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Community characteristics and regional variations in sepsis

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Abstract

Background: Sepsis may contribute to more than 200 000 annual deaths in the USA. Little is known about the regional patterns of sepsis mortality and the community characteristics that explain this relationship. We aimed to determine the influence of community characteristics upon regional variations in sepsis incidence and case fatality.

Methods: We performed a retrospective analysis of data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. Using US sepsis mortality data, we used two strategies for defining geographic regions: (i) Sepsis 'Belt' vs Non-Belt and (ii) Sepsis 'Cluster' vs Non-Cluster. We determined sepsis incidence and case fatality among REGARDS participants in each region, adjusting for participant characteristics. We examined the mediating effect of community characteristics upon regional variations in sepsis incidence and case fatality.

Results: Among 29 680 participants, 16 493 (55.6%) resided in the Sepsis Belt and 2958 (10.0%) resided in a Sepsis Cluster. Sepsis incidence was higher for Sepsis Belt than Non-Belt participants [adjusted hazard ratio (HR) = 1.14; 95% confidence interval (CI) = 1.02–1.24] and higher for Sepsis Cluster than Non-Cluster participants (adjusted HR = 1.18; 95% CI = 1.01–1.39). Sepsis case fatality was similar between Sepsis Belt and Non-Belt participants, as well as between Cluster and Non-Cluster participants. Community poverty mediated the regional differences in sepsis incidence.

Conclusions: Regional variations in sepsis incidence may be partly explained by community poverty. Other community characteristics do not explain regional variations in sepsis incidence or case fatality.

Key words: sepsis, epidemiology, poverty, region, mediation analysis

Key Messages

- Limited research has investigated regional patterns of sepsis incidence and case fatality among community-dwelling participants and the community characteristics that mediate this association.
- Our study provides evidence that persons living in 'Sepsis-Belt' and 'Sepsis Cluster' communities may be likely to develop sepsis due to higher community-level poverty.
- Community poverty may be a proxy for access to healthcare, healthcare utilization and healthcare literacy, therefore hindering treatment for community-acquired sepsis.

Introduction

Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection. In the USA, sepsis is a significant public health concern, associated with a high mortality rate, and may contribute to over 200 000 annual deaths.[1–4] Whereas prior studies have highlighted differences in regional sepsis mortality rates, few studies have examined these differences among participants in a large national prospective cohort.[3,5] Therefore, little is known about the regional patterns of sepsis mortality and the community characteristics that mediate this relationship.

The study of geographic patterns of disease is important because clustering in a specific area or region may represent associations with localized population or environmental characteristics. For example, individuals living in the southeastern USA are more likely to be obese and experience an increased risk of stroke.[6] Research also suggests that individuals living in communities with higher poverty, a proxy for lower socio-economic status, are at increased risk of morbidity, mortality and bloodstream infections.[7–10] Previous studies have reported that sepsis mortality in the USA may be characterized by two distinct patterns of regional variation: (i) a state-level 'belt' encompassing the states of Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee and (ii) county-level 'clusters' located in the Mississippi Valley, Central Appalachia and Middle Georgia.[3,5]

The underlying reasons for regional variations in sepsis mortality are unknown, but these patterns may be explained by differences in individual resident characteristics or characteristics related to their places of residence. The REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort is one of the nation's largest longitudinal population-based cohorts. In this study, we sought to determine the mediating effect of community characteristics upon regional variations in sepsis incidence and case fatality in the REGARDS cohort.

Methods

Ethics statement

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.

Study design and data source

We performed a retrospective analysis of prospectively collected data using REGARDS, a cohort of community-dwelling adults in the USA.[11] Designed to evaluate the origins for racial and geographic differences in stroke mortality, REGARDS includes 30 239 participants aged ≥45 years at baseline. The cohort is 45% male, 41% Black race and 69% >60 years old. REGARDS recruited participants between January 2003 and October 2007. At 6-month intervals until 31 December 2012, REGARDS contacted the participants by telephone to identify any hospitalizations experienced by the participant in the previous 6 months. Further details related to REGARDS study methods are described elsewhere.[11] Whereas the objective of REGARDS was to identify and characterize stroke events, the population of REGARDS included community-dwelling adults at healthy baseline.

