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Long-term mortality after community-acquired sepsis: a longitudinal population-based cohort study

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ABSTRACT

Objective: Prior studies have concentrated on the acute short-term outcomes of sepsis, with little focus on its long-term consequences. The objective of this study was to characterise long-term mortality following a sepsis event.

Design: Population-based data from the 30 239 community-dwelling individuals in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort.

Setting: USA.

Participants: Community-dwelling adults ≥45 years of age. Sepsis was defined as hospitalisation or emergency department treatment for a serious infection with the presence of ≥2 systemic inflammatory response syndrome criteria.

Outcomes: 6-year all-cause mortality. The analysis utilised a time-varying Cox model adjusted for participant's age, demographic factors, health behaviours and chronic medical conditions.

Results: The participants were observed for a median of 6.1 years (IQR 4.5–7.1). During this period, 975 individuals experienced a sepsis event. Sepsis hospital mortality was 8.9%. One-year, 2-year and 5-year all-cause mortality among individuals with sepsis were 23%, 28.8% and 43.8%, respectively, compared with death rates of 1%, 2.6% and 8.3% among those who never developed sepsis. On multivariable analysis, the association of sepsis with increased all-cause mortality persisted for up to 5 years, after adjustment for confounders; year 0.00–1.00, adjusted HR (aHR) 13.07 (95% CI 10.63 to 16.06); year 1.01–2.00 aHR 2.64 (1.85 to 3.77); year 2.01–3.00 aHR 2.18 (1.43 to 3.33); year 3.01–4.00 aHR 1.97 (1.19 to 3.25); year 4.01–5.00 aHR 2.08 (1.14 to 3.79); year 5.01+ aHR 1.41 (0.67 to 2.98).

Conclusions: Individuals with sepsis exhibited increased rates of death for up to 5 years after the illness event, even after accounting for comorbidities. Sepsis is independently associated with increased risk of mortality well after hospital treatment.

Strengths and limitations of this study

- Study uses data from the 30 329 participants in the REasons for Geographic And Racial Differences in Stroke REGARDS cohort.
- Participants were followed for over 6 years.
- Study characterised long-term survival after a sepsis episode.
- Robust analytic approach accounted for confounding effect for a wide range of participant characteristics.

INTRODUCTION

Sepsis, the syndrome of microbial infection complicated by systemic inflammation, is associated with an estimated 750 000 hospital admissions, 570 000 emergency department visits, 200 000 deaths and US$16.7 billion in medical expenditures annually in the USA.[1–3] While prior studies describe the acute care and course of individuals developing sepsis, relatively limited data characterise the long-term consequences of a sepsis event.[4] This gap in knowledge is important as the total public health impact of a disease encompasses not only the course of acute hospital care but also its downstream sequelae. Furthermore, compared with unaffected persons, an individual suffering from a disease—even after recovery from the acute illness—may also experience a higher risk of long-term death.

Prior studies describing mortality after sepsis have important limitations, including the lack of data describing health prior to the sepsis event, the use of hospital administrative data or data from single institutions or the focus on patients in intensive care units.[4–8] Few studies have characterised the excess risk of long-term death attributable to a sepsis event or identified the independent predictors of early death after sepsis.

The REasons for Geographic and Racial Differences in Stroke (REGARDS) study is one of the largest population-based longitudinal cohorts of community-dwelling adults in the USA. In this study, we sought to characterise long-term mortality after the hospital treatment for sepsis in the REGARDS cohort.

MATERIALS AND METHODS

Study design

This study utilised data from REGARDS, a national population-based longitudinal cohort.

