Trajectory of Cognitive Decline After Sepsis

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OBJECTIVES: Cognitive impairment is an important consequence of sepsis. We sought to determine long-term trajectories of cognitive function after sepsis.

DESIGN: Prospective study of the Reasons for Geographic and Racial Differences in Stroke cohort.

SETTING: United States.

PATIENTS: Twenty-one thousand eight-hundred twenty-three participants greater than or equal to 45 years, mean (SD) age 64.3 (9.2) years at first cognitive assessment, 30.9% men, and 27.1% Black.

MEASUREMENTS AND MAIN RESULTS: The main exposure was time-dependent sepsis hospitalization. The primary outcome was global cognitive function (Six-Item Screener range, 0–6). Secondary outcomes were incident cognitive impairment (Six-Item Screener score ≤ 4 [impaired] vs ≥5 [unimpaired]), new learning (Consortium to Establish a Registry for Alzheimer Disease Word List Learning range, 0–30), verbal memory (word list delayed recall range, 0–10), and executive function/semantic fluency (animal fluency test range, ≥ 30). Over a median follow-up of 10 years (interquartile range, 6–12 yr), 840 (3.8%) experienced sepsis (incidence 282 per 1,000 person-years). Sepsis was associated with faster long-term declines in Six-Item Screener (−0.02 points per year faster [95% CI, −0.01 to −0.03]; $p < 0.001$) and faster long-term rates of incident cognitive impairment (odds ratio 1.08 per year [95% CI, 1.02–1.15]; $p = 0.008$) compared with presepsis slopes. Although cognitive function acutely changed after sepsis (0.05 points [95% CI, 0.01–0.09]; $p = 0.01$), the odds of acute cognitive impairment (Six-Item Screener ≤ 4) immediately after sepsis was not significant (odds ratio, 0.81 [95% CI, 0.63–1.06]; $p = 0.12$). Sepsis hospitalization was not associated with acute changes or faster declines in word list learning, word list delayed recall, or animal fluency test.

CONCLUSIONS: Sepsis is associated with accelerated long-term decline in global cognitive function.

KEY WORDS: cognition; epidemiology; infections; sepsis

The crucial need to understand and reduce the long-term consequences of sepsis is an urgent priority for patients, providers, payers, and policymakers. Sepsis is a major public health burden, resulting in over 1.7 million hospitalizations, 860,000 emergency department visits, and 270,000 deaths annually in the United States (1–3). Although ample data describe the acute complications and care of sepsis, only limited attention has been paid to the devastating long-term consequences of sepsis such as worsening cognitive and functional impairment, comorbid burden, quality of life, healthcare utilization, and long-term mortality (4–9). Current international sepsis treatment guidelines do not address—or mention—postsepsis care (10).

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Cognitive impairment is an important, underrecognized, and poorly understood consequence of sepsis (11). Prior studies of postsepsis cognitive decline have important limitations, including the absence of adjudicated sepsis events, varying definitions for cognitive function, the absence of validated tools for measuring cognitive decline, the inability to compare cognitive impairment relative to nonhospitalized individuals, limited follow-up time, and the dearth of data on presepsis cognitive functioning (9, 12–14). Most notably, few studies have been able to characterize the influence of sepsis upon the longitudinal trajectory of cognitive function; that is, how sepsis alters or accelerates expected levels of cognitive decline with age. An enhanced understanding of the long-term cognitive course after sepsis may potentially shed light on the functional areas of the brain injured by sepsis. Filling these knowledge gaps could enhance understanding of the connection between sepsis and brain injury, potentially leading to strategies to improve sepsis care and outcomes.

A population-based cohort offers many strengths that overcome the limitations of prior studies of postsepsis cognitive function. The objective of this study was to characterize the association between sepsis hospitalizations and long-term trajectories of cognitive function in the Reasons for Geographic And Racial Differences in Stroke (REGARDS) cohort.

METHODS

Study Design, Participants, and Measurements

We conducted an observational study using prospectively collected data from the REGARDS cohort. The study was approved by the Institutional Review Boards of the University of Alabama at Birmingham and the University of Texas Health Science Center at Houston with waiver of the requirement for additional informed consent.

One of the nation's largest ongoing longitudinal cohorts, REGARDS is a prospective study of 30,239 community-dwelling Black and White adults 45 years old or older designed to evaluate the predictors of racial and geographic differences in stroke mortality (15). REGARDS encompasses representation from all regions of the continental United States. Participant representation focuses on the Southeastern United States, with 20% of the cohort originating from the coastal plains of North Carolina, South Carolina, and Georgia, and 30% originating from the remainder of North Carolina, South Carolina, and Georgia plus Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Approximately 45% of REGARDS participants are male, 41% are self-reported Black, and 69% are 60 years old or older. Baseline attributes of the cohort, including education and cognitive impairment, are similar to nationally reported figures (16, 17).

