ANESTHESIOLOGY

Association of Surgical Hospitalization with Brain Amyloid Deposition

The Atherosclerosis Risk in Communities–Positron Emission Tomography (ARIC–PET) Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hospitalization for medical illness and surgical procedures has been associated with subsequent cognitive decline in some older patients
- Animal models have suggested that surgery and anesthesia may lead to an increased production and accumulation of brain amyloid

What This Article Tells Us That Is New

- This study found no differences in brain amyloid levels measured by positron emission tomography scans more than a decade after hospitalization for a surgical procedure when compared with patients who were not hospitalized and did not have a surgical procedure
- When low-risk surgical procedures were removed from the analysis, there was a small but statistically significant increase in brain amyloid in patients who had high-risk surgical procedures when compared with all patients who did not have a surgical procedure
- On secondary analysis, patients with two or more surgical hospitalizations had a higher odds of elevated brain amyloid during late life when compared with participants with no surgical hospitalizations regardless of whether they had been hospitalized for medical reasons
- These data suggest that high-risk surgical procedures and multiple surgical procedures may be associated with increases in brain amyloid

ABSTRACT

Background: As more older adults undergo surgery, it is critical to understand the long-term effects of surgery on brain health, particularly in relation to the development of Alzheimer's disease. This study examined the association of surgical hospitalization with subsequent brain β-amyloid deposition in nondemented older adults.

Methods: The Atherosclerosis Risk in Communities–Positron Emission Tomography (ARIC–PET) study is a prospective cohort study of 346 participants without dementia who underwent florbetapir PET imaging. Active surveillance of local hospitals and annual participant contact were used to gather hospitalization and surgical information (International Classification of Disease, Ninth Revision, Clinical Modification codes) over the preceding 24-yr period. Brain amyloid measured using florbetapir PET imaging was the primary outcome. Elevated amyloid was defined as a standardized uptake value ratio of more than 1.2.

Results: Of the 313 participants included in this analysis (age at PET: 76.0 [SD 5.4]; 56% female), 72% had a prior hospitalization, and 50% had a prior surgical hospitalization. Elevated amyloid occurred in 87 of 156 (56%) participants with previous surgical hospitalization, compared with 45 of 87 (52%) participants who had no previous hospitalization. Participants with previous surgical hospitalizations did not show an increased odds of elevated brain amyloid (odds ratio, 1.32; 95% CI, 0.72 to 2.40; $P = 0.370$) after adjusting for confounders (primary analysis). Results were similar using the reference group of all participants without previous surgery (hospitalized and nonhospitalized; odds ratio, 1.58; 95% CI, 0.96 to 2.58; $P = 0.070$). In a prespecified secondary analysis, participants with previous surgical hospitalization did demonstrate increased odds of elevated amyloid when compared with participants hospitalized without surgery (odds ratio, 2.10; 95% CI, 1.09 to 4.05; $P = 0.026$). However, these results were attenuated and nonsignificant when alternative thresholds for amyloid-positive status were used.

Conclusions: The results do not support an association between surgical hospitalization and elevated brain amyloid.

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Cognitive impairment after surgery and anesthesia in older adults is increasingly recognized as common and important. Accordingly, the American Society of Anesthesiologists (Schaumburg, Illinois) recently established a perioperative Brain Heath Initiative to focus awareness on this issue. The highest risk period for postoperative cognitive change appears to be days to weeks after surgery.[1–3] Long-term cognitive impairment or increased risk of dementia has also been described,[3–5] although the evidence regarding the putative role for surgery and anesthesia

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is conflicting.[6,7] For example, a recent study found differing associations between surgical hospitalization and dementia risk across clinical and registry-based cohorts.[8] Risk factors for postoperative cognitive decline, such as critical illness,[9] and delirium[10,11] have been identified, but the neurobiologic mechanisms that might underlie cognitive decline after surgical hospitalization are not clear. One hypothesis is that perioperative events promote the deposition of β -amyloid (amyloid), a protein that is thought to play a key role in the pathogenesis of Alzheimer's disease.[12] Preliminary support for this hypothesis has emerged from cell culture and animal studies, which suggest that surgery- and anesthesia-related mechanisms, including volatile anesthetics and inflammation, may cause an increased production and accumulation of brain amyloid.[13–15] However, data from humans are scarce, and to the best of our knowledge, there are no large studies examining cortical amyloid deposition in humans after surgery. Thus, there is a clear need to understand the molecular brain changes associated with undergoing surgery in middle and late adulthood, in particular the role of amyloid deposition. If surgery or perioperative events influence cortical amyloid deposition, this would have meaningful implications for clinical decision making and management, especially for older adults at risk for dementia.

We used data from a cohort of older adults enrolled in the Atherosclerosis Risk in Communities–Positron Emission Tomography (ARIC–PET) study[16] to examine whether individuals hospitalized for a surgical procedure (henceforth referred to as "surgical hospitalization") in the decades leading up to older adulthood had elevated cortical amyloid levels, as measured using florbetapir PET imaging. We hypothesized that surgical hospitalization, particularly for a procedure with moderate to high cardiac risk, is associated with increased cortical amyloid in late life.