Selection of participants

Prior studies have described twofold increased stroke mortality in the Southeastern US (the 'stroke belt') and threefold increased stroke mortality along the coastal plains of North Carolina, South Carolina and Georgia (the 'stroke buckle').[9] In addition, other studies highlight the increased stroke mortality among African-Americans. Being one of the largest ongoing national cohorts of community-dwelling individuals in the USA, REGARDS was designed to identify the reasons for the geographical and racial disparities.[9]

REGARDS includes 30 239 community-dwelling adults ≥45 years from all regions of the continental US. Participant representation oversampled the Southeastern US, with 21% of the cohort originating from the coastal plains of North Carolina, South Carolina and Georgia (the 'stroke buckle'), and 35% originating from the remainder of North Carolina, South Carolina and Georgia plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas (the 'stroke belt'). The cohort is 42% African-American with 45% men and 69% of individuals are >60 years. The cohort does not include Hispanics where stroke mortality disparities are small to non-existent. The REGARDS cohort encompasses healthy community-dwelling adults—not just individuals with a history of stroke.

REGARDS enrolled participants during 2003–2007. REGARDS obtained baseline data for each participant using the phone interview and in-person evaluations, including medical history, functional status, health behaviours, physical characteristics (height and weight), physiological measures (blood pressure, pulse and ECG) and an inventory of medications. Each participant provided blood and urine specimens. Self-administered questionnaires evaluated diet, family history of diseases, psychosocial factors and prior residences. The study contacted participants at 6-month intervals by telephone, identifying the date, location and attributed reason for all emergency department visits and hospitalisations during the follow-up period. The study then retrieved medical records for specific health events. If the participant died, the study team reviewed death certificates and medical records and interviewed proxies to ascertain the circumstances of the participant's death.

Identification of sepsis events

Using the taxonomy of serious infections by Angus *et al*,[1] we identified all hospitalisations (emergency department visits and/or hospital admission) attributed by participants to a serious infection. Two trained abstractors independently reviewed all relevant medical records to identify clinical and laboratory information, confirm the presence of a serious infection on initial hospital presentation and to verify the relevance of the serious infection as a major reason for hospitalisation. Initial review of 1349 hospital records indicated excellent inter-rater agreement for the presence of a serious infection (κ=0.92) and the presence of sepsis (κ=0.90) on hospital presentation.

Sepsis consisted of presentation to the hospital with an infection plus two or more systemic inflammatory response syndrome (SIRS) criteria, including (1) heart rate >90 bpm, (2) fever (temperature >38.3°C or <36°C), (3) tachypnoea (>20 breaths/min) or partial pressure of carbon dioxide <32 mm Hg and (4) leukocytosis (white cell count >12 000 or <4000 cells/mm^3 or >10% band forms).[10] We defined SIRS using any asynchronous combination of the worst vital signs and laboratory test results for the initial 28 h of hospitalisation. We chose a 28 h time frame to account for emergency department and up to one full day of inpatient treatment. Because our study focused on 'community-acquired' sepsis rather than 'hospital-acquired' sepsis, we did not utilise vital signs or laboratory findings from later points during hospitalisation. The study follow-up period was from 5 February 2003 to 30 July 2012.

Outcomes

The primary outcome was all-cause mortality. The REGARDS study ascertained all-cause mortality through active follow-up with participants or proxies, plus searches of the Social Security Administration's Master Death File and the National Death Index. Observations were censored at the date of death or last follow-up. Available for a portion (74.5%) of deaths, cause of death was determined by dual-physician review and adjudication of death records, next-of-kin or proxy reports and hospitalisation records.

Covariates

Demographic characteristics included age, sex, race, geographical region and self-reported annual household income and education (years of school). As conducted for the parent REGARDS cohort, geographical region consisted of participant's residence in the stroke 'buckle,' stroke 'belt' and elsewhere.[9] Health behaviours included smoking status and alcohol use. Alcohol use categories included none, moderate (1 drink per day for women or 2 drinks per day for men) and heavy (>1 drink per day for women and >2 drinks per day for men).[11] To characterise baseline health status, we used quintiles of the physical composite score and mental composite score of the Short Form-12 (SF-12) health survey.

