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Mild Cognitive Impairment and Exposure to General Anesthesia for Surgeries and Procedures: A Population-Based Case Control Study

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Abstract

Objective—To examine whether exposure to general anesthesia for procedures at age 40 is associated with prevalent mild cognitive impairment (MCI) in the elderly.

Patients and Methods—A case-control study nested within a population-based cohort. Olmsted County, MN, residents ages 70–89 years, underwent baseline evaluations that included

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Juraj Sprung and Darrell Schroeder and Rosebud Roberts have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They also have final responsibility for the decision to submit for publication.

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the Clinical Dementia Rating scale, a neurologic evaluation, and neuropsychological testing. Individuals identified with MCI (*cases*) at enrollment were matched 1:2 on age, sex, education and apolipoprotein genotype with participants who were cognitively normal at the time of the index visit. Medical records from age 40 until the index visit were reviewed to determine exposures to general anesthesia. Conditional logistic regression, taking into account the matched set study design and adjusting for MCI risk factors, was used to assess whether exposure to anesthesia after the age of 40 was associated with prevalent MCI.

Results—A total of 387 MCSA participants (219 males, 168 females) were diagnosed with MCI at enrollment with mean age 81 ± 5 years. Exposure to general anesthesia after the age of 40 was not significantly associated with prevalent MCI when analyzed as a dichotomous variable (any *vs.* none, adjusted OR 0.97 [95% CI 0.68–1.40]) or the number of exposures OR 1.13 [0.74–1.72], 0.81 [0.53–1.22], and 1.03 [0.67–1.58] for 1, 2–3, and 4 exposures, respectively, with no exposure as the reference. Similar results were obtained for anesthesia exposure after the age 60, and during 5, 10 and 20 years prior to the first visit.

Conclusion—Exposure to general anesthesia for procedures at ages 40 years was not associated with prevalent MCI in the elderly.

Keywords

Aged humans; male; female; Anesthesia: general; Case-control study; Dementia; Alzheimer's dementia; Prevalent mild cognitive impairment; Surgery

INTRODUCTION

Preclinical studies suggest that some drugs that produce general anesthesia may induce neurohistological changes consistent with Alzheimer dementia (AD).^{1,2} In addition, surgical stimulation itself may increase levels of neuroinflammatory mediators that can result in cognitive impairment in aged mice.^{3,4} Nevertheless, findings regarding the potential association between exposure to anesthesia and long-term cognitive impairment have not been consistent in observational clinical studies.^{5–10} Much of this research utilizes dementia as the primary outcome.^{5,6} It is possible that less severe forms of cognitive impairment, such as the clinical diagnosis of mild cognitive impairment (MCI)^{11–13} would represent a more sensitive outcome to detect an association between anesthesia and long-term cognitive dysfunction, as a diagnosis of MCI often precedes the diagnosis of dementia.^{11–13}

MCI is a chronic condition with likelihood of onset increasing with age. When studying MCI it is important to distinguish between incidence and prevalence. Incidence corresponds to the rate at which new cases of MCI develop in the population, while prevalence corresponds to the percentage of the population who have MCI at a given point in time. The Mayo Clinic Study of Aging (MCSA), a population-based longitudinal cohort study, examines the incidence and prevalence of MCI and dementia in Olmstead County, MN, including risk factors for these outcomes. Roberts, 2008 #282} Using the MCSA, we recently analyzed the association between exposure to surgery and anesthesia at age 40 and the incidence of MCI in those who were cognitively normal at the time of entry into the MCSA, finding no overall association.¹⁴ However, because individuals were elderly at the

time of MCSA enrollment (mean age of 81 years in this analysis), excluding those who are not cognitively normal at the time of enrollment risks missing potentially relevant associations between anesthesia exposure and cognitive impairment with earlier onset. This may be particularly relevant if anesthesia exposure accelerates cognitive decline. Thus, an analysis of *prevalent cases* at the time of MCSA enrollment provides an additional opportunity to explore the potential association between lifetime exposure to surgical anesthesia and cognitive impairment. In the present study we use a case-control design to test the hypothesis that exposure to general anesthesia for surgery and procedures at age 40 is associated with prevalent MCI. In a supplementary analysis we also tested the hypothesis that exposure to general anesthesia for surgery and procedures at age 40 is associated with cognitive impairment, defined as prevalent MCI and dementia.