Recruitment of participants occurred between January 2003 and October 2007. At study enrollment, participants underwent comprehensive assessments of demographics, health behaviors, health status, and chronic medical conditions as well as collection of blood and urine samples. Since 2003, the study has contacted participants by telephone at 6-month intervals to identify health information and hospitalizations and at annual and biennial intervals to conduct cognitive assessments. Although the focus of REGARDS is upon ascertaining stroke outcomes, the cohort contains community-dwelling adults at stable baseline health, not just those experiencing stroke.

Identification of Sepsis Events

The primary exposure was first hospitalization for community-acquired sepsis during January 1, 2003, through December 31, 2012, defined as emergency department visit and/or hospital admission for a serious infection with the presence of at least two Systemic Inflammatory Response Syndrome (SIRS) criteria. We defined serious infections based upon infection taxonomies developed by Angus et al (1). Two trained abstractors independently reviewed the emergency department, hospital admission, and hospital discharge medical records to confirm the presence of a serious infection on hospital presentation and its relevance as a major reason for hospitalization.

SIRS criteria based included heart rate greater than 90 beats/min; fever (temperature > 38.3°C or < 36.0°C); tachypnea (> 20 breaths/min); or P_{CO_2} less than 32 mm Hg; and leukocytosis or leukopenia (WBCs > 12,000 or < 4,000 cells/mm^3 or > 10% band forms) (18). Although international consensus conferences (Sepsis-3) proposed new definitions for sepsis, we used the SIRS-based sepsis definition in the primary analysis because of its common use in prior sepsis epidemiology studies and its established prior application with the REGARDS cohort (19, 20). Also,

sepsis-SIRS is a precursor for more serious sepsis with organ dysfunction and shock. We used vital signs and laboratory test results during the initial 28 hours of hospitalization. Two independent reviewers evaluated medical record information for each event, resolving discordances with additional physician review as needed.

We did not use discharge diagnoses to detect sepsis events. We also did not measure hospital-acquired sepsis, which comprises only 11.3% of sepsis hospitalizations (21). We limited the analysis to the first sepsis event observed for each individual in the cohort. In a sensitivity analysis, we repeated the analysis using the Sepsis-3 definition for sepsis (infection + Sequential Organ Failure Assessment [SOFA] score ≥ 2) (19).

Cognitive Assessments

Trained research staff assessed cognitive status using standard instruments administered by telephone. Prior studies have validated the assessment of global cognitive function, word list learning (WLL), word list delayed recall (WLD), and verbal fluency reliably and precisely over the telephone in middle-aged and older adults, with scores virtually identical to those obtained in person (22, 23).

The primary outcome was cognitive function as indicated by the Six-Item Screener (SIS) (24). The SIS is a screen for cognitive impairment and consists of questions for three-item recall and three-item temporal orientation (score range, 0–6). The SIS has been validated for detecting cognitive impairment and dementia in community and clinical populations and can detect cognitive dysfunction in older patients experiencing acute medical illness (24, 25). The SIS correlates with the National Institute of Neurologic Diseases and Stroke (NINDS) 5-minute battery as well as with WLL and animal fluency (23, 26). We defined cognitive impairment as SIS less than or equal to 4, which has been validated as a measure of cognitive impairment in community-dwelling Black and White adults (24). The REGARDS study administered the SIS to participants upon study enrollment and annually.

Secondary outcomes included a three-test cognitive battery, which encompassed the Consortium to Establish a Registry for Alzheimer Disease (CERAD) word list learning (WLL), word list delayed recall (WLD), and animal fluency test (AFT) (27). Starting in 2006, REGARDS administered the three-test battery every 2 years. The WLL measures new learning (score range, 0–30). The WLD measures verbal memory (score range, 0–10). The AFT assesses executive function/semantic fluency (complex cognitive processing used in problem solving or complex action sequences, with scores representing number of animals generated in one minute). These cognitive measures are consistent with the Vascular Cognitive Impairment Harmonization Standards and have been validated for Black and White individuals (28–30). An additional secondary outcome was cognitive impairment defined by SIS score (≤ 4 [impaired] vs ≥ 5 [unimpaired]).

Although identification of sepsis events was limited to 2003–2012, to characterize postsepsis cognitive changes, we used cognitive assessments available through 2017.

Covariates

Covariates measured at the time of participant enrollment in REGARDS included sociodemographics, health behaviors, chronic medical conditions, depressive symptoms (CES-D), health status, and select biomarkers (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186).

