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Apolipoprotein E Genotype and Cognitive Dysfunction after Noncardiac Surgery

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Background: **Apolipoprotein E is important in recovery after neuronal damage. The ϵ4 allele of the apolipoprotein E gene has been shown as a risk factor for Alzheimer disease, poor outcome after cerebral injury, and accelerated cognitive decline with normal aging. The authors hypothesized that patients with the ϵ4 allele would have an increased risk of postoperative cognitive dysfunction (POCD) after noncardiac surgery.**

Methods: **In a multicenter study, a total of 976 patients aged 40 yr and older undergoing noncardiac surgery were tested preoperatively and 1 week and 3 months after surgery with a neuropsychological test battery comprising seven subtests. POCD was defined as a decline in test performance of more than 2 SD from the expected. Apolipoprotein E genotypes were determined by blood sample analysis at a central laboratory. Multivariate logistic regression analysis with POCD as the dependent variable assessed presence of the ϵ4 allele (yes/no) and other possible risk factors.**

Results: **The ϵ4 allele was found in 272 patients. One week after surgery, the incidence of POCD was 11.7% in patients with the ϵ4 allele and 9.9% in patients without the ϵ4 allele ($P = 0.41$). Three months later, POCD was found in 10.3% of patients with the ϵ4 allele and in 8.4% of patients without the ϵ4 allele ($P = 0.40$). Multivariate logistic regression analysis did not identify the ϵ4 allele as a risk factor at 1 week ($P = 0.33$) or 3 months ($P = 0.57$).**

Conclusions: **The authors were unable to show a significant association between apolipoprotein E genotype and POCD, but statistical power was limited because of a lower incidence of POCD than expected.**

FIRST discovered as a major determinant in lipoprotein metabolism and cardiovascular disease, apolipoprotein E (APOE) has emerged as an important molecule in several biologic processes not directly related to its lipid transport function, including Alzheimer disease and cognitive function.[1] There are three different isoforms of apolipoprotein E: E2, E3, and E4 which are encoded by the alleles ϵ2, ϵ3, and ϵ4 of the APOE gene, respectively. The ϵ3 allele is the wild type and is present in 75% of the native European population[2]; ϵ2 (8%) and ϵ4 (17%) are less frequent. The ϵ4 allele is associated with increased risk for atherosclerosis[3] and Alzheimer disease,[4–6] reduced neurite outgrowth,[7] and poor prognosis after cerebral injury.[8,9] There are data to indicate that presence of the ϵ4 allele may predict accelerated cognitive decline within a normal aging population.[10,11] However, the mechanism for this association is not clear because the ϵ4 allele predisposes to cerebrovascular disease and atherosclerosis of the aorta and carotid arteries,[3] which also accounts for considerable cognitive impairment.[12] An association between the ϵ4 allele and postoperative cognitive dysfunction (POCD) after cardiac surgery has been suggested by Tardiff *et al.*,[13] but the literature is conflicting because Steed *et al.*[14] did not confirm this relation.

Postoperative cognitive dysfunction is also a common complication after noncardiac surgery, with the incidence increasing with older age.[15,16] A multicenter study of patients undergoing noncardiac surgery was conducted as a part of the Second International Study of Postoperative Cognitive Dysfunction (ISPOCD2). We hypothesized that patients carrying the ϵ4 allele would have a greater risk of POCD than noncarriers.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

After approval from the local ethics committees (see "Data Collection Centers" in Appendix for locations of ethics committees) was obtained, a total of 976 patients were enrolled in 14 centers in 8 different countries after giving written informed consent. Blood samples were drawn from patients recruited for the three studies comprising the ISPOCD2 study: patients aged 60 yr and older undergoing minor surgery (< 1 h) with general anesthesia as inpatients or outpatients according to local practice (maximal hospital stay of 2 days),[17] patients aged 60 yr and older undergoing major surgery (> 1 h) and randomized for either general or regional anesthesia,[18] and patients aged 40–59 yr undergoing major surgery (> 1 h) with general anesthesia.[19] Patients scheduled to undergo cardiac surgery or neurosurgery were not eligible. Therefore, all patients were aged 40 yr or older and

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scheduled to undergo surgery with either general or regional anesthesia. The type and conduct of general anesthesia conformed to the usual institution practice, and apart from ensuring normocapnia, there were no restrictions. Some patients had a supplementary epidural for both perioperative and postoperative analgesia on the decision of the anesthesiologist in charge. Patients receiving epidural or spinal anesthesia during surgery were allowed sedation with propofol at a level compatible with prompt arousal to a verbal stimulus.

