Association of hospitalization with long-term cognitive and brain MRI changes in the ARIC cohort

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ABSTRACT

Objective: To determine whether hospitalization is associated with subsequent cognitive decline or changes on brain MRI in a community-based cohort.

Methods: Baseline and follow-up cognitive testing ($n = 2,386$) and MRI scans with standardized assessments ($n = 885$) were available from a subset of white and black participants in the Atherosclerosis Risk in Communities study. Cognitive tests included the Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT). Hospitalization characteristics were determined using ICD-9 codes. Regression models adjusted for demographics, education, comorbidities, and APOE $\epsilon 4$ were used to estimate the independent association of hospitalization with changes in cognition or neuroimaging.

Results: Over a mean 14.1 years between visits, 1,266 participants (53.1%) were hospitalized. Hospitalization compared with no hospitalization was associated with greater decline in DSST scores (1.25 points greater decline, $p < 0.001$) but no difference in DWRT or WFT score change. Each additional hospitalization, as well as a critical illness vs noncritical illness hospitalization, was associated with greater decline in DSST scores. A subset of participants ($n = 885$) underwent MRI scans separated by 10.5 years. Hospitalization ($n = 392$) compared with no hospitalization was associated with a 57% higher odds of increasing ventricular size at follow-up. Each additional hospitalization, as well as having a critical illness vs noncritical illness hospitalization, and having a hospitalization with major surgery vs no surgery was associated with greater odds of increased ventricular size.

Conclusions: Cognitive decline and neuroimaging changes may occur after hospitalization, independent of baseline demographics and comorbidities. *Neurology*® 2015;84:1443-1453

GLOSSARY

ARIC = Atherosclerosis Risk in Communities; **CCS** = Clinical Classification Software; **CI** = confidence interval; **DSST** = Digit Symbol Substitution Test; **DWRT** = Delayed Word Recall Test; **ICD-9** = International Classification of Diseases-9; **IMT** = intimal medial thickness; **LDL** = low-density lipoprotein; **OR** = odds ratio; **WFT** = Word Fluency Test; **WMH** = white matter hyperintensities.

Hospitalizations in older adults (>65 years) account for more than one third of community hospital stays and result in substantial morbidity and mortality.¹⁻³ Recently, evidence has emerged that hospitalization may be associated with long-term cognitive decline and incident dementia, even in the absence of hospitalization for stroke or head trauma.⁴⁻⁶ However, the association between hospitalization and cognitive decline has not been well-characterized, although establishing the magnitude and etiology of cognitive decline would be crucial to develop targeted prevention strategies.

In order to characterize the independent associations of hospitalization with cognitive change, accurate assessment of a patient's prehospitalization comorbidities is critical, since hospitalization might only be a marker of vulnerability. However, previous studies have been limited by excessive reliance on patient self-reported comorbidities, which may lead to misclassification with residual confounding, and lack of accounting for APOE $\epsilon 4$ status. The potential

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mechanism for cognitive decline following hospitalization for reasons other than stroke is unknown, although both patient and hospitalization characteristics may provide insight. Importantly, changes on brain imaging, including incident infarcts,⁷ brain atrophy,⁸ and increases in white matter hyperintensities (WMH)^{9,10} have all been associated with cognitive decline and may be more common after hospitalization.

The Atherosclerosis Risk in Communities (ARIC) study is a predominantly biethnic longitudinal cohort study with baseline and follow-up cognitive testing 15 years apart, baseline and follow-up brain MRI 10 years apart, and rigorous characterization of patient comorbidities. In this study, the association between hospitalization and cognitive decline and neuroimaging changes is examined in the ARIC cohort.

METHODS Study population. The ARIC study is a prospective, population-based cohort study conducted in a predominantly biethnic cohort of 15,792 participants enrolled between 1987 and 1989. Study design and procedures have been published.¹¹ All participants were invited for assessments at visits 2, 3, and 4, while only a subset of participants were invited for brain or carotid MRI visits. Briefly, the brain MRI cohort was >55 years old from Forsyth County, North Carolina, or Jackson, Mississippi, without exclusions for MRI, invited as an ancillary to visit 3 (1993–1995).^{12,13} The carotid MRI cohort was invited based on a stratified sampling plan from all sites, with a goal of recruiting 1,200 participants with high values of carotid arterial intimal medial thickness (IMT) and 800 individuals randomly sampled from the remainder of the IMT distribution.¹⁴

For the purpose of examining cognitive decline, we limited the analyzed population to participants who had cognitive testing at visit 2 (1990–1992, baseline) and either the brain¹² or carotid MRI visits¹⁴ (2004–2006, follow-up), since these visits provided the largest interval of cognitive testing.

For the purpose of examining changes on brain MRI, we limited the analyzed population to participants who had brain MRI scans at visit 3 (1993–1995, baseline) and the brain MRI visit (2004–2006, follow-up).

For all analyses, we excluded participants with a primary brain injury (ischemic or hemorrhagic stroke or head trauma) noted during hospitalization between baseline and follow-up, and patients on antimental, anticonvulsant, or antipsychotic medications at baseline. We did include patients hospitalized with conditions (besides stroke or head trauma) affecting the CNS. Participants missing baseline or follow-up cognitive testing or covariate data were excluded, and we disregarded hospitalizations in the year before follow-up visits (to reduce short-term effects of hospitalization). Figure 1 shows included patients.

Standard protocol approvals, registrations, and patient consents. All participants provided written informed consent, and the study was conducted with institutional review board approval at all study sites.