Materials and Methods

Participants and Procedures

ARIC is an ongoing community-based cohort study, which initially recruited 15,792 participants between 1987 and 1989 (visit 1) from four U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; the northwestern suburbs of Minneapolis, Minnesota; and Jackson, Mississippi (African Americans only).[17] As is illustrated in figure 1, participants were brought back for four additional visits until visit 5 (which occurred 2011 to 2013). At visit 5, approximately 2,000 participants (a group of participants with cognitive impairment and an age-matched group of cognitively normal participants) were selected to receive a brain magnetic resonance imaging (criteria for selection is outlined in the Supplemental Digital Content 1, http://links.lww.com/ALN/C304).[18] Among these, 346 participants at three ARIC sites (Forsyth County, North Carolina; Jackson, Mississippi; and Washington County, Maryland) without dementia, heavy current alcohol use, renal dysfunction (with creatinine levels greater than 2 mg/dl), or prolonged QT-c interval (more than 450 ms) were selected to take part in ARIC–PET.[16] Participant exclusion criteria are listed in figure 1, and a detailed study flowchart is provided in Supplemental Digital Content 2 (http://links.lww.com/ALN/C305). We excluded a small number of participants who did not meet ARIC–PET inclusion criteria (n = 3) or were missing important covariates (n = 4). We excluded another 26 participants who had missing International Classification of Disease, Ninth Revision codes because we could not ascertain the type of hospitalization. For the remainder of participants, we used a complete case analysis (with the underlying assumption of missing completely at random). All ARIC study protocols were approved by the Institutional Review Boards at each participating center: University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Johns Hopkins University, Baltimore, Maryland; University of Minnesota, Minneapolis, Minnesota; and University of Mississippi Medical Center, Jackson, Mississippi.

Measurement of Surgery Variables

All hospital events (surgical and nonsurgical) were identified using active surveillance of local hospitals and annual telephone contact between the time-of-study baseline (visit 1) until the time of the PET scan. All hospital discharge codes were reviewed and abstracted by trained staff. Based on methods that have been described previously,[19] we used International Classification of Disease, Ninth Revision, Clinical Modification codes and clinical classification software to categorize all surgical procedures documented during each hospitalization. International Classification of Disease, Ninth Revision, Clinical Modification codes have been validated as a method for the identification of hospital-based surgical procedures with generally good sensitivity and excellent specificity.[20] Surgical and other procedures were classified as either "low risk" or "moderate-to-high risk" by an experienced anesthesiologist according to 2014 American College of Cardiology/American Heart Association guidelines.[21] Of note, the primary analyses included endoscopic procedures in the low-risk group based on the American College of Cardiology/American Heart Association guidelines. A complete list of surgical procedures listed according to their level of risk is provided in Supplemental Digital Content 3 (http://links.lww.com/ALN/C306). Participants with missing International Classification of Disease, Ninth Revision, Clinical Modification codes for one or more hospitalization (n = 26) were excluded unless the participant had a separate hospitalization that included a moderate/high surgery.

Brain Positron Emission Tomography and Magnetic Resonance Imaging

The outcome of interest was cortical amyloid deposition, as defined by florbetapir PET imaging. Compared with

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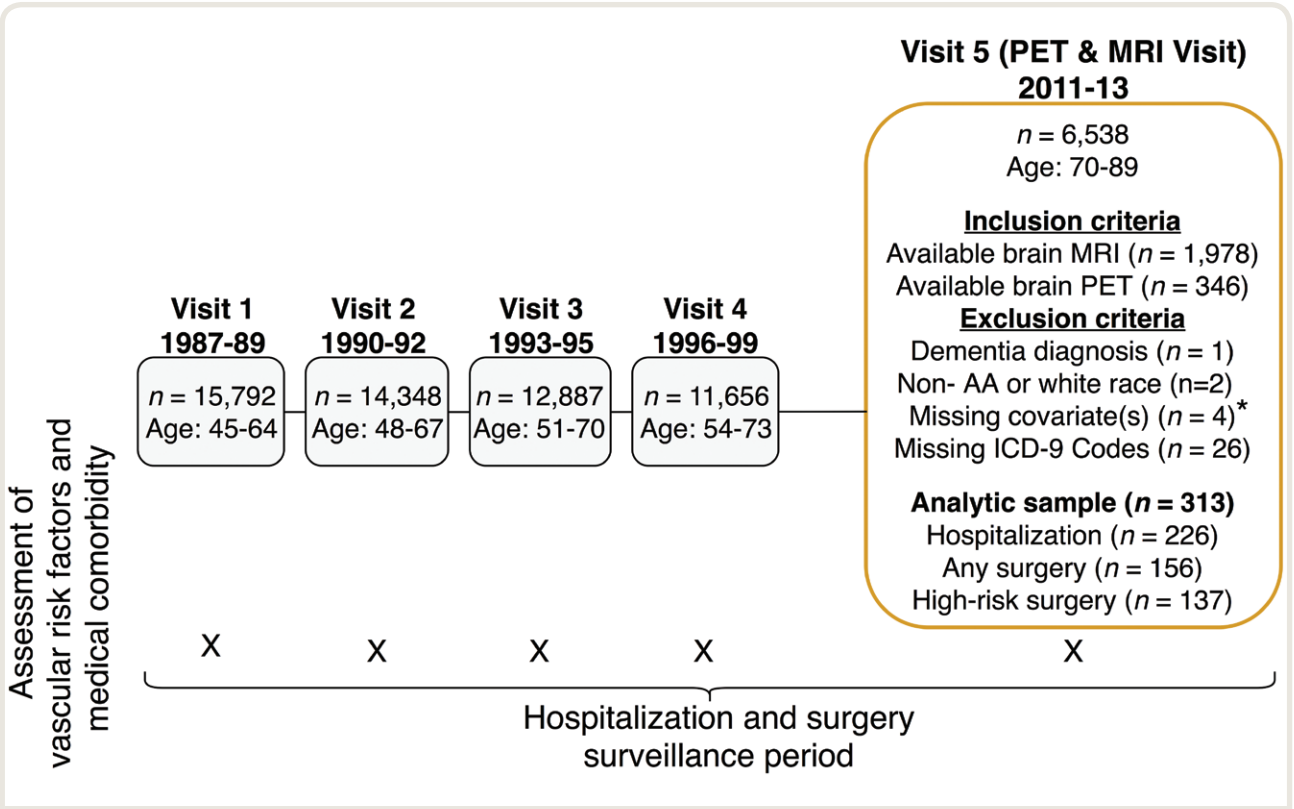

