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REPORTS OF ORIGINAL INVESTIGATIONS

# Apolipoprotein *epsilon* 4 genotype is associated with less improvement in cognitive function five years after cardiac surgery: a retrospective cohort study

# Le génotype *epsilon* 4 de l'apolipoprotéine est associé à une moindre amélioration de la fonction cognitive cinq ans après chirurgie cardiaque: une étude rétrospective de cohorte

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**Abstract**

**Purpose** *Cognitive performance after cardiac surgery can be impaired, and genetic risk factors have previously been suggested. When compared with other isoforms of the gene, the apolipoprotein epsilon 4 (APOE4) allele is associated with worse outcomes in many neurologic disorders. We hypothesized that the APOE4 allele is associated with less favourable cognitive function five years after surgery.*

**Methods** *Caucasian patients enrolled in previously reported prospective cognitive trials in both cardiac and non-cardiac surgery participated in this retrospective cohort study. Neuropsychological function was assessed at baseline and five years postoperatively. The relationship between change in cognitive index score and APOE was evaluated using multivariable linear regression. An additive genetic model toward the epsilon 4 allele was applied with adjustment for baseline cognition, years of education, age, presence of diabetes in both cohorts, and presence of coronary artery disease in the non-cardiac surgery cohort.*

**Results** *A total of 357 patients were included in this study. In the cardiac surgery group ($n = 233$), baseline cognitive index ($P < 0.001$), years of education ($P = 0.04$), age at time of surgery ($P < 0.001$), and the APOE4 allele ($P = 0.009$), were associated with a five-year change in cognitive index. Patients carrying the APOE4 allele showed less improvement in cognitive index scores five years after cardiac surgery compared with patients without the APOE4 allele. In the non-cardiac surgery ($n = 124$) group, no association was found*

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This article was conducted on behalf of the Neurologic Outcome Research Group (NORG) of the Duke Heart Center. Members of NORG are listed in the Appendix.

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*between APOE4 allele status and change in cognitive index.*

**Conclusion** *We report an association between APOE4 and neurocognitive function five years following cardiac surgery. Preoperative identification of patients with the APOE4 genotype may improve stratification of cardiac surgery patients at risk for a less favourable cognitive trajectory.*

**Résumé**

**Objectif** *Les performances cognitives peuvent être altérées après une chirurgie cardiaque et l'existence de facteurs de risque génétiques a déjà été suggérée. Quand on le compare aux autres isoformes du gène, l'allèle epsilon 4 de l'apolipoprotéine (APOE4) est associé à de moins bons aboutissements dans de nombreux troubles neurologiques. Nous avons émis l'hypothèse que l'allèle APOE4 est associé à une fonction cognitive moins favorable cinq ans après l'intervention chirurgicale.*

**Méthodes** *Des patients de race blanche recrutés dans des études cognitives prospectives déjà publiées en chirurgie cardiaque et non cardiaque ont participé à cette étude de cohorte rétrospective. La fonction neuropsychologique a été évaluée à la ligne de base et cinq ans après la chirurgie. La relation entre la modification du score de l'index cognitif et APOE a été évaluée au moyen d'une analyse de régression multifactorielle linéaire. Un modèle génétique additif visant l'allèle epsilon 4 a été appliqué avec ajustement pour la cognition, les années de scolarité, l'âge, l'existence d'un diabète (dans les deux cohortes), et l'existence d'une coronaropathie (dans la cohorte de chirurgie non cardiaque).*

**Résultats** *Un total de 357 patients a été inclus dans cette étude. Dans le groupe chirurgie cardiaque ($n = 233$), l'indice cognitif à la ligne de base ($P < 0{,}001$), les années de scolarité ($P = 0{,}04$), l'âge au moment de l'intervention chirurgicale ($P < 0{,}001$), et l'allèle APOE4 ($P = 0{,}009$) ont été associés à une modification de l'indice cognitif à cinq ans. Les patients porteurs de l'allèle APOE4 ont présenté une moindre amélioration des scores d'indice cognitif cinq ans après chirurgie cardiaque par rapport aux patients non porteurs de l'allèle APOE4. Dans le groupe de chirurgie non cardiaque ($n = 124$), aucune association n'a été trouvée entre le statut de l'allèle APOE4 et une modification de l'indice cognitif.*

**Conclusion** *Nous décrivons une association entre APOE4 et la fonction neurocognitive cinq ans après une chirurgie cardiaque. L'identification préopératoire des patients ayant le génotype APOE4 pourrait améliorer la stratification des patients devant subir une chirurgie cardiaque et à risque d'une évolution cognitive moins favorable.*