Chronic medical conditions included atrial fibrillation, cancer history, chronic lung disease, chronic kidney disease, coronary artery disease, deep vein thrombosis, diabetes, dyslipidaemia, hypertension, myocardial infarction, obesity, peripheral artery disease and stroke. We identified atrial fibrillation based on participants' self-report or baseline ECG evidence. Chronic kidney disease included individuals with an estimated

glomerular filtration rate <60 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration CKD-EPIequation.[12] Coronary artery disease included a history of myocardial infarction or coronary intervention. Diabetes included a fasting glucose ≥126 mg/L (or a glucose ≥200 mg/L for those not fasting) or the use of insulin or oral hypoglycaemic agents. Dyslipidaemia included individuals with self-reported high cholesterol or the use of lipid-lowering medications. Hypertension consisted of systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or the self-reported use of antihypertensive agents. Myocardial infarction included individuals with a self-reported history of myocardial infarction or baseline ECG evidence of myocardial infarction.

Obesity included those with a waist circumference >102 cm for men or >88 cm for women, or body mass index ≥30 mg/cm^2.[13] Participants self-reported the history of stroke (including transient ischaemic attacks) or deep vein thrombosis. Peripheral artery disease included a self-reported history of lower extremity arterial bypass or leg amputation. Because REGARDS did not collect information on pulmonary conditions such as asthma and chronic obstructive pulmonary disease, we defined participants' use of pulmonary medications as a surrogate for chronic lung disease, including β agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, ipratropium, cromolyn, aminophylline and theophylline.

For sepsis hospitalisations, we also identified organ dysfunctions using the Sequential Organ Failure Assessment (SOFA) based on the worst laboratory and physiological findings during the first 28 h of hospitalisation for respiratory, renal, hepatic, cardiovascular, haematological and neurological systems.[14]

Data analysis

We sought to compare the adjusted risk of all-cause mortality between sepsis and non-sepsis individuals as a function of follow-up time. Follow-up time consisted of (1) years after first sepsis event for individuals with sepsis, and (2) years after study enrolment for non-sepsis individuals. We assumed that non-sepsis participants were representative of the general population, exhibited relative constant risk and entered the study relative to no particular health event. Therefore, the start of the follow-up period for non-sepsis individuals could be defined relative to any arbitrary event.

Because of the non-proportional nature of the relative hazards of death, we fit a time-varying Cox regression model in a piecewise manner, calculating the hazards of death in 1-year intervals.[15] To account for differing observation start times, we adjusted the model for age at the start of the follow-up period (age decile at sepsis event for individuals with sepsis, and age decile at REGARDS enrolment for non-sepsis participants). We adjusted the hazard estimates for participants' demographic characteristics, baseline function, health behaviours and chronic medical conditions.

To account for potential clustering of deaths within each stroke belt region (stroke belt, stroke buckle and non-belt), we repeated the analysis (1) using a robust variance estimator, and (2) modelling stroke belt region as a shared frailty, which are two common approaches to analysing clustered data in time-to-event analysis. Owing to the time lag in observations and medical record retrieval, we could not review medical records for a portion of participants with reported hospitalisations for a serious infection over the observation period. We therefore repeated the analysis excluding these individuals from the non-sepsis group. We also repeated the analysis stratifying by uncomplicated sepsis (infection +SIRS criteria only) versus severe sepsis (sepsis+organ dysfunction).

To identify participant characteristics independently associated with early death after sepsis, among individuals with sepsis, only we fit a Cox model with age at sepsis, sex, race, tobacco and alcohol use, chronic medical conditions, infection type, admission to intensive care unit and SOFA score on hospital presentation in the regression model.

We conducted all analyses using Stata V.12.1 (Stata, Inc, College Station, Texas, USA).