METHODS

This study conformed to the requirements of the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) statement and was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center, Rochester, MN. At the time of enrollment all participants provided written informed consent for the study. This analysis included those MCSA participants who had also provided prior authorization for the use of their medical information in research (Minnesota Statute 144.335), such that their anesthesia and surgical records could be reviewed.

Study Design

We examined the association between adult-life exposure to general anesthesia for surgeries and procedures. Henceforth, we use term “*anesthetic exposure*” to denote exposure to general anesthesia for surgery or procedures. We accounted for exposure to anesthesia at age 40 until the day of first evaluation in the MCSA study (*index visit*). This age was selected to complement preclinical investigations, which found that exposure of 18-month old rats to anesthesia (thought by some authors to be equivalent to an ~45-year-old human)^{15,16} results in long-lasting impairment in spatial memory¹⁷ and the development of neuropathology consistent with AD.^{1,18} For this study two separate data resources are utilized. From the MCSA we obtained data regarding cognitive status on index visit (cognitively normal *vs.* prevalent MCI or dementia), and from medical records we obtained episodes of exposure to anesthesia and surgery.

This investigation utilizes a 1:2 matched case control design. Cases included all participants who were diagnosed with MCI or dementia at the index visit. The pool of potential controls included all participants who were evaluated and found to be cognitively normal at the index visit. For each case, 2 controls were randomly selected who matched the case on age (± 3 years), sex, education (≥ 12 years, ≥ 13 years), and apolipoprotein (APOE) genotype status. The medical and surgical records of all participants are available through the resources of the Rochester Epidemiology Project (REP), a medical records linkage system.¹⁹ For all participants medical records were abstracted for each episode of general anesthesia and type of surgery or procedure between age 40 and the date of the index study visit. This age was chosen to provide a relatively long exposure history useful to perform sensitivity (secondary)

analyses (see Statistical analysis). Exposures to anesthesia in Olmsted County hospitals were identified *via* REP procedure databases and abstracted as previously described,¹⁴ to ascertain information including the agents used for induction and maintenance of anesthesia, the type of surgery or procedure, and the duration of anesthesia. Episodes of anesthesia with regional block only, as well as those who received sedation and subcutaneous injection of local anesthetic, were excluded. All data were entered manually into the web-based Research Electronic Data Capture (REDCap[®]) system (Version 3.6.7, Vanderbilt University, Nashville, Tennessee).²⁰

Summary of MCSA study procedures—Details of the MCSA study protocol, including design, sampling, participation, baseline measures and sample characteristics, as well as comparison between participants and nonparticipants have been previously published,²¹ and were also summarized in our prior analysis of incident MCI cases.¹⁴ Briefly, a stratified random selection of subjects from the sampling frame of Olmsted County residents aged 70 to 89 years was conducted, followed by letter of invitation to participate and a recruitment telephone call. Upon signing the written informed consent, participants enrolled in the MCSA received detailed assessments of cognitive status at baseline and at 15 monthly follow-up visits. The Clinical Dementia Rating Scale (CDR)²² was administered to a study partner (informant) to assess functioning of the subject and dementia severity when present. The CDR score and the CDR sum of boxes were assessed independently of the results of the neuropsychological testing. In addition, the functional status of each subject was elicited from the study partner also using the Functional Activities Questionnaire.²³ If persons were judged to have no cognitive impairment according to published criteria^{12,24} and received a CDR of 0, they were enrolled as cognitively normal subjects. Subjects with a CDR >1 were classified as demented if they met DSM-IV criteria for dementia.²⁵ Subjects who received a CDR of 0.5 had a more intense evaluation (neurological, neuropsychological) to determine if they met criteria for MCI or for dementia.

The diagnosis of MCI was based on published criteria, including: 1) impairment in one of 4 assessed cognitive domains (memory, executive function, language, and visuospatial skills); 2) cognitive concerns by the subject, informant, examining nurse, or physician; 3) essentially normal functional activities, and; 4) absence of dementia (based on published criteria).^{11–13} Subjects who performed within the normal cognitive range and did not meet criteria for MCI or dementia were considered as cognitively normal. Those characterized as having MCI fulfilled all 4 criteria; however, the final MCI diagnosis was based on a review of all information collected for a participant and a consensus decision by the nurse and clinician who evaluated the participant and the neuropsychologist who reviewed the cognitive testing data.