Fig. 1. Study flow diagram and inclusion/exclusion criteria. *Participants missing one or more of the demographic covariates incorporated in model 1 were excluded from the analytic sample. AA, African American; ICD-9, International Classification of Disease, Ninth Revision; MRI, magnetic resonance imaging; PET, positron emission tomography.

the gold standard (neuropathologic studies of postmortem amyloid burden), florbetapir PET has demonstrated excellent validity and reliability in distinguishing individuals with absent or sparse cortical amyloid from those with moderate to frequent plaques.[22] Visit 5 magnetic resonance imaging scans were analyzed at the ARIC Magnetic Resonance Imaging Reading Center (Mayo Clinic) using previously described methods.[18] Florbetapir (amyloid) PET scans were performed within 1 yr of brain magnetic resonance imaging.[16] PET imaging procedures are detailed in the Supplemental Digital Content 4 (http://links.lww.com/ALN/C307). We calculated a global measure of florbetapir uptake using a volume-dependent weighted average of the following regions: orbitofrontal, prefrontal, and superior frontal cortices; the lateral temporal, parietal, and occipital lobes; and the precuneus, the anterior cingulate, and the posterior cingulate. We used an automated area of cerebellar gray matter as a reference region.[23] In accordance with previously published methods,[16,24,25] elevated cortical amyloid, defined *a priori* as a global standardized uptake value ratio above the sample median (1.2), was prespecified as the primary outcome. Sensitivity analyses evaluated alternative thresholds for elevated amyloid (standardized uptake value ratios of more than 1.11[26] and more than 1.25) and examined global and brain region-specific amyloid standardized uptake value ratio as a continuous variable (log transformed to correct for skewness).

Assessment of Covariates

Participant age, sex, education, center (Maryland/North Carolina/Mississippi), and race (white/African American) were obtained at baseline from participant self-report. *APOE* allele status was determined using the TaqMan assay (Applied Biosystems, USA). We incorporated physiologic variables assessed during visit 5: body mass index, calculated from recorded height and weight (kg/m^2); total cholesterol, measured using the enzymatic method[27]; and high density lipoprotein cholesterol, calculated using Friedewald's formula. Cigarette and alcohol use status (current/former/never) were determined based on participant self-report at visit 5.

We determined the presence/absence of the following medical conditions assessed at visit 5: hypertension, defined as antihypertensive medication use, or systolic or diastolic blood pressure of more than 140 mmHg and more than 90 mmHg, respectively; diabetes, defined as either participant report of a diabetes diagnosis from a physician, a fasting glucose level of at least 126 mg/dl, a nonfasting glucose level of at least 200 mg/dl, or current use of diabetes medication;

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coronary heart disease, adjudicated after visit 1 based on self-report or medical record evidence of previous myocardial infarction, coronary artery bypass graft, or angioplasty, or the presence of a myocardial infarction as determined by electrocardiogram; heart failure, defined as a previous heart failure–related hospitalization or heart failure medication use within the 2 weeks preceding the study visit; chronic obstructive pulmonary disease (COPD), defined based on participant report of previous COPD or emphysema diagnosis from a physician[28]; and chronic kidney disease, defined based on estimated glomerular filtration rate, which was calculated using demographic characteristics and serum creatinine.[29]

Statistical Analysis

A statistical plan for these hypotheses was developed before accessing the data and approved by the ARIC study publications committee on February 14, 2017. We used multivariable logistic regression to examine the association of surgical hospitalization with cortical amyloid deposition. We compared participants with one or more previous surgical hospitalization with participants who were not previously hospitalized during the follow-up period (prespecified primary analysis). Additionally, we conducted a series of secondary analyses to determine how the use of alternative nonsurgery comparison groups may influence the findings. First, we compared participants with surgical hospitalizations with a group of hospitalized participants who did not undergo surgery (prespecified secondary analysis). Second, we compared participants with surgical hospitalization to the total group of participants without surgical hospitalization (*i.e.*, the combined group of persons hospitalized without surgery and persons without previous hospitalization). Third, we examined the association of multiple surgical hospitalizations with cortical amyloid deposition by categorizing all participants into one of three groups based on the total number of surgical hospitalizations (zero, one, or at least two). Seventeen participants with one or more hospitalization with missing International Classification of Disease, Ninth Revision, Clinical Modification codes were excluded from the latter analysis. Findings from each of these secondary analyses are considered exploratory and should therefore be interpreted with caution.

