Published in final edited form as:

Am J Geriatr Psychiatry. 2015 October ; 23(10): 1029–1037. doi:10.1016/j.jagp.2014.12.192.

Does Apolipoprotein E Genotype Increase Risk of Postoperative Delirium?

Sarinnapha Vasunilashorn, PhD,

Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts

Harvard Medical School, Boston, Massachusetts

Long Ngo, PhD,

Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Harvard Medical School, Boston, Massachusetts

Cyrus M. Kosar, MA,

Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts

Tamara G. Fong, MD,

Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts

Corresponding Author: Sarinnapha Vasunilashorn, PhD Division of General Medicine and Primary Care Beth Israel Deaconess Medical Center 1309 Beacon St, Office 212 Brookline, MA 02446 svasunil@bidmc.harvard.edu Phone: +1 617 754 1424 Fax: +1 617 754 1440.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Contributions: Drs. Vasunilashorn and Marcantonio had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Vasunilashorn: Conception and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript, statistical analysis; obtained funding; administrative, technical, or material support; supervision

Ngo: Conception and design, analysis and interpretation of data; critical revision of manuscript; statistical analysis; administrative, technical, or material support

Kosar: Acquisition of data; analysis and interpretation of data; critical revision of manuscript; administrative, technical, or material support

Jones: Acquisition of data; analysis and interpretation of data; critical revision of the manuscript; administrative, technical, or material support

Fong: Acquisition of data; analysis and interpretation of data; critical revision of the manuscript; administrative, technical, or material support

Inouye: Study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript; obtained funding; administrative, technical, or material support; supervision

Marcantonio: Study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript; obtained funding; administrative, technical, or material support; supervision

Declarations: We have no conflicts of interest to declare.

Financial Disclosures: None reported.

Previous Presentations: This research was presented at the 4th Annual Meeting of the American Delirium Society, June 2, 2014, Baltimore, MD; at the Annual Scientific Meeting of the American Geriatrics Society, May 16, 2014, Orlando, FL; and at the 27th Annual Poster Symposium of the Massachusetts Alzheimer's Disease Research Center, March 4, 2014, Boston, MA.

Harvard Medical School, Boston, Massachusetts

Richard N. Jones, ScD,

Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts

Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, Rhode Island

Sharon K. Inouye, MD[#], and

Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts

Harvard Medical School, Boston, Massachusetts

Edward R. Marcantonio, MD[#]

Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts

Harvard Medical School, Boston, Massachusetts

[#] These authors contributed equally to this work.

Abstract

Objectives—To determine whether Apolipoprotein E (ApoE) is associated with postoperative delirium incidence, severity, and duration in older patients free of dementia at baseline.

Design, Setting, Participants—We examined 557 non-demented patients age ≥70 undergoing major non-cardiac surgery enrolled in the Successful Aging after Elective Surgery (SAGES) Study.

Measurements—We considered three ApoE measures: ε2, ε4 carriers vs. non-carriers, and a three-category ApoE measure. Delirium was determined using the Confusion Assessment Method (CAM) and chart review. We used generalized linear models to estimate the association between ApoE and delirium incidence, severity (peak CAM Severity [CAM-S] score), and days.

Results—ApoE ε2 and ε4 was present in 15% and 19% respectively, and postoperative delirium occurred in 24%. Among patients with delirium, the mean peak CAM-S score was 8.0 (standard deviation 4), with most patients experiencing one or two delirium days (51% or 28%, respectively). After adjusting for age, sex, surgical procedure, and preoperative cognitive function, ApoE ε4 and ε2 carrier status were not associated with postoperative delirium: RR for ε4=1.0, 95% confidence interval (CI) 0.7-1.5 and RR for ε2=0.9, 95% CI 0.6-1.4. No association between ApoE and delirium severity or number of delirium days was observed.

Conclusions—In older surgery patients free of dementia, our findings do not support the hypothesis that the ApoE genotype does not confer either risk or protection in postoperative

delirium incidence, severity, or duration. Thus, an important genetic risk factor for Alzheimer's Disease does not affect risk of delirium.

