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## REVIEW ARTICLE

# Anesthesia and Alzheimer disease – Current perceptions<sup>☆</sup>



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### Abstract

**Background and objectives:** It has been speculated that the use of anesthetic agents may be a risk factor for the development of Alzheimer disease. The objective of this review is to describe and discuss pre-clinical and clinical data related to anesthesia and this disease.

**Content:** Alzheimer disease affects about 5% of the population over 65 years old, with age being the main risk factor and being associated with a high morbidity. Current evidence questions a possible association between anesthesia, surgery, and long-term cognitive effects, including Alzheimer disease. Although data from some animal studies suggest an association between anesthesia and neurotoxicity, this link remains inconclusive in humans. We performed a review of the literature in which we selected scientific articles in the PubMed database, published between 2005 and 2016 (one article from 1998 due to its historical relevance), in English, which address the possible relationship between anesthesia and Alzheimer disease. 49 articles were selected.

**Conclusion:** The possible relationship between anesthetic agents, cognitive dysfunction, and Alzheimer disease remains to be clarified. Prospective cohort studies or randomized clinical trials for a better understanding of this association will be required.

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**PALAVRAS-CHAVE**

Doença de Alzheimer;  
Anestesia geral;  
Disfunção cognitiva  
pós-operatória

**Anestesia e doença de Alzheimer – Percepções atuais****Resumo**

*Justificativa e objetivos:* Tem sido especulado que o uso de agentes anestésicos possa ser um fator de risco para o desenvolvimento de doença de Alzheimer. O objetivo desta revisão é descrever e discutir dados pré-clínicos e clínicos relacionados com a anestesia e essa doença.

*Conteúdo:* A doença de Alzheimer afeta cerca de 5% da população com mais de 65 anos, a idade é o principal fator de risco e está associada a uma elevada morbidade. A evidência atual questiona uma possível associação entre anestesia, cirurgia e efeitos cognitivos em longo prazo, o que inclui a doença de Alzheimer. Embora os dados obtidos em alguns dos estudos animais sugiram uma associação entre anestesia e neurotoxicidade, esse elo permanece inconclusivo em humanos. Fizemos uma revisão da literatura em que foram selecionados artigos científicos na base de dados Pubmed, publicados entre 2005 e 2016 (um de 1998 pela relevância histórica), em inglês, que abordam a eventual relação entre anestesia e doença de Alzheimer. Foram eleitos 49 artigos.

*Conclusão:* A possível relação entre agentes anestésicos, disfunção cognitiva e doença de Alzheimer permanece por esclarecer. Serão necessários estudos de coorte prospectivos ou ensaios clínicos randomizados para melhor compreensão dessa associação.

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**Introduction**

Alzheimer disease is currently the most common form of dementia, estimated to reach 26.6 million people worldwide,<sup>1</sup> or about 5% of the population over 65 years of age.<sup>2</sup> The finding of a possible cognitive deterioration as a result of an anesthetic/surgical event led to the investigation of this phenomenon, also motivated by the greater concern and demand for information by patients and their families.<sup>3</sup>

Postoperative cognitive dysfunction is a well-known perioperative syndrome as a result of anesthesia and surgery but the exact cause remains unclear.<sup>4</sup> In what way postoperative cognitive dysfunction and Alzheimer disease may be linked remains a question under study. The biochemistry underlying the process of dementia, the study of the relationship between Alzheimer disease and postoperative cognitive dysfunction as a probable spectrum of the same disease, and the relationship of both with anesthetic agents motivate the exploration of this area.

We performed a search in Pubmed with the words "Alzheimer's disease", "Anesthesia", and "Postoperative Cognitive Dysfunction". We included scientific articles published in English between 2005 and 2016 (one from 1998 by historical relevance), which address the possible relationship between anesthesia and Alzheimer's disease. According to the inclusion criteria and their relevance, 49 articles were selected.

This review aims at summarizing the definition and pathophysiology of Alzheimer's disease, as well as discussing the scientific knowledge that relates the exposure to anesthetic agents with this dementia development.