Measures of hospitalization. The ARIC study obtains hospitalization information through annual telephone contact with participants and active surveillance of local hospitals. These data include all ICD-9 codes. We categorized each hospitalization as noncritical or critical illness, using the methodology of Ehlenbach et al.⁴ with the addition of sepsis (ICD-9 code 995.91) as a critical illness. Critical illness included shock/hypotension, sepsis, respiratory failure or prolonged mechanical ventilation, and respiratory/cardiac arrest. We further categorized each hospitalization into major surgical or non-surgical using Clinical Classification Software (CCS) (<http://www.hcupus.ahrq.gov/toolssoftware/ccs/ccsfactsheet.jsp>) from the Agency for Healthcare Quality and Research. We defined major surgical procedures as those with intermediate or high cardiac risk according to guidelines,¹⁵ generally spine, thyroid, cardiothoracic, vascular, gastrointestinal, hernia, or genitourinary procedures. We defined nonsurgical hospitalizations as not having CCS procedure codes (except radiologic imaging).

Outcome measures of cognitive function. Three cognitive tests were administered: (1) Delayed Word Recall Test (DWRT)¹⁶ (test of verbal learning and recent memory); (2) Digit Symbol Substitution Test (DSST)¹⁷ (test of executive function and processing speed); and (3) Word Fluency Test (WFT)¹⁸ (test of executive function and expressive language). For participants with cognitive testing at both the brain and carotid MRI visits, only the first score was used due to potential practice effects.¹⁹ The primary cognitive outcome was change in each cognitive test score, obtained by calculating visit 2 raw score minus the MRI visit raw score.

MRI measurement and outcomes. Details of the visit 3 and brain MRI visit scanning/interpretation protocols have been published.^{13,20,21} Infarcts were defined based on signal characteristics: bright on T2 and proton density scans and dark on T1 images. Ventricular size and sulcal width were estimated from axial T1-weighted images using a validated 0–9 scale.²¹ Outcomes of interest were presence of any new infarct, worsening of ≥ 1 grade of ventricular size (0–9 scale), and worsening of ≥ 1 grade of sulcal size (0–9 scale).

Change in WMH volume from visit 3 to the brain MRI visit was calculated by subtracting the WMH volume at the brain MRI visit²⁰ (using quantitative WMH volumes) minus the estimated WMH volume at visit 3 (using a validated prediction equation that related WMH volume to visit 3 visual grade) (0–9 scale) ($R^2 = 0.8$).²⁰ For WMH volume change, which was categorized into quintiles because of non-normal distribution, the outcome was odds of being in the top quintile of change compared to the bottom 4 quintiles, using prior methodology.²⁰ We also examined odds of being in the top quintile of WMH visual grade increase.

Statistical analysis. Characteristics of patients were compared using *t* tests or Wilcoxon rank-sum tests for continuous variables, χ^2 tests for binary variables, and Wilcoxon rank-sum tests for categorical variables.

Cognitive change analysis. First, multivariable linear regression models were used to estimate the change in each cognitive test score, comparing hospitalized vs nonhospitalized participants in the visit 2–MRI visit interval. Second, among participants with first hospitalization after visit 2, we used multilevel linear regression models with patient-level random intercepts, considering raw cognitive scores at visits 2, 3, 4, and MRI visit. For each subject, we defined time 0 as time of first hospitalization and calculated time from first hospitalization based on the dates of each visit. We estimated the change in raw cognitive scores before and after first hospitalization by including the main effect of time to estimate the slope prior to first hospitalization and a linear spline term that allowed the slope for time to change after the first hospitalization.

Figure 1 Flow diagram

Patients included and excluded for analysis of cognitive and brain MRI changes in the Atherosclerosis Risk in Communities study.

Neuroimaging analysis. MRI outcomes were dichotomized (increase of ≥ 1 grade of ventricular, or sulcal size, any new infarct, being in the top quintile of WMH volume change, or increase in visual grade). Multivariable logistic regression models were used to estimate the odds of each of these outcomes, comparing hospitalized vs nonhospitalized participants in the visit 3–MRI visit interval.

Secondary analyses. Additional exploratory characterizations of hospitalization were separately evaluated, including (1) number of hospitalizations (0, 1, 2, 3, 4, 5, ≥ 6), (2) critical illness vs noncritical illness hospitalization, (3) major surgical vs nonsurgical hospitalization, and (4) black vs white race. A potential role for neuroimaging changes on mediating cognitive changes was examined by adding neuroimaging changes to the adjusted model.

All models included age, sex, race/center, education (<high school, high school degree or vocational school, >high school), hypertension (diastolic blood pressure > 90 mm Hg or hypertension medications), systolic blood pressure, coronary heart disease (self-reported at visit 1 or subsequent adjudicated events), smoking status (never vs ever), diabetes (fasting plasma glucose > 126 mg/dL or any nonfasting glucose > 200 mg/dL, use of diabetes medications, or self-reported), self-reported or adjudicated stroke, carotid intimal medial thickness, number of *APOE* $\epsilon 4$ alleles (defined using single nucleotide polymorphisms rs429358 and rs7412 and coded 0, 1, or 2 alleles), low-density lipoprotein (LDL) concentration, kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m²

using the CKD-EPI equation²³), and the following self-reported diseases at visit 4: lung disease, hepatitis, lupus, rheumatoid arthritis, and cancer. To account for missing covariate data as a sensitivity analysis, we used multiple imputation by chained equations to create 5 imputed datasets using the missing data module in Stata.²³ Parameter estimates were averaged across imputed datasets. Standard errors of the estimates were calculated using Rubin's formula.²⁴

All *p* values are 2-sided, and *p* < 0.05 was considered statistically significant. Stata version 12 (StataCorp, College Station, TX) was used for analyses.