Introduction

Delirium is an acute alteration in cognition characterized by fluctuations in attention, disorganized thinking, and level of consciousness.^{1,2} Delirium after major surgery is associated with longer length of hospitalization,³ greater postoperative complications,⁴ and higher rates of discharge to nursing homes.⁵ Additionally, patients with post-surgical delirium have high in-hospital mortality (4-17%),^{2,3} and this mortality risk remains elevated over a 12 month period.⁵ Despite growing epidemiological evidence of its associated poor outcomes, our understanding of the pathophysiology of delirium remains superficial.² Understanding mechanisms is important for identifying patients at highest risk of delirium and designing better prevention and treatment strategies.^{6,7}

One major hypothesis that has emerged from the epidemiological and basic research characterizes delirium as an unmasking of an underlying but as yet asymptomatic cognitive decline.⁸ Furthermore, an association between delirium and dementia is well described.⁹ Apolipoprotein E (ApoE) ϵ 4 is considered a risk factor for Alzheimer's Disease (AD) and has been hypothesized as a genetic risk factor for delirium. The literature examining the relationship of ApoE with delirium, however, has reported mixed results. Some studies report an association between ApoE ϵ 4 and increased delirium incidence,¹⁰ others report an association with delirium days,¹¹ while still others observe no relationship at all.^{12,13} The majority of this work has been conducted in surgical patients,^{10,12-15} with some in ICU¹¹ and general medical populations.^{16,17} If the ApoE genotype is in-fact associated with delirium, then preventive efforts could target those patients at highest-risk for delirium.

Dementia may confound the relationship between ApoE and delirium, potentially resulting in the inconsistent findings in previous studies due to differential inclusion of patients with dementia. Our study aims to clarify the relationship between ApoE and postoperative delirium incidence, severity, and duration in a large sample of older adults undergoing major non-cardiac surgery who are free of any clinical evidence of preoperative dementia. Based on their effects in AD, we hypothesize that the ApoE ϵ 4 allele will be associated with increased delirium incidence, higher severity, and longer duration; and the ApoE ϵ 2 allele will be associated with decreased delirium incidence, severity, and duration.

Methods

Study Sample

The Successful AGing after Elective Surgery (SAGES) Study is a prospective observational study focused on furthering our understanding of the multifactorial delirium syndrome. Its primary goal is to investigate the contribution of delirium to long-term cognitive and functional decline. The SAGES study design and methodology has been previously published.¹⁸ Briefly, participants are enrolled from elective surgery rolls, and are assessed at baseline prior to surgery, and every day during their hospital stay.

There were 560 patients aged 70 years without recognized dementia or history of delirium scheduled for elective major surgery who were enrolled in SAGES. The major surgeries included: cervical, lumbar, or thoracic laminectomy; total hip or knee replacement; open abdominal aortic aneurysm repair; lower extremity vascular bypass; or colectomy. Exclusion criteria included: 1) active delirium on initial cognitive testing (using the Confusion Assessment Method [CAM]);¹ 2) hospitalization 3 months prior to study enrollment; 3) terminal conditions (e.g., advanced cancer, or receiving palliative care); 4) heavy alcohol consumption (to avoid confounding by delirium tremens); 5) legal blindness or severe deafness; 6) clinically evident dementia; 7) non-English speaking; and 8) history of schizophrenia or psychosis.

Dementia screening was conducted sequentially using three methods: initial review of the medical record, direct questions during telephone recruitment, and assessment of capacity and cognitive testing during the baseline enrollment interview. Patients were excluded from study participation if any of the following criteria for dementia were met: 1) diagnosis of dementia documented in the medical record, 2) diagnosis of dementia reported by the patient during telephone recruitment, 3) capacity assessment failed during the informed consent process, or 4) a score <69 or its education-adjusted equivalent on the Modified Mini-Mental (3MS)¹⁹ test at the baseline interview. Subsequently, all enrolled patients had their baseline cognitive status adjudicated by a clinical consensus panel using results from detailed baseline assessments including neuropsychological testing to classify individuals as: (1) no evidence of cognitive impairment or dementia; (2) cognitive impairment, no dementia (CIND); or (3) dementia. Patients who were enrolled but subsequently adjudicated by the consensus panel to have dementia at baseline were excluded from our analysis (n=6; see Figure 1 for details).

Among the 560 individuals enrolled without baseline dementia, 557 (99%) participants had information on ApoE genotype and at least two assessments to define delirium from postoperative day one until hospital discharge. Compared with the 557 participants included in the analysis, the three excluded individuals were not statistically different ($p>.05$) in age, sex, educational attainment, race, type of surgery, and preoperative cognitive function.