Neurologic injury is one of the most commonly reported adverse outcomes after cardiac surgery.[1] Postoperative cognitive dysfunction (POCD) is present in up to 30-50% of patients within six weeks of cardiac surgery, and only 45% of these patients recover to baseline cognitive function by one year after surgery.[2-4] While early studies suggested that cognitive dysfunction after coronary artery bypass surgery (CABG) is also associated with further decline at five years after surgery, subsequent studies showed that the pattern and degree of this decline is similar to patients with coronary artery disease who did not have surgical intervention.[5,6] Thus, long-term cognitive decline after surgery may be more a consequence of aging and the progression of chronic cardiovascular disease rather than any injury associated with surgery.[7]

Each of the apolipoprotein (ApoE) isoforms modulate lipoprotein metabolism according to its unique structure. In neurodegenerative disease, ApoE4 modulates the synthesis and clearance of amyloid-β. Indeed, the *APOE4* genotype has been independently associated with risk for Alzheimer's disease.[8] ApoE also mediates glial activation, neuroinflammation, and brain injury responses in an isoform-specific fashion. Apolipoprotein *epsilon* 4 is associated with increased glial activation, oxidative stress, and secondary neuronal injury following a central nervous system insult.[9] This mechanism may also play an important role in the poor outcomes observed in *APOE4* allele carriers following a variety of acute and chronic injuries such as cerebral amyloid angiopathy, traumatic brain injury, Down syndrome-associated dementia, subarachnoid and intracerebral hemorrhage, vascular dementia, and multiple sclerosis.[10-12]

Given the critical role of ApoE4 in common neurologic disorders, its role in POCD has been the focus of previous studies. The *APOE4* genotype was not associated with POCD following major non-cardiac surgery in 394 patients evaluated at six weeks and one year postoperatively.[13] A preliminary study in cardiac surgery patients indicated that the *APOE4* genotype plays a potential role in POCD at six weeks after surgery.[14] Nevertheless, more recent studies did not find such a relationship at four to seven weeks post CABG[15] or at three or 12 months after CABG surgery.[16] Furthermore, no link was found in 513 patients enrolled in a prospective cohort study that evaluated several genetic polymorphisms and cognitive function at six weeks after cardiac surgery.[17] In summary, these data suggest no connection between *APOE4* carrier status and cognitive function when assessed within one year of surgery.

Studies are lacking on the relationship between the *APOE4* genotype and longer-term cognitive function following cardiac surgery. Since long-term changes in cognition may be modulated by *APOE4*-related

progression of atherosclerotic disease or neurodegenerative pathology, we hypothesized that the *APOE4* allele is associated with less favourable cognitive function five years after cardiac surgery. Since pre-existing vascular pathology may be overrepresented in a cardiac surgery cohort, we also assessed the association between *APOE4* carrier status and long-term cognitive dysfunction in a non-cardiac surgery cohort.

## Methods

### Study population

The Duke University School of Medicine Institutional Review Board approved this study (November 25, 2013). Waiver of consent was approved for this retrospective study, but written informed consent was obtained from all subjects for the previously performed prospective cognitive trials.

The present study focused on a cohort of 334 patients who underwent CABG and/or cardiac valve surgery during 1996 to 2007 as well as a second cohort of 157 non-cardiac surgery patients. Both cohorts completed a follow-up five years after the previously performed and reported prospective studies.[13,17-22] Patients were not eligible for this study if they had a history of symptomatic cerebrovascular disease, psychiatric illness, plasma creatinine $> 2$ mg·dL$^{-1}$, less than a grade seven education, or a Mini Mental State Examination score $< 24$. Furthermore, we limited our study population to Caucasians because conducting genetic association tests in ethnically admixed populations can result in spurious associations as a consequence of population stratification. After excluding 36 patients of non-Caucasian ethnicity, 63 with missing *APOE4* allele information, and two with incomplete five-year follow-up neurocognitive examination results, 233 cardiac surgery patients were included in the final statistical analyses. In the second cohort, the 157 non-cardiac surgery patients who had similarly completed five-year cognitive follow-up were also examined. In this second cohort, 21 patients of non-Caucasian ethnicity were excluded, and 12 patients were excluded for incomplete test scores or lack of *APOE* status, leaving 124 patients in the final analysis.