**Alzheimer disease**

Alzheimer disease is a progressive dementia that leads to a decline in cognitive abilities. The vast majority of Alzheimer disease cases are late onset or sporadic and it is presumed to be a multifactorial disease resulting from the interaction between genetic and environmental factors.<sup>5</sup> The main risk factor is age, although others such as female, low educational level, family history, and specific genetic mutations (apolipoprotein E genotype)<sup>6,7</sup> may also contribute. A number of modifiable risk factors, such as cardiovascular disease, history of head trauma,<sup>6</sup> diabetes,<sup>8</sup> hypertension, and dyslipidemia have been described.<sup>9</sup> The association between environmental exposure to modifiable risk factors and Alzheimer disease provided a potential analogy for the possible role of general anesthesia in the pathogenesis of this disease. In this line of thinking, reducing these modifiable risk factors would reduce the incidence of dementia.

**Pathophysiology of Alzheimer disease**

Alzheimer disease is characterized by severe neurodegeneration, neuroinflammation, and progressive loss of cognitive abilities.<sup>10</sup> The diagnostic criteria for dementia released by the National Institute on Aging-Alzheimer's Association define dementia as the development of cognitive or behavioral symptoms associated with decline in the previous level of performance, involving several cognitive domains that may not be explained by delirium or psychiatric disorders.<sup>11</sup> Recently, the guidelines also included biomarkers as diagnostic criteria, such as decreased levels of amyloid protein

(by oligomerization) associated with increased total *tau* or phosphorylated *tau* protein in cerebrospinal fluid (CSF).<sup>12</sup> Moreover, the ratio between total *tau* protein and amyloid protein may also be used as an adjunct in Alzheimer disease diagnosis.<sup>13</sup>

The main disorder involved in its pathophysiology is abnormal protein folding. It has marked neuropathological characteristics, such as: 1) accumulation of senile plaques formed by aggregates of extracellular amyloid protein; 2) formation of intraneuronal neurofibrillary tangles of hyperphosphorylated *tau* protein.<sup>14,15</sup> These disorders induce oxidative stress, neuronal inflammation and dysfunction with eventual cell death.<sup>14</sup> Loss of hemostasis from *tau* protein phosphorylation may result from deregulation of the kinases and phosphatases involved in this process. Environmental factors may also contribute to changes in signal transduction leading to loss of this balance and culminating in neurofibrillary degeneration and cell death.<sup>16</sup> The amyloid hypothesis recognizes that deregulation between amyloid protein production and clearance leads to its accumulation.<sup>17</sup> This hypothesis also contemplates that some forms of amyloid peptide are neurotoxic and contribute to *tau* protein abnormal phosphorylation. Ultimately, this cascade culminates in mitochondrial damage, calcium deregulation, apoptosis, and neurodegeneration.<sup>18</sup>

Biomarker studies have shown that CSF amyloid protein concentrations are inversely related to the degree of Alzheimer's disease.<sup>19</sup> However, both amyloid plaques and amyloid protein declining can be found in the elderly without clinical signs of cognitive dysfunction, so amyloidosis alone appears to be insufficient for the development of dementia symptoms.<sup>20</sup>

Some neurotransmitters appear to play a role in the context of Alzheimer's dementia. Cholinergic dysfunction appears to be involved in the clinical symptoms of dementia. Alzheimer disease appears to be associated with loss of cholinergic neurons since acetylcholine modulates higher brain functions, such as attention, learning, and memory. Thus, the degree of cognitive dysfunction may be associated with the cholinergic deficit present, which raises the question about the potential role of acetylcholinesterase inhibitors.<sup>18</sup>

The attempt to relate environmental exposures such as anesthesia to Alzheimer disease development should be based on evidence between exposure and pathophysiological processes underlying the disease. In addition, surgery alone is considered to promote inflammatory stress response, which may promote the disease pathogenesis.<sup>21</sup>

## Animal models

Several studies have found evidence that anesthetic agents may contribute to or even exacerbate neurodegenerative diseases such as Alzheimer's disease.<sup>22,23</sup> While some studies have shown changes in cytokine and *tau* protein levels in human CSF fluid following anesthesia/surgery, coinciding with the levels found in patients with this dementia,<sup>21</sup> other studies did not find a significant contribution of anesthesia and surgery in its development.<sup>24,25</sup>