RESULTS Participant characteristics. For analysis of cognitive change, data were analyzed for 2,386 participants. Over a mean of 14.1 ± 1.0 years between baseline and follow-up visits, 1,266 participants (53.1%) were hospitalized at least once. For analysis of neuroimaging changes, data were analyzed for 885 participants. Over a mean of 10.5 ± 0.8 years between baseline and follow-up neuroimaging, 392 patients (44.3%) were hospitalized at least once. Figure 1 shows a flowchart of included patients.

Baseline characteristics of the study populations, as well as the overall ARIC population, are shown in

Table 1 Participant characteristics

	Cognitive analysis ^a (n = 2,386)				Neuroimaging analysis ^a (n = 885)			
	Not hospitalized (n = 1,120)	Hospitalized (n = 1,266)	p Value	Total ARIC cohort at visit 2 for comparison with cognitive analysis population (n = 14,348)	Not hospitalized (n = 493)	Hospitalized (n = 392)	p Value	Total ARIC cohort at visit 3 for comparison with neuroimaging analysis population (n = 12,887)
Age, y, mean ± SD	56.4 ± 5.2	57.8 ± 5.3	<0.001	57.0 ± 5.7	61.2 ± 4.4	62.7 ± 4.3	<0.001	60.0 ± 5.7
Female, n (%)	642 (57.3)	687 (54.3)	0.13	7,944 (55.4)	318 (64.5)	228 (58.2)	0.054	7,170 (55.6)
Race/center, n (%)			0.006				0.09	
Black								
Forsyth	39 (3.5)	26 (2.0)		380 (2.7)	31 (6.3)	12 (3.1)		333 (2.6)
Jackson	328 (29.3)	342 (27.0)		3,148 (21.9)	219 (44.4)	182 (46.4)		2,622 (20.4)
White								
Forsyth	341 (30.5)	362 (28.6)		3,280 (22.9)	243 (49.3)	198 (50.5)		2,994 (23.2)
Minneapolis	188 (16.8)	278 (22.0)		3,796 (26.5)	NA	NA		3,470 (26.9)
Washington	224 (20.0)	258 (20.4)		3,653 (25.5)	NA	NA		3,388 (26.3)
Education, n (%)			0.14				0.10	
Less than high school	198 (17.7)	234 (18.5)		3,144 (22.0)	96 (19.5)	99 (25.3)		2,625 (20.4)
High school degree/ vocational school	430 (38.4)	527 (41.6)		5,931 (41.4)	182 (36.9)	127 (32.4)		5,358 (41.6)
More than high school	492 (43.9)	505 (39.9)		5,249 (36.6)	215 (43.6)	166 (42.4)		4,884 (38.0)
Hypertension, ^b n (%)	243 (21.7)	374 (29.5)	<0.001	4,285 (30.0)	161 (32.7)	152 (38.8)	0.06	4,320 (33.7)
Systolic blood pressure, mm Hg, mean ± SD	117.9 ± 16.6	121.3 ± 17.5	<0.001	121.7 ± 18.9	124.3 ± 18.6	128.2 ± 20.3	0.003	124.6 ± 19.2
Prevalent coronary heart disease, ^c n (%)	22 (2.0)	59 (4.7)	<0.001	829 (5.9)	9 (1.8)	18 (4.6)	0.02	895 (7.1)
Prevalent stroke, ^d n (%)	4 (0.36)	11 (0.87)	0.11	275 (1.9)	3 (0.6)	4 (1.0)	0.49	252 (2.0)
Cigarette usage (ever), n (%)	601 (53.4)	750 (59.2)	0.007	8,629 (60.3)	253 (51.3)	210 (53.6)	0.51	7,571 (58.9)
LDL, mg/dL, mean ± SD	132.2 ± 36.1	133.7 ± 34.9	0.30	133.5 ± 36.8	126.2 ± 35.9	128.7 ± 34.1	0.29	127.3 ± 34.5
Diabetes mellitus, ^e n (%)	86 (7.7)	160 (12.6)	<0.001	2,159 (15.1)	41 (8.3)	58 (14.8)	0.002	1,654 (12.9)
Kidney disease, ^f n (%)	7 (0.6)	14 (1.1)	0.21	309 (2.2)	6 (1.2)	4 (1.0)	0.78	228 (1.8)
Lung disease, ^g n (%)	29 (2.6)	61 (4.8)	0.004	722 (5.0)	12 (2.4)	21 (5.4)	0.02	586 (4.6)
Hepatitis, ^g n (%)	40 (3.6)	70 (5.5)	0.02	590 (4.1)	9 (1.8)	20 (5.1)	0.007	587 (4.6)
Lupus, ^g n (%)	6 (0.54)	8 (0.63)	0.76	86 (0.6)	3 (0.6)	4 (1.0)	0.49	85 (0.7)
Cancer, ^g n (%)	66 (5.9)	84 (6.6)	0.46	949 (6.6)	22 (4.5)	27 (6.9)	0.12	808 (6.3)
Rheumatoid arthritis, ^g n (%)	39 (3.5)	73 (5.8)	0.008	609 (4.2)	19 (3.9)	25 (6.4)	0.09	602 (4.7)
Carotid intimal medial thickness, mm, mean ± SD	0.72 ± 0.15	0.77 ± 0.20	<0.001	0.74 ± 0.19	0.79 ± 0.17	0.82 ± 0.20	0.002	0.82 ± 0.22
Number of APOE ε4 alleles, ^h n (%)			0.28				0.42	
0	787 (70.3)	851 (67.2)		9,521 (69.1)	346 (70.2)	262 (66.8)		8,593 (69.5)
1	308 (27.5)	382 (30.2)		3,886 (28.2)	136 (27.6)	117 (29.9)		3,440 (27.8)
2	25 (2.2)	33 (2.6)		370 (2.7)	11 (2.2)	13 (3.3)		330 (2.7)