To adjust for potential confounders, we used two regression models. The first model (model 1) adjusted for demographic factors (age, sex, education, race, center, and *APOE* ε4 status). We used a second model to account for the confounding effects of cardiovascular risk factors and chronic medical comorbidity.[24] This second model (model 2) adjusted additionally for late-life physiologic variables (body mass index, total cholesterol, and high-density lipoprotein), alcohol and cigarette use, and individual prevalent disease (hypertension, diabetes, coronary heart disease, heart failure, chronic kidney disease, and COPD) diagnosed at the time of visit 5. *Post hoc* analyses were conducted to examine whether findings differed when amyloid standardized uptake value ratio was parameterized as a continuous variable, and when the potential effects of selection into the ARIC–PET study were accounted for using inverse probability weighting (Supplemental Digital Content 5, http://links.lww.com/ALN/C308). Additionally, *APOE* ε4 status (defined as 0 *vs.* at least 1 ε4 alleles) was examined as an effect modifier. Additional sensitivity analyses examined the potential effect of reverse causation (*i.e.*, amyloid brain changes increasing surgery risk) by excluding participants with an initial surgical hospitalization within the span of 5 yr before PET imaging and evaluated alternative thresholds for elevated amyloid. A minimum clinically meaningful odds ratio for elevated amyloid standardized uptake value ratio was not defined because of a lack of empirical data to guide this choice. The sample size for this analysis was derived based on available data from the ARIC–PET study.[16,24] A two-sided P value < 0.05 was used as the cutoff for statistical significance. Analyses were conducted using Stata, version 14 (StataCorp, USA).

Results

Of the 313 participants included in the analytic sample, 56% (n = 175) were women, 40% (n = 125) were African American, 74% (n = 232) were cognitively normal, and 26% (n = 81) met criteria for mild cognitive impairment. Participants were 52.4 ± 5.2 yr of age (± SD) at study baseline and 76.0 ± 5.4 yr of age at the time of the PET scan. The average time between the baseline visit and PET scan was 25.2 ± 0.9 yr. Of the 226 (72%) participants who were hospitalized during the study period, 156 (69%) had one or more surgical hospitalizations, and 137 (61%) had one or more hospitalizations for a moderate to high-risk surgery. The average time between initial surgery and PET scan was 13.7 ± 7.4 yr; Supplemental Digital Content 6, http://links.lww.com/ALN/C309, histogram of the number of years between initial surgery and PET scan). As displayed in table 1, participants with a surgical hospitalization were slightly older and had greater prevalence of coronary heart disease compared with participants without a previous surgical hospitalization. Participants with one or more moderate-to-high-risk surgical hospitalization showed a similar pattern of a greater prevalence of heart disease and were less likely to possess a single *APOE* ε4 allele, compared with participants without surgical hospitalization. Group characteristics for participants with moderate to high-risk surgery are presented in Supplemental Digital Content 7 (http://links.lww.com/ALN/C310).

Primary Analysis of Surgical Hospitalization and Late-life Brain Amyloid

The prevalence of elevated amyloid levels among surgery, nonsurgery hospitalized, and nonhospitalized groups is displayed in figure 2A. In the primary analysis of 243 participants,

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Table 1. Participant Characteristics at Visit 5 (Positron Emission Tomography/Magnetic Resonance Imaging Visit; 2011 to 2013)

Characteristic	Surgical Hospitalization before PET Imaging (n = 156)	Nonsurgical Hospitalization before PET Imaging (n = 70)	No Hospitalization before PET Imaging (n = 87)
Demographic variables			
Age*	76.8 ± 5.7	75.4 ± 5.1	75.1 ± 4.7
Female (%)	85 (54.5)	38 (54.3)	52 (59.8)
African American (%)	65 (41.7)	21 (30.0)	39 (44.8)
Education (%)			
Less than high school	25 (16.0)	13 (18.6)	10 (11.5)
High school/general equivalency diploma/vocational	72 (46.2)	25 (35.7)	40 (46.0)
College/graduate/professional	59 (37.8)	32 (45.7)	37 (42.5)
Apolipoprotein E ε4 alleles (%)			
0	112 (71.8)	48 (68.6)	57 (65.5)
1	38 (24.4)	22 (31.4)	29 (33.3)
2	6 (3.9)	0 (0)	1 (1.1)
Physiologic and lab variables			
Body mass index, kg/m^2*	29.5 ± 5.7	28.9 ± 5.2	28.2 ± 4.6
Total cholesterol, mg/dl*	177.8 ± 36.9	177.6 ± 38.6	187.9 ± 39.0
High-density lipoprotein, mg/dl†	51.8 ± 13.2	48.0 ± 12.8	52.2 ± 13.2
Low-density lipoprotein, mg/dl*	101.8 ± 31.0	103.7 ± 30.6	110.5 ± 33.6
Cigarette smoking status (%)			
Current	6 (3.9)	7 (10.0)	1 (1.2)
Former	82 (53.6)	32 (45.7)	42 (48.8)
Never	65 (42.5)	31 (44.3)	43 (50.0)
Alcohol consumption (%)			
Current	54 (34.6)	32 (45.7)	38 (43.7)
Former	56 (35.9)	22 (31.4)	25 (28.7)
Never	46 (29.5)	16 (22.9)	24 (27.6)
Prevalent medical comorbidity (%)*			
Hypertension	111 (72.1)	51 (72.9)	59 (67.8)
Diabetes mellitus	67 (43.5)	21 (30.0)	26 (30.6)
Coronary heart disease*†	21 (13.7)	2 (2.9)	1 (1.2)
Heart failure*	8 (5.1)	4 (5.7)	0 (0)
Cancer	5 (3.2)	2 (2.9)	1 (1.2)
Chronic obstructive pulmonary disease	10 (6.5)	7 (10.0)	2 (2.3)
Chronic kidney disease	51 (32.7)	17 (24.3)	22 (25.3)
Cognitive status (%)			
Cognitively normal	109 (69.9)	57 (81.4)	66 (75.9)
Mild cognitive impairment	47 (30.1)	13 (18.6)	21 (24.1)

The values are displayed as mean ± SD for continuous variables and frequency (column and percentage) for categorical variables, unless otherwise specified.
*$P < 0.05$ for difference between the surgical hospitalization and no hospitalization group. †$P < 0.05$ for difference between the surgical hospitalization and nonsurgical hospitalization group.
PET, positron emission tomography.