The use of animal models allows the exploration of mechanisms through which anesthetics may be involved in the Alzheimer disease pathogenesis. A pilot in vitro study using a free cell model demonstrated that volatile anesthetics, such as halothane, isoflurane, and sevoflurane could potentiate the oligomerization and cytotoxicity of Alzheimer's disease-related amyloid peptides.<sup>26</sup> It should be noted that amyloid protein oligomerization with halothane was dose-dependent and the doses used were high (~4 MAC). The effect remained for hours after the volatile anesthetic washout. In vitro and animal studies have shown that the use of 1.4% isoflurane and 2.5% sevoflurane for 2 h potentiates the processing of amyloid precursor protein into amyloid protein, increasing its brain levels in wild type mice (five months old), which leads to caspase-3 activation and causes neuronal apoptosis.<sup>27,28</sup> A recent study reported that anesthesia with 2.1% sevoflurane for 6 h can induce caspase-3 activation and increase amyloid protein levels in brains of six-day naive mice and transgenic mice models of Alzheimer disease (mutation of amyloid precursor protein) which may be more vulnerable to neurotoxicity.<sup>29</sup> Thus, it has been shown that certain mouse models have an increased risk for developing Alzheimer's disease.

In 2008, a working group exposed 12-month-old transgenic mice (mutation for human amyloid precursor protein expression) and their non-transgenic littermates to isoflurane and halothane for 120 min per day for five days. It was concluded that in the transgenic mouse there was overload of amyloid protein plaques after halothane use and *tau* protein aggregation after exposure to isoflurane.<sup>30</sup> However, no change in cognitive performance was found in mutant mice, no effect of volatile anesthetics on apoptosis was found in either the transgenic or control mice, and there was no dissociation between amyloid generation (halothane – mutant mice) versus decline of cognitive performance (isoflurane – control mice). Later, with the same mice model, the animals were exposed to isoflurane for 20–30 min twice weekly for three months and were found to exhibit behavioral decrease and increased mortality. Similar responses to Alzheimer disease were also identified in transgenic mice, such as increased numbers of apoptotic cells, reduced autophagy, reduced astroglia and increased microglia response, as well as increased amyloid protein aggregates.<sup>31</sup>

In 2011, a study using triple-mutated mice models for Alzheimer disease exposed one group to general anesthesia with halothane or isoflurane 5 h a week for four weeks (at three different ages: 2, 4, and 6 months) and another had no exposure to inhaled anesthetics.<sup>32</sup> No differences were found in cognitive decline of mutant mice exposed to volatile anesthetics compared to mutant mice that were not exposed. Although phosphorylated *tau* protein levels were increased in the hippocampus two months after surgery, no amyloid, caspase, microglia, or synaptophysin changes were found. These results appeared to indicate that exposure to these inhalational agents during the pre-symptomatic period of Alzheimer disease is not related to cognitive decline acceleration.

Intravenous anesthetic agents, particularly propofol, are also associated with increased *tau* protein in rat hippocampus, and this effect appears to be due to a direct action of

the drug and not to secondary physiological effects (such as hypothermia).<sup>33</sup>

Given the possible link between surgery and/or anesthesia and pathophysiological changes related to Alzheimer's disease, one of the major difficulties in this evaluation is the separation between exposure to anesthetics and effects of surgery.

The presence of cognitive decline after surgery is reasonably well established and there are many animal studies examining this interaction. Post-surgical cognitive decline in aged mice has been associated with microgliosis, amyloid protein production, and *tau* protein hyperphosphorylation in the hippocampus.<sup>34</sup> The role of neuroinflammation in post-surgical cognitive dysfunction and its relation to Alzheimer disease has also been studied. In wild type young mice, surgery, not anesthesia, caused neuroinflammation and acute cognitive losses, and both microgliosis and cognitive deficits were reduced by anti-inflammatory agents.<sup>35-37</sup> Surgery leads to the formation of tumor necrosis factor- $\alpha$ , which causes damage to the blood-brain barrier and allows the infiltration of inflammatory macrophages, especially in the hippocampus.<sup>34</sup> Mice undergoing surgery compared to mice that were only anesthetized without undergoing any surgical intervention had increased levels of interleukin-1 $\beta$  and interleukin-6.<sup>37</sup>

It should be mentioned that animal studies are not able to completely separate anesthesia from surgery, as each surgical procedure is always performed with an anesthetic agent and it has become more evident that anesthetics are able to modulate the immune-inflammatory response.

