Supplemental Table 1: Detailed definitions and technical information for sociodemographics, health behaviors, and chronic medical conditions.

Characteristic	Definition and/or Technical Information
Sociodemographics	
Age	Age in years
Gender	Male, female
Race	Black, white
Education	Participant reported: - Less than high school - High school graduate - Some college - College or higher - Missing
Income	Participant reported: - <$20k - $20k-$34k - $35k-$74k - ≥$75k - Missing (not reported)
Geographic Region	Participant residence: - Stroke Buckle (coastal plains of North Carolina, South Carolina and Georgia) - Stroke Belt (remainder of North Carolina, South Carolina and Georgia, plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas) Non-Belt/Buckle (other states)
Health Behaviors	
Smoking Status	Participant reported: - Current - Past - Never
Alcohol use	Participant reported: - None - Moderate (up to 1 drink per day for women or 2 drinks per day for men) - Heavy (>1 drink per day for women and >2 drinks per day for men).[63]
Chronic Medical Conditions	
Atrial Fibrillation	Participant reported history of atrial fibrillation.
Chronic Lung Disease	Participant use of pulmonary medications (beta agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, ipratropium, cromolyn, aminophylline and theophylline) as a surrogate for chronic lung disease.
Coronary Artery Disease	Participant reported history of myocardial infarction, coronary artery bypass grafting, or cardiac angioplasty or stenting, or baseline electrocardiographic evidence of

	myocardial infarction.
Chronic Kidney Disease	Defined as measured glomerular filtration rate of<60 ml/min based upon serum creatinine.
Diabetes	Fasting glucose ≥126 mg/L (or a glucose ≥200 mg/L for those not fasting) or participant reported use of insulin or oral hypoglycemic agents.
Deep Vein Thrombosis	Participant reported history of deep vein thrombosis.
Dyslipidemia	Low-density lipoprotein cholesterol >130 mg/dL or participant reported use of lipid lowering medications.
Hypertension	Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or participant reported antihypertensive agent use.
Myocardial Infarction	Participant reported history of myocardial infarction or baseline electrocardiographic evidence of myocardial infarction.
Obesity	{Waist circumference [>102 cm for males or >88 cm for females]} or {body mass index ≥30 kg/m^2}.
Peripheral Artery Disease	Participant reported history of lower extremity arterial bypass or leg amputation.
Stroke	Participant reported history of stroke or transient ischemic attack.
Medications	
Aspirin use	Self-reported participant chronic use of aspirin at baseline.
Statin use	Self-reported participant chronic use of statins at baseline.
Steroid use	Steroid use is the reported use of oral or injectable hydrocortisone, dexamethasone, fludrocortisone, prednisone, methyl prednisone, budesonide, and stanozolol.
Albumin-to-Creatinine Ratio (ACR)	Abnormal defined as ACR ≥30 mcg/mg. Albumin assay by nephelometry (BN ProSpec Nephelometer, Dade Behring, Siemens Healthcare, Deerfield, Illinois, USA). Urinary creatinine assay determined by rate blanked Jaffé procedure (Modular-P analyzer, Roche/Hitachi, Roche Diagnostics, Indianapolis, Indiana, USA).
Cystatin C	Abnormal defined as Cyst-C measurements above the fourth quartile (≥1.11 mg/dL) Assay by particle-enhanced immunonephelometry (N Latex Cyst-C, Siemens AG, Munich, Germany).
High Sensitivity C-Reactive Protein (hsCRP)	Abnormal defined as hsCRP >3.0 mg/dL Assay by particle-enhanced immunonephelometry (N High-sensitivity CRP, Siemens AG, Munich, Germany).

Supplemental Table 2: Mediating effects [1] of indicators of frailty on the association between risk of sepsis after cancer survivorship, excluding cancer deaths within 3 years. Among 27,878 REGARDS participants with 1305 first sepsis events.

	Mediation Analysis				
	Natural Indirect Effect[2] (Mediation Effect)		Natural Direct Effect[3]		Percent Mediated[4] (%) (Log Hazard Scale)
	HR	95% CI[5]	HR	95% CI[5]	
Mediators					
Weakness	1.007	1.006 – 1.012	2.614	2.394 – 2.842	0.77%
Exhaustion	1.005	1.002 – 1.010	2.632	2.411 – 2.861	0.50%
Low Physical Activity	1.003	1.000 – 1.006	2.622	2.398 – 2.860	0.26%
Frailty	1.009	1.005 – 1.016	2.607	2.389 – 2.849	0.92%
# Frailty Indicators	1.008	1.004 – 1.015	2.628	2.410 – 2.861	0.85%

	Total Effect (Risk of Sepsis)			
	N	No. Sepsis Events (%)	Mean Survival Time (95% CI)[6]	Hazard Ratio (95% CI)
Cancer Survivors	25,155	346 (12.71)	8.57 (8.49 – 8.65)	2.62 (2.31 – 2.97)
No Cancer History	2723	959 (3.81)	9.19 (9.17 – 9.20)	Ref

[1] Models adjusted for age, sex, race, and comorbidity score.
[2] Natural Indirect Effect (i.e., the effect of the cancer on sepsis incidence *through* the mediator)
[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)
[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.
[5] 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.
[6] Mean survival time in years.