Continued

Table 1 Continued

	Cognitive analysis ^a (n = 2,386)				Neuroimaging analysis ^a (n = 885)			
	Not hospitalized (n = 1,120)	Hospitalized (n = 1,266)	p Value	Total ARIC cohort at visit 2 for comparison with cognitive analysis population (n = 14,348)	Not hospitalized (n = 493)	Hospitalized (n = 392)	p Value	Total ARIC cohort at visit 3 for comparison with neuroimaging analysis population (n = 12,887)
Visit 2 cognitive scores, mean ± SD								
Delayed Word Recall Test	6.8 ± 1.4	6.7 ± 1.5	0.06	6.6 ± 1.5	NA	NA		NA
Digit Symbol Substitution Test	45.5 ± 13.7	44.1 ± 12.9	0.01	44.6 ± 14.2	NA	NA		NA
Word Fluency Test	34.5 ± 12.3	33.8 ± 11.9	0.17	33.1 ± 12.5	NA	NA		NA
Visit 3 MRI data								
Ventricular grade, ⁱ median (IQR)	NA	NA		NA	2 (2-3)	2 (2-3)	0.67	
Sulci grade, ⁱ median (IQR)	NA	NA		NA	2 (1-2)	2 (2-3)	0.47	
WMH volume, cm ³ , median (IQR)	NA	NA		NA	6.3 (6.3-10.8)	6.3 (6.3-10.8)	0.06	
WMH visual grade, ⁱ median (IQR)	NA	NA		NA	1 (1-2)	1 (1-2)	0.06	
Prevalent infarcts, n (%)	NA	NA		NA	34 (6.9)	53 (13.5)	0.001	

Abbreviations: ARIC = Atherosclerosis Risk in Communities; IQR = interquartile range, reported in the table as the 25th and 75th percentile; LDL = low-density lipoprotein; NA = not applicable; WMH = white matter hyperintensity.

^a All characteristics are reported from the baseline visit, visit 2 for the cognitive analysis, and visit 3 for the neuroimaging analysis, unless otherwise stated.

^b Hypertension is defined as diastolic blood pressure >90 mm Hg or use of hypertension medications.

^c Prevalent coronary disease is defined as reported coronary heart disease at visit 1 or subsequent adjudicated coronary events (myocardial infarction, silent myocardial infarction, coronary artery bypass surgery, angioplasty, or fatal coronary heart disease).

^d Prevalent stroke is defined as self-reported stroke or adjudicated stroke.

^e Diabetes is defined as fasting plasma glucose >126 mg/dL or any nonfasting glucose >200 mg/dL, use of diabetes mellitus medications, or self-reported history.

^f Kidney disease is defined as estimated glomerular filtration rate <60 mL/min/1.73 m² using the CKD-EPI equation.

^g Lung disease, hepatitis, rheumatoid arthritis, lupus, and cancer are all defined as self-reported diseases by the participant at visit 4.

^h APOE ε4 genotype is defined using the single nucleotide polymorphisms rs429358 and rs7412 and coded as having 0, 1, or 2 alleles.

ⁱ Ventricle volume, sulcal size, and WMH visual grade at visit 3 were estimated using a validated scale from 0 to 9.

table 1. Hospitalized participants were generally older, were more likely to be men, and were more likely to have more carotid atherosclerosis and comorbidities, including hypertension, diabetes, coronary heart disease, kidney disease, and lung disease. Baseline cognitive scores were slightly lower among hospitalized participants. Brain MRI characteristics at baseline were generally similar, although there were more prevalent infarcts among hospitalized participants.

Hospitalization and cognitive change. In adjusted models (table 2), there was more decline in DSST scores among participants with a hospitalization between ARIC visit 2 and the MRI visits, compared to participants without hospitalization in that interval (greater decline by 1.25 symbol pairs). However, the adjusted decline in both WFT and DWRT scores during the visit 2–MRI visits interval was not different among hospitalized vs nonhospitalized participants.

Because of baseline differences in participants, we also examined trajectories of cognitive change before hospitalization compared to after hospitalization. Before hospitalization, the average rate of DSST decline was 0.38 digit-symbol pairs/year (95% confidence interval [CI] 0.34–0.42), which after hospitalization worsened by an additional 0.20 digit-symbol pairs/year (95% CI 0.12–0.27; $p < 0.001$). Similarly, the average rate of WFT decline before hospitalization was 0.10 words/year (95% CI 0.05–0.14), which after hospitalization worsened by an additional 0.09 words/year (95% CI 0.02–0.17, $p = 0.02$). There was no statistical difference in average rate of DWR decline before hospitalization (0.032 words/year [95% CI 0.023–0.041]) compared to after hospitalization (worsening by 0.016 more words/year [95% CI –0.001 to 0.032; $p = 0.06$]). Inferences regarding cognitive change were not different when multiple imputation was used to account for missing covariate data.