Science and scientific investigation in this area did not stagnate and as early as 2008 there was a study that supported the low concentrations of amyloid as a potential neurotransmitter modulating role,<sup>38</sup> which contradicted the guilty attitude of the scientific community in general.

## Clinical evidence

### Prospective studies

Given the evidence that anesthesia causes a decrease in cognitive abilities in susceptible subjects after elective surgery, it is suggested that the pathological mechanisms underlying the postoperative cognitive dysfunction mimic those of Alzheimer disease.<sup>39</sup>

The first large international study of postoperative cognitive dysfunction (ISPOCD study) reported an incidence of 25% in patients undergoing non-cardiac surgery after one week and 9.9% after three months.<sup>40</sup> There is a limited number of prospective studies investigating the association between exposure to anesthetic agents and Alzheimer disease. From the original ISPOCD study, 701 patients were followed for 8.5 years. In the study, patients who developed postoperative cognitive dysfunction had higher mortality rate and increased risk of social dependence, but no reference was made to the incidence of dementia.<sup>41</sup> The same author, in a separate evaluation, followed 686 subjects involved in the ISPOCD study from 1994 to 1996 and 1998 to 2000 up to July 1, 2011, through the Danish National Registry of Patients and the Central Registry of Psychiatric

Research, of these only 32 developed dementia and no statistically significant relationship was found between post-operative cognitive dysfunction and dementia.<sup>42</sup> Recently, a prospective randomized study was conducted with a group of 180 patients diagnosed with amnesic cognitive impairment, a subtype of cognitive dysfunction with predominance of memory impairment, with the objective of evaluating the effect of anesthesia on this disorder progression to Alzheimer disease during a 2-year follow-up period.<sup>23</sup> Sixty outpatients with the same diagnosis were designated as control group, while the remainder underwent spinal lumbar surgery and randomized to receive sevoflurane, propofol or epidural anesthesia with lidocaine. Through neuropsychological tests and evaluation of levels of amyloid peptide, total *tau* protein, and phosphorylated *tau*, the investigators concluded that the number of cases of emerging Alzheimer disease did not differ between groups. The number of cases of progressive amnesic cognitive dysfunction was greater in sevoflurane group than in control group ( $p=0.001$ ), but patients who received epidural anesthesia with lidocaine or intravenous anesthesia with propofol had the same rate of progression as the control group. The rate of progression to dementia was faster in sevoflurane group, although this value was not statistically significant.<sup>23</sup>

### Retrospective observational studies

A large part of the literature aiming to examine the relationship between exposure prior to anesthesia/surgery and the subsequent risk of developing dementia has turned to databases and epidemiological (observational) techniques for this purpose. Note that it is a challenge to independently examine the effects of anesthesia and surgery (Table 1).

### Cohort studies

In 2005, a retrospective cohort study was carried out to evaluate the risk of developing Alzheimer disease after myocardial revascularization under general anesthesia compared to another group undergoing transluminal percutaneous angioplasty under sedation (without general anesthesia).<sup>43</sup> A total of 5216 and 3954 patients, respectively, were selected from the veterans' health system database. The study population included all patients aged 55 and over, without previous diagnosis of dementia, undergoing coronary revascularization or transluminal percutaneous angioplasty between October 1996 and September 1997. Patients were followed-up from the date of the intervention to September 2002, until the diagnosis of Alzheimer disease or until death. The results showed that 119 patients (78 undergoing myocardial revascularization and 41 undergoing percutaneous transluminal angioplasty) developed Alzheimer disease during the follow-up period. The relative risk of Alzheimer disease was compared in both groups. In the adjusted final model, myocardial revascularization under general anesthesia was associated with 1.71 times greater risk of developing Alzheimer disease compared to percutaneous angioplasty without general anesthesia (risk ratio = 1.71; 95% CI between 1.02 and 2.87,  $p=0.04$ ).