Identification of sepsis incidence and fatality

The primary outcomes of this study were (i) first incident sepsis events and (ii) fatality after the sepsis event (case fatality). We included hospitalization events reported from 1 January 2003 through 31 December 2012. Using the taxonomy of Angus *et al.* (2001), we identified all hospitalizations (Emergency Department visits and/or hospital admission) attributed by participants to a serious infection (i.e. all hospitalizations with a bacterial, fungal or viral

infectious process).[1] We defined a sepsis event as a hospital admission for serious infection with the presence of at least two Systemic Inflammatory Response Syndrome (SIRS) criteria, including heart rate >90 beats/minute, fever (temperature >38.3°C or <36°C), tachypnea (>20 breaths/min) or $PCO_2 < 32$ mmHg and leukocytosis (white blood cells >12 000 or <4000 cells/mm^3 or >10% band forms).[1] Based on medical records and/or death certificates, we defined sepsis case fatality as an either in-hospital death attributed to sepsis or death within 30 days after hospital discharge of a physician-adjudicated sepsis event.

We assessed vital signs and laboratory findings within the first 28 hours of hospitalization to include Emergency Department care and up to 1 full day of inpatient care. Our analysis focused on community-acquired sepsis, so we did not assess vital signs, laboratory findings or development of sepsis at later time points. Initial review of 1329 hospital records indicated excellent inter-rater consensus for the presence of serious infection (kappa = 0.92) and the presence of sepsis (kappa = 0.90) at the time of hospital presentation.

International consensus conferences ('Sepsis-3') have proposed new definitions for sepsis.[12] Because of its common use in prior sepsis epidemiology studies, we used the SIRS-based sepsis definition as the primary analysis. However, in a sensitivity analysis, we repeated the analysis using the Sepsis-3 definition of sepsis as the presence of a serious infection plus a sequential organ failure assessment (SOFA) score ≥2.[12]

Definition of sepsis geographic regions

We previously described two strategies for characterizing regional sepsis variations using 2003–12 US national mortality data.[3,5] In short, we defined sepsis deaths as all deaths attributed to an infection.[3,13] We identified age- and sex-adjusted sepsis mortality rates for each US county.[3] We observed that sepsis mortality was higher along a contiguous group of states encompassing the south-eastern USA (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee); we defined this region as the 'Sepsis Belt'. We categorized all REGARDS participants as residing in 'Sepsis Belt' or 'Non-Belt' regions (Figure 1).

In a subsequent analysis, we identified sepsis county 'hot spots' of increased sepsis mortality using three geospatial autocorrelation measures [Empirical Bayes (EB) smoothed sepsis mortality rates, Local Indicators of Spatial Association (LISA)[14] and the Getis-Ord Gi* statistic[15]]; these regions were localized to the Mississippi Valley, Central Appalachia and Middle Georgia. From this prior analysis, US counties were designated as 'Sepsis Clusters' if they were identified as counties of high sepsis mortality based on at least two of the three geospatial methods.[5] In this study, we categorized REGARDS participants as residing in 'Sepsis Cluster' or 'Non-Cluster' counties.

Participant characteristics

REGARDS participant demographics included self-reported age, race, sex, income, education and geographic location. Health behaviours included tobacco and alcohol use. Smoking status included current, past and never. We defined alcohol use as moderate (one drink per day for women or two drinks per day for men) and heavy alcohol use (more than drink per day for women and more than two drinks per day for men), per the National Institute on Alcohol Abuse and Alcoholism classification.[16] Baseline medical conditions included atrial fibrillation, chronic lung disease, coronary artery disease, deep vein thrombosis, diabetes, dyslipidemia, hypertension, myocardial infarction, obesity, peripheral artery disease and stroke. We have provided detailed information regarding participant characteristics in Appendix A (available as Supplementary Data at *IJE* online).

Community characteristics

We determined the characteristics of REGARDS participant communities using 2010 American Community Survey (ACS) data available from the National Historical Geographic Information System (NHGIS).[13,17] The ACS 2010 provides demographic information for each county for 2006–10. We determined community characteristics for this study based on publicly available variables that characterize county-level socio-economic status and healthcare availability, including median household income, percentage of the population completing college, percentage of the population below the poverty line, percentage of population without medical insurance coverage, unemployment rate, percentage of urban population and number of active medical doctors per 100 000 persons.[5,18]

Statistical analysis

We compared differences in participant and community characteristics between 'Sepsis Belt' vs 'Non-Belt' and 'Sepsis Cluster' vs 'Non-Cluster' participants. We used a chi-square test for categorical characteristics, analysis of variance (ANOVA) for normally distributed continuous characteristics and Kruskal-Wallis test for non-parametric continuous variables.