Exclusion criteria were daily use of major tranquilizers or antipsychotic medication, or extensive use of alcohol (> 5 U/day). We also excluded patients with known disease of the central nervous system (such as psychiatric, degenerative or metabolic disease, infection, tumor, earlier severe head trauma or parkinsonism) or a score of less than 24 of 30 points on the Mini-Mental State Examination.[20] A full medical history was recorded, including all medications given and complications occurring during admission. At the 3-month follow-up, new medications and complications were also recorded.

APOE Genotyping

A blood sample was drawn into an evacuated tube containing K_2-EDTA. Three samples each of approximately 50 μl were dropped onto filter paper (Marchery-Nagel, Düren, Germany) and air-dried. The filter papers were refrigerated until shipment to Statens Serum Institute, Copenhagen, Denmark, where they were stored at −20°C until analysis. DNA was extracted from filter paper using the QIAamp Minikit (QIAGEN GMBH, Hilden, Germany) as recommended by the manufacturer. An APOE fragment of 231 base pairs was amplified from purified genomic DNA by polymerized chain reaction using the primers APOE FWD (5'-GCGGGCACG-GCTGTCCAAG-3') and APOE REV (5'-GCCCCGGCCTG-GTACACTGC-3'). The polymerized chain reaction conditions were 94°C for 4 min followed by 38 cycles of 94°C for 20 s, 65°C for 20 s, and 72°C for 40 s, ending with a 7-min extension at 72°C. Genotyping was performed by means of combined *Hae*II and *Afl*III enzyme digestion followed by separation on a 3% Metaphor agarose (Medinova, Glostrup, Denmark).[21] The APOE alleles $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ were discernible by the appearance of fragments of the sizes 168, 145, and 195 base pairs, respectively.

Each patient was given a patient code at the local study center at enrollment. Blinding of APOE genotype was obtained because the identity of the individual patient was not known at the central laboratory analyzing blood samples or at the data analysis center.

Neuropsychological Testing

The patients underwent neuropsychological testing using the ISPOCD Test Battery[15] comprising seven subtests at three occasions: preoperatively and approximately 1 week and 3 months after surgery.

Statistical Analysis

Assuming an incidence of POCD of 20% at 1 week after surgery in patients with the $\epsilon 4$ allele and 10% in noncarriers, a sample size of 700 patients was required, accepting a type 1 error of 5% and a power of 95%. SAS software (Cary, NC) was used for data analysis. A P value below 5% was considered statistically significant. In the text, population average values are reported as medians with 5–95% range and population proportions as percentages with 95% confidence intervals.

Normative neuropsychological data were available for each of the two age groups, 40–59 yr[19] and 60 yr and older.[15] The controls were age-matched healthy individuals not staying in the hospital or undergoing surgery in the study period. They were recruited as spouses of patients or by advertisements in local papers. We analyzed test results of 352 controls tested using the same test battery at the same intervals. The mean changes were taken as estimated learning effects. We calculated the change in test results from the preoperative baseline value for patients and expressed the differences as Z scores for each by comparison with the control population. The Z score is therefore a continuous parameter describing the number of SDs that the change in test results of the individual patient is from the mean change of the normative data. By adding the subtest Z scores, a combined Z score was calculated, a measure of change in overall test performance of the patient at the postoperative test session. We defined POCD as a combined Z score greater than 1.96 or a Z score greater than 1.96 in at least two of the seven subtests.[15] If patients refused or were not able to complete a specific test, the Z score for that test was considered 0.

Baseline test results between patients with and without the $\epsilon 4$ allele were compared to investigate whether patients with the $\epsilon 4$ allele had poorer performance at baseline.

The variables of interest were the dichotomous POCD indicators (yes/no) at the two postoperative test sessions. APOE genotype, age, sex, and education level were used as covariates, and additional risk factors were identified in the three ISPOCD2 studies: alcohol, epidural, hospitalization, type of surgery, duration of anesthesia, and center.[17–19]

In a univariate analysis, APOE genotype was classified in two ways: a gene-dosage effect was tested by a division into three groups—0, 1, and 2 $\epsilon 4$ alleles—and an overall effect was tested by a division into two groups—presence of the $\epsilon 4$ allele (yes/no). The latter, dichotomous, classification of APOE genotype was used in a multivariate logistic regression model to assess the influence of the APOE genotype on POCD in the presence of the other covariates. The prevalence of the $\epsilon 4$ allele is known to vary in different populations[2] and with age,[22] and a significant interaction with education was found in a similar study.[13] Therefore, the significance of the effect