Statistical Analyses

We followed the analytic strategy of Levine et al (31), who characterized cognitive decline after incident stroke in the REGARDS cohort. We conceptualized that a first sepsis event might result in: 1) an acute decline in cognitive function and 2) faster cognitive decline compared with the presepsis trajectory (**eFig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). We excluded participants with baseline cognitive impairment, who lacked at least one cognitive assessment before the sepsis event, lacked a baseline or follow-up SIS, or had missing values for covariates.

We treated each cognitive assessment (SIS, WLL, WLD, AFT) as a continuous measure because continuous variables may be better able to detect average interindividual change and heterogeneity in interindividual cognitive function changes (32). For each measure of cognition, we fit separate multivariable linear mixed-effects models to measure changes in cognitive performance over time, adjusting for participant factors. The models included random effects

for intercept and slope to accommodate correlation of repeated cognitive measures within participants over time, baseline cognitive score, sociodemographics, health behaviors, chronic medical conditions, and select biomarkers (eTable 1, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). Time was expressed as the years from the date of the first cognitive assessment of each cognitive outcome. All available cognitive observations were used in the analysis. We assumed that the presepsis slopes were the same for sepsis as nonsepsis persons. We inspected residual plots to examine the assumptions of linearity and normality of the linear mixed-effects models.

We first estimated the acute change in cognition (change in intercept) associated with the first sepsis event; that is, we assessed the change in cognition indicated by the last measure before and the first measure after the sepsis hospitalization (Model A). We fit SIS as a continuous measure and included a time-varying first sepsis variable (with value changing from 0 to 1 on the date of the first sepsis) to estimate the acute change in cognitive function at the time of the sepsis event. We next determined the change in cognitive trajectory (slope) after the first sepsis event (Model B), adding a (years since sepsis) term to Model A in order to estimate the rate of change in cognitive function (slope) after first sepsis. We adjusted these models for sociodemographics, health behaviors, chronic medical conditions, biomarkers, and baseline depressive symptoms; we excluded variables that did not reach statistical significance (defined as $p < 0.05$). We performed a similar analysis using generalized linear mixed-effects models to estimate the odds of incident cognitive impairment (SIS ≤ 4) after sepsis. Although the linear mixed-effect model is an approximation and may not work well at the tails of the distribution, we verified linearity and normality of residual errors assumptions of the model by inspecting residual plots.

We constructed graphs illustrating participant-specific predicted cognitive values for an exemplar participant (with/without first sepsis at year three, age = 70 yr, female, White race, high school graduate, lowest income quintile, stroke belt region, no tobacco or alcohol use, diabetic, obese, no peripheral artery disease, no history of stroke, no history of myocardial infarction, depressive symptoms four-item CES-D = 0.9, normal CRP, normal ACR, normal eGFR, and normal Cystatin-C).

We conducted a series of sensitivity analyses including the use of multiple imputation for missing baseline covariates, limiting to participants with at least two cognitive evaluations after each sepsis event, excluding individuals experiencing incident stroke before the first sepsis event (defined by the parent study using structured adjudication of hospital records by physician reviewers and published guidelines), censoring cognitive measures after repeat sepsis events, and applying the Sepsis-3 definition of sepsis (infection + SOFA score ≥ 2) (19). All analyses were performed using Stata Version 15.0 (StataCorp, College Station, TX).

RESULTS

Of 30,239 participants, we included 21,823 in the analysis (**Fig. 1**). Over a median follow-up period of 10 years (interquartile range, 6–12 yr), 840 (3.9%) experienced a sepsis hospitalization (incidence, 282 sepsis hospitalizations per 1,000 person-years [95% CI, 294–302]), most due to lung infections (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). Sepsis participants were older, more likely to be White, reported less education and lower income, were more likely to exhibit past or current tobacco use, and were more likely to have chronic medical conditions and abnormal biomarkers (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). Repeat sepsis hospitalizations occurred in 129 participants (15.4%).

First SIS scores were similar between sepsis (mean 5.8 [SD 0.4]) and sepsis-free (5.8 [0.4]) participants (**eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). First assessments of WLL, WLD, and AFT were slightly lower in participants who subsequently developed sepsis than sepsis-free individuals (**eTables** 3 and **5**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). Median time from the first SIS to first sepsis hospitalization was 3.5 years (IQR, 1.6–5.3 yr). The median time from the last preceding SIS to first sepsis hospitalization was 0.6 years (IQR, 0.4–0.9 yr). Median time from first sepsis hospitalization to the next SIS was 0.5 years (IQR, 0.3–0.8 yr). Median time from first sepsis hospitalization to last SIS was 5.3 years (IQR, 2.7–7.6 yr).