Statistical analyses

To test the hypothesis that anesthetic exposure at age 40 is associated with MCI, the primary analyses included only cases of prevalent MCI and their matched controls. Subsequent supplementary analyses included prevalent cases who were not cognitively normal (i.e., both prevalent MCI and dementia), along with their matched controls.

Anesthesia exposure was quantified as any *vs.* none, number of exposures, and cumulative duration of exposure. The number of exposures was treated both as a continuous variable and as a categorical variable, using 4 categories (no exposure, 1 exposure, 2–3 exposures and 4 exposures). The cumulative duration of exposure was also analyzed as both a continuous variable and as a categorical variable (no exposure, 1–120 minutes, 121–240 minutes, 241–480 minutes and 481 minutes). Separate analyses were performed for each approach used to quantify anesthesia exposure. For the primary analyses the values for these variables were those calculated for both cases and controls using all surgeries from age 40 up to the first MCSA visit (i.e., adult life exposure). Data were analyzed using conditional logistic regression taking into account 1:2 matched study design. Cases and controls were matched on age, sex, education, and APOE genotype. The decision to use 1:2 matching was made based on resource constraints not on a formal statistical power analysis. In addition to anesthesia exposure variable, covariates were included in all models, and specifically those are the variables found to be associated with MCI in previous publications²⁶ and included: marital status, smoking status, alcohol, midlife diabetes, midlife hypertension, midlife dyslipidemia, atrial fibrillation, Charlson Comorbidity Index, history of congestive heart failure, stroke, and coronary artery disease. In addition, since cases and controls were not matched exactly for age and number of years of education, these variables were also included as covariates.

Additional secondary analyses were planned *a priori*. To explore the concept that risk produced by exposure to anesthesia and procedures increases with age, the primary analyses were repeated including only exposures to anesthesia after age 60 (i.e., not including exposures prior to age 60). In addition, analyses were performed which included only exposures to anesthesia which occurred in the 5, 10, and 20 year periods prior to the index visit. Finally, in order to assess whether specific types of surgery may be associated with MCI a series of additional analyses were performed. The types of surgery of specific interest included major vascular, cardiac with and without cardiopulmonary bypass, and orthopedic procedures, which are frequently studied in populations in association with postoperative cognitive dysfunction.^{27,28} For each of these surgery types a binary variable was created to indicate patients who underwent one or more procedure of the given type. For each participant these variables had a value of 1 if the participant underwent one or more of the given type of surgery, and a value of 0 if the participant did not have exposure to any surgery. Using this approach the same reference group was used for all procedure types.

In all cases, results are summarized using odds ratio estimates and corresponding 95% confidence intervals. Unadjusted, two-tailed P values are presented. To account for the fact that anesthesia exposure was quantified using 3 approaches (any *vs* none, number of exposures, and cumulative duration of exposure), P-values < 0.017 were considered statistically significant. Analyses were performed using SAS statistical software (Version 9.3, SAS Institute, Inc, Cary, NC).

Sample size/statistical power considerations—This investigation includes all prevalent cases of MCI identified in the MCSA during the study period (n=387). The decision to include 2 controls per case (n=774) was made based on resource constraints given that medical records of both cases and controls needed to be manually reviewed in

order to identify anesthesia exposures. No formal power analysis was performed when making the decision to include 2 controls per case. However, based on the observed frequency of anesthesia exposure among controls in a recent case-control study of Alzheimer's disease (reference here), our sample-size would provide statistical power (two-tailed, $\alpha = 0.017$) of 80% to detect an odds ratio of 1.6 when assessing the association between anesthesia exposure (any vs none) and prevalent MCI.

RESULTS

A total of 454 MCSA participants were not cognitively normal (387 with prevalent MCI and 67 with prevalent dementia) at their first enrollment visit and had authorized the use of their medical records for research. For our primary analyses assessing the association between exposure to anesthesia and MCI we include the 387 prevalent MCI cases. For these cases, the mean age at the time of enrollment was 81 ± 5 years. These MCI cases were matched to 774 participants who were cognitively normal at the time of the first visit. Matching variables and risk factors for MCI found in a previous study²⁶ are summarized in Table 1. Cases and controls were matched exactly on sex, education category and APOE status. For all matched sets, age was matched within ± 3 years and for 85.8% within ± 1 year. As expected from previous reports^{29–32} several major cardiovascular morbidities were more prevalent in MCI cases.