Study Measures

Apolipoprotein E. Phlebotomy was performed on the entire cohort at baseline. To determine ApoE genotype, DNA was extracted from whole blood using a previously described technique,²⁰ which yields high quantities of purified DNA of relatively high molecular weight that can be amplified using polymerase chain reaction (PCR) and restriction enzyme digestion. DNA was extracted, allele specific PCR assays were conducted in the Brigham Research Assay Core, and ApoE genotyping was determined from the Partners Center for Personalized Medicine. The genotype frequencies were in Hardy-Weinberg equilibrium ($\chi^2 = 2.44$, $df = 3$, $p \approx 0.49$). To consider both the potential effects of ApoE $\epsilon 4$ and $\epsilon 2$, we constructed several alternative formulations of ApoE genotype: $\epsilon 4$ allele carriers (in the absence of an $\epsilon 2$ allele); $\epsilon 2$ allele carriers (in the absence of an $\epsilon 4$ allele); and a three-category variable ($\epsilon 2\epsilon 2$ or $\epsilon 3\epsilon 2$; $\epsilon 3\epsilon 3$; $\epsilon 4\epsilon 3$ or $\epsilon 4\epsilon 4$ -- $\epsilon 4\epsilon 2$ was excluded because this

genotype includes one risk allele [$\epsilon 4$] and one protective allele [$\epsilon 2$] and their combined effect is unclear) based on previous work.²¹

Delirium—Postoperative delirium was assessed through a structured assessment²² performed daily throughout hospitalization for the scheduled surgery. Delirium was determined using a combination of results from the daily interviews using the CAM and a validated chart review method, described below.

CAM delirium—CAM, the primary method for determining delirium, was rated by trained SAGES field staff. CAM delirium required evidence of an acute change in mental status or fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness.¹ The CAM has high specificity (89%) and sensitivity (94%) compared with delirium ratings by geriatric psychiatrists.²³

Chart review delirium—The secondary method for determining delirium was a validated chart review method^{24,25}, which was used to detect delirium during times when the CAM could not be administered (e.g., the middle of the night). All chart review diagnoses were adjudicated by at least two experts, and any disagreements were resolved through consensus.

Final delirium determination—Patients were considered to be delirious if delirium was present by either the CAM or the chart review method on one or more postoperative days; otherwise, patients were considered non-delirious. The combination of interview and chart methods is considered optimal for identification of delirium.²⁵

Delirium Severity and Delirium Days—To further explore the relationship between ApoE and postoperative delirium, we considered delirium severity and number of delirium days among the patients with postoperative delirium. Delirium severity was quantified using the CAM Severity (CAM-S) score, as previously described.²⁶ The CAM-S long form is the sum of ten CAM items (range 0-19, 19 most severe), which includes fluctuating course, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation, and sleep-wake disturbance, each scored 0-absent, 1-present, mild, 2-present, severe, except for fluctuating course, which is scored 0-absent, 1-present. CAM-S scores were obtained for each post-surgical day. For our analysis, we used the peak CAM-S score from all available CAM-S scores among the delirious patients. Number of delirium days was determined by summing the number of postoperative days the patient was considered delirious by either the CAM or chart review methods.

Covariates—We examined covariates that have been associated with ApoE and postoperative delirium, including age, sex, surgical procedure, and preoperative cognitive functioning. Surgical procedures were categorized into three types: (1) orthopedic (total hip replacement or revision, single or bilateral; total knee replacement or revision, single, or bilateral; lumbar laminectomy; cervical laminectomy); (2) vascular: lower extremity bypass surgery; abdominal aortic aneurysm repair [open procedure, not endovascular]; thoracoabdominal aortic aneurysm repair, and (3) gastrointestinal (open or laparoscopic colectomy). Preoperative cognitive functioning was measured by a composite variable, the

General Cognitive Performance (GCP), described previously.^{27,28} The GCP was created from the SAGES battery of commonly used neuropsychological measures,²⁷ which were selected to reflect domains considered vulnerable to the impact of delirium. GCP demonstrates excellent psychometric properties with little floor and ceiling effects spanning a broad range of values²⁷ and was scaled to the US older adult population using the Aging, Demographics, and Memory Study (ADAMS).²⁸ Our analysis considered the GCP as a continuous variable.