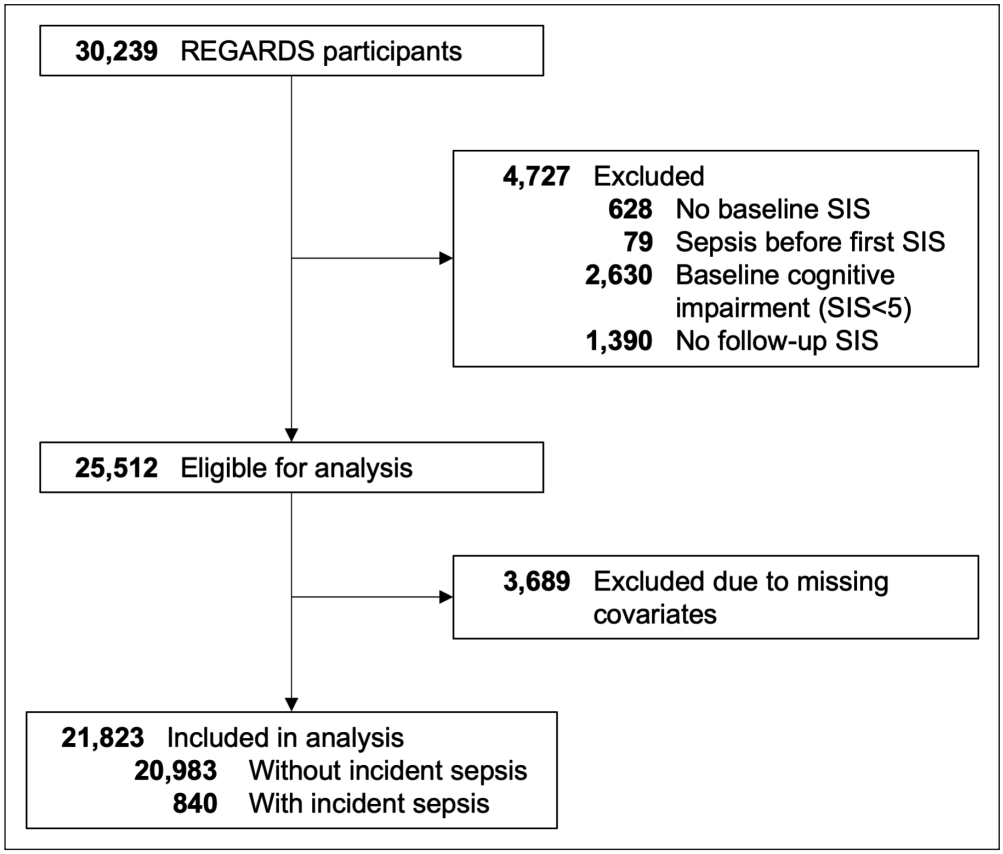

Figure 1. Overview of study cohort. *Missing data for covariates included cystatin-C ($n = 1,688$), C-reactive protein ($n = 1,574$), albumin-to-creatinine ratio ($n = 1,105$), estimated glomerular filtration rate ($n = 1,022$), history of diabetes ($n = 913$), history of atrial fibrillation ($n = 557$), alcohol use ($n = 459$), history of myocardial infarction ($n = 462$), four-item depression scale ($n = 193$), smoking ($n = 98$), history of stroke ($n = 79$), history of hypertension ($n = 63$), history of peripheral artery disease ($n = 39$), obesity ($n = 37$), and education ($n = 15$). Categories for missing data on covariates are not mutually exclusive. REGARDS = Reasons for Geographic And Racial Differences in Stroke, SIS = Six-Item Screener.

Changes in SIS After Sepsis

In the overall cohort, there was a decline in SIS over time before sepsis (adjusted decrease in SIS, −0.003 points per year [95% CI, 0.002–0.005]; $p < 0.001$) (Model A, **Table 1** and **Fig. 2**). Compared with presepsis slopes, there was an increase in SIS acutely after sepsis (adjusted increase in SIS, 0.05 points [95% CI, 0.01–0.09]; $p = 0.01$). Participants with sepsis, compared with those without sepsis, demonstrated faster declines in SIS over the long-term after sepsis controlling for presepsis slopes (adjusted SIS decline −0.02 points per year faster than presepsis slopes [95% CI, −0.03 to −0.01]; $p < 0.001$) (Model B, Table 1).

We also assessed incident cognitive impairment using SIS less than or equal to 4 as a binary outcome. Sepsis was not associated with incident cognitive impairment acutely after the event (adjusted odds ratio, 0.81 [95% CI, 0.63–1.06]; $p = 0.12$). However, sepsis was associated with faster rates of incident cognitive impairment compared with the presepsis rate (adjusted odds ratio, 1.08 per year [95% CI, 1.02–1.15]; $p = 0.008$) (**Table 2**).