The objective of our analysis were to test for the mediating effect of community characteristics and not potential

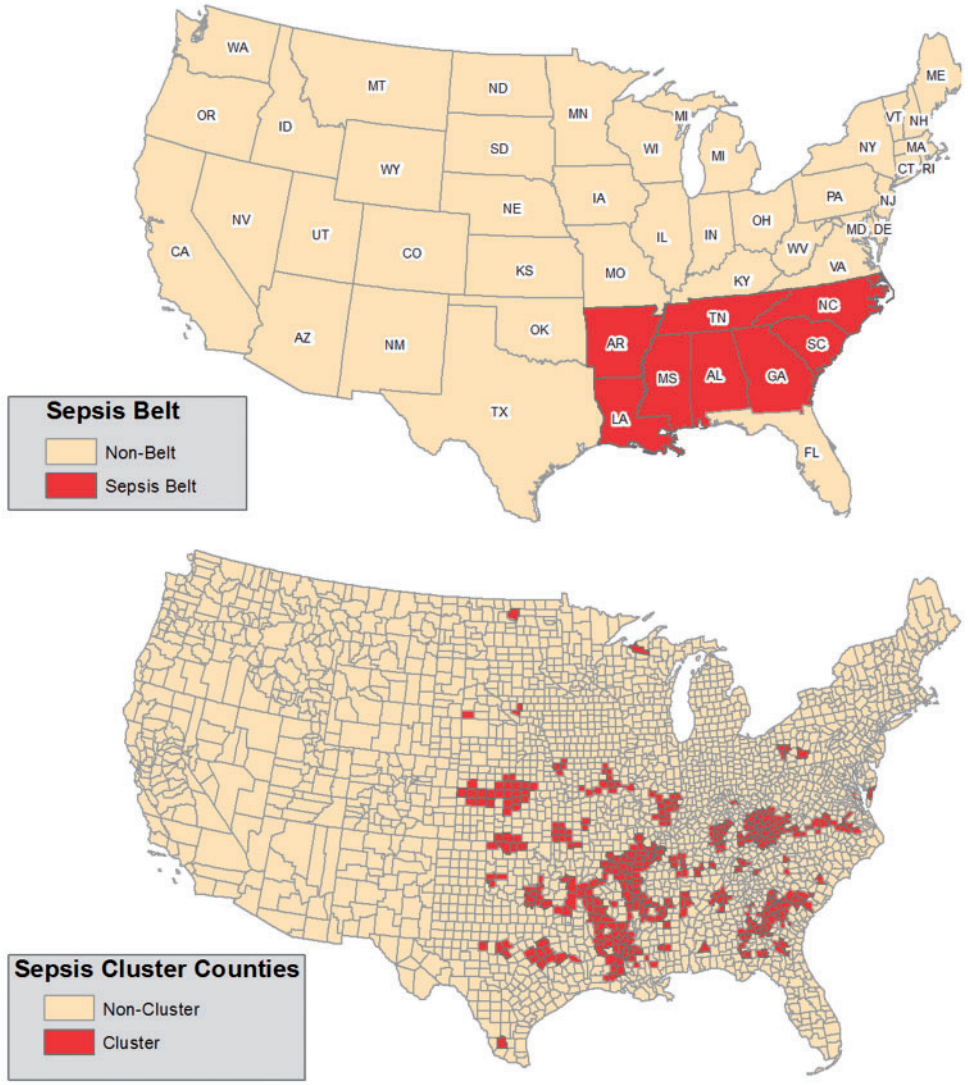

Figure 1. Sepsis exposure regions.

for effect modification. Therefore, we examined the mediating effect of community characteristics upon regional differences in sepsis incidence and case fatality. Mediators (or intervening/intermediary variables) are variables that are causally located between exposure and outcome variables, and that explain, in part, the effect of exposure on outcome.[19–23] In a mediation model, the indirect (or mediation) effect represents the pathway in which an exposure affects an outcome indirectly through the mediator(s).[19–23] In addition, the exposure can have a direct association with the outcome of interest, independently of the mediator variable.[20–22]

We determined the mediating effect of community characteristics on the association between region (Sepsis Cluster and Sepsis Belt) and the odds of sepsis and case fatality using PROCESS—a statistical macro developed by Hayes (2013) for mediation analysis.[20–22] As all community characteristics may serve as equivalent mediators,[24] we chose to fit four parallel logistic regression mediation models with the seven community characteristics. The first model examined the mediating effect of community characteristics upon differences in sepsis incidence between the Sepsis Belt and Non-Belt participants. We then repeated the analysis comparing Sepsis Cluster with Non-Cluster participants. We repeated these models using sepsis case fatality as the primary outcome.