RESULTS

Valid follow-up data were available for 29 664 REGARDS participants, including 970 sepsis and 28 694 non-sepsis individuals. Median follow-up time was 6.1 years (IQR 4.5–7.1). Sepsis incidence was 5.8/1000 person-years (95% CI 5.4 to 6.2). Median time to the first sepsis event was 1.9 years (IQR 3.5–5.0). The most common infection types associated with incident sepsis were pneumonia,

Table 1 Infection types associated with first hospitalisations for sepsis

Infection type	Number of first sepsis hospitalisations N (%)
Pneumonia	412 (42.5)
Kidney and urinary tract infections	155 (16.0)
Abdominal	137 (14.1)
Bronchitis, influenza and other lung infections	88 (9.1)
Skin and soft tissue	74 (7.6)
Sepsis	58 (6.0)
Fever of unknown origin	15 (1.6)
Catheter (intravenous/central/dialysis)	5 (0.5)
Surgical wound	7 (0.7)
Meningitis	3 (0.3)
Unknown/other	16 (16.5)

Total of 970 first-sepsis events.

Table 2 Baseline patient characteristics

Characteristics	Sepsis (n=970) N (%)	Non-sepsis (n=28 694) N (%)	p Value*
Demographics			
Age decile			
<50	14 (1.4)	1460 (5.1)	<0.001
50–59	171 (17.6)	7581 (26.4)	
60–69	343 (35.4)	10 835 (37.8)	
70–79	311 (32.1)	6839 (23.8)	
≥80	131 (13.5)	1979 (6.9)	
Gender			
Male	508 (52.4)	12 812 (44.7)	<0.001
Female	462 (47.6)	15 882 (55.4)	
Race			
White	662 (68.3)	16 802 (58.6)	<0.001
Black	308 (31.8)	11 892 (41.4)	
Education			
Less than high school	153 (15.8)	3547 (12.4)	<0.001
High school graduate	275 (28.4)	7387 (25.7)	
Some college	272 (28.0)	7670 (26.7)	
College or higher	268 (27.6)	10 069 (35.1)	
Unknown	2 (0.2)	21 (0.01)	
Income			
<US$20k	238 (24.5)	5102 (17.8)	<0.001
US$20k–US$34k	272 (28.0)	6892 (24.0)	
US$35k–US$74k	254 (26.2)	8552 (29.8)	
≥US$75k	103 (10.6)	4587 (16.0)	
Unknown (refused)	970 (10.6)	3561 (12.4)	
Geographical region			
Stroke buckle	209 (21.6)	6003 (20.9)	0.04
Stroke belt	367 (37.8)	9910 (34.5)	
Non-belt/buckle	394 (40.6)	12 781 (44.5)	
Health status—physical composite score			
Quintile 1 (≤37.002)	352 (36.3)	5314 (18.5)	<0.001
Quintile 2 (37.006–46.949)	208 (21.4)	5482 (19.1)	
Quintile 3 (46.951–52.111)	145 (15.0)	5545 (19.3)	
Quintile 4 (52.112–55.501)	136 (14.0)	6126 (21.4)	
Quintile 5 (≥55.502)	76 (7.8)	4945 (17.2)	
Missing	53 (5.46)	1282 (4.47)	
Health status—mental composite score			
Quintile 1 (≤49.591)	224 (23.1)	5442 (19.0)	<0.001
Quintile 2 (49.592–55.282)	188 (19.4)	5481 (19.1)	
Quintile 3 (55.282–57.827)	143 (14.9)	5741 (20.0)	
Quintile 4 (57.828–59.872)	144 (14.9)	5459 (19.0)	
Quintile 5 (≥59.872)	218 (22.5)	5289 (18.4)	
Missing	53 (5.5)	1282 (4.5)	
Health behaviours			
Tobacco use			
Current	173 (17.8)	4106 (14.3)	<0.001
Past	471 (48.6)	11 432 (39.8)	
Never	323 (33.3)	13 045 (45.5)	
Unknown	3 (0.3)	111 (0.4)	
Alcohol use			
Heavy	39 (4.0)	1136 (4.0)	0.07
Moderate	279 (28.8)	9406 (32.8)	
None	631 (65.1)	17 593 (61.3)	
Unknown	21 (2.2)	559 (2.0)	
Chronic medical conditions			
Atrial fibrillation	128 (13.2)	2418 (8.4)	<0.001
Cancer history	131 (13.5)	3484 (8.7)	<0.001