Changes in WLL, WLD, and AFT After Sepsis

In the overall cohort, WLL and WLD learning exhibited baseline increases over time, whereas AFT decreased over time (**Table 3** and Fig. 2). In contrast to SIS, acute changes in the three-test battery were not statistically significant: WLL −0.03 points (95% CI, −0.50 to 0.44; $p = 0.89$); WLD −0.11 (−0.25 to 0.03; $p = 0.09$); AFT −0.09 (−0.56 to 0.39; $p = 0.73$). Long-term slopes of the three-test battery after sepsis were not significantly different compared with presepsis slopes (adjusted slopes after sepsis: WLL −0.09 points per year [95% CI, −0.20 to 0.03], $p = 0.13$; WLD −0.02 [−0.03 to 0.07], $p = 0.35$; AFT −0.01 [−0.13 to 0.11], $p = 0.84$).

Sensitivity Analyses

When we applied multiple imputation for the 3,689 participants with missing covariates, results were similar (**eTable 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). We observed similar results when restricting to subjects with at least two postsepsis cognitive assessments before and after the sepsis event (**eTables 7** and **8**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186), excluding individuals who experienced incident stroke before sepsis (**eTable 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186) and censoring

TABLE 1.
Association of First Sepsis Events With Changes in Six-Item Screener

	SIS			
	Model A		Model B	
No. of First Sepsis Events/No. of Participants	840/21,823 (3.8%)		840/21,823 (3.8%)	
Variables	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*
Baseline SIS trajectory (slope) without sepsis, per year (full cohort)	−0.004 (−0.005 to −0.002)	< 0.001	−0.003 (−0.005 to −0.002)	< 0.001
Acute SIS change after first sepsis event	0.002 (−0.03 to 0.04)	0.90	0.05 (0.01–0.09)	0.01
Change in postsepsis SIS trajectory (slope), per year	Not applicable		−0.02 (−0.03 to −0.01)	< 0.001

SIS = Six-Item Screener.

The SIS ranges from 0 to 6, with higher scores indicating better performance. The SIS was analyzed as a continuous measure. The analysis includes 840 first sepsis events among 21,823 participants. Linear mixed-effects models included a random intercept and a random effect for slope, follow-up time, age, gender, race education, income, region, tobacco use, alcohol use, diabetes, peripheral artery disease, stroke, history of myocardial infarction, obesity, depressive symptoms, high sensitivity C-reactive protein, albumin-to-creatinine ratio, estimated glomerular filtration rate, and cystatin-C. Model A included a time-varying first sepsis variable to estimate the acute cognitive change after first sepsis. Model B added (years since sepsis) to Model A in order to estimate the change in cognitive trajectory (slope) after the first sepsis event. Interpretative example for the SIS score as a continuous measure: At baseline, an average participant's SIS declined −0.003 SIS points per year (95% CI, −0.005 to −0.002; $p < 0.001$). An average sepsis survivor's SIS score acutely increased 0.05 points after a sepsis event (95% CI, 0.01–0.09; $p = 0.01$). After the first sepsis event, the average sepsis survivor's SIS score declined −0.02 points per year faster (95% CI, −0.03 to −0.01; $p < 0.001$) compared with the baseline SIS trajectory.

cognitive measures after a repeat sepsis hospitalization (**eTable 10**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186).

When we used the Sepsis-3 definition for sepsis hospitalization, the postsepsis trajectory of cognitive decline was twice that observed with the Sepsis-SIRS definition for sepsis hospitalization (adjusted SIS decline after sepsis, –0.04 points per year faster [95% CI, –0.05 to –0.02]; $p < 0.001$) (**eTable 11**, Supplemental Digital Content 1, http://links.lww.com/CCM/G186). The yearly odds of cognitive impairment (SIS ≤ 4) was also higher with Sepsis-3 than Sepsis-SIRS (odds ratio, 1.11 [95% CI, 1.03–1.20]; $p = 0.005$). With the use of Sepsis-3 definition, the downward trajectory of WLL was statistically significant (adjusted WLL decline after sepsis, –0.18 points per year faster [95% CI, –0.34 to –0.02]; $p = 0.02$). Trajectories of WLD and AFT after sepsis were not significantly different than presepsis slopes.

DISCUSSION

Our study provides new perspectives on the trajectories of cognitive decline after community-acquired sepsis. As indicated by the SIS, first sepsis events were associated with an almost seven-fold accelerated rate of cognitive decline compared with presepsis trajectories. Compared with the presepsis rate, the odds of incident cognitive impairment (SIS ≤ 4) also increased by 8% for each year following the sepsis event. Cognitive changes greater than 0.5 SDs are considered clinically important, have been correlated with clinically meaningful declines in global cognition, and, for the CERAD battery, have been correlated with other measures of cognitive decline in older adults with dementia (33–35). In this series, given the baseline SIS SD of 0.4, the observed accelerated SIS decline trajectory (–0.023 SIS points per year) over a 10-year span would result in cognitive changes exceeding the 0.5 SD threshold. With use of the higher acuity Sepsis-3 definition, we observed an additional two-fold acceleration of cognitive decline (19). Our observations suggest that monitoring of long-term cognitive function may be important after a sepsis hospitalization and that the total number of persons with postsepsis cognitive decline may multiply in the years following a sepsis event.