A total of 947 participants (627 [81.0%] controls and 320 [82.7%] MCI cases) were exposed to general anesthesia at age 40 and prior to the index visit. The most frequent surgeries were general and orthopedic operations (Table 2). Most surgeries (86% and 92% of cases and controls, respectively) included the use of halogenated inhalational agents with the specific agent used reflective of the era when the procedure was conducted (Figure 1). Anesthesia induction was most frequently performed with sodium thiopental (67% and 69% of cases and controls, respectively) or propofol (29% and 28% of cases and controls, respectively), and the maintenance anesthetic typically included the use of nitrous oxide (79% and 82% of cases and controls, respectively).

In the primary analyses, there was no significant association between anesthesia exposure at age 40 and prevalent MCI (OR 0.97 [95% CI 0.68 to 1.40]) for any exposure *vs.* no exposure after age 40] (Table 3). The lack of association persisted when exposures were quantified according to number and total duration (Table 3). Similar results were obtained from sensitivity analyses that quantified anesthesia exposure after the age of 60, and during the 5, 10 and 20 years periods prior to the index visit (Table 4). Furthermore, when separate analyses were performed to assess specific types of major surgeries thought to potentially be associated with an increased risk of postoperative cognitive decline and possibly MCI no significant associations were detected (Table 5).

Analyses were repeated using all cases who were not cognitively normal (i.e., both prevalent MCI and dementia), along with their matched controls. In these analyses a total of 1,116 participants (742, 81.7%, controls, and 374, 82.4% MCI/dementia cases) were exposed to general anesthesia at age 40 and prior to the index visit. The most frequent surgeries were general and orthopedic operations (Figure 1 Appendix). The findings from these analyses

are presented in Appendix Tables 1–5. In all analyses, exposure to general anesthesia for surgeries and procedures at age 40 were not associated with cognitive impairment.

DISCUSSION

The main finding of our study is that exposure to general anesthesia for surgery and procedures at age 40 was not associated with *prevalent MCI* in a cross-sectional, population-based sample of the elderly. These results are consistent with our previous report indicating that exposure to anesthesia at age 40 is not associated with the development of *incident MCI* in individual who were cognitively normal on enrollment in the MCSA and followed for subsequent development of MCI.¹⁴

There is no doubt that elderly patients may develop transient postoperative cognitive dysfunction.^{27,28,33–38} Whether this can lead to long-term cognitive impairment remains controversial.^{9,10,39} Although a detailed review of this literature is beyond the scope of present paper,^{5,9,40} the results from both our current (prevalent MCI) and prior (incident MCI)¹⁴ analyses are consistent those studies which have not found an association between anesthesia exposure and long-term cognitive impairment.^{5,6,8–10,41,42}

Although we did not find an association between anesthesia exposure and incident MCI, in our prior analysis, we could not exclude the possibility that recent anesthetic exposure (within previous 10 or 20 years) to anesthetic was associated with incident MCI.¹⁴ This finding was only observed in patients who underwent major vascular operations, which may also be a marker for patients with advanced atherosclerotic disease who are known to be at risk for vascular dementia.^{30,31} In contrast, in the present study we did not find an association between anesthetic exposure and prevalent MCI for exposure at any age.

To control for known risk factors, we matched cases and controls on age, sex, APOE status and education. Comparing cases *vs.* controls we found that some cardiovascular comorbidities were more prevalent in MCI cases. This finding is not surprising and is consistent with the notion that cardiovascular pathology is frequently associated with atherosclerosis, and in particular atherosclerotic cerebrovascular disease poses a risk factor for dementia.^{29–31} This and other known risk factors were included as adjustor variables when analyzing the role of anesthesia exposure in MCI.