Table 2 Relative decline in cognitive test scores for hospitalized vs nonhospitalized participants and other exploratory characterization of hospitalizations

		Unadjusted			Adjusted ^a			Comparison p value ^b
		β-coefficient	95% CI	p Value	β-coefficient	95% CI	p Value	
Association of any hospitalization with change in cognitive test scores ^c								
DWRT	0.12	−0.02 to 0.26	0.10	0.07	−0.08 to 0.21	0.35	NA	
DSST	1.80	1.21 to 2.40	<0.001	1.25	0.66 to 1.84	<0.001	NA	
WFT	0.74	0.10 to 1.38	0.02	0.53	−0.12 to 1.18	0.11	NA	
Exploratory characterization of hospitalizations								
Number of hospitalizations ^d								
DWRT	0.04	−0.002 to 0.09	0.06	0.03	−0.02 to 0.08	0.20	NA	
DSST	0.77	0.57 to 0.97	<0.001	0.58	0.38 to 0.78	<0.001	NA	
WFT	0.35	0.14 to 0.56	0.001	0.27	0.05 to 0.49	0.02	NA	
Severity of hospitalization ^e								
DWRT							0.75	
Noncritical illness	0.12	−0.02 to 0.26	0.10	0.07	−0.07 to 0.21	0.34		
Critical illness	0.15	−0.50 to 0.80	0.65	−0.04	−0.70 to 0.62	0.91		
DSST							0.046	
Noncritical illness	1.73	1.13 to 2.32	<0.001	1.20	0.61 to 1.80	<0.001		
Critical illness	5.17	2.39 to 7.95	<0.001	3.96	1.23 to 6.68	0.004		
WFT							0.46	
Noncritical illness	0.70	0.06 to 1.35	0.03	0.52	−0.14 to 1.17	0.12		
Critical illness	2.26	−0.72 to 5.24	0.14	1.64	−1.36 to 4.64	0.28		
Nonsurgical or major surgical hospitalization ^f								
DWRT							0.48	
No surgery	0.18	−0.05 to 0.41	0.13	0.13	−0.10 to 0.36	0.28		
Major surgery ^g	0.08	−0.09 to 0.24	0.35	0.04	−0.13 to 0.21	0.66		
DSST							0.74	
No surgery	1.43	0.43 to 2.42	0.005	1.07	0.10 to 2.05	0.03		
Major surgery ^g	1.90	1.19 to 2.61	<0.001	1.25	0.54 to 1.96	0.001		
WFT							0.17	
No surgery	0.25	−0.80 to 1.31	0.64	0.02	−1.04 to 1.09	0.97		
Major surgery ^g	1.01	0.25 to 1.77	0.01	0.81	0.04 to 1.59	0.04		

Abbreviations: CI = confidence interval; DSST = Digit Symbol Substitution Test; DWRT = Delayed Word Recall Test; NA = not applicable; WFT = Word Fluency Test.

^aAdjusted for age, sex, education, race/center, hypertension, systolic blood pressure, low-density lipoprotein, coronary heart disease, history of ever smoking, diabetes mellitus, history of stroke, carotid intima media thickness, number of APOE ϵ 4 alleles, kidney disease, lung disease, hepatitis, lupus, rheumatoid arthritis, and cancer.

^bThe comparison p value is a test of the statistical difference between 2 subgroups. For instance, participants with noncritical illness compared to no hospitalizations had greater decline in DSST scores by 1.20 digit symbols. Similarly, participants with critical illness compared to no hospitalizations had greater decline in DSST scores by 3.96 digit symbols. The comparison p value tested whether these changes in DSST decline between the noncritical illness and critical illness groups were statistically different.

^cThe β -coefficient indicates the amount of cognitive decline (visit 2 to MRI visit) of the hospitalized group compared to the reference group of no hospitalization. A positive β -coefficient indicates that the cognitive decline of the observed hospitalization group was greater (i.e., more decline in cognitive function) compared to the reference group of no hospitalization.

^dThe β -coefficient indicates the amount of cognitive decline associated with each increasing number of hospitalization. The number of participants in each group of number of hospitalizations are as follows: 0 (n = 1,120), 1 (n = 594), 2 (n = 312), 3 (n = 153), 4 (n = 81), 5 (n = 49), and ≥ 6 (n = 77).

^eThe β -coefficient indicates the amount of cognitive decline in the group with noncritical illness hospitalizations (n = 1,238) compared to no hospitalizations (n = 1,120), and in the group with critical illness hospitalizations (n = 28) compared to no hospitalizations (n = 1,120).

^fThe β -coefficient indicates the amount of cognitive decline in the group with nonsurgical hospitalizations (n = 266) compared to no hospitalizations (n = 1,120), and in the group with surgical hospitalizations (n = 671) compared to no hospitalizations (n = 1,120).

^gMajor surgery refers to procedures recognized as intermediate or high cardiac risk according to the 2007 American Heart Association guidelines on perioperative evaluation,¹⁵ and generally included spine, thyroid, thoracic, cardiac, vascular, gastrointestinal, hernia repair, and genitourinary procedures.

Table 3 Adjusted odds of neuroimaging outcomes from visit 3 to the MRI visits by hospitalization status, and other exploratory characterization of hospitalizations