which compared participants with one or more previous surgical hospitalization (87 of 156 [56%] amyloid-positive) with participants without previous hospitalization (45 of 87 [52%] amyloid-positive), there was no difference in odds of elevated brain amyloid after adjusting for demographic factors or after additionally adjusting for cardiovascular risk factors and prevalent disease (table 2). Similarly, in an analysis of 224 participants (excluding participants with only low-risk surgery), those with one or more moderate to high-risk surgeries (77 of 137 [56%] amyloid-positive) compared with participants without previous hospitalization (45 of 87 [52%] amyloid-positive) did not show increased odds of elevated brain amyloid after adjusting for demographic factors or after additionally adjusting for cardiovascular risk factors and prevalent disease (table 2). These results were similar in *post hoc* analyses that modeled amyloid as a continuous variable (Supplemental Digital Content 8, http://links.lww.com/ALN/C311), in analyses that used inverse probability weighting to account for selection (Supplemental Digital Content 9, http://links.lww.com/ALN/C312), in analyses that excluded individuals who underwent procedures that are generally performed with sedation alone (such as endoscopy and other minor procedures; Supplemental Digital Content 10, http://links.lww.com/ALN/C313), and in analyses that additionally adjusted for cognitive status and white matter hyperintensity volume (data not shown). There was no evidence for effect modification by *APOE* ε4 status (Supplemental Digital Content 11, http://links.lww.com/ALN/C314) or age (< 76 *vs.* ≥ 76, the sample median; Supplemental Digital Content 12, http://links.lww.com/ALN/C315).

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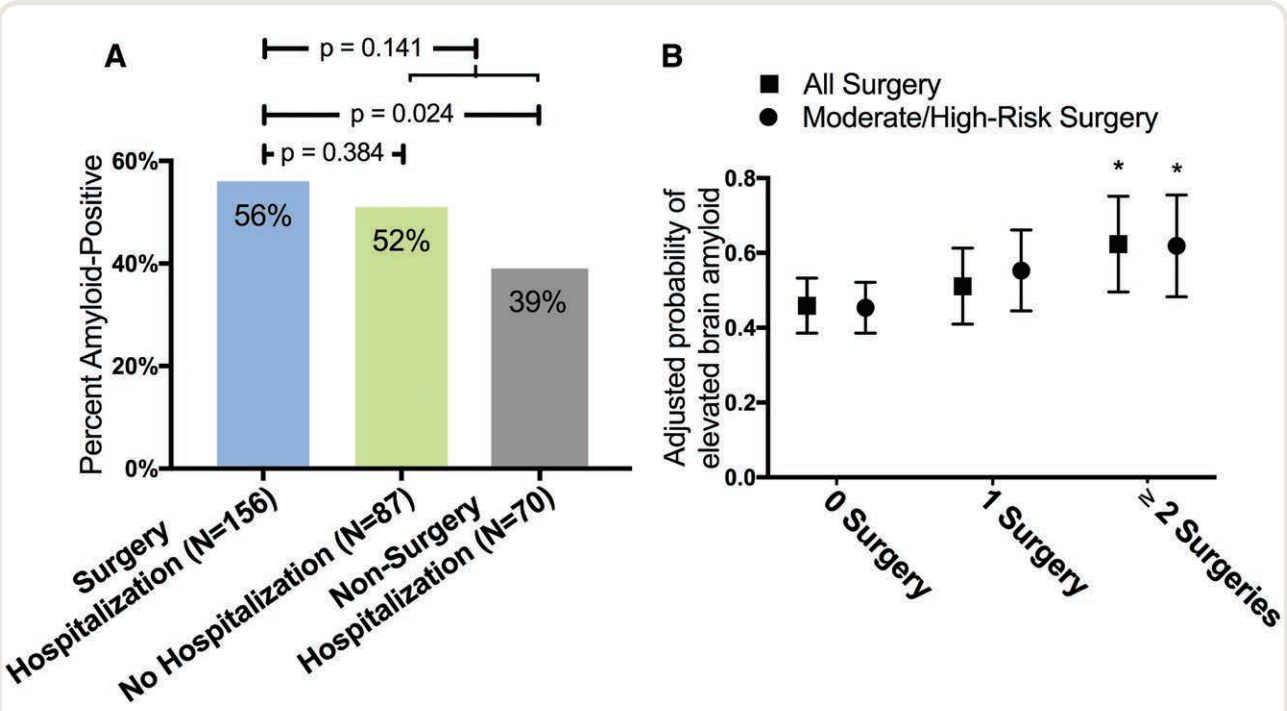

Fig. 2. The prevalence and probability of elevated cortical amyloid according to surgical hospitalization. (*A*) The prevalence of elevated cortical amyloid levels among participants with previous surgical hospitalization and among each nonsurgery comparison group. Of note, the prevalence of amyloid-positive status among the combined group of participants without surgery was 46%. The *P* values were calculated using logistic regression models that adjusted for demographic factors, cardiovascular risk factors, and prevalent disease. (*B*) The estimated adjusted probability of elevated late-life (visit 5) brain amyloid according to the number of surgical hospitalizations. The values represent estimates from fully adjusted logistic regression models. Of the 280 participants included in this analysis, 54% (n = 151), 28% (n = 79), and 18% (n = 50) of participants had 0, 1, and at least 2 surgeries, respectively; 60% (n = 169), 25% (n = 69), and 15% (n = 42) of participants had 0, 1, and at least 2 moderate/high-risk surgeries, respectively. The test for differences among the all surgery groups and the moderate/high-risk surgery groups were nonsignificant with *P* values of $P = 0.123$ and $P = 0.089$, respectively. *$P < .05$ compared with the no-surgery group.