Limitations and strengths of the study

Our study also has several limitations. As with any observational study, potential confounders related to nature of comorbidities necessitating surgery and hospitalization may themselves may be associated with cognitive decline;⁴³ however, in the absence of associations this and similar factors become less relevant. For prevalent MCI cases the time of development of the cognitive impairment is not known, so that some of the anesthesia exposures among cases may have occurred following the onset of MCI. Nonparticipation bias is also a potential limitation, as patients who died prior to age 70 were not considered for inclusion in the present MCSA cohort. Therefore, our findings apply only to persons who survived to 70 years of age and agreed to participate in MCSA. Anesthetic agents and techniques have changed over the last several decades (Figure 1), so that the results may not

reflect the effects of contemporary anesthetic practice (which hopefully continues to improve over time as perioperative “brain health” attracts more attention). The secondary analyses restricted to more recent exposures presumably better reflects contemporary practice, yet no associations were observed. Our study is restricted to surgeries that required general anesthesia. Current evidence suggests that there is no difference in incidence of POCD following regional vs. general anesthesia.⁴⁴ Thus, since surgeries performed under regional anesthesia only are not included in our study we cannot generalize our study results to reflect the association between any surgical exposure and the development of MCI. Furthermore, hospitalization without surgery, which may be associated with cognitive decline, was not accounted in any of our analyses.⁴⁵ Finally, the racial and ethnic composition of Olmsted County residents of this age group is less diverse than the overall US population, so our results may not apply to populations underrepresented in Olmsted County.

Important strengths of this study include sensitive methods used by an experienced team of neurologists, nurses and a neuropsychologist to detect early cognitive dysfunction that is consistent with a diagnosis of MCI based on a consensus decision. The REP¹⁹ is a unique database that provides rich information regarding medical comorbidity and anesthesia history for Olmsted County residents, which for many individuals encompasses their entire lifetime. Obtaining the medical and surgical data from REP provides greater precision of retrospective data collection when compared to self-reported recollection of surgical and anesthetic exposures.¹⁰

In conclusion, exposure to general anesthesia for surgeries and procedures at age 40 or later was not significantly associated with prevalent MCI in a population-based cohort of elderly subjects. With all acknowledged limitations of prevalent case-control study design, our findings are in line with a preponderance of the literature which has failed to show a significant association between exposure to surgical anesthesia and sustained cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Alphabetical List of Abbreviations

AD Alzheimer’s dementia

MCI	mild cognitive impairment
MCSA	Mayo Clinic Study of Aging
POCD	postoperative cognitive dysfunction
REP	Rochester Epidemiology Project

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Summary statement

In this population-based Mayo Clinic Study of Aging there was no association between exposure to general anesthesia for surgery and procedures at age 40 and prevalent mild cognitive impairment.

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Figure 1.

Volatile anesthetic agents used during the study period (the use of cyclopropane and nitrous oxide not shown). This figure includes prevalent MCI cases and their respective controls. The numbers in parentheses represent the total number of surgeries and procedures performed during the given calendar period. Each color in a column denotes a partition of specific inhalational agent use during the respective year range.

Table 1

Clinical characteristics in MCI cases and controls.

Clinical Characteristics	Cognitively Normal N=774 N (%)	MCI N=387 N (%)	OR (95% CI)	P Value*
Age (y) (mean ± SD)	81.0 ± 4.9	81.3 ± 5.1	--	--
Gender				
Female	336 (43)	168 (43)	--	--
Male	438 (57)	219 (57)	--	--
Education, years				
12	428 (55)	214 (55)	--	--
>12	346 (45)	173(45)	--	--
APOE epsilon 4 allele				
No	528 (68)	264 (68)	--	--
Yes	246 (32)	123 (32)	--	--
Smoking status				0.975
Never	389 (50)	192 (50)	Ref.	
Former	355 (46)	180 (47)	1.03 (0.79 to 1.35)	
Current ^a	34 (4)	16 (4)	1.02 (0.53 to 1.94)	
Marital status				0.485
Married	469 (61)	231 (60)	Ref.	
Widowed ^b	235 (30)	113 (29)	0.98 (0.72 to 1.34)	
Single ^b	70 (9)	43 (11)	1.29 (0.82 to 2.02)	
Ever diagnosed alcohol problem (n=1359)^{a,b}				0.056
No	749 (96)	366 (95)	Ref.	
Yes	24 (3)	21 (5)	1.80 (0.99 to 3.29)	
Midlife diabetes^a				0.184
No	740 (96)	363 (94)	Ref.	
Yes	38 (4)	24 (6)	1.44 (0.84 to 2.47)	
Midlife hypertension^a				0.563
No	519 (67)	253 (65)	Ref.	
Yes	255 (33)	134 (35)	1.08 (0.83 to 1.40)	
Midlife dyslipidemia^a				0.930
No	498 (64)	246 (64)	Ref.	
Yes	276 (36)	141 (36)	1.04 (0.80 to 1.35)	
Atrial fibrillation^{a,b}				0.020
No	622 (80)	287 (74)	Ref.	
Yes	152 (20)	100 (26)	1.43 (1.07 to 1.92)	
Congestive heart failure				0.044
No	667 (80)	316 (82)	Ref.	
Yes	107 (14)	71 (18)	1.40 (1.01 to 1.95)	
Stroke^{a,b}				0.002