Table 1. Patient Characteristics

(N = 976)	ε4 Allele Absent (n = 704)	ε4 Allele Present (n = 272)	*P* Value, Chi-square
Center: Nordic/United Kingdom/Mediterranean/American	389/154/143/18	168/62/35/7	0.06
Age: older than 70 yr *vs.* 40–69 yr	216/488	88/184	0.61
Duration of anesthesia: > 2 h *vs.* 0–2 h†	329/361	118/146	0.41
Sex: female *vs.* male	451/253	182/90	0.40
Education: less than high school/high school/more than high school*	426/138/139	164/50/56	0.90
Type of surgery: minor *vs.* major	218/486	84/188	0.98
Epidural: yes *vs.* no†	89/601	30/234	0.52

* Recordings were missing in 2 patients. † Recordings were missing in 22 patients.

of APOE genotype and of the other covariates was assessed in a model that included interactions between APOE genotype and center, age, and education, respectively. An indication of effect size was based on a similar multivariate logistic regression model but without the interactions.

A protective effect of the ϵ2 allele on cognitive function has been demonstrated.[23] To take this possible interference into account, analysis of the influence of the APOE genotype on POCD was done in two ways. First, carriers of the ϵ2 allele were eliminated from the multivariate logistic regression analysis (without interactions), and second, an effect of the ϵ2 allele was specifically allowed by adding it to the covariate list in the multivariate logistic regression analysis (without interactions).

Supplementary data analyses were performed to avoid overlooking a significant association between APOE genotype and POCD due to the chosen cutoff level or cognitive decline in specific cognitive domains. For this purpose, multivariate linear regression models containing the covariates listed above (but not the interactions) were fitted to the continuous score variables, *i.e.*, the combined Z score and the seven separate subtest Z scores. Multiple testing decreases the significance level in this analysis to a *P* value of less than 0.006 through a Bonferroni correction.

Results

One hundred eighty-three controls (133 women and 50 men) were included in the group aged between 40 and 60 yr, with a median age of 51 (41–59) yr,[19] and 176 controls (75 women and 101 men) were included in the group aged 60 yr and older, with a median age of 67 (61–81) yr.[15]

A total of 976 patients with a median age of 65 (43–80) yr were included in the study. The median duration of anesthesia was 113 (25–255) min. The median duration of hospital stay was 4 (0–16) days. Other characteristics are given in table 1: Patients from the Mediterranean centers had a lesser prevalence of the ϵ4 allele. The distribution of patients with the six different genotypes is shown in table 2 and gave the following allele frequencies ϵ2: 7.9%; ϵ3: 75.1%; ϵ4: 17.0%.

Neuropsychological data were obtained at the first postoperative test session for 895 patients and at 3 months' follow-up for 842 patients. Infectious, respiratory, and cardiovascular complications and cases in which second surgery was needed were few in the study period. Accordingly, postoperative complications were not included in the risk factor analysis.

Neuropsychological Test Results

At the preoperative test session, we found no difference in baseline test results between patients with or without the ϵ4 allele (table 3). The first postoperative test session was completed by 895 patients after a median of 7 (2–17) days, and 93 had POCD, corresponding to an incidence of 10.4% (8.5–12.3%). At the second postoperative test session, after a median of 99 (77–160) days, 75 of 842 patients had POCD, *i.e.*, an incidence of 8.9% (7.0–10.8%). In the control group 13 of 352 controls, *i.e.*, 3.7% (2.7–4.7%), fulfilled the criteria of cognitive dysfunction after 1 week, and 12 of 345 controls fulfilled the criteria of cognitive dysfunction after 3 months, corresponding to an incidence of 3.5% (2.6–4.4%). Accordingly, the incidence of POCD among patients was significantly higher than among controls ($P < 0.001$ for both 1 week and 3 months).

The number of patients completing both postoperative

Table 2. Distribution of Patients with the Six Different APOE Genotypes (N = 976)

	ε2ε2	ε2ε3	ε2ε4	ε3ε3	ε3ε4	ε4ε4
This study	1 (0.1%)	121 (12.4%)	22 (2.3%)	582 (59.6%)	235 (24.1%)	15 (1.5%)
Expected*	6 (0.6%)	117 (12.0%)	26 (2.7%)	550 (56.3%)	249 (25.5%)	28 (2.9%)

* Based on allele frequencies reported by Gerdes *et al.*[2]

APOE = apoliprotein E.