We adjusted the estimates for participant sociodemographics, health behaviours and chronic medical conditions significant in univariate analysis (p-value ≤ 0.05). Our outcomes were binary, so we presented the indirect (mediation) effects and mediator-to-outcome associations (path b) as odds ratios (ORs) and their associated 95% confidence intervals (CIs), determined using a bootstrapping technique with 1000 resamples and with

replacement.[20–22,25] As our mediators were normalized continuous variables, we presented the exposure to mediator associations as parameter estimates (β estimates) and their associated standard errors (SEs), estimated from linear regression. We used SAS version 9.4, Stata version 13 and GeoDa version 1.6.7.9 for all statistical analyses. We used ArcGIS version 10.4 for all maps.

Results

Baseline participant characteristics

Among 30 239 REGARDS participants, there were a total of 1526 sepsis events, with the majority being attributed to pneumonia (38.2%), urinary tract infections (16.9%) and abdominal (15.5%) infections (Table 1). We excluded 559 participants from the analysis due to incomplete follow-up time, missing geocode data or missing county information. Among the 29 680 remaining in the analysis, 16 493 (55.6%) resided in the Sepsis Belt and 13 187 (44.4%) resided in Non-Belt areas (Table 2). Non-Belt participants were older and more likely to have Black race and male gender. Sepsis Belt participants reported lower education and income ($p < 0.001$). Current tobacco use was more common among Sepsis Belt participants, whereas Non-Belt participants were more likely to have moderate to heavy alcohol consumption. Sepsis Belt participants were more likely to have deep vein thrombosis, diabetes, dyslipidemia and hypertension ($p < 0.05$). There was a similar distribution of all other baseline medical conditions.

Among the 29 680 REGARDS participants, 2958 (10%) resided in a Sepsis Cluster and 26 722 (90%) resided in a Non-Cluster community (Table 2). Sepsis Cluster participants were younger than Non-Cluster participants. Sepsis Cluster participants had a larger proportion of women and participants with White race than Non-Cluster participants. Non-Cluster participants reported higher education and income. Sepsis Cluster participants reported slightly higher current tobacco use (15.3% vs 14.4%) than Non-Cluster participants. Non-Cluster participants were more likely to be moderate to heavy alcohol users than Sepsis Cluster participants ($p < 0.001$). Sepsis Cluster participants were more likely to have a history of coronary artery disease, deep vein thrombosis, diabetes, dyslipidemia, hypertension, myocardial infarction and obesity ($p < 0.05$).

Table 1. Infection characteristics of 1526 sepsis events

	N (%)
Infection type	
Pneumonia	583 (38.2)
Urinary tract infections	258 (16.9)
Abdominal	236 (15.5)
Bronchitis	142 (9.3)
Skin	138 (9.0)
Sepsis	95 (6.2)
Fever of unknown origin	29 (1.9)
Catheter/other	45 (2.9)
Sequential organ failure assessment score	
0	432 (28.3)
1	375 (24.6)
≥2	719 (47.1)

Community characteristics

Sepsis Belt participants lived in communities with lower median household income, value of housing units and a lower proportion of population that completed college when compared with Non-Belt participants ($p < 0.001$) (Table 3). Non-Belt participants lived in communities with lower poverty rates, greater population density and percentage urban ($p < 0.001$). Sepsis Belt participants lived in communities with a greater number of medical resources, characterized by larger proportions of primary care physicians, hospitals, beds and medical doctors per 100 000 persons ($p < 0.001$). Non-Belt participants resided in communities with lower uninsured population and lower unemployment rates (<0.001).

Sepsis Cluster participants resided in communities with lower median household income, value of housing units and a lower proportion of population that completed college compared with Non-Cluster participants ($p < 0.001$). Sepsis Cluster participants lived in communities with higher poverty rates, lower population density and percentage urban ($p < 0.001$). Non-Cluster participants lived in communities with a lower number of medical resources, characterized by smaller proportions of primary care physicians, hospitals, beds and medical doctors per 100 000 persons ($p < 0.001$) when compared with Sepsis Cluster participants. Non-Cluster participants resided in communities with lower uninsured population and lower unemployment rates ($p < 0.001$).