Secondary Analysis of Alternative Comparison Groups

In a prespecified secondary analysis (n = 226) that compared participants who had one or more surgical hospitalization (87 of 156 [56%] amyloid-positive) with participants who were hospitalized without surgery (27 of 70 [39%] amyloid-positive), surgical hospitalization was associated with a 2.10 greater odds (95% CI, 1.09 to 4.05) of elevated brain amyloid during late life after adjusting for demographic variables (small to medium effect size).[30] Similar results were observed after additionally adjusting cardiovascular risk factors (odd radio, 2.45; 95% CI, 1.13 to 5.33; table 3). Participants with one or more moderate-to-high-risk surgeries (77 of 137 [56%] amyloid-positive) also had a significantly higher odds of elevated brain amyloid during late life compared to participants who were previously hospitalized without moderate-to-high-risk surgery (37 of 89 [42%] amyloid-positive; table 3).

In an analysis of 313 participants that expanded the nonsurgery comparison group to include all participants (hospitalized and nonhospitalized) without a surgical hospitalization, participants with one or more surgical hospitalization (87 of 156 [56%] amyloid-positive) did not differ significantly from the nonsurgery group (72 of 157 [46%] amyloid-positive) with regard to odds of elevated amyloid (table 3). The results of *post hoc* analyses were largely similar when amyloid was modeled as a continuous variable (Supplemental Digital Content 13, http://links.lww.com/ALN/C316).

Secondary Analysis of Number of Surgical Hospitalizations and Late-life Brain Amyloid

In an analysis of 280 participants not missing International Classification of Disease, Ninth Revision, Clinical Modification codes, participants with two or more surgical hospitalizations had 2.33 higher odds of elevated amyloid (95% CI, 1.04 to 5.24) during late life, compared with participants with no surgical hospitalizations (both hospitalized and nonhospitalized; table 4). Figure 2B displays the estimated probability of elevated amyloid according number of surgical hospitalizations.

Sensitivity and *Post Hoc* Analyses

The results were largely similar in analyses that excluded participants (n = 29) who had an initial surgery within 5 yr

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Table 2. Association of Surgical Hospitalization with Elevated Late-life (Visit 5) Brain β-Amyloid Deposition

	Surgery Group	Comparison Group	Model 1		Model 2	
	n/N (% Amyloid+)	n/N (% Amyloid+)	OR (95% CI)*	*P* Value	OR (95% CI)*	*P* Value
All surgery *vs.* never hospitalized	87/156 (56%)	45/87 (52%)	1.32 (0.72, 2.40) N = 243	0.370	1.36 (0.68, 2.72) N = 228	0.384
Moderate/high-risk surgery *vs.* never hospitalized	77/137 (56%)	45/87 (52%)	1.39 (0.75, 2.59) N = 224	0.299	1.46 (0.71, 2.99) N = 210	0.306

Model 1 is adjusted for age, center, race, sex, education, and *APOE* ε4 status. Model 2 is additionally adjusted for body mass index, total cholesterol, high-density lipoprotein, alcohol use and smoking status, and prevalent hypertension, diabetes, coronary heart disease, heart failure, chronic kidney disease, and COPD, as assessed at visit 5. Sixteen participants included in model 1 were excluded from model 2 because of missing one or more model 2 covariate. The moderate/high-risk surgery comparison excluded 19 participants with only a previous low-risk surgery.

*OR represents the adjusted odds for elevated brain amyloid of the surgery group as compared with the no-surgery referent group

COPD, chronic obstructive pulmonary disease; n, number of amyloid-positive participants; N, total number of participants; OR, odds ratio.

Table 3. Secondary Analyses Examining the Association of Surgical Hospitalization with Elevated Late-life (Visit 5) Brain β-Amyloid Deposition

	Surgery Group	Comparison Group	Model 1		Model 2	
	n/N (% Amyloid+)	n/N (% Amyloid+)	OR (95% CI)*	*P* Value	OR (95% CI)*	*P* Value
All surgery						
All surgery *vs.* hospitalization without surgery	87/156 (56%)	27/70 (39%)	2.10 (1.09, 4.05) N = 226	0.026	2.45 (1.13, 5.33) N = 215	0.024
All surgery *vs.* no surgery†	87/156 (56%)	72/157 (46%)	1.58 (0.96, 2.58) N = 313	0.070	1.52 (0.87, 2.66) N = 297	0.141
Moderate/high-risk surgery						
Moderate/high-risk surgery *vs.* hospitalization without moderate/high-risk surgery	77/137 (56%)	37/89 (42%)	2.12 (1.13, 3.96) N = 226	0.018	2.64 (1.26, 5.56) N = 215	0.010
Moderate/high-risk surgery *vs.* no moderate/high-risk surgery†	77/137 (56%)	82/176 (47%)	1.69 (1.02, 2.80) N = 313	0.041	1.74 (0.99, 3.08) N = 297	0.055

Model 1 is adjusted for age, center, race, sex, education, and *APOE* ε4 status. Model 2 is additionally adjusted for body mass index, total cholesterol, high-density lipoprotein, alcohol use and smoking status, and prevalent hypertension, diabetes, coronary heart disease, heart failure, chronic kidney disease, and COPD, as assessed at visit 5. Sixteen participants included in model 1 were excluded from model 2 because of missing one or more model 2 covariate.

*OR represents the adjusted odds for elevated brain amyloid of surgery group as compared with the no-surgery referent group. †The reference group is participants without surgery (both hospitalized and nonhospitalized).