Continued

Table 2 Continued

Characteristics	Sepsis (n=970) N (%)	Non-sepsis (n=28 694) N (%)	p Value*
Chronic lung disease	201 (20.7)	2529 (8.8)	<0.001
Chronic kidney disease	210 (21.7)	3034 (10.6)	<0.001
Coronary artery disease	277 (28.6)	4948 (17.2)	<0.001
Deep vein thrombosis	89 (9.2)	1464 (5.1)	<0.001
Diabetes	328 (33.8)	6369 (22.2)	<0.001
Dyslipidaemia	618 (63.7)	16 331 (56.9)	<0.001
Hypertension	666 (68.7)	16 863 (58.8)	<0.001
Myocardial infarction	205 (21.1)	3510 (12.2)	<0.001
Obesity (elevated waist circumference or body mass index ≥30 kg/m^2)	609 (62.8)	15 328 (53.4)	<0.001
Peripheral artery disease	46 (4.7)	615 (2.1)	<0.001
Stroke	107 (11.0)	1786 (6.2)	<0.001

*From χ^2 test.

kidney and urinary tract infections and abdominal infections (table 1). Compared with non-sepsis participants, individuals with sepsis were older, more likely to be male, had lower income and education, were more likely to use alcohol or tobacco and were more likely to have chronic medical conditions (table 2).

There were 324 deaths among 970 individuals with sepsis (33.4%) and 3155 deaths among 28 694 non-sepsis individuals (11%). The incidence of death was 141/1000 person-years for sepsis and 19.2/1000 person-years for non-sepsis individuals (table 3). Adjudicated cause of death was available for 84.6% of sepsis and 73.5% of non-sepsis deaths; the most common adjudicated causes of death among individuals with sepsis were infection, lung disease and cancer (table 4).

Among all first-sepsis events, 86 (8.9%) patients died in the hospital, with a median time to death of 7 days (IQR 3–15). One-year, 2-year and 5-year all-cause mortality among individuals with sepsis were 23%, 28.8% and 43.8%, respectively (figure 1). One-year, 2-year and 5-year all-cause mortality among non-sepsis individuals were 1%, 2.6% and 8.3%, respectively. Compared with non-sepsis persons, the rate of death was high among individuals with sepsis in the first year after the event (adjusted HR 13.07; 95% CI 10.63 to 16.06; figure 2 and see online supplementary appendix 1). Among those who survived for at least 1 year, individuals with sepsis exhibited twofold increased rates of death for up to 5 years after the sepsis event.

To account for potential clustering of deaths within stroke belt region, we repeated the analysis using a robust variance estimator; we observed similar associations between sepsis and rates of long-term mortality; however, the higher rate of death among individuals with sepsis was statistically significant in the sixth year of follow-up. When repeating the analysis modelling stroke belt region as a shared frailty, we observed no major changes in the associations between sepsis and rates of all-cause mortality. When repeating the analysis excluding the 1310 non-sepsis individuals who had unadjudicated possible sepsis events, we observed similar associations between sepsis and long-term mortality.

We stratified the analysis by uncomplicated sepsis (n=257) versus severe sepsis (n=713). Compared with non-sepsis individuals, the adjusted rate of death was twofold higher for 1 year among those experiencing uncomplicated sepsis (see online supplementary appendix 2). Among those who survived at least 1 year, the

Table 3 Incidence of death for sepsis and non-sepsis individuals

Activity	Person-time (person-years)	Deaths	Incidence (deaths per 1000 person-years)
Non-sepsis	163 520	3140	19.2 (18.5–19.9)
Sepsis	2241	316	141.0 (126.3–157.5)
Lung infection	1132	176	155.4 (134.1–180.2)
Kidney infection	366	51	139.4 (105.9–183.4)
Abdominal infection	388	25	64.4 (43.5–95.3)
Skin infection	168	23	137.1 (91.1–206.4)
'Sepsis' NOS	82	25	306.2 (206.9–453.2)
Other infections	105	16	152.2 (93.2–248.4)
Overall	165 761	3456	20.8 (20.2–21.6)

Sepsis incidence further stratified by infection type.
NOS, not otherwise specified.