Sepsis incidence and case fatality

The odds of sepsis were higher among Sepsis Belt than Non-Belt participants after adjustment for age, sex, race, education, income, health behaviours, cancer, deep vein thrombosis, diabetes, dyslipidemia and hypertension (adjusted total effect OR = 1.14; 95% CI = 1.02–1.24, *p*-value = 0.02). The mediation effect of poverty on the association between Sepsis Belt residents and sepsis incidence did not reach significance (indirect effect OR = 1.08; 95% CI = 1.00–1.18; *p*-value = 0.06). Further, the mediation

Table 2. REGARDS participant characteristics stratified by geographic region

	Geographic region					
	Sepsis Belt[a] (*N* = 16 493)	Non-Belt (*N* = 13 187)	*p*-value*	Sepsis Cluster[b] (*N* = 2958)	Non-Cluster (*N* = 26 722)	*p*-value*
Age[†]	64.3 (9.3)	65.6 (9.5)	<0.01	64.1 (9.4)	65.0 (9.4)	<0.01
Race (%)						
Black	6258 (37.9)	5956 (45.2)	<0.01	1029 (35.5)	11 165 (41.8)	<0.01
White	10 235 (62.1)	7231 (54.8)		1909 (64.5)	15 557 (58.2)	
Sex (%)						
Male	7040 (42.7)	6289 (47.7)	<0.01	1268 (42.9)	12 061 (45.1)	0.02
Female	9453 (57.3)	6898 (52.3)		1690 (57.1)	14 661 (54.9)	
Education (%)						
≤High school	2307 (14.0)	1400 (10.6)	<0.01	510 (17.3)	3197 (12.0)	<0.01
High-school graduate	4434 (26.9)	3231 (24.5)		880 (29.8)	6785 (25.4)	
Some college	4331 (26.3)	3616 (27.5)		733 (24.8)	7214 (27.0)	
≥College graduate	5413 (32.8)	4925 (37.4)		833 (28.2)	9505 (35.6)	
Income (%)						
≤$20 000	3204 (19.4)	2137 (16.2)	<0.01	643 (21.7)	4698 (17.6)	<0.01
$20 000–$34 000	3974 (24.1)	3199 (24.3)		732 (24.8)	6441 (24.1)	
$35 000–$74 000	4823 (29.2)	3981 (30.2)		837 (28.3)	7967 (29.8)	
≥$75 000	2390 (14.5)	2306 (17.5)		370 (12.5)	4326 (16.2)	
Refused	2102 (12.7)	1564 (11.9)		376 (12.7)	3290 (12.3)	
Tobacco use (%)						
Never	7577 (46.1)	5802 (44.2)	<0.01	1394 (47.2)	11 985 (45.0)	<0.01
Past	6416 (39.1)	5489 (41.8)		1106 (37.5)	10 799 (40.6)	
Current	2436 (14.8)	1846 (14.1)		451 (15.3)	3831 (14.4)	
Alcohol use (%)						
None	10 861 (67.0)	7377 (57.3)	<0.01	2105 (72.3)	16 133 (61.6)	<0.01
Moderate	4739 (29.2)	4948 (38.4)		717 (24.6)	8970 (34.3)	
Heavy	615 (3.8)	560 (4.4)		89 (3.1)	1086 (4.2)	
Chronic medical conditions (%)						
Atrial fibrillation	1454 (9.0)	1094 (8.5)	0.10	273 (9.4)	2275 (8.7)	0.19
History of cancer	1534 (9.3)	1425 (10.8)	<0.01	269 (9.1)	2690 (10.1)	0.09
Chronic lung disease	1540 (9.3)	1191 (9.0)	0.37	267 (9.0)	2464 (9.2)	0.73
Coronary artery disease	2902 (17.9)	2326 (18.0)	0.93	584 (20.1)	4644 (17.7)	<0.01
Deep vein thrombosis	916 (5.6)	639 (4.9)	<0.01	187 (6.4)	1368 (5.1)	<0.01
Diabetes	3872 (23.6)	2826 (21.5)	<0.01	755 (25.6)	5943 (22.3)	<0.01
Dyslipidemia	9559 (60.1)	7393 (58.4)	<0.01	1807 (63.0)	15 145 (58.9)	<0.01
Hypertension	9902 (60.2)	7637 (58.1)	<0.01	1846 (62.6)	15 693 (58.9)	<0.01
Myocardial infarction	2045 (12.6)	1672 (12.9)	0.47	416 (14.3)	3301 (12.6)	0.01
Obesity	8858 (53.8)	7002 (53.2)	0.27	1644 (55.7)	14 216 (53.3)	0.01
Peripheral artery disease	360 (2.2)	303 (2.3)	0.51	68 (2.3)	595 (2.2)	0.80
Stroke	1023 (6.2)	873 (6.6)	0.15	199 (6.8)	1697 (6.4)	0.43

[†]Mean (Standard deviation).

*Significance determined using ANOVA or chi-square test. (%) Denotes column percentages.

[a]States with increased sepsis mortality (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee).