Table 3. Comparison of Baseline Test Results between Patients (median [range 5–95%])

(N = 976)	ε4 Allele Absent (n = 704)	ε4 Allele Present (n = 272)	*P* Value*
Visual verbal learning test			
Cumulative of words in three trials	26 (15–37)	26 (15–36)	0.13
No. of words in delayed recall	9 (4–14)	8 (3–13)	0.10
Concept shifting test part C			
Time (s)	42.4 (24.6–93.4)	44.4 (23.9–92.4)	0.14
No. of errors	0 (0–5)	0 (0–3)	0.95
Stroop color word test part 3			
Time (s)	49.4 (32.5–95.3)	49.9 (32.7–94.3)	0.36
No. of errors	0 (0–7)	0 (0–5)	0.85
Letter–digit coding task			
No. of correct answers	26 (10–41)	26 (11–40)	0.47

* Mann–Whitney test.

test sessions was 840, and of those, 18 had POCD at both test sessions. POCD 1 week after surgery was found in an additional 69 patients who recovered 3 months later. On the other hand, 57 patients who did not exhibit early POCD fulfilled the criteria 3 months postoperatively.

In the univariate analysis (table 4), presence of the ϵ4 allele was not a significant risk factor for POCD after 1 week or after 3 months. Few patients were homozygous for the ϵ4 allele, so we were unable to assess a possible gene-dosage effect on POCD. Results from the multivariate logistic regression model for POCD after 1 week are given in table 5; age, duration of anesthesia, and avoidance of alcohol were significant risk factors for POCD 1 week after surgery. At the 3-month test session (table 6), no significant risk factors were identified. Presence of the ϵ4 allele was not a significant risk factor at 1 week or 3 months. There were no significant interactions.

An additional multivariate logistic regression analysis was repeated after omitting carriers of the ϵ2 allele to avoid interference of the presumably protective effect of this allele. The ϵ4 allele was still not a risk factor for POCD at 1 week ($P = 0.38$) or 3 months ($P = 0.91$). In the analysis of the ϵ2 allele as a protective factor, no statistical significance was found in the full model of multivariate logistic regression of POCD after 1 week ($P = 0.44$) or POCD after 3 months ($P = 0.34$). Presence of the ϵ4 allele was not a predictor of cognitive decline in any of the seven separate subtests or the overall test performance of test results at the test session after 1 week or 3 months ($P > 0.02$ with significance level 0.006 in this supplementary analysis).

Discussion

This study investigated a possible genetic predisposition to POCD after noncardiac surgery. We found no statistically significant association between APOE geno-

Table 4. Proportion of Patients with Postoperative Cognitive Dysfunction (POCD) at 1 Week and 3 Months by Risk Factors (Chi-square)

	1 week (n = 895)			3 months (n = 842)		
Risk factor	Number of Patients	Patients with POCD	*P* Value	Number of Patients	Patients with POCD	*P* Value
Duration of anesthesia						
0–2 h	481	30 (6.2%)		449	30 (6.7%)	
> 2 h	414	63 (15.2%)	< 0.0001	393	45 (11.5%)	0.015
Hospitalization						
In-patient	749	89 (11.9%)		699	70 (10.0%)	
Out-patient	146	4 (2.7%)	0.0009	143	5 (3.5%)	0.013
Alcohol						
Yes	514	39 (7.6%)		479	39 (8.1%)	
No	381	54 (14.2%)	0.001	363	36 (9.9%)	0.37
Age (years)						
40–69	620	51 (8.2%)		587	43 (7.3%)	
> 70	275	42 (15.3%)	0.001	255	32 (12.6%)	0.015
ε4 allele						
No	648	64 (9.9%)		618	52 (8.4%)	
Yes	247	29 (11.7%)	0.41	224	23 (10.3%)	0.40
Number of ε4 alleles						
0	648	64 (9.9%)		618	52 (8.4%)	
1	234	27 (11.5%)		211	21 (10.0%)	
2	13	2 (15.4%)	0.65	13	2 (15.4%)	0.57

Table 5. Analysis of Risk Factors in Relation to the First Postoperative Test Session (n = 895)