Statistical Analysis

We estimated generalized linear models (GLM) with a log link and binomial error term to assess the association (unadjusted and adjusted relative risks [RR]) between ApoE and postoperative delirium incidence. For severity and days of delirium, we used generalized linear identity-link models. We conducted our analysis for three outcomes: postoperative delirium incidence, severity, and days. The latter two outcomes were examined only among patients who developed postoperative delirium. For all three outcomes, separate unadjusted models examined postoperative delirium risk by three parameterizations of ApoE: ApoE ϵ 2 carrier status, ApoE ϵ 4 carrier status, and a three-ApoE genotype categorization (described above). We examined these relationships further by adjusting for age, sex, type of surgery, and preoperative GCP (adjusted models). Poisson models were used for delirium-days analyses. Prior to analyzing the full SAGES study sample, power analysis was conducted to determine the sample size required to observe a 12% effect of ApoE ϵ 4 on delirium (effect size: 12% absolute difference in risk of incident delirium between ϵ 4 carriers and non- ϵ 4 carriers, assuming type-I error 0.05). All analyses were conducted in SAS Version 9.3, Cary NC. Informed consent for study participation was obtained from all subjects according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, the two surgical sites, and Hebrew SeniorLife, the study coordinating center, all located in Boston, MA.

Sensitivity Analysis

To test the possibility that either exclusion of patients with dementia or inclusion of patients with CIND may have influenced the lack of association between ApoE and delirium, we conducted two sets of post-hoc sensitivity analyses. The first sensitivity analysis, which considered the impact of exclusion of patients with dementia, considered two scenarios which re-introduced dementia patients into the cohort: 1) Add back the 51 patients excluded from our sample (including those not enrolled in SAGES) because of dementia (see Figure 1) and assume a maximally plausible prevalence of 40% ApoE ϵ 4 carriers and 70% incidence of postoperative delirium based on the literature^{29,30}, and 2) Increase the prevalence of dementia to that observed in ADAMS³¹ by adding 145 patients with dementia (20% prevalence) to the SAGES sample and again assume the maximally plausible prevalence of 40% ApoE ϵ 4 carriers and 70% incidence of delirium. The second sensitivity analysis excluded SAGES participants with evidence of CIND (n=38). CIND diagnosis, made by expert panel, was based on a detailed neurocognitive battery assessed at baseline. Unadjusted GLM models were rerun using the simulated data (for sensitivity analysis 1) and the available data (for sensitivity analysis 2) to obtain the alternative RRs. See eAppendix for details.

Results

Table 1 reports the clinical characteristics of our study sample. On average, our sample was older but not exceptionally old, was highly educated, and had a higher than U.S. average preoperative GCP score (Table 1). Most individuals had a score of 3 (indicating severe systemic disease) for the American Society of Anesthesiology (ASA) class, a classification system assessing the patient's physical state prior to surgery. Slightly more than half of the study sample was women and most underwent orthopedic surgery with fewer vascular and gastrointestinal surgeries. Among the participants who developed postoperative delirium (24%), the peak CAM-S score indicated moderate to high delirium severity, with most patients experiencing delirium on one or two postoperative days.

Table 2 reports the ApoE parameter characteristics of the study sample. There were slightly fewer ApoE $\epsilon 2$ carriers than ApoE $\epsilon 4$ carriers. Among our three ApoE genotype categories, about two-thirds had an $\epsilon 3\epsilon 3$ genotype, one-fifth had an $\epsilon 3\epsilon 4$ or $\epsilon 4\epsilon 4$ genotype, and the fewest proportion had $\epsilon 2\epsilon 2$ or $\epsilon 3\epsilon 2$ genotype (Table 2).

Table 3 shows the incidence and RR of postoperative delirium among ApoE $\epsilon 2$ carriers (vs. non-carriers), ApoE $\epsilon 4$ carriers (vs. non-carriers), and the three ApoE genotype categories. Unadjusted and adjusted models for each of the three ApoE parameterizations indicated no association between ApoE and postoperative delirium. ApoE $\epsilon 2$ carriers had a non-significant lower risk of postoperative delirium compared to non- $\epsilon 2$ carriers, and ApoE $\epsilon 4$ carriers had a non-significant higher risk of incident postoperative delirium relative to their non- $\epsilon 4$ counterparts. Among the 132 patients who developed postoperative delirium, non-significant associations between the three ApoE parameterizations and CAM-S scores were observed (Table 4). Among participants with postoperative delirium, all models yielded non-significant associations between ApoE and number of delirium days (Table 4). Altogether, our findings suggest an absence of an association between ApoE and postoperative delirium incidence, severity, and days.