Clinical Characteristics	Cognitively Normal N=774 N (%)	MCI N=387 N (%)	OR (95% CI)	P Value*
No	716 (93)	336 (87)	Ref.	0.016
Yes	58 (7)	51 (13)	1.89 (1.26 to 2.83)	
Coronary artery disease				
No	459 (59)	201 (52)	Ref.	
Yes	315 (41)	186 (48)	1.36 (1.06 to 1.75)	

Values are mean $\pm$ SD or N (%). Age, sex, education and APOE allele were included as matching variables, and therefore not analyzed as potential risk factors. These characteristics were identified as predictors for MCI in the clinical risk model for women (^a) and men (^b).²⁶

Table 2Surgeries and procedures performed under general anesthesia in cases and controls^a

Type of Surgery or Procedure	Cognitively Normal (N=774) N (%)	MCI (N=387) N (%)
Any surgery or procedure	627 (81)	320 (83)
General		
Colorectal	53 (7)	26 (7)
Hepatobiliary	23 (3)	49 (13)
Other general	276 (36)	93 (24)
Orthopedic	219 (28)	110 (28)
Genitourinary/reproductive		
Obstetrics / gynecology	151 (20)	81 (21)
Urological	125 (16)	74 (19)
Cardiac with bypass	88 (11)	52 (13)
Cardiovascular without bypass		
Vascular	66 (9)	45 (12)
Cardiac without bypass	15 (2)	9 (2)
Neurosurgery	62 (8)	43 (11)
Thoracic	19 (2)	8 (2)
Head and neck		
Ear, nose and throat	71 (9)	30 (8)
Oral and maxillofacial	47 (6)	22 (6)
Plastic		
Breast	56 (7)	28 (7)
Plastic reconstructive	15 (2)	16 (4)
Miscellaneous	46 (6)	42 (11)
Surgeries		
Ophthalmologic	29 (4)	16 (4)
Dermatologic	7 (1)	2 (1)
Procedures		
Endoscopy	2 (0)	2 (1)
Electroconvulsive therapy	1 (0)	0 (0)
Interventional radiology	0 (0)	0 (0)
Angiography	0 (0)	2 (1)

^a 947 individuals underwent 3,039 surgeries or procedures after the age of 40, but prior to the initial study visit. The data presented correspond to the number (%) of individuals who underwent at least one surgery in the given category (i.e., patients who underwent multiple surgeries of the same type are counted only once). For this reason, the sum across categories does not equal the total number of surgeries performed.

Table 3

Primary analysis assessing association between exposure to general anesthesia for surgeries and procedures at age 40 and MCI.

Anesthetic Characteristic	Cognitively Normal N=774 N (%)	MCI N=387 N (%)	OR (95% CI)	P Value*
Any anesthesia exposure				0.885
No	147 (19)	67 (17)	Ref.	
Yes	627 (81)	320 (83)	0.97 (0.68 to 1.40)	
Count of anesthesia exposures (n)				
Continuous, per exposure			1.03 (0.97 to 1.10)	0.328
Categorical				0.323
0	147 (19)	67 (17)	Ref.	
1	164 (21)	84 (22)	1.13 (0.74 to 1.72)	
2–3	262 (34)	115 (30)	0.81 (0.53 to 1.22)	
4 or more	201 (26)	121 (31)	1.03 (0.67 to 1.58)	
Duration of anesthetic exposure (min)				
Continuous, per 60 min			1.01 (0.99 to 1.03)	0.461
Categorical				0.554
0	147 (19)	67 (17)	Ref.	
1–120	66 (9)	39 (10)	1.31 (0.78 to 2.22)	
121–240	144 (19)	61 (16)	0.87 (0.55 to 1.39)	
241–480	199 (26)	94 (24)	0.87 (0.57 to 1.34)	
481 or more	218 (28)	126 (33)	1.00 (0.65 to 1.52)	

Odds ratios (OR) and P-values are from conditional logistic regression. OR greater than 1 indicates an increased risk for MCI. Separate models were used to assess anesthesia exposure quantified as any anesthetic, number of exposures (0, 1, 2–3, 4) and cumulative duration of exposure in minutes (0, 1–120, 121–240, 241–480, and >480). Cases and controls were matched on age, sex, education, and *APOE ε4* genotype. In addition, covariates were included in all models for age, education, marital status, smoking status, alcohol, midlife diabetes, midlife hypertension, midlife dyslipidemia, atrial fibrillation, Charlson comorbidity index, history of congestive heart failure, stroke, and coronary artery disease.