	Unadjusted			Adjusted ^a			Comparison p value ^b
	OR	95% CI	p Value	OR	95% CI	p Value	
Association of any hospitalization with odds of neuroimaging outcomes ^c							
Top quintile of WMH volume change ^d	1.77	1.26-2.47	0.001	1.55	1.08-2.23	0.02	NA
Top quintile of increase in WMH visual grade ^d	1.44	1.05-1.96	0.02	1.26	0.90-1.76	0.17	NA
Incident infarcts	1.31	0.99-1.73	0.06	1.08	0.80-1.45	0.63	NA
Ventricular size worsening ≥1 grade	1.72	1.24-2.37	0.001	1.57	1.11-2.21	0.01	NA
Sulcal widening ≥1 grade	1.55	1.15-2.09	0.004	1.35	0.99-1.85	0.06	NA
Exploratory characterization of hospitalizations							
Number of hospitalizations ^e							
Top quintile of WMH volume change ^d	1.25	1.13-1.39	<0.001	1.23	1.09-1.38	0.001	NA
Top quintile of increase in WMH visual grade ^d	1.14	1.03-1.27	0.01	1.10	0.98-1.24	0.10	NA
Incident infarcts	1.23	1.12-1.36	<0.001	1.17	1.05-1.30	0.004	NA
Ventricular size worsening ≥1 grade	1.23	1.08-1.41	0.002	1.21	1.05-1.40	0.007	NA
Sulcal widening ≥1 grade	1.07	0.96-1.19	0.21	1.01	0.90-1.13	0.93	NA
Severity of hospitalization ^f							
Top quintile of WMH volume change ^d							0.18
Noncritical illness	1.70	1.21-2.39	0.002	1.51	1.05-2.17	0.03	
Critical illness	5.30	1.50-18.7	0.01	3.95	0.97-16.1	0.06	
Top quintile of increase in WMH visual grade ^d							0.41
Noncritical illness	1.41	1.03-1.93	0.03	1.24	0.89-1.74	0.21	
Critical illness	2.94	0.78-11.14	0.11	2.32	0.53-10.26	0.26	
Incident infarcts							0.67
Noncritical illness	1.31	0.99-1.73	0.06	1.08	0.80-1.47	0.60	
Critical illness	1.44	0.40-5.18	0.58	0.80	0.19-3.27	0.75	
Ventricular size worsening ≥1 grade							0.02
Noncritical illness	1.67	1.21-2.31	0.002	1.52	1.08-2.14	0.02	
Critical illness	g	g	g	g	g	g	
Sulcal widening ≥1 grade							0.86
Noncritical illness	1.54	1.14-2.09	0.005	1.35	0.98-1.85	0.06	
Critical illness	1.78	0.37-8.68	0.47	1.57	0.30-8.25	0.60	
Nonsurgical or major surgical hospitalization ^h							
Top quintile of WMH volume change ^d							0.58
No surgery	1.93	1.14-3.26	0.02	1.31	0.74-2.31	0.35	
Major surgery ⁱ	1.74	1.16-2.62	0.01	1.56	1.00-2.44	0.05	
Top quintile of increase in WMH visual grade ^d							0.57
No surgery	1.81	1.11-2.94	0.02	1.28	0.76-2.17	0.35	
Major surgery ⁱ	1.20	0.81-1.77	0.36	1.08	0.71-1.65	0.71	
Incident infarcts							0.37
No surgery	1.48	0.94-2.32	0.09	1.19	0.74-1.93	0.47	
Major surgery ⁱ	1.20	0.85-1.70	0.31	0.94	0.64-1.36	0.73	
Ventricular size worsening ≥1 grade							0.04
No surgery	1.18	0.70-1.96	0.54	0.94	0.55-1.63	0.83	
Major surgery ⁱ	2.01	1.31-3.09	0.001	1.89	1.19-2.99	0.007	

Continued

Table 3 Continued

	Unadjusted			Adjusted ^a			Comparison <i>p</i> value ^b
	OR	95% CI	<i>p</i> Value	OR	95% CI	<i>p</i> Value	
Sulcal widening ≥ 1 grade							0.24
No surgery	1.21	0.74-1.97	0.45	1.12	0.68-1.87	0.65	
Major surgery ⁱ	1.91	1.29-2.83	0.001	1.60	1.06-2.42	0.03	

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio; WMH = white matter hyperintensity.

^aAdjusted for age, sex, education, race/center, hypertension, systolic blood pressure, low-density lipoprotein, coronary heart disease, history of ever smoking, diabetes mellitus, history of stroke, carotid intima media thickness, number of APOE $\epsilon 4$ alleles, kidney disease, lung disease, hepatitis, lupus, rheumatoid arthritis, and cancer.

^bThe comparison *p* value is a test of the statistical difference between 2 subgroups, similar to table 2.

^cCompared to the reference group of no hospitalizations.

^dCompared to bottom 4 quintiles.

^eThe OR refers to the odds of the outcome with each increasing number of hospitalizations. The number of participants in each group of number of hospitalizations is as follows: 0 (*n* = 493), 1 (*n* = 188), 2 (*n* = 97), 3 (*n* = 54), 4 (*n* = 20), 5 (*n* = 10), and ≥ 5 (*n* = 23).

^fThe OR refers to the odds of each outcome in the group with noncritical illness hospitalizations (*n* = 382) compared to no hospitalizations (*n* = 493), and in the group with critical illness hospitalizations (*n* = 10) compared to no hospitalizations (*n* = 493).

^gIndicates that all participants with critical illness hospitalization had increasing ventricle size on follow-up neuroimaging.

^hThe OR refers to the odds of each outcome in the group with nonsurgical hospitalizations (*n* = 96) compared to no hospitalizations (*n* = 493), and in the group with major surgery hospitalizations (*n* = 196) compared to no hospitalizations (*n* = 493).

ⁱMajor surgery refers to procedures recognized as intermediate or high cardiac risk according to the 2007 American Heart Association guidelines on perioperative evaluation,¹⁵ and generally included spine, thyroid, thoracic, cardiac, vascular, gastrointestinal, hernia repair, and genitourinary procedures.

Hospitalization and changes on MRI studies. As shown in table 3, the odds of ventricular size increasing from baseline to follow-up were 1.57-fold greater among hospitalized compared to nonhospitalized participants. The odds of sulcal size increasing were also greater, although not significant (*p* = 0.06), among hospitalized participants, and there was no difference in incident infarcts by hospitalization status.