### DNA isolation and APOE4 genotype analysis

Blood samples were collected preoperatively, and isolation of genomic DNA was performed from whole blood. The *APOE4* genotype was determined either by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on a Sequenom MassARRAY® system (Sequenom, San Diego, CA, USA) at Agencourt Bioscience Corporation, Beverly, MA, as previously described,[17] or by polymerase chain reaction amplification followed by restriction enzyme digestion, also as previously described.[23]

### Assessment of cognitive function

Cognitive function was assessed on the day prior to surgery and at five years postoperatively. Investigators experienced in neurocognitive testing were blinded to the *APOE* genotype status. Five cognitive tests that yielded ten cognitive raw scores were administered as previously described.[13,17]

1. Randt (Short Story) Memory Test: This is a test to assess discourse memory (immediate and delayed) and oral language comprehension. Subjects are asked to repeat a brief paragraph that has been read aloud to them.[24]
2. Modified Visual Reproduction Test from the Wechsler Memory Scale: This test measures short- and long-term figural memory. Subjects are asked to reproduce several geometric shapes from memory.[25]
3. Digit Span from the WAIS-R: This is a test of short-term auditory memory and attention. A series of digits is presented orally to subjects, and they are then asked to repeat the digits in order and, in an independent test, in reverse order.[26]
4. Digit Symbol from the WAIS-R: This test measures psychomotor processing speed and attention. Subjects are allowed a brief look at a coding scheme that pairs digits with symbols, and they are then given 90 sec to reproduce as many coded symbols as possible in blank boxes beneath randomly generated digits.[26]
5. Trail Making Test, Part B: This is a test of processing speed and attention. Subjects connect a series of numeric and alphabetic circles in order, e.g., 1-A-2-B, as quickly as possible.[27]

### Statistical analysis

Cognitive function was assessed using a continuous cognitive index score calculated by performing a factor analysis on the raw scores of the test battery above and averaging the resulting four domain scores.[4,17] We used the continuous score rather than a dichotomous outcome in order to maximize statistical power. Preoperative scores from 1,134 eligible patients in our ongoing prospective post-CABG cognitive database were used for the factor analysis in the cardiac surgery group.[4,17] The cognitive factor scores for the non-cardiac surgery patients were calculated using the factor weights developed from a sample of 339 patients[13] and used in their respective group. The weighting of each test on a factor was performed to generate comparable domain scores at each time of follow-

up. Hence, the domains tested were identified at baseline and were not changed during subsequent examinations.

All tests were scored so that higher scores represented better performance (SAS® PROC). A principal components method without priors was used for factor analysis. Factors were rotated with an orthogonal varimax transformation yielding uncorrelated rotated factors. A factor solution with four factors was selected to optimize data reduction, total variance, and clinical interpretability. The first four factors, representing the cognitive domains of 1) verbal memory, 2) abstraction and visuospatial orientation (i.e., executive function), 3) visual memory, and 4) attention and concentration, cumulatively accounted for 83.3% of the total variance among the ten raw scores in the cardiac surgery group.

For the primary outcome variable, i.e., change in cognitive index score from preoperative baseline to five years after surgery (ΔCI-5), we assessed the statistical power by Quanto (http://biostats.usc.edu/Quanto.html) based on the sample size of 233 and the characteristics of clinical and *APOE* data in our cardiac surgery group. Assuming an allele frequency of 0.13 with an additive genetic model and the population mean (SD) of ΔCI-5 as 0.136 (0.3), a sample the size of our dataset ($n = 233$) has 82% power to detect a 3.5% ΔCI-5 variation ($R^2_G$) explained by the *APOE4* allele or a 0.117 decrease of ΔCI-5 (regression coefficient, β) by carrying an additional *APOE4* allele under a two-sided significance level of 0.05.

The relationship between the change in cognitive index score (from preoperative baseline to five years postoperatively) and *APOE4* allele status was evaluated using multivariable linear regression. An additive genetic model toward the *E4* allele was applied with adjustment for age, years of education, diabetes, baseline cognition, and presence of coronary artery disease in the non-cardiac surgery group. Comparisons of the demographic group characteristics were made using Student's *t* test for continuous variables and Chi square test for categorical variables. SAS statistical software, version 9.3 (SAS Inc., Cary, NC, USA) was used. All reported *P* values are two sided.

## Results

Demographic characteristics of the patient cohorts analyzed in this study are presented in Table 1. There were 357 patients analyzed; 233 of these patients underwent cardiac surgery and 124 had non-cardiac surgery.