Multivariate Logistic Regression	*P*	Odds Ratio*	90% CI*
Age: older than 70 yr *vs.* younger than 70 yr	0.004†	2.04	1.37–3.03
Duration of anesthesia: > 2 h *vs.* 0–2 h	0.01	2.00	1.27–3.13
Alcohol: yes *vs.* no	0.04	0.61	0.41–0.91
Hospitalization: in-patient *vs.* out-patient	0.10	2.69	0.99–7.34
ε4 allele: yes *vs.* no	0.33‡	1.22	0.81–1.82
Type of surgery: minor *vs.* major	0.58	0.84	0.45–1.56
Education:	0.67†		
more than high school *vs.* less than high school		0.98	0.56–1.71
high school *vs.* less than high school		0.99	0.61–1.62
Sex: female *vs.* male	0.71	1.05	0.69–1.61
Epidural: yes *vs.* no	0.97	0.97	0.56–1.68
Center	0.48†	—	—
Interactions:			
ε4 allele × center	0.15		
ε4 allele × age	0.11		
ε4 allele × education	0.31		

* Based on a model without interactions. † Test for joint significance of main effect and interaction with ε4 allele. ‡ Test for joint significance of main effect and interactions with center, age, and education.

type and POCD at 1 week or 3 months after noncardiac surgery, but low statistical power could be an important limitation. Logistic regression analysis identified age, duration of anesthesia, and avoidance of alcohol as risk factors for POCD after 1 week. Three months later, no significant risk factors were found.

The frequencies and distribution of genotypes found in this study population corresponds well to previous reports (table 2), and a lesser prevalence of the ε4 allele in Mediterranean countries compared to Northern Europe is well known.[2] We did not analyze APOE genotype among controls, but the patients with the ε4 allele did not have a poorer baseline performance (table 3) than the rest of the study population. If that had been the case, floor effects could have impaired the detection of decline among patients with the ε4 allele.[24]

The incidence of POCD 1 week after surgery was only 10.4%, which is less than in the ISPOCD1 study,[15] where an incidence of 25.8% was found among elderly patients undergoing major surgery with general anesthesia. However, in the current study, the median age of the population was lower, perioperative complications were few, and some patients had only minor surgery with short hospital stay if any, all conditions associated with a lower incidence of POCD.[17,19]

After 3 months, the incidence of POCD was 8.9%, which is comparable to that of the ISPOCD1 study (9.9%).[15] During the 3 months after surgery, the incidence of POCD did not change significantly in this study in contrast to the ISPOCD1 study.[15] Early POCD after major surgery might mainly be due to residual drug effects and complications that depress cognitive function shortly after surgery, where the etiology of long-term POCD might be different. The patients with POCD after 3 months did not all exhibit POCD at the test session after 1 week; only 18 patients had POCD at both

Table 6. Analysis of Risk Factors in Relation to the Second Postoperative Test Session (n = 842)

Multivariate Logistic Regression	*P*	Odds Ratio*	90% CI*
Age: older than 70 yr *vs.* younger than 70 yr	0.17†	1.67	1.09–2.50
Duration of anesthesia: > 2 h *vs.* 0–2 h	0.34	1.32	0.79–2.13
Alcohol: yes *vs.* no	0.69	1.09	0.70–1.71
Hospitalization: in-patient *vs.* out-patient	0.16	2.26	0.87–5.85
ε4 allele: yes *vs.* no	0.57‡	1.30	0.83–2.04
Type of surgery: minor *vs.* major	0.79	0.89	0.46–1.74
Education:	0.22†		
more than high school *vs.* less than high school		0.50	0.26–0.95
high school *vs.* less than high school		0.62	0.35–1.11
Sex: female *vs.* male	0.14	0.66	0.42–1.03
Epidural: yes *vs.* no	0.44	0.74	0.39–1.42
Center	0.19†	—	—
Interactions:			
ε4 allele × center	0.49		
ε4 allele × age	0.91		
ε4 allele × education	0.50		

* Based on a model without interactions. † Test for joint significance of main effect and interaction with ε4 allele. ‡ Test for joint significance of main effect and interactions with center, age, and education.

postoperative test sessions. First, patients who were not fit enough for testing after 1 week were not registered as having POCD at this time point. Patients withdrawing from studies are known to have lower baseline test results[18] and may be most likely to experience cognitive decline. This leads to an underestimation of the incidence of early POCD. Second, it is known from similar studies of cardiac[25,26] and noncardiac surgery[27] that there is a discrepancy between results from repeated test sessions. Some patients may be able to compensate for a period of time and then relapse into the group of patients fulfilling the criteria of POCD.