The odds of being in the top quintile of WMH volume change compared to the bottom 4 quintiles were 1.55 times higher for hospitalized compared to nonhospitalized participants. However, when we examined change in WMH using visual grade¹⁶ (0–9 scale) to account for potential imprecision in continuous volumetric estimates, we found no difference in the odds of being in the top quintile of increase in WMH visual grade by hospitalization status. Inferences were unchanged when multiple imputation was used to account for missing covariate data.

Exploratory characterizations of the hospital exposure.

Number of hospitalizations. There was a general dose effect in the association of each additional hospitalization and decline in DSST scores (0.58 symbol-digit pair decline with each hospitalization) and WFT scores (0.27 symbol-digit pair decline with each hospitalization) (figure 2 and table 2). With regard to neuroimaging outcomes, each additional hospitalization was associated with increased odds of being in the top quintile of WMH volume progression (odds ratio [OR] 1.23), of incident infarct (OR 1.17), and of ventricular size increase (OR 1.21) (table 3).

Severity of hospitalization. The number of participants with critical illness was small (*n* = 28 for

cognitive change and *n* = 10 for neuroimaging), thus limiting the ability to make rigorous comparisons. Nevertheless, there was significantly greater decline in DSST scores for participants hospitalized with critical compared to noncritical illness (table 2). With regard to neuroimaging outcomes, ventricular size increased by at least 1 grade in every participant hospitalized with critical illness, and this increase was significant compared to ventricular changes in participants with noncritical illness hospitalization (*p* = 0.02) (table 3).

Major surgical vs nonsurgical hospitalization. There were no large differences in cognitive outcomes among participants hospitalized with major surgery compared to no surgery (table 2). With regard to neuroimaging outcomes (table 3), the odds of worsening ventricle size were significantly increased among participants hospitalized with major surgery compared to no surgery (table 3).

Effect of race. Changes in cognitive and neuroimaging outcomes were examined according to race, and there was no significant race interaction for the association of hospitalization with any outcome (all *p* interactions > 0.05).

Potential mediation of cognitive changes by neuroimaging outcomes. We examined whether changes in ventricular size, white matter, or infarcts from the visit 3–MRI visit mediated the decline in DSST scores that was observed after hospitalization from visit 2–MRI visit. We found a 25% attenuation of estimated change in DSST scores when the amount of ventricle change was added to the model, indicating a modest mediating effect on decline in DSST scores. We found

Figure 2 Adjusted decline in cognitive test scores by number of noncritical illness hospitalizations

Adjusted decline in test scores for participants by number of hospitalizations, compared to the reference group of test score decline in participants with no hospitalizations. A (+) value for decline indicates that test scores worsened between baseline and follow-up, while a (–) value for decline indicates that test scores improved between baseline and follow-up. *Above each bar indicates a p value < 0.05 for the comparison of cognitive decline for that particular number of hospitalizations compared to the reference of no hospitalizations. Overall p value refers to the overall association between each additional hospitalization and decline in individual test score.

only small attenuation of cognitive coefficients (<15%) with the addition of WMH volume change, WMH visual grade increase, or incident infarcts to the model, indicating no substantial mediating effect.

DISCUSSION In this study of a subset of ARIC participants, hospitalizations were independently associated with a decline on one test of executive function (DSST), similar to results of previous studies,^{4,5} even with inclusion of more precise comorbidity measures. Further, hospitalizations were associated with increased ventricular size on brain MRI.

There are many potential explanations for the observed cognitive decline. Events during hospitalization have been associated with cognitive decline, including delirium,^{25–27} hypotension,²⁸ sedation,²⁹ acute lung injury,³⁰ and sepsis.³¹ Older adults may be particularly susceptible because of less cognitive reserve or increased susceptibility to inflammation.³² To better understand the etiology of decline in DSST scores, we examined characteristics of hospitalizations and found that both number of hospitalizations and critical illness were associated with increased decline in DSST scores, implying a potential dose effect of insults during hospitalization. There was no difference in DSST score change by race, or by nonsurgical vs major surgical hospitalization, implying that factors driving cognitive change may not be unique to the perioperative period.

We were particularly interested in the effect of hospitalization on changes in brain MRI, since we hypothesized that hospitalization might lead to structural brain changes and subsequent cognitive decline. Our results demonstrate increased ventricular size after hospitalization compared to no hospitalization, with both critical illness and major surgical hospitalizations even more highly associated with worsening ventricular size. These results are consistent with prior studies that have demonstrated associations between events during hospitalization (acute respiratory distress syndrome³³ or surgery³⁴) and increased cerebral atrophy, but the length of follow-up and the adjustment for important covariates distinguish our results.

We examined the potential mediating role of changes in ventricular size or WMH on cognitive decline, since both cerebral atrophy^{35,36} and WMH severity³⁷ and progression^{38,39} have been associated with decreases in cognition. Our results suggest that increased ventricular size (a marker of cerebral atrophy), but not changes in WMH, may mediate a portion of decline in DSST scores, although it appears that a large portion of cognitive change occurs independent of structural changes observable on brain MRI. However, these results are limited because MRI changes were assessed from visit 3–MRI visits, while cognitive change was assessed from visit 2–MRI visits, and thus should be considered hypothesis-generating.

An alternative explanation for our results is that underlying comorbidities may predispose patients to both hospitalizations and further cognitive or MRI

changes. To account for this possibility, previous studies have adjusted for patient self-reported comorbidities, thus leading to potential misclassification bias. We adjusted our models using precise comorbidity definitions or actual physiologic or genetic data from a well-characterized cohort. Additionally, we examined cognitive trajectories before and after hospitalization with each participant serving as his or her own control. Similar to our main results, we found worsening trajectory of decline in cognitive scores after hospitalization compared to before hospitalization.