Multivariable linear regression was performed to evaluate the relationship between individual patient genotype and cognitive change five years after cardiac surgery. A higher level of education was associated with greater improvement in cognitive test scores, whereas baseline preoperative cognitive index and age were associated with less improvement in performance during neuropsychological testing at the five-year mark. Patients with the *APOE4* allele had a less favourable cognitive change at five years after surgery compared with those without the *APOE4* allele (Table 2). The improvement in cognitive index score from preoperative baseline to five years following cardiac surgery was greater in patients who did not carry the *APOE4* allele (Figure).

In patients who had non-cardiac surgery, a higher level of education was associated with greater improvement in cognitive scores at five years postoperatively, whereas baseline cognitive index and advanced age were associated with less improvement. Unlike the cardiac surgery group, *APOE4* allele status was not associated with performance during neurocognitive testing at five years (Table 3).

## Discussion

Our primary finding is that the *APOE4* genotype is associated with less favourable neurocognitive outcome at five years following cardiac surgery, thus confirming our hypothesis. This relationship was found in an analysis using multivariable linear regression in a cohort of 233 Caucasian patients previously enrolled in prospective cognitive trials. These results indicate that *APOE4* carrier status may be relevant to the long-term cognitive trajectory of cardiac surgery patients.

Apolipoprotein *epsilon* is a 34 kDa polymorphic glycoprotein containing 299 amino acid residues arising from three alleles at a single gene locus. The three isoforms – ApoE2, ApoE3, and ApoE4 – differ only in the substitution of amino acids at two possible sites (112 and 158). In the normal isoform, ApoE3, cysteine is present at residue 112 and arginine at 158, and in the ApoE4 isoform, arginine is present at both locations.[28] This substitution results in significant changes to the tertiary structure of ApoE4, increasing its affinity to bind very low-density lipoproteins.[29] Patients with the *APOE4* allele have elevated levels of low-density lipoprotein and triglyceride and corresponding low levels of high-density lipoprotein, thereby promoting a pro-atherogenic milieu. Although the responsible molecular mechanisms are not completely understood, impaired recycling of intracellular ApoE4 is thought to lead to intracellular cholesterol accumulation and adverse downstream effects on low-density lipoprotein and triglyceride-rich lipoprotein metabolism.[30] Reflective of this atherosclerosis-promoting pathophysiology, it is not surprising that *APOE4* carrier status has been associated with the need for CABG surgery at an earlier age[31] and increased aortic arch atheroma in cardiac surgery patients.[32]

**Table 1** Demographic characteristics of the two patient cohorts studied

| | Cardiac patients, $n = 233$ | Non-cardiac patients, $n = 124$ | $P$ value |
|---|---|---|---|
| Cardiac surgery type | | | |
| CABG / CPB | 201 (86.3%) | | |
| CABG / OP | 10 (4.3%) | | |
| CABG + Valve | 5 (2.1%) | | |
| Valve | 15 (6.4%) | | |
| Other | 2 (0.9%) | | |
| Non-cardiac surgery type | | | |
| Orthopedic | | 102 (82.3%) | |
| Vascular | | 8 (6.5%) | |
| Thoracic | | 1 (0.8%) | |
| Other | | 13 (10.5%) | |
| Female | 65 (27.9%) | 56 (45.2%) | 0.001 |
| Age (SD) | 63.2 (10.7) | 66.8 (7.1) | <0.001 |
| Education (SD) | 13.0 (3.1) | 14.6 (3.1) | <0.001 |
| CI-0 (SD) | 0.08 (0.45) | 0.22 (0.4) | |
| Coronary artery disease | 217 (93.1%) | 24 (19.4%) | <0.001 |
| Diabetes | 67 (28.8%) | 13 (10.5%) | <0.001 |
| Hypertension | 150 (64.4%) | 73 (53.9%) | 0.306 |
| Number of *APOE4* alleles | | | 0.743 |
| 0 | 175 (75.1%) | 96 (77.4%) | |
| 1 | 54 (23.2%) | 25 (20.2%) | |
| 2 | 4 (1.7%) | 3 (2.4%) | |

Comparisons between groups were made using Student's $t$ test for continuous dependent variables. Chi square test was used for categorical dependent variables. No $P$ value is provided for CI-0 as the factor loadings differ between the cardiac and non-cardiac groups. Age = age at surgery, Education = years of education, CI-0 = baseline cognitive index, SD = standard deviation; *APOE4* = apolipoprotein *epsilon* 4; CABG = coronary artery bypass surgery; CPB = cardiopulmonary bypass; OP = off-pump; Valve = valve surgery