COPD, chronic obstructive pulmonary disease; n, number of amyloid-positive participants; N, total number of participants; OR, odds ratio.

of PET imaging (Supplemental Digital Content 14, http://links.lww.com/ALN/C317) and in analyses that examined participants with their first surgical hospitalizations occurring proximal and distal to the time of PET imaging (distal defined as a surgical hospitalization at least 14 yr before PET imaging [median time]; Supplemental Digital Content 15, http://links.lww.com/ALN/C318). We also repeated analyses using alternative thresholds to define amyloid positive status.[26] Using a more liberal (standardized uptake value ratio of more than 1.11) and a more conservative (standardized uptake value ratio or more than 1.25) threshold, associations between surgical hospitalization and amyloid positive status were generally attenuated and were no longer statistically significant (Supplemental Digital Content 16 and 17, http://links.lww.com/ALN/C319 and http://links.lww.com/ALN/C320, respectively). *Post hoc* analyses that looked at the association of hospitalization with continuous markers of cortical amyloid across distinct brain regions are presented in Supplemental Digital Content 18 (http://links.lww.com/ALN/C321). The primary comparison showed no region-specific differences.

Discussion

In a community sample of nondemented older adults enrolled in the ARIC–PET study, we did not find support for an association between past surgical hospitalization and elevated cortical amyloid levels in the primary analysis. Participants with one or more surgical hospitalizations did not differ significantly from participants without previous

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Table 4. Association of Total Number of Surgical Hospitalizations with Late-life Brain β-Amyloid Deposition

	All Surgery (N = 280)		Moderate/High-Risk Surgery (N = 280)	
Number of Hospitalizations	OR (95% CI)* n/N (% Amyloid+)	*P* Value	OR (95% CI)* n/N (% Amyloid+)	*P* Value
No surgery	Reference 70/151 (46%)	—	Reference 79/169 (47%)	—
1 surgery	1.30 (0.68, 2.49) 40/79 (51%)	0.423	1.66 (0.85, 3.27) 37/69 (54%)	0.139
2 surgeries	2.33 (1.04, 5.24) 31/50 (62%)	0.041	2.35 (1.01, 5.44) 25/42 (60%)	0.046

The results are adjusted for age, center, race, sex, education, *APOE* ε4 status, body mass index, total cholesterol, high-density lipoprotein, alcohol use and smoking status, and prevalent hypertension, diabetes, coronary heart disease, heart failure, chronic kidney disease, and chronic obstructive pulmonary disease, as assessed at visit 5. All participants missing one or more International Classification of Disease, Ninth Revision, Clinical Modification codes (n = 17) were excluded from the current analysis. Additionally, 16 participants were excluded from this analysis because of missing one or more model 2 covariate.

*OR represents the adjusted odds for elevated brain amyloid as compared to the no surgery referent group.

n, number of amyloid-positive participants; N, total number of participants.; OR, odds ratio; —, no *P* value was calculated for the No Surgery reference group.

hospitalization with regard to odds of elevated amyloid, after adjusting for potentially confounding variables. The results were similar when the subset of participants with one or more moderate to high-risk surgeries was compared with participants without a previous hospitalization.

Few human studies have examined the association between surgery and brain amyloid deposition. A recent study measured florbetapir (amyloid) PET in a small number of patients 6 weeks and 1 yr after cardiac surgery. The authors found 1-yr increases in amyloid in the cardiac surgery group that were greater than that which has been reported previously in nonsurgery cohorts.[31] However, this study was limited by a small sample size, the absence of a nonsurgery comparison group, and the exclusive focus on cardiac surgery patients limits the generalizability of these findings. Two human studies examined cerebral spinal fluid after surgery. Although these studies found a decreased amyloid/Tau ratio after surgery (indicative of greater Alzheimer's disease burden), this change was largely due to an increase in Tau rather than changes in amyloid.[32,33]

Several studies have highlighted plausible mechanistic pathways through which the events associated with surgery may promote cortical amyloid deposition. First, animal models have indicated that common anesthetics, including sevoflurane and isoflorane, can increase the activation of caspases, leading to apoptosis and greater amyloid precursor protein processing.[13,34,35] Alzheimer's disease transgenic mice have been shown to be particularly vulnerable to the effects of anesthesia because of an increased neuroinflammatory response.[34] Oligomerization of A β may also be increased after exposure to specific anesthetics such as isoflurane.[15] Additionally, tissue injury resulting from surgery can generate damage-associated molecular patterns that can initiate a systemic inflammatory response. Systemic inflammation can subsequently trigger or exacerbate neuroinflammation, which itself is hypothesized to play a key role in amyloid deposition and cognitive change after surgery.[36] Additionally, sleep is commonly disrupted after surgery and is thought to play a key role in clearance of amyloid.[37,38] In spite of suggestive preclinical data, the results of the current study suggest that other mechanisms may be more important in the pathophysiology of cognitive change after surgery than brain amyloid deposition.

The results of the current study do not support the hypothesis that hospitalization for a surgical procedure during the mid- to late-life period increases the risk of elevated cortical amyloid. Surprisingly, we found the lowest rates of amyloid positivity among the group of participants who were previously hospitalized without surgery. It is unclear why participants with a previous nonsurgical hospitalization would have a lower prevalence of elevated amyloid than participants in the nonhospitalized group, because cardiovascular risk factors and other comorbidities have been associated with elevated brain amyloid.[24] One explanation for this unexpected finding may be selection bias. Given that persons with dementia were not included in the ARIC–PET study, it is possible that the comparatively higher prevalence of elevated amyloid among the nonhospitalized group represents a result of differential selection whereby persons without previous hospitalization (and without associated medical comorbidity) are more likely to remain nondemented in spite of a higher burden of amyloid and thus were not excluded from the ARIC–PET study.