Supplemental Table 3: Mediating effects [1] of indicators of frailty on the association between cancer and sepsis. Among 26158 REGARDS participants with 1224 first sepsis events. Further adjusted for biomarkers and baseline medications.

	Mediation Analysis				
	Natural Indirect Effect[2] (Mediation Effect)		Natural Direct Effect[3]		Percent Mediated[4] (%) (Log Hazard Scale)
	HR	95% CI[5]	HR	95% CI[5]	
Mediators					
Weakness	1.005	1.002 – 1.009	2.601	2.384 – 2.879	0.49%
Exhaustion	1.004	1.001 – 1.008	2.613	2.396 – 2.890	0.40%
Low Physical Activity	1.002	0.999 – 1.006	2.604	2.382 – 2.890	0.22%
Frailty	1.006	1.002 – 1.012	2.595	2.383 – 2.883	0.65%
# Frailty Indicators	1.006	1.002 – 1.011	2.595	2.383 – 2.883	0.60%

	Total Effect (Risk of Sepsis)		
	No. Sepsis Events (%)	Mean Survival Time (95% CI)[6]	Hazard Ratio (95% CI)
Cancer Survivors	325 (12.56)	8.56 (8.48 – 8.64)	2.61 (2.29 – 2.97)
No Cancer History	899 (3.81)	9.19 (9.17 – 9.21)	Ref

[1] Models adjusted for age, sex, race, comorbidity score, Cystatin-C, and aspirin use.
[2] Natural Indirect Effect (i.e., the effect of the cancer on sepsis incidence *through* the mediator)
[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)
[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.
[5] 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.
[6] Mean survival time in years.

Supplemental Table 4: Mediating effects [1] of indicators of frailty on the association between cancer and sepsis. Among 10,586 Black participants with 408 first sepsis events. Further adjusted for biomarkers and baseline medications.

	Natural Indirect Effect[2] (Mediation Effect)		Natural Direct Effect[3]		Percent Mediated[4] (%) (Log Hazard Scale)
Mediators	**HR**	**95% CI[5]**	**HR**	**95% CI[5]**	
Weakness	1.001	0.997 – 1.006	2.846	2.189 – 3.672	0.05%
Exhaustion	1.003	0.996 – 1.008	2.834	2.183 – 3.664	0.27%
Low Physical Activity	1.002	0.999 – 1.005	2.837	2.184 – 3.641	0.18%
Frailty	1.002	1.000 – 1.005	2.834	2.184 – 3.641	0.18%
# Frailty Indicators	1.002	1.000 – 1.005	2.837	2.184 – 3.641	0.17%

	Total Effect (Risk of Sepsis)		
	No. Sepsis Events (%)[6]	**Mean Survival Time (95% CI)[7]**	**Hazard Ratio (95% CI)[8]**
Cancer Survivors	89 (11.51)	8.10 (7.97 – 8.24)	3.00 (2.36 – 3.82)
No Cancer History	319 (3.25)	9.22 (9.19 – 9.24)	Ref

[1] Models adjusted for age, sex, race, comorbidity score, Cystatin-C, and aspirin use.
[2] Natural Indirect Effect (i.e., the effect of the cancer on sepsis incidence *through* the mediator)
[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)
[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.
[5] 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.
[6] % represents the proportion within cancer group with sepsis event.
[7] Mean survival time in years.
[8] Estimated from Cox proportional hazards model.

Supplemental Table 5: Mediating effects [1] of indicators of frailty on the association between cancer and sepsis. Among 15,572 White participants with 816 first sepsis events. Further adjusted for biomarkers and baseline medications.

	Natural Indirect Effect[2] (Mediation Effect)		Natural Direct Effect[3]		Percent Mediated[4] (%) (Log Hazard Scale)
Mediators	**HR**	**95% CI[5]**	**HR**	**95% CI[5]**	
Weakness	1.004	1.001 – 1.012	2.507	2.383 – 2.761	0.48%
Exhaustion	1.002	1.000 – 1.007	2.513	2.392 – 2.760	0.26%
Low Physical Activity	1.004	0.999 – 1.009	2.503	2.377 – 2.748	0.48%
Frailty	1.004	0.999 – 1.009	2.503	2.377 – 2.748	0.48%
# Frailty Indicators	1.004	0.999 – 1.009	2.514	2.389 – 2.761	0.48%

	Total Effect (Risk of Sepsis)		
	No. Sepsis Events (%)	**Mean Survival Time (95% CI)[7]**	**Hazard Ratio (95% CI)[8]**
Cancer Survivors	236 (13.00)	8.54 (8.44 – 8.64)	2.45 (2.10 – 2.86)
No Cancer History	580 (4.22)	8.82 (8.80 – 8.84)	Ref

[1] Models adjusted for age, sex, race, comorbidity score, Cystatin-C, and aspirin use.
[2] Natural Indirect Effect (i.e., the effect of the cancer on sepsis incidence *through* the mediator)
[3] Natural Direct Effect (i.e., the effect of the cancer on sepsis incidence *NOT through* mediator)
[4] Percent Mediated = Percent of the total association between the cancer and sepsis incidence that was mediated on the log hazard scale.
[5] 95% Confidence intervals (CIs) estimated using 500 bootstrapped resamples.
[6] % represents the proportion within cancer group with sepsis event.
[7] Mean survival time in years.
[8] Estimated from Cox proportional hazards model.