Table 4

Secondary analyses assessing association between MCI and exposure to general anesthesia for surgeries and procedures after age 60, and during 20, 10 and 5-year periods prior to the index visit.

Anesthetic Exposure	Cognitively Normal N=774 N (%)	MCI N=387 N (%)	OR (95% CI)	P Value*
Exposures between age 60 and first visit				
Any anesthesia exposure				0.795
No	234 (30)	109 (28)	Ref.	
Yes	540 (70)	278 (72)	0.96 (0.71 to 1.30)	
Count of anesthesia exposures (n)				
Continuous, per exposure			1.03 (0.96 to 1.11)	0.380
Categorical				0.930
0	234 (30)	109 (28)	Ref.	
1	204 (26)	97 (25)	1.01 (0.70 to 1.45)	
2–3	241 (31)	120 (31)	0.91 (0.63 to 1.29)	
4 or more	95 (12)	61 (16)	1.00 (0.63 to 1.58)	
Duration of anesthetic exposure (min)				
Continuous, per 60 min			1.01 (0.98 to 1.03)	0.507
Categorical				0.814
0	234 (30)	109 (28)	Ref.	
1–120	62 (8)	30 (8)	1.21 (0.72 to 2.04)	
121–240	145 (19)	75 (19)	1.00 (0.67 to 1.49)	
241–480	174 (22)	85 (22)	0.88 (0.59 to 1.31)	
481 or more	159 (21)	88 (23)	0.89 (0.60 to 1.33)	
Exposures during the 20 years prior to first visit				
Any anesthesia exposure				0.438
No	237 (31)	114 (30)	Ref.	
Yes	537 (69)	273 (70)	0.89 (0.66 to 1.20)	
Count of anesthesia exposures (n)				
Continuous, per exposure			1.03 (0.96 to 1.11)	0.393
Categorical				0.840
0	237 (31)	114 (30)	Ref.	
1	217 (28)	105 (27)	0.91 (0.63 to 1.30)	
2–3	232 (30)	115 (30)	0.85 (0.60 to 1.21)	
4 or more	88 (11)	53 (14)	0.95 (0.59 to 1.53)	
Duration of anesthetic exposure (min)				
Continuous, per 60 min			1.01 (0.98 to 1.03)	0.535
Categorical				0.835
0	237 (31)	114 (30)	Ref.	
1–120	68 (9)	34 (9)	1.01 (0.61 to 1.69)	
121–240	144 (19)	72 (17)	0.94 (0.63 to 1.40)	
241–480	173 (22)	85 (21)	0.81 (0.55 to 1.20)	

