001
Underweight/normal	20.6	22.1	25.3	31.1	
Overweight	33.3	35.4	38.0	40.8	
Obese	46.2	42.5	36.7	28.1	
Missing, No. (%)	81 (1.2)	43 (0.7)	32 (0.5)	38 (0.6)	
Biomarkers, %					
eGFR <60 mg/min/1.73 m^2	12.5	11.6	10.4	9.4	<.001
hs-CRP >3.0 mg/dL	45.4	41.1	36.0	29.7	<.001
Functional status					
Weakness (SF-12 PCS <75), %	40.0	33.9	26.5	19.3	<.001
Missing, No. (%)	135 (2.0)	123 (1.9)	91 (1.4)	59 (0.9)	
Participant-reported exhaustion, %	18.2	16.0	12.2	9.5	<.001
Missing, No. (%)	21 (0.3)	27 (0.4)	27 (0.4)	19 (0.3)	
Low physical activity, %	39.0	36.1	34.7	28.1	<.001
Missing, No. (%)	142 (2.1)	99 (1.5)	74 (1.1)	84 (1.3)	

Total of 26 604 Reasons for Geographic and Racial Differences in Stroke (REGARDS) participants. nSES composite score ranges provided for nSES quartiles.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; nSES, neighborhood socioeconomic status; PCS, physical composite score; SD, standard deviation; SF-12, 12-Item Short-Form Health Survey.

[a] *P* values from analysis of variance for continuous variables (age) and Pearson χ^2 tests of association for categorical variables.

Table 3. Relative Infection Hazard by Neighborhood Socioeconomic Status Score

nSES Score Quartile	Infections, No. (%)	Infection Incidence per 1000 PY (95% CI)	Crude	Add Race	Add Other Demographics[a]	Add Behaviors[b] + Chronic Conditions[c] + Biomarkers[d]	Add Functional Status[e]
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Q1: –11.79 to –3.90 [Lowest]	605 (9.1)	15.6 (14.4–16.9)	Ref	Ref	Ref	Ref	Ref
Q2: –3.89 to –0.93	630 (9.5)	15.7 (14.5–17.0)	1.00 (.90–1.12)	0.90 (.81–1.01)	0.96 (.86–1.08)	1.00 (.89–1.12)	1.01 (.90–1.14)
Q3: –0.92 to 3.08	585 (8.8)	14.0 (12.9–15.2)	0.89 (.80–1.00)	0.76 (.68–.86)	0.85 (.75–.96)	0.93 (.82–1.06)	0.94 (.83–1.07)
Q4: 3.09–28.95 [Highest]	505 (7.6)	11.7 (10.7–12.8)	0.74 (.66–0.84)	0.59 (.52–.68)	0.68 (.60–.78)	0.81 (.70–.93)	0.84 (.73–.97)
Trend *P* value			<.001	<.001	<.001	.002	.011

Total of 26 604 Reasons for Geographic and Racial Differences in Stroke (REGARDS) participants. HRs estimated using Cox proportional hazards regression. *P* values represent tests for linear trends across nSES score quartiles.

Abbreviations: CI, confidence interval; HR, hazard ratio; nSES, neighborhood socioeconomic status; PY, person-years.

[a]Age, gender, region, income, and education.

[b]Smoking status and alcohol use.

[c]Body mass index category, chronic lung disease, diabetes, hypertension, myocardial infarction, and stroke.

[d]High-sensitivity C-reactive protein and estimated glomerular filtration rate.

[e]Weakness, exhaustion, and low physical activity.

regression to model the odds of sepsis, we did not observe an association between nSES and sepsis (Supplementary Table 3).