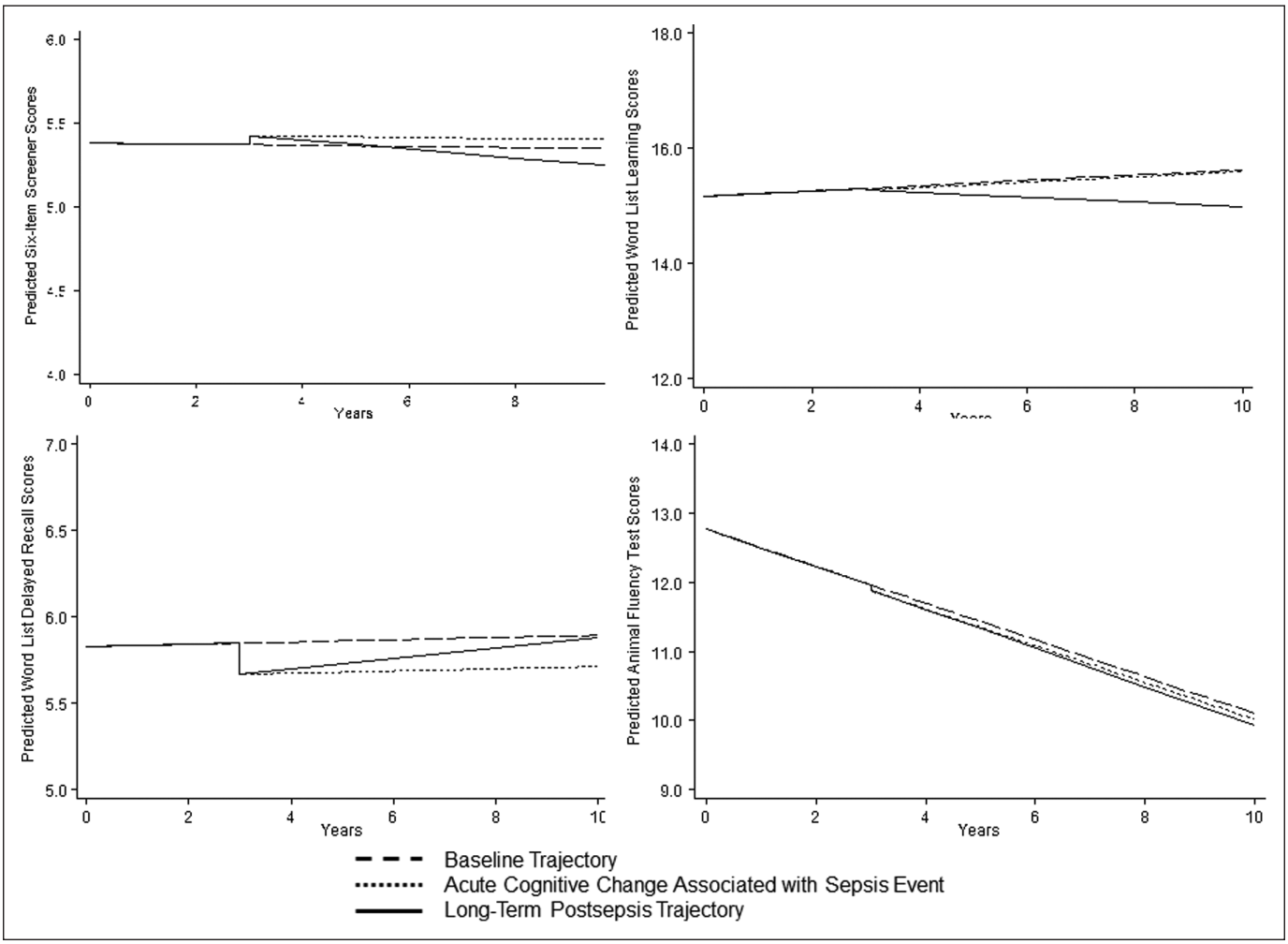

Figure 2. Predicted mean changes in cognitive function test scores before and after sepsis. Graphs reflect participant-specific predicted cognitive trajectories for exemplar participant with/without first sepsis at year 3: age = 70 yr, female, White race, high school graduate, lowest income quintile, stroke belt region, no tobacco or alcohol use, diabetic, obese, no peripheral artery disease, no history of stroke, no history of myocardial infarction, depressive symptoms four-item Center for Epidemiological Studies-Depression scale = 0.9, normal high sensitivity C-reactive protein, normal albumin-to-creatinine ratio, normal estimated glomerular filtration rate, and normal Cystatin-C.