Sensitivity Analyses

For sensitivity analysis 1, scenario 1 (including patients with dementia at 8% prevalence, as observed in SAGES) resulted in a non-significant association between ApoE $\epsilon 4$ and postoperative delirium, while scenario 2 (including patients with dementia at 20% prevalence) yielded a significant association between ApoE $\epsilon 4$ and delirium. Sensitivity analysis 2, which excluded enrolled individuals with CIND, had little impact on our results, and did not substantively alter either the magnitude or statistical significance of our results. See eAppendix for additional details.

Discussion

This study examined the association between ApoE polymorphisms and postoperative delirium incidence, severity, and days in non-demented older adults undergoing major non-cardiac surgery, and we observed no significant associations. Contrary to our hypotheses, the ApoE $\epsilon 4$ allele was not a risk factor for postoperative delirium, and the ApoE $\epsilon 2$ allele was not protective against postoperative delirium. Our results demonstrate that an important

risk factor for AD did not affect risk of delirium in our non-demented sample. A significant corollary of this conclusion is that the cognitive decline and dementia that have been reported following delirium in non-demented individuals may not represent an “unmasking” of preclinical AD.

The absence of an association between ApoE and delirium onset is consistent with some studies but incongruent with others. Our findings differ from those of three reported studies: one conducted in a non-cardiac surgery population,¹⁰ one in a medical and hip fracture population,¹⁶ and one in a medical and surgical population.¹⁴ Subsequently a meta-analysis, which included many of the studies above, also reported an association between ApoE and delirium.¹⁶ Additionally, there was one study conducted in ICU patients,¹¹ that found an association between ApoE ϵ 4 carrier status and delirium days but not delirium incidence. Conversely, our findings agree with the lack of an association between ApoE and delirium reported in 5 studies, two conducted in medical populations,^{12,13} one in a cardiac surgery population,¹⁴ one in a stroke population,¹⁷ and one in patients undergoing major non-cardiac surgery.¹⁵

One possible explanation for the widely divergent findings of the relationship between ApoE genotype and delirium is variation in study sample characteristics, specifically the inclusion or exclusion of patients with dementia. Notably, most of the above cited studies did not conduct detailed cognitive evaluations of the participants, and thus, we are not able to make accurate determinations of the prevalence of dementia in the study samples. Many of the studies enrolled medical, hip fracture, or ICU patients, who were already sick at the time of presentation, precluding assessment of baseline cognitive function. One study that enrolled elective surgical patients¹⁰ completed only a brief cognitive screening test (the Telephone Interview for Cognitive Status). A unique strength of our study was the careful assessment and exclusion of patients with dementia through a multi-stage process, culminating with a full neurocognitive assessment with adjudication by an expert panel. Moreover, our sensitivity analyses suggest that the exclusion of patients with dementia is unlikely to explain the absence of an association between ApoE and delirium in the SAGES sample. However, the inclusion of patients with dementia could explain the previously reported associations between ApoE and delirium observed in the literature,^{10,14,16} particularly if the prevalence of dementia is 20% or higher in these study samples.

Dementia is an established risk factor for delirium.³² There is also a growing literature that among patients without dementia, those who develop delirium may be at increased risk of cognitive decline or dementia in the future. This suggests that the development of delirium may be an indicator of a dysfunctional response in the brain, which may represent an underlying vulnerability to subsequent dementia. Most studies that have examined the relationship between dementia and postoperative delirium have not characterized dementia subtypes; therefore it remains unknown whether delirium is preferentially associated with AD or other forms of dementia. Since ApoE ϵ 4 is the most penetrant genetic risk factor known for AD, the absence of an association between ApoE ϵ 4 and delirium observed in our study suggests, but does not explicitly test, the possibility that delirium and dementia may not originate from the same pathological process. Therefore, the associations observed between delirium and dementia are not attributable to the strongest genetic risk factor for

AD. Ultimately, this suggests delirium is unlikely to represent simply an unmasking of pre-clinical dementia. We are confident in our results given that our sample size was substantial and our study sufficiently powered to detect a clinically significant effect attributable to $\epsilon 4$ (See Methods), if it was present.