The mechanistic basis for the association of the *APOE4* genotype with long-term cognitive dysfunction after surgery likely lies within functions of the ApoE4 protein that extend beyond lipoprotein metabolism.[10] For example, ApoE4 increases amyloid-β synthesis in neuronal cell cultures[33] and promotes amyloid-β aggregation to form potentially more neurotoxic macromolecular filaments.[34] Furthermore, ApoE4 seems to promote neuronal cell death, possibly by inducing lysosomal leakage via amyloid-β.[35] Accordingly, the link between the *APOE4* genotype and the risk for developing Alzheimer's disease is well established.[8] Since *APOE4* status is associated with less favourable outcomes in other neurologic diseases, such as traumatic brain injury, subarachnoid and intracerebral hemorrhage, vascular dementia, multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis,[10-12] a key role in neurologic injury after cardiac surgery seems biologically plausible.

The association between the *APOE4* genotype and cognitive dysfunction at five years should be interpreted in light of previous studies that investigated postoperative cognitive trajectories. Although earlier observations at three to six months postoperatively suggested a worse outcome in operatively managed coronary artery disease (CAD) patients, these findings do not seem to be sustained over prolonged periods of time.[6,36] In a prospective non-randomized study of 395 patients (CABG, on-pump CABG, or non-surgical CAD therapy patients) and a healthy control group, no differences in cognitive outcome were detected after six years, regardless of the management technique for CAD.[5]

In summary, these data suggest that differences in cognitive outcomes early after surgery could result from perioperative neurologic insults and that the more pronounced cognitive decline over longer periods of time found in CAD patients *vs* healthy controls likely results from progression of underlying cardiovascular or cerebrovascular disease. Indeed, others have found more pronounced cardinal findings of Alzheimer's disease in postmortem histopathologic preparations of brain tissue in CAD subjects that also carried the *APOE4* allele.[37] Our study adds to previously reported findings as it extends the

**Table 2** Cardiac surgery group – relationship between apolipoprotein *epsilon* 4 (*APOE4*) allele status and change in cognitive index score

| Outcome | Variables | *n* | Beta | SE | *P* value |
|---|---|---|---|---|---|
| ΔCI-5 | CI-0 | 233 | −0.187 | 0.051 | <0.001 |
| | Education | 233 | 0.014 | 0.007 | 0.040 |
| | Age | 233 | −0.011 | 0.002 | <0.001 |
| | Diabetes | 233 | −0.036 | 0.041 | 0.376 |
| | *APOE4* | 233 | −0.102 | 0.039 | 0.009 |
| Outcome | # of *APOE4* alleles | *n* | ΔCI-5 Mean (SD) | ΔCI-5 Min | ΔCI-5 Max |
| ΔCI-5 | 0 | 175 | 0.163 (0.273) | −0.520 | 1.026 |
| | 1 | 54 | 0.053 (0.376) | −1.138 | 0.664 |
| | 2 | 4 | 0.057 (0.218) | −0.244 | 0.260 |

An additive genetic model toward the *APOE4* allele with adjustment for baseline cognition (CI-0), years of education (Education), age, and presence of diabetes (Diabetes) was applied to describe the relationship between *APOE4* allele status and change in cognitive index score from preoperative baseline to five years postoperatively (ΔCI-5) ($n = 233$). Beta coefficients describe the effect of any one independent variable on the dependent variable (ΔCI-5) in a standardized fashion (allowing for comparison of effects even though the independent variables have different units of measurement). The summary statistics for the primary outcome (ΔCI-5) relative to the *APOE4* allele status are shown in the lower part of the table. SD = standard deviation, SE = standard error

reported postoperative follow-up period significantly and finds an association between *APOE4* and long-term cognitive change after cardiac surgery - possibly as a consequence of the progression of underlying atherosclerotic disease. The lack of a genetic association in the non-cardiac surgery cohort may simply reflect the lower prevalence of vascular disease in this population.