[c]Counties with high sepsis mortality (fulfilling two of three criteria for geographic clustering).

pathway explained that Sepsis Belt residents were more likely to live below the poverty line (β = 0.90; SE = 0.01; *p*-value < 0.01); however, living below the poverty line was non-significantly associated (mediator-to-outcome OR = 1.09; 95% CI = 0.99–1.19; *p*-value = 0.06) with higher odds of sepsis (Figure 2A and Appendix B, available as Supplementary Data at *IJE* online).

The odds of sepsis were also higher for Sepsis Cluster than Non-Cluster participants after adjustment for age, sex, race, education, income, health behaviours, CAD, deep vein thrombosis, diabetes, dyslipidemia, hypertension, MI and obesity (adjusted total effect OR = 1.18; 95% CI = 1.01–1.39, *p*-value = 0.046). In addition, the mediation pathway explained that Sepsis Cluster residents were more likely to

Table 3. REGARDS participant community characteristics stratified by geographic region

	Geographical region					
	Sepsis Belt[a] ($N = 16\,493$)	Non-Belt[b] ($N = 13\,187$)	*p*-value*	Sepsis Cluster[b] ($N = 2958$)	Non-Cluster ($N = 26\,722$)	*p*-value*
Community characteristic						
Household Income[†]	39 048 (8771)	47 245 (12 656)	<0.01	39 400 (9090)	43 055 (11 597)	<0.01
% Completed college[†]	17.1 (7.8)	20.2 (8.9)	<0.01	16.3 (6.4)	18.7 (8.6)	<0.01
% Below poverty line[†]	19.5 (6.6)	13.7 (4.7)	<0.01	19.3 (6.9)	16.7 (6.4)	<0.01
% Urban[†]	42.1 (29.1)	52.5 (28.3)	<0.01	45.3 (27.5)	46.8 (29.4)	<0.01
Medical doctors[€†]	40.2 (163.7)	22.5 (153.2)	<0.01	65.8 (252.7)	28.6 (144.9)	<0.01
% Without insurance coverage[†]	20.4 (3.1)	17.0 (5.4)	<0.01	20.9 (2.8)	18.7 (4.7)	<0.01
Unemployment rate[†]	0.06 (0.02)	0.05 (0.02)	<0.01	0.06 (0.02)	0.05 (0.02)	<0.01

Community determined by participant residence.

[†]Mean (Standard deviation).

[€]Ratio per 100 000 persons.

[a]States with increased sepsis mortality (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina and Tennessee).

[b]Counties with high sepsis mortality (fulfilling two of three criteria for geographic clustering).

*Significance determined using ANOVA or Wilcoxon test.

live below the poverty line ($\beta = 0.39$; SE = 0.02; *p*-value < 0.01) and living below line was associated (mediator-to-outcome OR = 1.11; 95% CI = 1.01–1.21; *p*-value = 0.04) with higher odds of sepsis (Figure 2B and Appendix C, available as Supplementary Data at *IJE* online). No other community characteristics exhibited mediating effects upon the relationship between region and odds of sepsis.

Among REGARDS participants, there were a total of 197 sepsis deaths among participants. Sepsis case fatality was similar between Sepsis Belt and Non-Belt participants (adjusted total effect OR = 1.21; 95% CI = 0.87–1.66). Sepsis Case fatality was similar between Sepsis Cluster and Non-Cluster participants (adjusted total effect OR = 1.48; 95% CI = 0.96–2.30). Community characteristics did not mediate the associations between geographic region and sepsis case fatality (Appendices D and E, available as Supplementary Data at *IJE* online).

In sensitivity analysis, community characteristics did not mediate associations between region with sepsis or sepsis case fatality when sepsis was defined as infection plus a SOFA score ≥ 2 (Appendices F and G, available as Supplementary Data at *IJE* online).

Discussion

The objectives of this study were to determine the mediating effect of community characteristics upon regional variations in sepsis incidence and sepsis case fatality among the REGARDS cohort. In this study, we found that the association between region and sepsis was explained mostly by individual level factors as the regional differences in sepsis attenuated after adjustment for participant characteristics. Among community characteristics, community poverty explained the remaining variation in sepsis incidence, corresponding to the greatest mediating factor for both Sepsis Belt and Sepsis Clusters. We did not observe regional differences in risk of sepsis case fatality, and thus community-level mediating factors were not associated.