Our current study has a number of strengths that underscore its innovation. SAGES represents the first study conducted in a large patient sample who were free of dementia at baseline. Enrolling patients scheduled for major non-cardiac surgery enabled us to carefully characterize their baseline cognitive status, exclude individuals with dementia, and ultimately clearly distinguish between risk factors for delirium and dementia. These strengths distinguish our study from previous studies examining the relationship of ApoE and delirium. Another strength of our study is the use of state-of-the art delirium measures, including delirium incidence, severity, and duration. The consistent findings across all three outcomes underscore the robustness of our results and strengthen our conclusion of a lack of an association between ApoE and delirium.

We also note some study limitations. The restricted enrollment of non-demented older adults along with the high education of the SAGES sample reflect findings that may not be generalizable to the entire population of older adults. While acknowledging this threat to generalizability, this restriction enabled us to conduct a more pristine analysis of the relationship between ApoE and postoperative delirium in the absence of dementia. Our sample of non-demented adults aged ≥ 70 may also represent a population with high reserve, which may protect against the detrimental effects of ApoE $\epsilon 4$ on dementia and delirium. We also enrolled from two academic medical centers in a single geographical region, and had relatively low minority representation. Our findings should be reproduced in other settings with more diverse samples.

In summary, in this study of older adults without dementia undergoing major elective non-cardiac surgery, we found no association between ApoE genotype and delirium incidence, severity, or duration. Our findings do not support the role of ApoE genotype in conferring protection or risk in the development of postoperative delirium. We conclude that in our non-demented older surgical sample, an important genetic risk factor for AD does not affect risk of delirium. Our results are consistent with the possibility that delirium is not merely an unmasking of preclinical AD and that efforts to address delirium may represent a fruitful avenue to prevent the post-operative cognitive decline that is frequently observed in older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This research was supported by grants from the National Institute on Aging T32AG023480 (Vasunilashorn), P01AG031720 (Inouye), K07AG041835 (Inouye), R01AG030618 (Marcantonio), and K24AG035075 (Marcantonio).

Role of the Sponsor: The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

References

1. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The confusion assessment methods. A new method for detection of delirium. *Ann Intern Med.* 1990; 113:941–948. [PubMed: 2240918]
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014; 383:911–922. [PubMed: 23992774]
3. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. *JAMA.* 2012; 308:73–81. [PubMed: 22669559]
4. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA.* 1994; 271:134–139. [PubMed: 8264068]
5. Marcantonio ER, Flacker JM, Michaels M, et al. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc.* 2000; 48:618–624. [PubMed: 10855596]
6. Maldonado J. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry.* 2013; 21:1190–1222. [PubMed: 24206937]
7. Kamholz B, Blazer DG. Progress in delirium. *Am J Geriatr Psychiatry.* 2013; 21:1169–1172. [PubMed: 24206936]
8. Nadelson MR, Sanders RD, Avidan MS. Perioperative cognitive trajectory in adults. *Br J Anaesth.* 2014; 112:440–451. [PubMed: 24384981]
9. Stritmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high activity binding to β -amyloid and increased frequency for type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA.* 1993; 90:1977–1981. [PubMed: 8446617]
10. Leung JM, Sands LP, Wang Y, et al. Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. *Anesthesiology.* 2007; 107:406–411. [PubMed: 17721242]
11. Ely EW, Girard TD, Shintani AK, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Crit Care Med.* 2007; 35:112–117. [PubMed: 17133176]
12. Adamis D, Treloar A, Martin FC, et al. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. *Int J Geriatr Psychiatry.* 2007; 22:688–694. [PubMed: 17203511]
13. van Munster BC, Korevaar JC, de Rooij SE, et al. The association between delirium and the apolipoprotein E4 allele in the elderly. *Psychiatr Genetics.* 2007; 17:261–266.
14. Tagarakis GI, Tsolaki-Tagaraki F, Tsolaki M, et al. The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations. *Am J Amzheimers Dis Other Dement.* 2007; 22:223–28.
15. Abelha FJ, Fernandes V, Botelho M, et al. Apolipoprotein E e4 does not increase the risk of early postoperative delirium after major surgery. *J Anesth.* 2012; 26:412–21.
16. van Munster BC, Korevaar JC, Zwinderman AH, et al. The association between delirium and the apolipoprotein E Epsilon 4 allele: New study results and a meta-analysis. *Am J Geriatr Psychiatry.* 2009; 17:856–62. [PubMed: 19910874]
17. Oldenbeuwing AW, de Kort PLM, Kappelle LJ, et al. Delirium in the acute phase after stroke and the role of Apolipoprotein E. *Am J Geriatr Psychiatry.* 2013; 21:935–37. [PubMed: 23969090]
18. Schmitt EM, Marcantonio ER, Alsop DC, et al. Novel risk markers and long-term outcomes of delirium: The Successful Aging after Elective Surgery (SAGES) Study Design and Methods. *JAMDA.* 2012; 13:1–10. [PubMed: 22119549]
19. Teng EL, Chui HC. The Modified Mini-Mental State Examination. *J Clin Psychiatry.* 1987; 48:314–318. [PubMed: 3611032]
20. Ciulla TA, Sklar RM, Hauser SI. A simple method for DNA purification from peripheral blood. *Anal Biochem.* 1988; 174:485–488. [PubMed: 3239751]