Anesthetic Exposure	Cognitively Normal N=774 N (%)	MCI N=387 N (%)	OR (95% CI)	P Value*
481 or more	152 (20)	82 (22)	0.86 (0.58 to 1.29)	
Exposures during the 10 years prior to first visit				
Any anesthesia exposure				0.789
No	372 (47)	179 (46)	Ref.	
Yes	402 (53)	208 (54)	0.96 (0.73 to 1.27)	
Count of anesthesia exposures (n)				
Continuous, per exposure			1.07 (0.97 to 1.17)	0.183
Categorical				0.703
0	372 (47)	179 (45)	Ref.	
1	234 (30)	104 (27)	0.88 (0.64 to 1.22)	
2–3	136 (18)	78 (21)	1.05 (0.71 to 1.55)	
4 or more	32 (4)	26 (7)	1.25 (0.66 to 2.34)	
Duration of anesthetic exposure (min)				
Continuous, per 60 min			1.01 (0.98 to 1.04)	0.633
Categorical				0.261
0	372 (47)	179 (46)	Ref.	
1–120	60 (7)	35 (9)	1.40 (0.85 to 2.31)	
121–240	143 (18)	59 (15)	0.75 (0.51 to 1.10)	
241–480	126 (17)	73 (19)	1.08 (0.72 to 1.60)	
481 or more	73 (10)	41 (11)	0.90 (0.55 to 1.47)	
Exposures during the 5 years prior to first visit				
Any anesthesia exposure				0.554
No	524 (68)	289 (64)	Ref.	
Yes	250 (32)	165 (36)	1.08 (0.83 to 1.41)	
Count of anesthesia exposures (n)				
Continuous, per exposure			1.15 (1.01 to 1.31)	0.039
Categorical				0.177
0	524 (68)	289 (64)	Ref.	
1	177 (23)	99 (22)	0.92 (0.68 to 1.25)	
2–3	63 (8)	50 (11)	1.40 (0.90 to 2.17)	
4 or more	10 (1)	16 (4)	2.44 (1.01 to 5.85)	
Duration of anesthetic exposure (min)				
Continuous, per 60 min			1.04 (0.99 to 1.08)	0.129
Categorical				0.197
0	524 (68)	248 (64)	Ref.	
1–120	46 (6)	28 (7)	1.29 (0.74 to 2.23)	
121–240	107 (14)	41 (11)	0.75 (0.48 to 1.16)	
241–480	69 (9)	48 (12)	1.40 (0.90 to 2.19)	
481 or more	28 (4)	22 (6)	1.32 (0.67 to 2.61)	

Odds ratio (OR) and P-values are from conditional logistic regression. CI, confidence interval. OR >1.00 indicates an increased risk for MCI. Separate models were used to assess anesthesia exposure quantified as any anesthetic, number of exposures (0, 1, 2–3, 4) and cumulative duration of exposure in minutes (0, 1–120, 121–240, 241–480, and ≥481). Cases and controls were matched on age, sex, education, and APOE genotype. In addition, covariates were included in all models for age, education, marital status, smoking status, alcohol, midlife diabetes, midlife hypertension, midlife dyslipidemia, atrial fibrillation, Charlson comorbidity index, history of congestive heart failure, stroke, and coronary artery disease.

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Table 5

Secondary sensitivity analyses assessing association between MCI and specific types of surgery after age 40, and 60, and during the 20, 10 and 5-year period prior to the index visit.

Surgery Specific Exposure	OR (95% CI)	P Value*
Exposure between age 40 and first visit		
No anesthesia exposure	Ref.	
Major vascular	1.19 (0.69 to 2.06)	0.525
Cardiac with bypass	0.77 (0.41 to 1.45)	0.414
Cardiac without bypass	0.65 (0.22 to 1.95)	0.442
Orthopedic	0.86 (0.58 to 1.30)	0.481
Exposure between age 60 and first visit		
No anesthesia exposure	Ref.	
Major vascular	1.24 (0.66 to 2.32)	0.510
Cardiac with bypass	0.79 (0.42 to 1.50)	0.475
Cardiac without bypass	0.55 (0.17 to 1.73)	0.303
Orthopedic	0.96 (0.62 to 1.47)	0.846
Exposure 20 years prior to first visit		
No anesthesia exposure	Ref.	
Major vascular	1.12 (0.59 to 2.15)	0.728
Cardiac with bypass	0.79 (0.41 to 1.50)	0.467
Cardiac without bypass	0.55 (0.17 to 1.73)	0.303
Orthopedic	0.90 (0.58 to 1.40)	0.651
Exposure 10 years prior to first visit		
No anesthesia exposure	Ref.	
Major vascular	1.11 (0.53 to 2.32)	0.780
Cardiac with bypass	0.90 (0.45 to 1.80)	0.758
Cardiac without bypass	0.42 (0.11 to 1.64)	0.212
Orthopedic	1.03 (0.64 to 1.65)	0.905
Exposure 5 years prior to first visit		
No anesthesia exposure	Ref.	
Major vascular	1.68 (0.71 to 3.98)	0.236
Cardiac with bypass	0.99 (0.42 to 2.35)	0.985
Cardiac without bypass	0.66 (0.13 to 3.31)	0.613
Orthopedic	0.89 (0.51 to 1.55)	0.677

Odds ratio (OR) and P-values are from conditional logistic regression. CI, confidence interval. OR >1.00 indicates an increased risk for MCI. Separate models were used to assess exposure to each surgery type. In all cases the reference group was no anesthesia exposure to any surgery type.