Although the primary analyses did not support our hypothesis, we found some support for an association between previous surgical hospitalization and elevated cortical amyloid in secondary analyses that compared participants with surgical hospitalization to participants who were previously hospitalized without surgery and among participants who were hospitalized for two or more surgeries.

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However, the significant associations derived from secondary analyses were not robust to the use of alternative thresholds for defining elevated amyloid and therefore should be interpreted with caution. A recent study demonstrated that *APOE* genotype modified the association between hospitalization and dementia risk.[8] However, our results do not support the hypothesis that *APOE* ε4 allele possession influences the relationship between surgical hospitalization and amyloid deposition.

The current study has several strengths, including the use of a unique, well characterized cohort followed over 24 yr, with measurement of hospitalization events, important cardiovascular risk factors, and medical comorbidity. There are also several limitations to consider. First, we found that the results varied based on the comparison group used. As discussed above, this may be due to a selection effect, whereby healthier nonhospitalized participants with elevated amyloid were able to remain nondemented and therefore be included in the original ARIC–PET study. Participants in the ARIC–PET cohort were selected to be dementia-free and able to undergo magnetic resonance and PET imaging. As such, this group may not be representative of the larger population of older adults, which is likely to have poorer health (see Supplemental Digital Content 19, http://links.lww.com/ALN/C322, participant characteristics stratified by inclusion in the ARIC–PET study). The selective attrition of persons with higher levels of medical comorbidity and the exclusion of persons with dementia from the ARIC–PET study, who presumably have a higher rate of surgical hospitalization and amyloid deposition, may have attenuated the associations found in the present study. Interpretation of the results may also be limited by potential bias caused by residual confounding from unmeasured covariates or subclinical disease.

Given that amyloid is known to increase for one to two decades and then plateau in older adults who go on to develop dementia,[39] the extended duration of time between surgery and amyloid assessment may mask surgery-related increases in amyloid deposition. As with other studies that measure brain amyloid levels, interpretation of the current results may also be limited by the lack of consensus regarding what characterizes a clinically meaningful threshold for (or difference in) brain amyloid levels. We have provided an estimate of the sample size needed to detect a group difference given the observed odds ratio of 1.32 from our primary analysis; however, it is unknown whether this observed effect is clinically meaningful (Supplemental Digital Content 20, http://links.lww.com/ALN/C323). The understanding of the effect of surgical hospitalization on amyloid deposition would be improved by the ability to assess how amyloid levels change after surgery. As such, the lack of baseline amyloid measurement represents a limitation of the current study. Another potential limitation, the use of International Classification of Disease, Ninth Revision, Clinical Modification codes to capture and categorize surgical procedures, may have introduced bias resulting from misclassification of the exposure variable. Last, use of these codes precluded the consideration of important exposures, such as type of anesthesia, postoperative complications, delirium, and drugs.

Despite these limitations, our results add to a growing body of evidence about the potential effects of surgery on the brain of aging adults. Although the primary analysis does not support an association between surgical hospitalization and elevated cortical amyloid, evidence from secondary analyses provides conflicting evidence. For older adults, preservation of cognitive and functional capacity are key patient-centered goals; however, there are a limited number of guidelines for evaluation and management strategies to preserve brain health after surgery. Thus, there is a need for more research to understand the neurobiologic mechanisms that underlie cognitive decline after surgery. Future studies with larger sample sizes, particularly studies that evaluate the level of cortical amyloid (or other potentially pathogenic proteins) both before and after surgery, may be especially important for providing more definitive evidence in this area.

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Competing Interests

Dr. Gottesman serves as Associate Editor for *Neurology*. Dr. Knopman serves on a data safety monitoring board

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for the Dominantly Inherited Alzheimer Network study and is an investigator in clinical trials sponsored by Biogen (Cambridge, Massachusetts), Lilly Pharmaceuticals (Indianapolis, Indiana), and the Alzheimer's Disease Cooperative Study. Dr. Wong receives funding from Avid/Lilly research collaboration, Roche Neuroscience (Basel, Switzerland), Lundbeck (Copenhagen, Denmark), Five Eleven Pharma (Philadelphia, Pennsylvania), and Cerveau (Knoxville, Tennessee) research collaboration, and his spouse is an intramural NIH scientist in a related field of the publication, but not a coauthor. Dr. Brown has consulted for and participates in a data-sharing agreement with Medtronic. The other authors declare no competing interests.

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Shadowing the Abbess: Wood Library-Museum Exhibit Designer John Byrne and His "Superior" Spouse

Son of the cryptographer behind the unsolvable secret code, Chaocipher (1918), John Francis Byrne, Jr. (1929 to 2008, *upper left*), designed window dressing for Manhattan department stores. When he designed to marry Broadway soprano Patricia "Pat" Neway, John observed wrily that he was also marrying a Mother Superior. Indeed Pat was the 1960 Tony Award winning singer, whose character, the Mother Abbess (*lower left*), had sung "Climb Ev'ry Mountain" in the original *Sound of Music*. After resonating as an operatic singer, she retired to acting as a sounding board for John's exhibit designs. Using noncomputerized, old-fashioned cut-and-paste techniques in their retirement home in East Corinth, Vermont, John fashioned the Wood Library-Museum's early annual exhibits. Sadly, on November 29, 2008, he succumbed to lung cancer metastatic to his brain. John had battled just long enough to reach his fortieth wedding anniversary with his "Superior" wife. Papers, secrets, and blueprints (*backdrop*) for John Senior's insoluble code were eventually deposited in the National Cryptologic Museum. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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