21. Ewbank DC. Mortality differences by APOE genotype estimated from demographic synthesis. *Genet Epidemiol.* 2002; 22:146–155. [PubMed: 11788960]
22. Simon SE, Bergman MA, Jones RN, et al. Reliability of a structure assessment for non-clinicians to detect delirium among new admissions to post-acute care. *J Am Med Dir Assoc.* 2006; 7:412–415. [PubMed: 16979083]
23. Wei LA, Fearing MA, Sternberg EJ, et al. The Confusion Assessment Method: a systematic review of current usage. *J Am Geriatr Soc.* 2008; 56:823–830. [PubMed: 18384586]
24. Inouye SK, Leo-Summers L, Zhang Y, et al. A chart-based method for identification of delirium: Validation compared with interviewer ratings using the Confusion Assessment Method. *J Am Geriatr Soc.* 2005; 53:312–318. [PubMed: 15673358]
25. Saczynski JS, Kosar CM, Xu G, et al. A tale of two methods: chart and interview methods for identifying delirium. *J Am Geriatr Soc.* 2014; 62:518–524. [PubMed: 24512042]
26. Inouye SK, Kosar CM, Tommet D, et al. The CAM-S, a new scoring system for delirium severity: Association with clinical outcomes. *Ann Intern Med.* 2014; 150:526–533. [PubMed: 24733193]
27. Jones RN, Rudolph JL, Inouye SK, et al. Development of a unidimensional composite measure of neuropsychological functioning in older cardiac surgery patients with good measurement precision. *J Clin Exp Neuropsych.* 2010; 32:1041–1049.
28. Gross AL, Jones RN, Fong TG, et al. Calibration and validation of an innovative approach for estimating general cognitive performance. *Neuroepidemiology.* 2014; 42:144–153. [PubMed: 24481241]
29. Bullido MJ, Artiga MJ, Recuero M, et al. A polymorphism in the regulatory region of ApoE associated with risk for Alzheimer's dementia. *Nat Genet.* 1998; 18:69–71. [PubMed: 9425904]
30. Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc.* 2001; 49:516–522. [PubMed: 11380742]
31. Plassman B, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology.* 2007; 29:125–132. [PubMed: 17975326]
32. Davis DH, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: A population-based cohort study. *Brain.* 2012; 135:2809–2816. [PubMed: 22879644]

Figure 1.

Number of participants excluded based on sequential dementia screening steps in the Successful Aging after Elective Surgery (SAGES) Study

Table 1

Clinical Characteristics of the Study Sample

Characteristic	Mean $\pm$ SD or N (%)
Age (mean $\pm$ SD)	76.6 $\pm$ 5.2
Female, N (%)	324 (58)
Educational attainment (years)	15.0 $\pm$ 3.0
Non-White or Hispanic, N (%)	42 (8)
Type of Surgery, N (%)	
Orthopedic	451 (81)
Vascular	35 (6)
Gastrointestinal	71 (13)
General cognitive performance (externally scaled, mean $\pm$ SD) ^a	57.6 $\pm$ 7.3
American Society of Anesthesiology class, N (%) ^b	
1	2 (0)
2	203 (37)
3	347 (62)
4	5 (1)
Any postoperative delirium, N (%)	132 (24)
Confusion Assessment Method-Severity score (long form, mean $\pm$ SD) ^{c,d}	8.0 $\pm$ 3.6
Total days with delirium, N (%) ^c	
1	67 (51)
2	37 (28)
3+	28 (21)

Notes: Participant N=557. SD: standard deviation; ApoE: Apolipoprotein E.