Table 4 Adjudicated causes of death.

Adjudicated cause of death	Sepsis (n=274) N (%)	Non-sepsis (n=2318) N (%)
Infection	88 (32.1)	187 (8.1)
Chronic lung disease	36 (13.1)	92 (4.0)
Cancer	31 (11.3)	647 (27.9)
Sudden death	23 (8.4)	272 (11.7)
Myocardial infarction	18 (6.6)	253 (10.9)
Heart failure	15 (5.5)	147 (6.3)
Cerebrovascular accident	11 (4.0)	160 (6.9)
End-stage renal disease	8 (2.9)	65 (2.8)
Accident, injury, suicide or homicide	3 (1.1)	92 (4.0)
Liver disease	2 (0.7)	30 (1.3)
Dementia	1 (0.4)	55 (2.4)
Pulmonary embolism	0 (0.0)	24 (1.0)
Other cardiovascular condition	11 (4.0)	93 (4.0)
Other non-cardiovascular condition	17 (6.2)	129 (5.6)
Unclassifiable	10 (3.7)	72 (3.1)

Adjudicated cause of death not available for 274 of 324 (84.6%) deaths among individuals with sepsis and 2318 of 3155 (73.5%) deaths among non-sepsis individuals.
Includes 274 deaths among sepsis individuals and 2318 deaths among non-sepsis individuals.

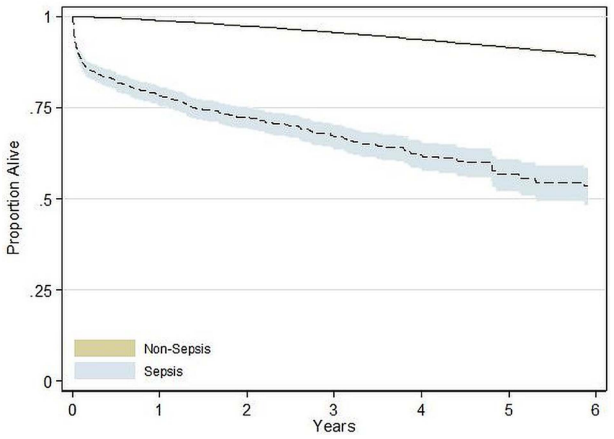


Figure 1 Kaplan-Meier curves and 95% CIs for long-term survival after sepsis. Sepsis versus non-sepsis. Includes 970 sepsis and 28 694 non-sepsis individuals. Analysis censored at 6 years.

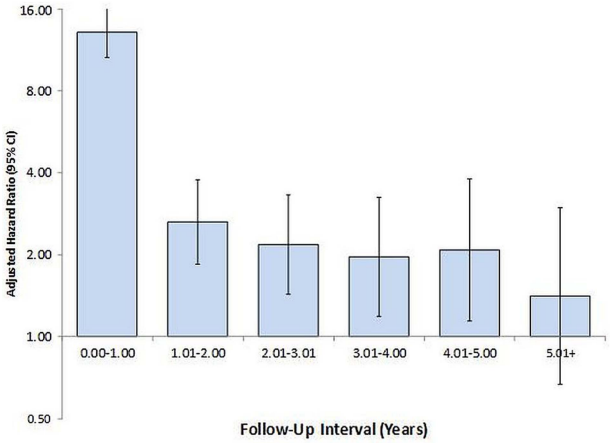
adjusted rates of death were twofold higher for up to 5 years among those experiencing severe sepsis.

In the sepsis subset, participant characteristics independently associated with increased rates of death after the sepsis event included male sex, health status (physical component score), cancer history, chronic kidney disease, deep vein thrombosis, diabetes, dyslipidaemia, hypertension and obesity (table 5 and see online supplementary appendix 3). Among hospital course characteristics, death rates were higher among participants with increased sequential organ failure scores or admission to the intensive care unit. Rates of long-term death were lower for sepsis due to abdominal infections.