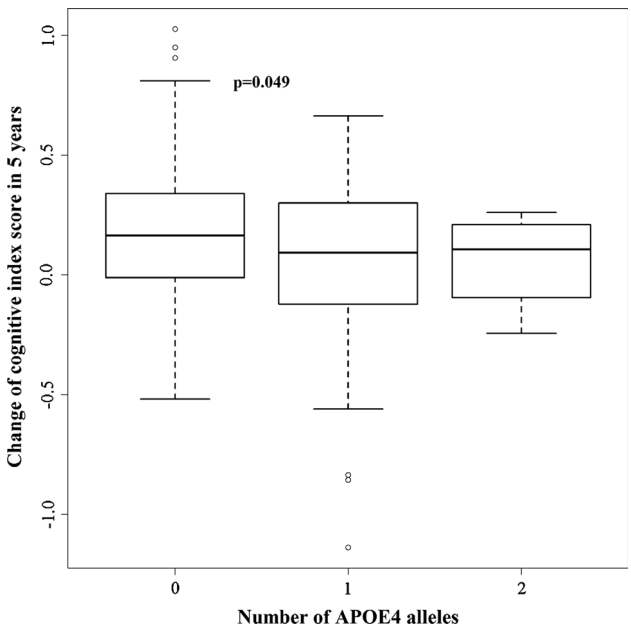


**Figure** Box plots depict the relationship between change in cognitive index score (from preoperative baseline to five years post cardiac surgery) and apolipoprotein *epsilon* 4 (*APOE4*) allele status in Caucasian patients following cardiac surgery ($n = 233$). Univariate comparison reveals a significant difference ($P = 0.049$) between patients with 0 and 1 allele present

## Limitations

Our sample size of 233 patients for this study is relatively large considering the limited access to the patients and a long-term follow-up. The estimated ΔCI-5 variation contributed by the *APOE4* allele ($R^2_G$) from our dataset was slightly lower (2.3%) than in the power calculation, which may be the reason that we detect only a nominal significant effect of *APOE4*. An even larger sample size might enhance the evidence presented here.

Another limitation is that this cohort study did not include non-surgically managed control patients. Hence, while our findings are relevant to patients undergoing cardiac and non-cardiac surgery, we cannot compare these findings with patients with similar medical comorbidities who did not undergo surgery. A potential limitation in our factor analysis was that it was deliberately performed on separate cohorts for the cardiac and non-cardiac samples. This was done in order to allow for potential differences and to obtain the most accurate estimates of change within each group. Thus, direct comparisons of the neurocognitive testing raw scores were not appropriate. Nevertheless, the results did not change when the factor analysis was performed on the combined cohort (data not shown). Furthermore, when the same factor loadings are applied to both cohorts, the baseline (SD) cognitive index score (CI-0) differs between the two groups: [cardiac: 0.08 (0.45) *vs* non-cardiac: 0.45 (0.42); $P < 0.001$].

**Table 3** Non-cardiac surgery group – relationship between apolipoprotein E *epsilon* 4 (*APOE4*) allele status and change in cognitive index score

| Outcome | Variables | *n* | Beta | SE | *P* |
|---|---|---|---|---|---|
| ΔCI-5 | CI-0 | 124 | −0.251 | 0.082 | 0.003 |
| | Education | 124 | 0.034 | 0.010 | < 0.001 |
| | Age | 124 | −0.010 | 0.004 | 0.016 |
| | CAD | 124 | −0.027 | 0.067 | 0.684 |
| | Diabetes | 124 | −0.141 | 0.088 | 0.110 |
| | APOE4 | 124 | 0.004 | 0.055 | 0.948 |
| Outcome | # of APOE4 alleles | *n* | ΔCI-5 Mean (SD) | ΔCI-5 Min | ΔCI-5 Max |
| ΔCI-5 | 0 | 96 | −0.051 (0.308) | −0.795 | 0.660 |
| | 1 | 25 | −0.057 (0.252) | −0.567 | 0.393 |
| | 2 | 3 | −0.127 (0.559) | −0.745 | 0.342 |

An additive genetic model toward the *APOE4* allele – with adjustment for baseline cognition (CI-0), years of education (Education), age, presence of coronary artery disease (CAD), and presence of diabetes (Diabetes) – was applied for multivariable linear regression to describe the relationship between *APOE4* allele status and change in cognitive index score from preoperative baseline to five years postoperatively (ΔCI-5) ($n = 124$). The summary statistics for the primary outcome (ΔCI-5) relative to the *APOE4* allele status are shown in the lower part of the table. SD = standard deviation, SE = standard error