Strengths of this study include a well-defined cohort with precise comorbidity definitions and both cognitive and MRI testing separated by ≥ 10 years. However, there are several limitations. First, as an observational study, our results could be explained by residual unmeasured confounding. Second, analysis of potentially important hospitalization characteristics may be underpowered to detect a difference among groups, and other factors (besides critical illness or major surgery) might be important in cognitive or brain MRI changes. Additionally, the association of white matter change with hospitalization was only significant when white matter change was considered as a continuous (not categorical) variable. Third, because the study population was slightly healthier than the general ARIC population, results may not be generalizable to all patients. Finally, cognitive testing was limited to 3 tests, which may not adequately characterize cognitive change. Recently, ARIC participants underwent extensive neurocognitive testing and dementia classification, so further studies in ARIC participants will be able to address this limitation.

The results of this study highlight cognitive consequences of hospitalization in a community cohort. The results provide a rationale for research to characterize the timing and etiology of cognitive and brain MRI changes after hospitalization, to determine modifiable risk factors, and to determine whether increased prevention, monitoring, or rehabilitation efforts can improve cognitive outcomes after hospitalization.

AUTHOR CONTRIBUTIONS

Charles Brown helped design the study, perform the statistical analysis, draft and review the manuscript, and approved the final manuscript. A. Richey Sharrett helped design the study, revise the manuscript, and approved the final manuscript. Josef Coresh provided input into the analysis, helped revise the manuscript, and approved the final manuscript. Andrea L.C. Schneider provided input into the statistical analysis, helped revise the manuscript, and approved the final manuscript. Alvaro Alonso provided input into the analysis, helped revise the manuscript, and approved the final manuscript. David S. Knopman provided input into the analysis, helped revise the manuscript, and approved the final manuscript. Thomas H. Mosley provided input into the analysis, helped revise the manuscript, and approved the final manuscript. Rebecca F. Gottesman helped design the study, provided input into the statistical analysis, helped revise the manuscript, and approved the final manuscript.

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DISCLOSURE

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REFERENCES

1. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002;39:930–936.
2. Mahoney JE, Palta M, Johnson J, et al. Temporal association between hospitalization and rate of falls after discharge. *Arch Intern Med* 2000;160:2788–2795.
3. Walter L, Brand R, Counsell S, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;285:2987–2994.
4. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA* 2010;303:763–770.
5. Wilson RS, Hebert LE, Scherr PA, Dong X, Leurgans SE, Evans DA. Cognitive decline after hospitalization in a community population of older persons. *Neurology* 2012;78:950–956.
6. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
7. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler M. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2013;348:1215–1222.
8. Jack CR, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology* 2004;62:591–600.
9. DeBette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010;341:c3666.
10. Schmidt R, Petrovic K, Ropele S, Enzinger C, Fazekas F. Progression of leukoaraiosis and cognition. *Stroke* 2007;38:2619–2625.

11. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol* 1989;129:687–702.
12. Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement* 2009;5:207–214.
13. Liao D, Cooper L, Cai J, et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control: the ARIC study. *Stroke* 1996;27:2262–2270.
14. Wagenknecht L, Wasserman B, Chambless L, et al. Correlates of carotid plaque presence and composition as measured by MRI. *Circ Cardiovasc Imaging* 2009;2:314–322.
15. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2007;50:1707–1732.
16. Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Arch Neurol* 1989;46:141–145.
17. Wechsler D. Manual for the Wechsler Adult Intelligence Scale, First Edition. San Antonio, TX: Psychological Corporation; 1955.
18. Benton AL, Eslinger PJ, Damasio AR. Normative observations on neuropsychological test performances in old age. *J Clin Neuropsychol* 1981;3:33–42.
19. Schneider AL, Sharrett AR, Patel MD, et al. Education and cognitive change over 15 years: the Atherosclerosis Risk in Communities Study. *J Am Geriatr Soc* 2012;60:1847–1853.
20. Gottesman R, Coresh J, Catellier D, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2010;41:3–8.
21. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology* 2011;76:1879–1885.
22. Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): a new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
23. Royston P. Multiple imputation using missing values: update. *Stata J* 2005;5:118–201.
24. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: Wiley; 1987.
25. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;367:30–39.
26. Rudolph JL, Marcantonio ER. Postoperative delirium: acute change with long-term implications. *Anesth Analg* 2011;112:1202–1211.
27. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev* 2004;14:87–98.
28. Yocum GT, Gaudet JG, Teverbaugh LA, et al. Neurocognitive performance in hypertensive patients after spine surgery. *Anesthesiology* 2009;110:254–261.
29. Pandharipande P, Pun B, Herr D, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298:2644–2653.
30. Herridge MS, Cheung AM, Tansey CM. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–693.
31. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–1794.
32. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol* 2007;7:161–167.
33. Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. *Brain Inj* 2006;20:263–271.
34. Kline RP, Pirraglia E, Cheng H, et al. Surgery and brain atrophy in cognitively normal elderly subjects and subjects diagnosed with mild cognitive impairment. *Anesthesiology* 2012;116:603–612.
35. Jack CR, Shiung MM, Weigand SD, et al. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnesic MCI. *Neurology* 2005;65:1227–1231.
36. Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology* 1999;52:1687–1689.
37. Verdelho A, Madureira S, Moleiro C, et al. White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology* 2010;75:160–167.
38. Longstreth WT, Arnold AM, Beauchamp NJ, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The Cardiovascular Health study. *Stroke* 2004;36:56–61.
39. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology* 2012;79:442–448.