DISCUSSION

For almost a decade, the Surviving Sepsis Campaign guidelines have advocated best practices for sepsis care with the goal of reducing the mortality associated with this condition.[16] Drawing on REGARDS, one of the nation's largest population-based cohorts of community-dwelling adults, our study highlights that excess long-term all-cause mortality persists among those suffering from sepsis. Compared with individuals who did not develop sepsis, rates of death among individuals experiencing sepsis were twofold higher for up to 5 years after the sepsis event. Our analysis adjusted for a range of potential confounders and observed relatively small attenuation of risk, suggesting that comorbidities are not playing the major role in this extended risk.

Our findings add to the body of knowledge highlighting the downstream consequences of sepsis. As highlighted in Winters *et al*'s[4] systematic review, most sepsis mortality studies have focused on shorter endpoints,



Follow-up Time Interval (Years)	Unadjusted HR (95% CI) for Death	Adjusted HR (95% CI) for Death
0.00-1.00	25.63 (21.44-30.64)	13.07 (10.63-16.06)
1.01-2.00	4.97 (3.63-6.79)	2.64 (1.85-3.77)
2.01-3.00	4.22 (2.90-6.15)	2.18 (1.43-3.33)
3.01-4.00	3.65 (2.31-5.77)	1.97 (1.19-3.25)
4.01-5.00	3.85 (2.22-6.68)	2.08 (1.14-3.79)
5.01+	1.84 (0.87-3.87)	1.41 (0.67-2.98)

Figure 2 Adjusted HRs for association of sepsis with long-term survival. Time-dependent effects described using a Cox regression model with all sepsis defined as a time-varying covariate. Analysis censored at 6 years. Each bar reflects the HR for death among individuals alive at the beginning of that time segment. Graph depicts observation time ≥6 months only. Adjusted for age, sex, race, region, health status, smoking, alcohol use, obesity and chronic medical conditions, as reported at the beginning of the REasons for Geographic And Racial Differences in Stroke REGARDS study.

Table 5 Participant characteristics associated with rates of mortality after first sepsis events

Characteristics	HR (95% CI)	p Value
Demographics		
Sex (male vs female)	1.37 (1.002 to 1.88)	0.048
Health status—physical composite score		
Quintile 1	Referent	
Quintile 2	0.68 (0.46 to 1.01)	0.06
Quintile 3	0.55 (0.36 to 0.84)	0.006
Quintile 4	0.51 (0.33 to 0.79)	0.002
Quintile 5	0.59 (0.35 to 0.99)	0.045
Chronic medical conditions		
Cancer history	1.68 (1.24 to 2.27)	0.001
Chronic kidney disease	1.43 (1.05 to 1.95)	0.02
Deep vein thrombosis	0.63 (0.38 to 1.04)	0.07
Diabetes	1.57 (1.17 to 2.11)	0.003
Dyslipidaemia	0.73 (0.55 to 0.98)	0.04
Hypertension	1.46 (1.07 to 2.00)	0.02
Obesity (elevated waist circumference or body mass index ≥30 kg/m^2)	0.74 (0.56 to 0.99)	0.04
Hospital course		
Infection type		
Lung	Referent	
Kidney	0.80 (0.55 to 1.17)	0.24
Abdominal	0.48 (0.29 to 0.78)	0.004
Skin	0.79 (0.43 to 1.43)	0.43
Sepsis	0.98 (0.58 to 1.67)	0.96
Other	1.33 (0.72 to 2.46)	0.37
Admission to intensive care unit	2.02 (1.40 to 2.91)	<0.001
Sequential organ failure score		
0	Referent	
1	1.10 (0.71 to 1.71)	0.68
2	1.25 (0.79 to 2.00)	0.34
3–4	1.66 (1.06 to 2.58)	0.03
5+	3.62 (2.23 to 5.88)	<0.001