The findings of this study suggest that community impoverishment may partly explain the association between geographic region and sepsis risk. Impoverishment may impact health through access to personal health care providers, quality of care, healthcare literacy and availability of effective medical treatments.[18] We found that counties in Sepsis Cluster or Sepsis Belt regions had larger numbers of medical physicians per 100 000 persons, but lower education and income. Our study delineates that persons living in regions with otherwise higher 'access to care' are still at greater odds for sepsis.[5] As explained by Gulliford *et al.* (2002), 'access' to healthcare is a complex concept that involves multiple components and the process in which a person actually 'gains access' depends on financial, organizational, social and cultural barriers that limit the utilization of services.[26]

Our results highlight that residents of the Sepsis Cluster counties live in areas that are commonly affected by poorer health outcomes due to increased poverty.[11,27–36] Areas of greater unemployment and lower SES are subsequently victim to greater health disparities that alternatively perpetuate cultural patterns which further reduce access to healthcare and opportunities for sustainable disease prevention.[37] A possible explanation of regional differences in sepsis risk is that individuals from socio-economically disadvantaged communities are more likely adopt unhealthy diets.[38] As explained by Gutierrez *et al.* (2015), an

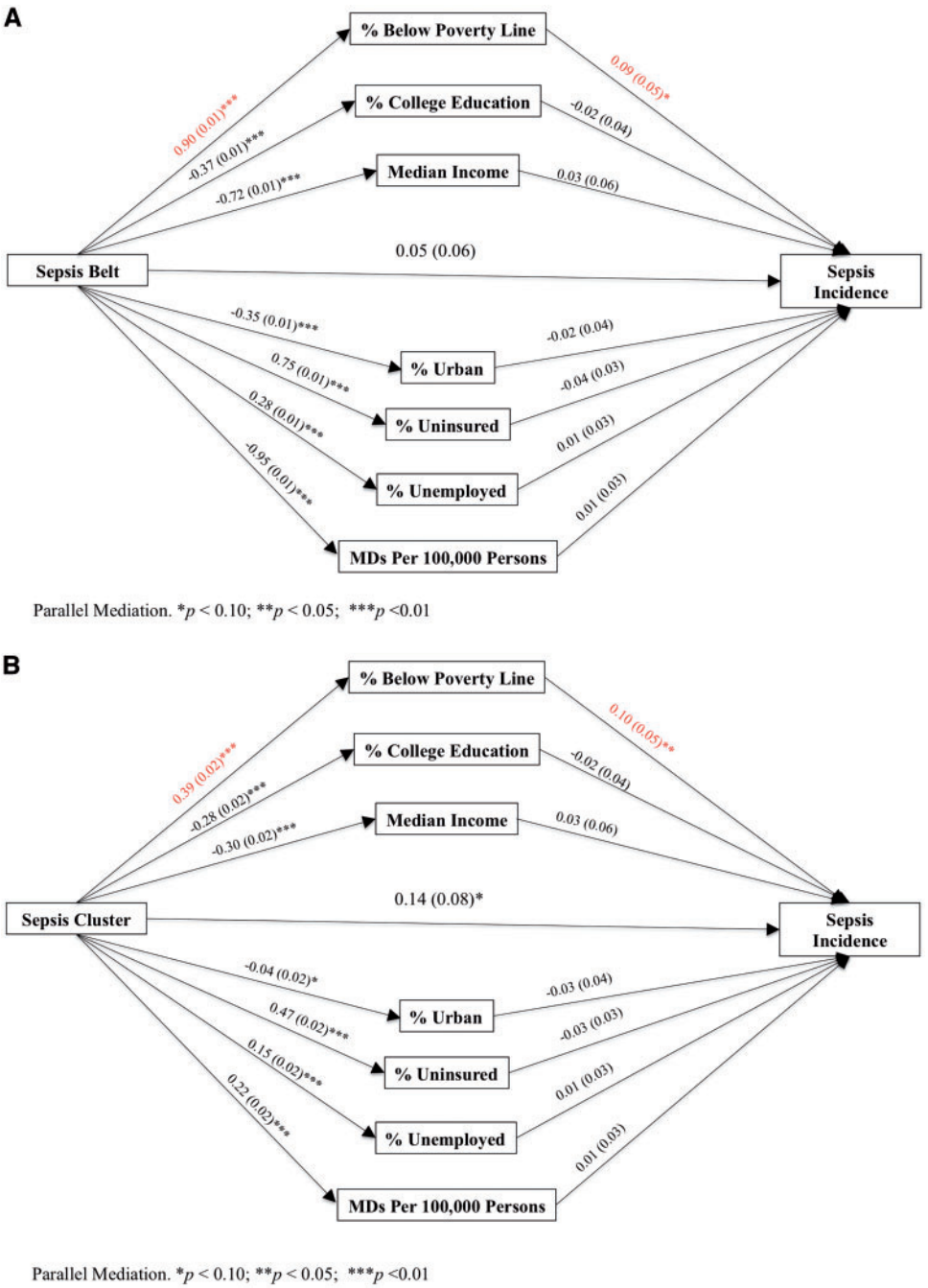

Figure 2. Parallel mediation models for the associations between Sepsis Region, potential community mediators and sepsis incidence. Pathways represent the association between variables. For example, in Figure 2A, the Sepsis Belt has an effect of β = 0.90 on the percentage of population below poverty line, and poverty has an effect of β = 0.09 on sepsis incidence. Pathways are presented as β estimates (Standard Error) from logistic regression.