**Table 1** Relevant studies that demonstrated the relationship between dementia and surgery/anesthesia.

Author, year	Type of study	Population	Results
Lee, 2005	Retrospective cohort study	Adults undergoing myocardial revascularization under general anesthesia ( $n = 5216$ ) and percutaneous transluminal angioplasty under sedation ( $n = 3954$ ).	Myocardial revascularization surgery under general anesthesia increased risk of developing Alzheimer disease (hazard ratio = 1.71, $p = 0.04$ ).
Avidan, 2005	Retrospective cohort study	Adults with some degree of dementia (365) and without dementia (214): 1) no history of cardiac surgery; 2) no history of illness; 3) control group ( $n = 575$ ).	Group with dementia without difference in cognitive trajectory between groups, group without dementia progression to clinical dementia, similar between groups.
Steinmetz, 2009	Prospective study	Adults undergoing surgery, with or without development of POCD DCPO, without dementia ( $n = 686$ ).	32 developed dementia, with no statistically significant relationship between POCD and dementia.
Vanderweye, 2010	Retrospective cohort study	Adults undergoing hernia repair under general or regional anesthesia ( $n = 3769$ ) and prostatic surgery under general or regional anesthesia ( $n = 6511$ ).	No association between general anesthesia and increased risk of Alzheimer disease compared with regional anesthesia in both studies.
Seitz, 2011	Meta-analysis of case-control studies	Adults undergoing general anesthesia vs. non-surgical patients or undergoing regional anesthesia; 15 studies (1752 cases, 5261 controls).	Absence of a statistically significant relationship between general anesthesia and Alzheimer disease development.
Liu, 2013	Prospective randomized study	Adults with ACD undergoing spinal surgery ( $n = 180$ ).	Higher incidence of progressive ACD in sevoflurane group ( $p = 0.001$ ).
Sprung, 2013	Case-control study	Adults diagnosed with Alzheimer disease ( $n = 877$ ) compared with disease-free adults ( $n = 877$ ).	No association between exposure to general anesthesia and Alzheimer disease diagnosis ( $p = 0.27$ ).
Chen, 2014	Case-control study	Adults diagnosed with dementia ( $n = 5345$ ) compared with disease-free adults ( $n = 21,830$ ).	Exposure to general anesthesia associated with increased risk of developing dementia.

POCD, postoperative cognitive disease; ACD, amnesic cognitive disease.

In 2009, a retrospective cohort study identified three groups of patients selected through the University of Washington Alzheimer's Research Center: 1) no history of cardiac surgery; 2) no history of illness; 3) control group. And a long-term follow-up of cognitive function was performed before and after surgery and disease.<sup>25</sup> These patients underwent annual exams and, of the 575 selected patients, 214 had no dementia, while 361 had mild or very mild dementia at the time of recruitment. The authors found that in

the group of patients without dementia there was progression to clinical dementia throughout the study, similarly in all three groups, with older patients being more likely to show progression ( $p < 0.0001$ ). In the group of patients with dementia *ad initium* it was anticipated that the postoperative cognitive dysfunction could manifest itself as an increase in the rate of cognitive decline; however, no difference was found in the cognitive trajectories between groups.



Surgical procedures that can be performed under general or regional anesthesia are possible sources for comparing the effects of general anesthesia on Alzheimer disease development. In this sense, a retrospective cohort study was carried out in 2010 with two groups of surgical patients (prostatic surgery and hernia surgery), in order to compare the risk of developing Alzheimer disease after exposure to general or regional anesthesia.<sup>44</sup> In the hernia study 3769 patients were selected of which 2658 (70.5%) underwent general anesthesia and 1111 (29.5%) regional anesthesia. Hazard ratio adjusted for age, hospital stay, number of previous procedures, and number of diagnoses at the time of admission showed no association between general anesthesia and increased risk of Alzheimer disease compared to regional anesthesia (hazard ratio=0.65, 95% CI 0.49–0.85). In the prostate study, 6511 patients were included, 2820 (43.3%) underwent general anesthesia and 3691 (56.7%) regional anesthesia. Similar to that found in the hernia study, the risk of developing Alzheimer disease in subjects undergoing general anesthesia was not high compared to regional anesthesia (hazard risk=0.71, 95% CI 0.49–1.04).

#### Meta-analysis and case-control studies

A meta-analysis of case-control studies was published in 2011 assessing the association between exposure to general anesthesia and Alzheimer disease development.<sup>45</sup> This work defined exposure to general anesthesia as any history of surgery under general anesthesia compared with absence of history of surgery under general anesthesia. Control group included non-surgical patients or surgical patients under regional anesthesia. Under these conditions, 15 studies were included, with 1752 cases and 5261 controls. The primary outcome was diagnosis of Alzheimer disease of any severity. Secondary outcomes were related to time to development of Alzheimer disease and development of early (<65 years) or late onset (>65 years). The analysis revealed no statistically significant association between general anesthesia and development of Alzheimer disease, with a combined odds ratio of 1.05;  $p=0.43$ . Two of the analysis subgroups of this study aimed to compare exposure to general anesthesia with exposure to regional anesthesia and the association between the number of previous general anesthesia or the cumulative exposure to general anesthesia and Alzheimer disease. No statistically significant difference was found in the development of Alzheimer disease between general and regional anesthesia or the association between cumulative exposure to general anesthesia and the development of this type of dementia.