Prior studies of cognitive impairment after sepsis have important limitations, including focus on ICU survivors, limited information on presepsis functioning, limited short-term follow-up, and the absence of comparisons with sepsis-free individuals (9, 13, 14, 36). Our study overcomes these limitations with the use of a population-based cohort with systematically collected baseline health information, the ability to compare with sepsis-free participants, longitudinal follow-up of up to 15 years, and inclusion of a majority of individuals not admitted to the ICU. Among similar studies using population-based cohorts, Iwashyna et al (7) found that sepsis was associated with a tripling of the odds of subsequent cognitive impairment in the Health and Retirement Study, and Shah et al (37) found that pneumonia-associated sepsis doubled the risk of subsequent dementia in the cardiovascular health study. Our current study extends upon these prior works, demonstrating that a sepsis event of any severity (including lower acuity sepsis) is associated with a faster rate of decline in cognitive function and incident cognitive impairment.

Although numerous studies have linked critical illness with subsequent cognitive impairment, these series were relatively limited in size and represented a range of different medical conditions besides sepsis (38–41). REGARDS did not collect data on all hospitalizations, and therefore, we could not differentiate if the observed cognitive decline is specifically due to sepsis or hospitalization in general. However, we would expect distinct patterns of brain injury and cognitive impairment to result from different pathophysiologic processes. For example, stroke is often associated with focal vascular lesions, whereas sepsis is

TABLE 2.
Association of First Sepsis Events With Incident Cognitive Impairment

	Incident Cognitive Impairment (Six-Item Screener ≤ 4)			
	Model A		Model B	
No. of First Sepsis Events/No. of Participants	840/21,823 (3.8%)		840/21,823 (3.8%)	
Variables	OR (95% CI)	*p*	OR (95% CI)	*p*
Baseline cognitive impairment trajectory—odds of cognitive impairment without sepsis, per year (full cohort)	0.95 (0.94–0.97)	< 0.001	0.95 (0.94–0.97)	< 0.001
Odds of acute cognitive impairment after sepsis event	1.03 (0.86–1.24)	0.75	0.81 (0.63– 1.06)	0.12
Postsepsis cognitive impairment trajectory—odds of cognitive impairment per year after sepsis event	Not applicable		1.08 (1.02–1.15)	0.008

OR = odds ratio.

The Six-Item Screener (SIS) ranges from 0 to 6, with higher scores indicating better performance. Cognitive impairment defined as SIS ≤ 4. The analysis includes 840 first sepsis events among 21,823 participants. Linear mixed-effects models included a random intercept and a random effect for slope, follow-up time, age, gender, race, education, income, region, tobacco use, alcohol use, diabetes, peripheral artery disease, stroke, history of myocardial infarction, obesity, depressive symptoms, high sensitivity C-reactive protein, albumin-to-creatinine ratio, estimate glomerular filtration rate, and cystatin-C. Generalized linear mixed-effects models for a binary outcome were used for estimating the odds of incident cognitive impairment. Model A included a time-varying first sepsis variable to estimate the acute cognitive change after the first sepsis event. Model B added (years since sepsis) to Model A in order to estimate the change in cognitive trajectory (slope) after the first sepsis event. "Interpretative example for incident cognitive impairment as a binary measure (SIS ≤ 4 [impaired] vs ≥ 5 [unimpaired])": The OR is the odds of developing cognitive impairment per year. Prior to the first sepsis event, the odds of developing cognitive impairment for all participants was 5% lower for each year (OR, 0.95; 95% CI, 0.94–0.97; $p < 0.001$). Sepsis events were not associated with acute cognitive impairment (OR, 0.81 [95% CI, 0.63–1.03]; $p = 0.12$). However, after the first sepsis event, the odds of cognitive impairment was 1.08 times greater with each successive year (95% CI, 1.02–1.15; $p = 0.008$).

likely associated with cerebral hypoperfusion, diffuse vascular injury, endothelial dysfunction, and inflammation (11, 42). In a study of cognitive decline after stroke in the same REGARDS cohort, Levine et al (31) observed an decrease in SIS but not a significant increase in risk of cognitive impairment acutely after stroke followed by accelerated faster decline in SIS and rate of incident cognitive impairment, in addition to acute decreases in WLL and WLD and faster declines in AFT. Our contrasting findings are not surprising given the differing disease processes.