Hospital course data based on first sepsis episode only. Only variables associated with early death are listed—full model listed in online supplementary appendix 3.
Includes individuals experiencing sepsis only.

inadequately controlled for baseline comorbidities, and relied on population norms as matched controls. Other studies focused on intensive care unit patients with sepsis, used data from single or smaller groups of centres or utilised discharge diagnoses to identify sepsis events.[6–8] Our contrasting study utilised a large (>30 000 persons) and diverse population-based sample of community-dwelling individuals in the USA and entailed follow-up of up to 6 years. Rather than relying on hospital discharge diagnoses, a process that may underdetect sepsis cases, we identified sepsis through review of hospital records.[1 17] We were able to account and adjust for baseline comorbidities that may affect the outcomes of sepsis and non-sepsis individuals.

It is unclear whether increased sepsis mortality reflects the increased susceptibility of those with heightened comorbid burden or whether sepsis triggers an independent pathophysiological process leading to early death.[18] Where adjudicated cause of death was available, 70% of deaths following a sepsis event were attributed to a range of other conditions, including cardiovascular and pulmonary diseases. We also identified that select chronic medical conditions such as diabetes, chronic kidney disease and chronic lung disease were independent predictors of early death among individuals with sepsis. Other described sequelae of sepsis include acute kidney injury, atrial fibrillation, cognitive impairment, functional disability and impaired quality of life.[19–22] Additional study must confirm the mechanisms by which sepsis creates or complicates the management of these other conditions. For example, does sepsis increase long-term mortality by causing acute kidney injury and subsequent chronic kidney disease? Another important question is whether prevention or optimal management of these parallel conditions might reduce the long-term rates of sepsis death. For example, could optimal management of sepsis-triggered chronic kidney alter an individual's risk of death?

Some limitations of this analysis should be noted. The REGARDS cohort contains individuals over 45 years only, and thus we could not characterise sepsis in younger individuals, who would likely exhibit lower rates of long-term mortality after a sepsis event. We could not identify sepsis events not reported by participants. We did not examine the influence of repeat sepsis events, which could conceivably increase the risk of mortality. We identified individuals who presented to the hospital with sepsis, but did not include those who acquired sepsis during their hospitalisation; we would expect inclusion of the latter individuals to amplify the observed mortality differences. We did not evaluate cognitive impairment, functional disability or impacts on quality of life.

REGARDS was designed to study stroke, not sepsis. However, our novel study takes advantage of important features of REGARDS, including the large participant base, extensive baseline information and extended observation period. There have been no population-based cohorts designed specifically to study sepsis, and few studies on sepsis have had access to comprehensive 'baseline' information as is in our study. It would be logistically and financially difficult to replicate a cohort of this scale.

By design, the REGARDS cohort includes only African-Americans and Caucasians, and thus these results may not generalise to other ethnic groups. Select medical conditions not identified by REGARDS may have exhibited associations with risk of sepsis as well as mortality; for example, a history of immunosuppression. As with all observational studies, residual confounding is always a concern. However, our risk adjustment strategy accounted for a comprehensive range of variables that were systematically identified for each participant at the beginning of the REGARDS study. While we accounted

for the presence of baseline participant characteristics and chronic medical conditions, we could not account for changes in these patterns over time.

CONCLUSION

In the REGARDS cohort, individuals with sepsis exhibited increased rates of long-term death, even after accounting for comorbidities. Sepsis is independently associated with increased mortality risk well after hospital treatment.

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Competing interests MMS reports the following potential conflicts of interest: Amgen—salary support to study patterns of statin use in Medicare and other large databases; diaDexus—salary support for a research grant on lipids and coronary heart disease outcomes; diaDexus—consulting to help with Food and Drug Administration FDA application; National Institutes of Health, Agency for Healthcare Research and Quality—salary support for research grants. Dr Wang, Dr Szychowski, Dr Griffin, Dr Shapiro and Dr Howard do not report any related conflicts of interest.

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