DISCUSSION

We examined the association of nSES with 10-year risk of hospitalization for infection and sepsis in the REGARDS study, one of the largest contemporary cohorts of community-dwelling adults in the United States. Compared to low nSES, participants residing in high-nSES neighborhoods demonstrated lower rates of infection, but no difference in odds of sepsis at presentation. This suggests that the association between nSES and sepsis may be explained by differences in infection risk. Our study also demonstrates that physical function, individual income, and comorbid diabetes mediate the association,

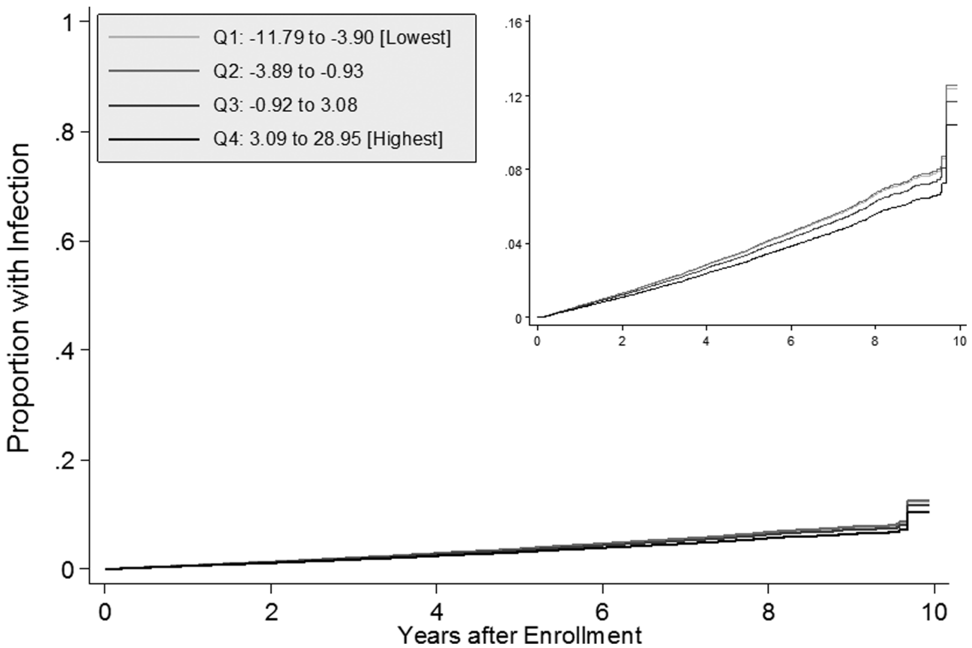

Figure 1. Adjusted failure curves for time to infection by neighborhood socioeconomic status (nSES) score. Total of 26 604 Reasons for Geographic and Racial Differences in Stroke (REGARDS) participants. Q1–Q4 represent quartiles of nSES score in the REGARDS cohort. All failure functions estimated among white, male, nonsmoking, and non-alcohol-consuming participants residing in the non–Stroke Belt region, with no history of comorbidities, normal biomarker levels, and no functional status impairments (all binary variables set to zero and all categorical variables set to the reference groups).

Table 4. Mediation of the Association Between Neighborhood Socioeconomic Status Score and Infection

	Natural Indirect Effect[a]		Natural Direct Effect[b]		
Characteristic	HR	(95% CI)[c]	HR	(95% CI)[c]	Percentage Mediated (Log Hazard Scale)
Adjusted (Q4 [highest] vs Q1 [lowest])[d]	…	…	0.76	(.65–.90)	…
Potential mediators					
Weakness (SF-12 PCS <75)	0.94	(.92–.96)	0.81	(.69–.95)	21.5
Individual income	0.96	(.92–.99)	0.80	(.68–.94)	16.5
Diabetes	0.97	(.96–.98)	0.78	(.67–.92)	10.7
Exhaustion	0.98	(.97–.99)	0.78	(.67–.92)	8.5
BMI (obese vs nonobese)	0.98	(.97–1.00)	0.78	(.66–.91)	6.1
Low physical activity	0.99	(.98–1.00)	0.77	(.66–.91)	4.5

Total of 12 463 Reasons for Geographic and Racial Differences in Stroke (REGARDS) participants in lowest or highest quartiles of nSES score with complete covariate data. Characteristics added as the only additional covariate relative to the adjusted model.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; nSES, neighborhood socioeconomic status; PCS, physical composite score; SF-12, 12-Item Short-Form Health Survey.