^a General cognitive performance, a composite measure of neuropsychological measures reflecting cognitive domains vulnerable to delirium.²¹

^b American Society of Anesthesiology class, a classification system assessing the patient's physical state prior to surgery.

^c Among participants with postoperative delirium (n=132).

^d Confusion Assessment Method-Severity score range 0-19, 19 most severe.

Table 2

Apolipoprotein E Parameters of the Study Sample

ApoE parameter	N (%)
ApoE genotypes	
ε2ε2	4 (1)
ε3ε3	358 (64)
ε3ε2	78 (14)
ε4ε2	9 (2)
ε4ε3	104 (18)
ε4ε4	4 (1)
ApoE ε2 carrier ^a (vs. non-ε2 carrier)	82 (15)
ApoE ε4 carrier ^b (vs. non-ε4 carrier)	108 (19)
ApoE category ^c	
ε2ε2 or ε3ε2	82 (15)
ε4ε3 or ε4ε4	108 (20)
ε3ε3	358 (65)

Notes: Participant N = 557. ApoE: Apolipoprotein E.

^aIn the absence of an ε4 allele

^bIn the absence of an ε2 allele

^cExcludes ε4ε2 (n=9)

Table 3

Generalized Linear Log-Link Models Predicting Postoperative Delirium by Apolipoprotein E

		<u>Unadjusted Model</u>		<u>Adjusted Model^a</u>	
Parameters	Delirium Incidence (%)	RR	(95% CI)	RR	(95% CI)
ApoE ε2 carrier status					
ε2 carrier (vs. non-ε2 carrier)	20	0.8	(0.5-1.3)	0.9	(0.6-1.4)
ApoE ε4 carrier status					
ε4 carrier (vs. non-ε4 carrier)	24	1.0	(0.7-1.5)	1.0	(0.7-1.5)
ApoE categories					
ε2ε2 or ε3ε2	20	0.8	(0.5-1.3)	0.9	(0.5-1.4)
ε4ε3 or ε4ε4	24	1.0	(0.7-1.4)	1.0	(0.7-1.5)
ε3ε3	25	Reference		Reference	

Notes: Participant N = 557. RR: relative risk; CI: confidence interval; ApoE: Apolipoprotein E.

Maximum-likelihood-estimation derived Wald chi-square with 1 df for the ApoE carrier status and categorical variables in all models.

^a Adjusted Model: Adjusted for age, sex, type of surgery, and preoperative general cognitive performance using generalized linear log-link regression.

Table 4

Generalized Linear Identity-Link Models Predicting Postoperative Delirium Severity and Delirium Days by Apolipoprotein E Parameterizations among Patients with Postoperative Delirium

Parameters	CAM-S Score			# Days with Delirium		
	Unadjusted Model		Adjusted Model ^a	Unadjusted Model		Adjusted Model ^a
	β	p-value	β	p-value	β	p-value
ApoE $\epsilon 2$ carrier status						
$\epsilon 2$ carrier (vs. non- $\epsilon 2$ carrier)	1.7	0.08	1.6	0.2	0.63	0.1
ApoE $\epsilon 4$ carrier status						
$\epsilon 4$ carrier (vs. non- $\epsilon 4$ carrier)	-0.7	0.38	-0.6	0.3	0.30	0.2
ApoE categories						
$\epsilon 2\epsilon 2$ or $\epsilon 3\epsilon 2$	1.5	0.11	1.4	0.3	0.49	0.2
$\epsilon 4\epsilon 3$ or $\epsilon 4\epsilon 4$	-0.5	0.57	-0.4	0.4	0.25	0.2
$\epsilon 3\epsilon 3$	Reference	Reference	Reference	Reference	Reference	Reference

Notes: Participant N = 132. ApoE: Apolipoprotein E; CAM-S: Confusion Assessment Method Severity; B: Beta estimate (defined as points on the CAM-S score or number of days with delirium)

Maximum-likelihood-estimation derived Wald chi-square with 1 df for the ApoE carrier status and categorical variables in all models.

^a Adjusted Model: Adjusted for age, sex, type of surgery, and preoperative general cognitive performance using generalized linear identity-link models; since these are linear models, the beta estimates represent CAM-S points (for the first two columns) and delirium days (for the last two columns).