The lower prevalence of coronary artery disease in the non-cardiac *vs* the cardiac surgery group (19.4% *vs* 93.1%, respectively) is also a limitation. Accordingly, it is possible that an ApoE4-mediated effect on cognitive performance could have manifested in non-cardiac surgery patients if the sample size for this group had been larger. A common factor in many similar studies, our study also lacks replication analysis in an independent cohort. This limitation is due to the inherent difficulties in collecting neurocognitive follow-up data five years postoperatively on patients who have been genotyped. We also did not perform a functional analysis on the impact of the *APOE4* allele in cardiac surgery patients. Unfortunately, the molecular mechanisms that lead to a pro-atherogenic milieu are not completely understood at this time.[28]

A final limitation is that using the cognitive index as an indicator of cognitive dysfunction is not universally accepted as a clinically relevant measure of postoperative cognitive dysfunction. Nevertheless, use of the cognitive index was based on published recommendations from a consensus conference.[38] Furthermore, the cognitive index has been a reliable measure of perioperative cognitive performance in multiple clinical studies and, most importantly, has been associated with impaired quality of life.[4,19-21,39,40]

Despite the above considerations, the major strength of our study lies within its five-year follow-up period. The relationship of long-term neurologic outcomes and individual patient genotypes is of particular relevance to perioperative medicine. An improved understanding of this correlation will potentially help clinicians to stratify risk more precisely and inform approaches to protect the brain in the perioperative period. Similarly, prior to surgery, patients could make more informed decisions that are based on individual risk.

## Conclusions

In summary, we found an association between less favourable cognitive performance and the *APOE4* genotype in a cohort of 233 Caucasian patients five years after cardiac surgery. We did not find this association in a cohort of 124 patients five years following non-cardiac surgery. Identification of cardiac surgery patients with the *APOE4* genotype may improve stratification of patients at risk for long-term cognitive decline. Future studies should include non-surgical controls and attempt to investigate this relationship prospectively.

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**Conflicts of interest** None declared.