unhealthy 'Southern' diet consisting of greater consumption of energy intake derived from fats at the expense of protein and carbohydrates was associated with a 40% increased risk of sepsis.[39] Neighbourhood poverty and lower personal income are associated with greater adherence to poorer dietary patterns due to the higher cost of healthy foods and availability of healthy, nutrient rich, affordable food within poorer neighbourhoods (i.e. food deserts).[38] Therefore, it is important that US policy focuses on increasing employment opportunities in effort to remedy the disparities in health outcomes among those living in underserved communities. Interventions specifically focused on reducing sepsis risk may include targeting factors at both the community (e.g. cultural competence and customer service skills of medical professionals) and personal (e.g. health literacy and education) levels.[40]

Investigating the mediating role of community characteristics in the risk of sepsis allows for the possibility of intervening with health policy and implementation of needed healthcare resources. In the USA, socio-economic status remains an important determinant of health and mortality.[7,41,42] Whereas geographic and socio-economic differences in diseases such as cancer and cardiovascular disease have been extensively researched,[11,18,27,28,43–45] very few studies have attempted to uncover the community characteristics that predict sepsis risk. We found that community poverty was a weak mediator of the association between region and odds of sepsis, and similarly other studies have indicated that neighbourhood poverty and income are associated with bloodstream and bacterial infections.[8,42,46] For example, Mendu *et al.* (2012) observed that, among critically ill patients, those living in communities with higher neighbourhood poverty rates were at a 49% increased risk of developing acute bloodstream infections. Possible explanations for the increased risk of bacterial infections among individuals from poorer communities is that individuals from lower SES environments are less likely to vaccinate and may have weakened immune function as a result of their environment.[47–49] Another explanation for increased sepsis incidence among individuals of socio-economically disadvantaged communities is that these patients are likely to present with more complicated infections.[50] Earlier treatment with intravenous fluid resuscitation and antibiotic administration is pivotal for reducing risk of sepsis complications.[51,52] However, patients from historically underserved populations and impoverished environments are less likely to seek and obtain healthcare resources and have a lower level of trust in medical professionals.[53] Whereas timing is key in the treatment of septic patients,[51,52,54] impetus for individuals of lower SES communities receiving timely healthcare may be promoted through an affordable/universal healthcare system.[55]

Limitations

Whereas the REGARDS sepsis cohort provided a unique opportunity to explore the odds of sepsis and case fatality within a longitudinal cohort of community-dwelling adults, our study has several important limitations. REGARDS is a longitudinal study intended to investigate stroke among a racially dichotomous cohort of Black and White participants, and not sepsis outcomes. The current analysis is not a surveillance study and thus we may not have achieved complete ascertainment of all sepsis events. In addition, we did not observe any regional differences in sepsis case fatality, although these estimates were likely underpowered due to small number of sepsis deaths. We did not have information regarding the hospitals that REGARDS sepsis patients admitted to, and therefore were unable to address hospital sepsis quality and antibiotic resistance. A future longitudinal study dedicated to the surveillance and identification of sepsis among a nationally representative cohort could further delineate socio-demographic differences in risk of sepsis. In addition, we used county-level characteristics to approximate state-level community characteristics. Further, the mediation effect of poverty on the association between Sepsis Belt region and sepsis incidence did not reach statistical significance ($p = 0.06$) and should be interpreted accordingly. Nevertheless, the current study provides a foundational observation of the existing regional differences in sepsis incidence.

Conclusion

Using definitions of the 'Sepsis Belt' and 'Sepsis Clusters' previously defined using US mortality data, we found that, in the REGARDS cohort, participants living in the Sepsis Belt and Sepsis Cluster counties were at increased risk of sepsis but not at increased risk of case fatality following sepsis. The most significant mediating community characteristic on the relationship between region and sepsis incidence was the proportion of the population living below the poverty level. Future efforts should focus on sepsis prevention for participants residing in socio-economically disadvantaged communities.

Supplementary Data

Supplementary data are available at *IJE* online.

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