[a]Natural indirect effect represents the component of the exposure effect that is mediated, reported on the hazard ratio scale.

[b]Natural direct effect represents the component of the exposure effect not mediated, reported on the hazard ratio scale.

[c]Confidence intervals estimated using the delta method.

[d]Initial hazard ratio comparing lowest to highest quartile of nSES score (lowest as referent) from Cox proportional hazards model adjusted for age, sex, race, education, geographic region, chronic lung disease, hypertension, stroke, myocardial infarction, smoking, alcohol use, C-reactive protein, and estimated glomerular filtration rate (chronic kidney disease).

Table 5. First Infection Hospitalization Characteristics by Neighborhood Socioeconomic Status Score

	nSES Quartile				
Participant Characteristic	Q1 [Lowest] nSES Score (–11.79 to –3.90) (n = 605)	Q2 nSES Score (–3.89 to –0.93) (n = 630)	Q3 nSES Score (–0.92 to 3.08) (n = 585)	Q4 [Highest] nSES Score (3.09–28.95) (n = 505)	*P* Value[a]
Primary infection type, %					.65
Respiratory	41.0	40.2	39.3	40.4	
Urinary/kidney	18.0	19.8	19.2	16.8	
Abdominal	16.2	17.9	20.2	20.0	
Skin/soft tissue	13.7	11.9	12.8	13.5	
Sepsis	5.3	4.9	2.7	4.8	
Other	5.8	5.2	5.8	4.6	
≥2 SIRS[b] criteria, %	54.1	54.1	53.7	49.7	.41
≥2 SOFA[c] points, %	38.7	37.8	35.6	34.1	.37
≥2 qSOFA[d] points, %	12.6	11.4	9.9	12.3	.49
SOFA score category, %					.54
0	36.2	37.1	40.0	40.4	
1	25.1	25.1	24.4	25.5	
2	14.6	17.5	15.2	13.3	
3–4	15.4	13.8	14.2	15.1	
5	8.8	6.5	6.2	5.7	
Admitted length of stay[e], d, median (25th–75th percentile)	5 (3–8)	4 (3–7)	5 (3–7)	4 (3–7)	.03
Admitted to ICU vs floor[e], %	11.0	11.2	6.8	10.3	.08
In-hospital death, %	7.4	6.5	5.0	5.5	.30
Discharged to nursing home, %	9.3	8.7	6.7	9.1	.35

Total of 2325 participants hospitalized with a first infection event.

Abbreviations: ICU, intensive care unit; nSES, neighborhood socioeconomic status; qSOFA, "quick" sepsis-related organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sepsis-related organ failure assessment.

[a]*P* values from Kruskal-Wallis tests of equal distribution for continuous variables (length of stay) and Pearson χ^2 tests of association for categorical variables.

[b]Sepsis-SIRS defined as infection event meeting ≥2 SIRS criteria.

[c]Sepsis-SOFA defined as infection event with ≥2 SOFA points.

[d]Sepsis-qSOFA defined as infection event meeting ≥2 qSOFA criteria.

[e]Includes only participants admitted as an inpatient with inpatient records available.

highlighting potential pathways through which nSES could impact infection risk.

Prior studies have examined associations between markers of SES and sepsis using administrative databases [4, 27–29]. O'Brien et al studied the association between insurance type and admission for sepsis as well as sepsis outcomes [4]. Among discharges of individuals aged ≥18 years in the 2003 Nationwide Inpatient Sample, those with Medicaid or Medicare experienced higher risk-adjusted odds of sepsis compared to discharged patients with private insurance. Mendu et al examined critical care discharges from 2 hospitals in the northeastern United States, finding that census tract poverty was significantly associated with bloodstream infection [28]. In addition, using data from nonfederal hospitals in South Carolina, Goodwin et al found that residence in a medically underserved area was associated with increased incidence of sepsis admission and higher mortality [29]. However, the authors did not find similar associations with ZIP code–level SES measures.