An unexpected finding was the absence of acute decrease in cognition after a sepsis event; in fact, SIS seemed to increase slightly after a sepsis hospitalization before exhibiting an accelerated downwards trajectory. SIS assessments in REGARDS occurred at 1-year intervals, which may not have been frequent enough to capture cognitive changes in the immediate postsepsis period. Intensive rehabilitation after the sepsis event may have mitigated acute cognitive decreases. We note that the subsequent change in SIS trajectory was considerably larger, perhaps signaling that long-term changes are more prominent than short-term changes as a result of sepsis. We also found no associations between sepsis and changes in WLL, WLD, and AFT; the smaller number of participants and fewer cognitive observations might have obscured our ability to detect cognitive changes in these domains.

Although characterizing long-term cognitive patterns, our results do not indicate the mechanisms triggering accelerated cognitive decline in sepsis survivors nor potential interventions to mitigate cognitive damage. Mechanisms proposed to explain sepsis-associated brain injury include hypoperfusion, inflammation, endothelial activation, damage of the blood-brain barrier, microglial activation, reduced clearance of beta-amyloid, hippocampal atrophy, and thalamocortical dysfunction (11). Existing studies hint at potential targets for improving brain recovery after sepsis, including optimizing acute care, cognitive and physical rehabilitation, intensive ambulatory care, increased screening for acute and chronic diseases, management of medications,

TABLE 3.
Adjusted Associations of First Sepsis Events With Changes in Word List Learning, Word List Delayed Recall, and Animal Fluency Test Over Time

	Word List Learning				Word List Delayed Recall				Animal Fluency Test			
	Model A		Model B		Model A		Model B		Model A		Model B	
No. of First Sepsis Events/No. of Participants	368/14,423 (2.6%)		368/14,423 (2.6%)		361/14,204 (2.5%)		361/14,204 (2.5%)		364/15,615 (2.3%)		364/15,615 (2.3%)	
Variables	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*
Baseline cognitive trajectory (slope) without sepsis, per year (full cohort)	0.05 (0.03–0.06)	< 0.001	0.05 (0.03–0.06)	< 0.001	0.007 (0–0.01)	0.05	0.006 (0–0.1)	0.06	−0.27 (−0.28 to −0.25)	< 0.001	−0.27 (−0.28 to −0.25)	< 0.001
Acute cognitive change after sepsis event	−0.28 (−0.62 to 0.05)	0.10	−0.03 (−0.50 to 0.44)	0.89	−0.11 (−0.25 to 0.03)	0.13	−0.18 (−0.39 to 0.02)	0.09	−0.12 (−0.46 to 0.22)	0.49	−0.09 (−0.56 to 0.39)	0.73
Postsepsis change in cognitive trajectory (slope), per year	NA		−0.09 (−0.20 to 0.03)	0.13	NA		0.02 (−0.03 to, 0.07)	0.35	NA		−0.01 (−0.13 to 0.11)	0.84

NA = not applicable.

Model A included a time-varying first sepsis variable to estimate acute changes in word list learning (WLL), word list delayed recall (WLD), and animal fluency test (AFT) after first sepsis. Model B added a years since sepsis term to Model A in order to estimate the changes per year in WLL, WLD, and AFT after the sepsis hospitalization and cognitive trajectory (slope) after the first sepsis event. Models adjusted for age, gender, education, income, region, tobacco use, alcohol use, diabetes, peripheral artery disease, stroke, history of myocardial infarction, obesity, depressive symptoms, high sensitivity C-reactive protein, albumin-to-creatinine ratio, estimated glomerular filtration rate, and Cystatin-C.

and increased social support (43). Clinical trials of regimented outpatient care and early physical rehabilitation, including cognitive rehabilitation, have been proposed to foster sepsis recovery (44, 45). Research on postsepsis cognitive decline is needed to better understand its biological basis, develop effective treatments to reduce cognitive impairment in sepsis survivors, and identify high-risk groups to target with interventions.

Limitations of the study include the absence of data on the severity of comorbid conditions and the inclusion of only non-Hispanic Black and White participants greater than or equal to 45 years. Because REGARDS was not designed as a sepsis surveillance study, we may not have been able to detect all sepsis events. Although stroke may be a risk factor for infection and sepsis, a sensitivity analysis excluding patients with incident stroke before sepsis showed similar results (46). The structure of REGARDS did not allow identification of all other hospitalizations, and therefore, we could not distinguish if the observed cognitive declines were due to sepsis or hospitalization in general. We did not adjust for time-varying depressive symptom scores

because depressive symptoms are often comorbid with cognitive decline and therefore on the causal pathway. Although use of the SIRS criteria for sepsis could misclassify patients without sepsis as having sepsis and bias results toward the null, sensitivity analyses further restricting the case definition of sepsis confirmed the robustness of our findings. We did not measure hospital-acquired sepsis. Misclassifying patients with hospital-acquired sepsis as sepsis-free patients would reduce our ability to detect differences in cognitive trajectories by sepsis status.

CONCLUSION

Sepsis is associated with accelerated long-term decline in cognitive function.

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