Patients with the $\epsilon 4$ allele were observed to have a 20% greater risk of POCD than noncarriers in the univariate analysis, but we assumed a 100% higher risk as the basis of our sample size calculation. To detect a true difference between 9.9% and 11.7%, at least 10,000 patients would be required. On one hand, the $\epsilon 4$ allele would, accordingly, not be a major risk factor for POCD. On the other hand, it could be argued that in general, a 20% difference in an outcome associated with potential substantial decrease in quality of life would have a clinical significance. The clinical impact of POCD is difficult to assess, but we have previously demonstrated a significant correlation between a decline in the activities of daily living and POCD after 3 months.[15,19] Maybe the sample size defined should be assessed within the confines of other interventions within the population. As an example, antiplatelet treatment reduced vascular mortality by 15% and nonfatal vascular events by 30% in a meta-analysis of a total of 29,000 patients.[28] Also, it should be noted that, had the incidence of early POCD been as high as in the ISPOCD1 study[15] (25.8%) and given a 20% risk reduction determined by APOE genotype, only a sample size of 3,500 would be needed. Hence, the importance of APOE genotype could be demonstrated in fewer patients by studying a high-risk population.

The methodology is comparable to previous studies on cognitive decline and APOE genotype.[10,11] Some population-based studies have found an association between decline in specific cognitive domains such as memory functions[29,30] and APOE genotype. When evaluating a broad measure of cognitive performance, whether it is a dichotomous or a continuously dependent variable, such a specific impairment might be overlooked. Hence, we also assessed changes in performance in each of the seven subtests constituting the ISPOCD Test Battery but found no relation between decline in a specific cognitive domain and APOE genotype.

Tardiff *et al.*[13] studied 65 patients undergoing cardiac bypass grafting. They used a less rigorous definition of POCD and found a significant association between the $\epsilon 4$ allele and decline in short-term memory 6 weeks after surgery. However, there was a significant interaction between APOE genotype and education level. They regarded their results as preliminary due to the small sample size that permitted the analysis of only a few covariates. Steed *et al.*[14] aimed to replicate this work with a sample size of 111 patients but found no association between the $\epsilon 4$ allele and cognitive decline. Moreover, this was a secondary analysis of pooled data from a negative drug trial aimed at reducing neurologic injury after cardiac surgery, and a possible interaction between the neuroprotective drug and the $\epsilon 4$ allele was not evaluated. So far, the literature is conflicting regarding importance of APOE genotype on POCD after cardiac surgery.

The etiology of POCD is unknown, but the high incidence after cardiac surgery has been attributed to the use of cardiopulmonary bypass. More recently, studies on cognitive functioning after on-pump *versus* off-pump surgery have been published. Conclusions conflict with some studies reporting a significantly lower incidence of POCD among patients in the off-pump technique group,[31] and others find no difference.[32] During cardiopulmonary bypass, embolic events combined with periods of cerebral hypoperfusion do occur.[33,34] Even though emboli may also occur during major joint replacement, patients undergoing noncardiac surgery do not face the same risks of potentially damaging incidents. Accordingly, other mechanisms may be responsible, and therefore, APOE genotype might be connected with POCD after on-pump cardiac surgery but not after noncardiac surgery. APOE genotype may determine outcome only after the specific neuronal damage of cardiac surgery during cardiopulmonary bypass.

Some of the risk factors identified in this study at the test session 1 week after surgery, such as age, and duration of anesthesia are the same as those found in the ISPOCD1 study.[15] Complications in the perioperative period were few in the current study, so these were not entered as covariates in further analyses. The greater incidence of POCD in patients who avoided alcohol could be explained if patients who use alcohol regularly are less sensitive to anesthetics. It could be speculated also that patients who never drink alcohol might have different genetic, social, educational, or environmental backgrounds making them more susceptible to POCD.

In this study, age failed to reach the level of significance ($P = 0.17$) at the second postoperative test session. In the ISPOCD1 study,[15] age was the only identified risk factor after 3 months. The hypothesis that APOE genotype would add to in the explanation of prolonged POCD could not be supported in this study. The mechanisms behind POCD must still be elucidated to provide additional information regarding this serious complication to surgery.

In conclusion, we were not able to show a significant association between APOE genotype and POCD after noncardiac surgery. It must be taken into consideration that the sample size of the study did not allow a firm conclusion because of a lower incidence of POCD than expected.

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Appendix: ISPOCD2 (International Study of Postoperative Cognitive Dysfunction) Investigators

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