## Appendix: The Neurologic Outcome Research Group (NORG) of the Duke Heart Center

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## References


1. *Bartels K*, *McDonagh DL*, *Newman MF*, *Mathew JP*. Neurocognitive outcomes after cardiac surgery. Curr Opin Anaesthesiol 2013; 26: 91-7.
2. *Newman MF*, *Mathew JP*, *Grocott HP*, *et al*. Central nervous system injury associated with cardiac surgery. Lancet 2006; 368: 694-703.
3. *Fontes MT*, *Swift RC*, *Phillips-Bute B*, *et al*. Predictors of cognitive recovery after cardiac surgery. Anesth Analg 2013; 116: 435-42.
4. *Newman MF*, *Kirchner JL*, *Phillips-Bute B*, *et al*. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344: 395-402.
5. *Selnes OA*, *Grega MA*, *Bailey MM*, *et al*. Do management strategies for coronary artery disease influence 6-year cognitive outcomes? Ann Thorac Surg 2009; 88: 445-54.
6. *Sweet JJ*, *Finnin E*, *Wolfe PL*, *et al*. Absence of cognitive decline one year after coronary bypass surgery: comparison to nonsurgical and healthy controls. Ann Thorac Surg 2008; 85: 1571-8.
7. *Uysal S*, *Reich DL*. Neurocognitive outcomes of cardiac surgery: a review. J Cardiothorac Vasc Anesth 2013; 27: 958-71.
8. *Corder EH*, *Saunders AM*, *Strittmatter WJ*, *et al*. Gene dose of apolipoprotein-E type-4 allele and the risk of Alzheimer's disease in late-onset families. Science 1993; 261: 921-3.
9. *Laskowitz DT*, *Vitek MP*. Apolipoprotein E and neurological disease: therapeutic potential and pharmacogenomic interactions. Pharmacogenomics 2007; 8: 959-69.
10. *Verghese PB*, *Castellano JM*, *Holtzman DM*. Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurol 2011; 10: 241-52.
11. *Li YJ*, *Hauser MA*, *Scott WK*, *et al*. Apolipoprotein E controls the risk and age at onset of Parkinson disease. Neurology 2004; 62: 2005-9.
12. *Li YJ*, *Pericak-Vance MA*, *Haines JL*, *et al*. Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis. Neurogenetics 2004; 5: 209-13.
13. *McDonagh DL*, *Mathew JP*, *White WD*, *et al*. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology 2010; 112: 852-9.
14. *Tardiff BE*, *Newman MF*, *Saunders AM*, *et al*. Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. Ann Thorac Surg 1997; 64: 715-20.
15. *Steed L*, *Kong R*, *Stygall J*, *et al*. The role of apolipoprotein E in cognitive decline after cardiac operation. Ann Thorac Surg 2001; 71: 823-6.
16. *Silbert BS*, *Evered LA*, *Scott DA*, *Cowie TF*. The apolipoprotein E epsilon4 allele is not associated with cognitive dysfunction in cardiac surgery. Ann Thorac Surg 2008; 86: 841-7.
17. *Mathew JP*, *Podgoreanu MV*, *Grocott HP*, *et al*. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. J Am Coll Cardiol 2007; 49: 1934-42.
18. *Grigore AM*, *Mathew J*, *Grocott HP*, *et al*. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. Anesthesiology 2001; 95: 1110-9.
19. *Grigore AM*, *Grocott HP*, *Mathew JP*, *et al*. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. Anesth Analg 2002; 94: 4-10.
20. *Mathew JP*, *Mackensen GB*, *Phillips-Bute B*, *et al*. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. Anesthesiology 2007; 107: 577-84.
21. *Mathew JP*, *Mackensen GB*, *Phillips-Bute B*, *et al*. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke 2009; 40: 880-7.
22. *Mathew JP*, *White WD*, *Schinderle DB*, *et al*. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. Stroke 2013; 44: 3407-13.
23. *Hixson JE*, *Vernier DT*. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 1990; 31: 545-8.
24. *Randt C*, *Brown E*. Administration Manual: Randt Memory Test. New York, NY: Life Sciences Associates; 1983 .
25. *Wechsler D*. The Wechsler Memory Scale-Revised (Manual). New York, NY: Psychological Corp; 1987 .
26. *Wechsler D*. The Wechsler Adult Intelligence Scale-Revised (Manual). New York, NY: Psychological Corp; 1981 .
27. *Reitan RM*. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills 1958; 8: 271-6.
28. *Mahley RW*, *Rall SC Jr*. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 2000; 1: 507-37.
29. *Altman R*, *Rutledge JC*. The vascular contribution to Alzheimer's disease. Clin Sci (Lond) 2010; 119: 407-21.
30. *Heeren J*, *Beisiegel U*, *Grewal T*. Apolipoprotein E recycling: implications for dyslipidemia and atherosclerosis. Arterioscler Thromb Vasc Biol 2006; 26: 442-8.
31. *Newman MF*, *Laskowitz DT*, *White WD*, *et al*. Apolipoprotein E polymorphisms and age at first coronary artery bypass graft. Anesth Analg 2001; 92: 824-9.
32. *Ti LK*, *Mackensen GB*, *Grocott HP*, *et al*. Apolipoprotein E4 increases aortic atheroma burden in cardiac surgical patients. J Thorac Cardiovasc Surg 2003; 125: 211-3.

33. *Ye S*, *Huang Y*, *Mullendorff K*, *et al*. Apolipoprotein (apo) E4 enhances amyloid beta peptide production in cultured neuronal cells: apoE structure as a potential therapeutic target. Proc Nat Acad Sci U S A 2005; 102: 18700-5.
34. *Ma J*, *Yee A*, *Brewer HB Jr*, *Das S*, *Potter H*. Amyloid-associated proteins alpha 1-antichymotrypsin and apolipoprotein E promote assembly of Alzheimer beta-protein into filaments. Nature 1994; 372: 92-4.
35. *Ji ZS*, *Miranda RD*, *Newhouse YM*, *Weisgraber KH*, *Huang Y*, *Mahley RW*. Apolipoprotein E4 potentiates amyloid beta peptide-induced lysosomal leakage and apoptosis in neuronal cells. J Biol Chem 2002; 277: 21821-8.
36. *Selnes OA, Grega MA, Borowicz LM Jr, Royall RM, McKhann GM, Baumgartner WA*. Cognitive changes with coronary artery disease: a prospective study of coronary artery bypass graft patients and nonsurgical controls. Ann Thorac Surg 2003; 75: 1377-84; discussion 1384-6.
37. *Beeri MS*, *Rapp M*, *Silverman JM*, *et al*. Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers. Neurology 2006; 66: 1399-404.
38. *Murkin JM*, *Newman SP*, *Stump DA*, *Blumenthal JA*. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995; 59: 1289-95.
39. *Grocott HP*, *Mackensen GB*, *Grigore AM*, *et al*. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. Stroke 2002; 33: 537-41.
40. *Phillips-Bute B*, *Mathew JP*, *Blumenthal JA*, *et al*. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 2006; 68: 369-75.