The current study expands on prior efforts in that we were able to examine outcomes prospectively and isolate the effects of nSES on infection risk and odds of sepsis. In contrast to previous studies, our results indicate that residing in a low nSES neighborhood is associated with an increased risk hospitalization for infection, but not event severity among those hospitalized. Although our prospective design may explain this discordance, several alternative explanations are possible. To define "neighborhood," we used census block groups, which represent a smaller and more granular geographic unit than previously studied. We also used a comprehensive summary score incorporating multiple domains to define nSES, as opposed to focusing our analyses on a single factor. In addition, we identified hospitalizations for serious infection and sepsis via record review, while many prior studies have employed discharge diagnosis code algorithms. Thus, the observed differences could be explained by the infection population in the current study being lower acuity as compared with sepsis patients identified using discharge diagnoses.

Our findings could help to inform approaches for reducing the national burden of sepsis. Specifically, our results suggest that strategies for sepsis prevention may need to target infection risk prior to a sepsis event, as opposed to focusing exclusively on improvements in the provision of acute care. We have also identified several potential mechanisms that could be incorporated into focused efforts to ameliorate SES disparities in sepsis. The mediating role of individual income suggests that factors associated with living in poverty, such as reduced food availability, lack of transportation, and social isolation, could be targeted for intervention [30]. Mediation of the association by physical weakness suggests that mobility, neighborhood walkability, blight, and physical safety could also be important factors to consider in efforts to reduce sepsis disparities. In addition, reducing diabetes prevalence may also serve as an important component of efforts to prevent infection. Further research must develop and evaluate effective community-based interventions for reducing infection and sepsis risk among populations with limited resources, such as individuals living in low-nSES neighborhoods.

Our study has notable strengths, including substantial heterogeneity and variety in neighborhoods, comprehensive baseline participant data, and nearly 10 years of follow-up. However, our results must be interpreted in light of several important limitations. Although outcomes were defined via a rigorous abstraction and medical record review process, due to the fact that events were participant reported, it is possible that hospitalizations were missed. In addition, for the analysis of qSOFA criteria, we did not identify a large number of events, which could explain the change in magnitude of association after adjustment for participant characteristics. To define nSES, we used a widely published summary score calculated at the block group level. Although census data are available for larger geographic units, we believed that the block group provided the most granular impression of participant nSES. It is possible that participants could have moved or neighborhood characteristics could have changed over follow-up, leading to potential misclassification of nSES. However, we limited our analyses to nSES as defined at baseline to characterize the exposure at the time of enrollment in REGARDS. There is the potential for unmeasured confounding due to factors not included in our models as well as the potential that other important mediators were missed (eg, measures of realized access to care). These factors could attenuate the observed association or play important mediating roles. However, we made use of a wide range of data collected at baseline enrollment among REGARDS participants in all models. Generalizability of our findings could also be limited by specific characteristics of the study population: Participants were enrolled in a long-term cohort study, nearly 70% of the population was >60 years old, and only 6% of the population lacked health insurance at the time of enrollment.

We examined the association of nSES with risk of infection and sepsis over a 10-year period using data from a national cohort of community-dwelling adults. Compared to low nSES, participants residing in high-nSES neighborhoods had an increased risk of hospitalization for infection, even after adjustment for participant characteristics. However, we found no association between nSES and odds of sepsis at presentation. Physical weakness, individual income, and comorbid diabetes mediated the association of nSES and infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author contributions. J. P. D. and H. E. W. conceived of the study. H. E. W. and M. M. S. organized and oversaw data collection. J. P. D. and S. L. conducted the analysis and all authors contributed to review of results.

J. P. D. produced an initial draft of the manuscript and all authors contributed to its editorial review and revision. J. P. D. and H. E. W. assume responsibility for the work as a whole.

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