Recently, a group of investigators published a population-based case-control study using the Rochester epidemiological project and the registry of patients with Alzheimer disease at Mayo Clinic.<sup>24</sup> Between January 1st, 1985, and December 31, 1994, 877 incidental cases of Alzheimer disease were identified and, for each case, a disease-free control, paired according to sex and age, was randomly selected for each case, according to the index year. The medical records of each patient from the age of 45 up to the index year were examined to determine exposure to anesthesia. Among the cases of dementia, 615 (70%) underwent procedures under general anesthesia versus 636

controls (72.5%) under the same circumstances and no statistically significant association was found between exposure and diagnosis ( $p=0.27$ ). Furthermore, the authors found no significant association between quantitative variables (number of exposures to anesthesia) and the development of dementia.

Another population-based case-control study published in 2014 sought to evaluate the association between prior exposure to various types of general anesthesia and the incidence of dementia.<sup>6</sup> To that end, data on one million patients covered by universal Thai health insurance between 2005 and 2009 were used. Subjects without dementia ( $n=21,830$ ) were matched for sex, age, and date of diagnosis. General anesthesia was allocated into three groups: 1) general anesthesia with intratracheal intubation; 2) general anesthesia using intravenous injection or general anesthesia using intramuscular injection; and 3) deep sedation. The authors concluded that subjects undergoing general anesthesia with intratracheal intubation (OR = 1.34, 95% CI 1.25–1.44) and general anesthesia with intravenous or intramuscular injection (OR = 1.28, 95% CI, 1.14–0.43) were at higher risk of developing dementia, this risk increased with increasing exposure ( $p < 0.0001$ ). There was no difference between groups regarding exposure to deep sedation.

#### Currently

New studies have emerged in this area. A prospective longitudinal study of 2016 involved first-time coronary bypass patients who were initially enrolled in a cognitive outcome comparison study after randomization to receive either low or high doses of fentanyl. After 12-month evaluation, the same patients were invited to participate in a follow-up study at 7.5 years after surgery.<sup>46</sup> Of the 326 initial patients, aged 55 years or over, 193 were assessed. Patients were evaluated for development of dementia and postoperative cognitive dysfunction was also investigated at three months, 12 months, and 7.5 years after surgery. However, it was only possible to evaluate 113 patients for both dementia and postoperative cognitive dysfunction. At 7.5 years after surgery, the prevalence of dementia was 30.8% in patients aged over 55 years at the time of intervention. The authors attribute this high prevalence of dementia to anesthesia/surgery or the natural decline of cognitive abilities with aging and in patients with severe cardiovascular disease. They add that since there was no follow-up of a non-surgical control group, this will be an important limitation of the study. Postoperative cognitive dysfunction was detected in 32.8%. Of the 113 patients evaluated for both entities, 44% of those with dementia were also classified with postoperative cognitive dysfunction. Pre-existing cognitive deficit and peripheral vascular disease were both associated with dementia at 7.5 years after coronary artery bypass, and postoperative cognitive dysfunction at either three or eight months was associated with increased mortality at 7.5 years.

Another research group assessed 8503 pairs of middle-aged (<70 years) and advanced age Danish twins ( $\geq 70$  years). There were two groups: 1) those who had undergone at least one surgery (18–24 years before the cognitive

evaluation); 2) those who had not undergone any surgical intervention. In addition, subjects who underwent surgery were allocated into four groups: 1) major surgeries; 2) knee and hip arthroplasty; 3) minor surgeries; 4) others. Results from five cognitive studies were compared between twins. Confounding of genetic and environmental factors were assessed in intra-pair analysis of 87 monozygotic and 124 dizygotic same-sex twin pairs with and without history of surgery, respectively.<sup>47</sup> Twins who underwent major surgeries scored slightly worse on cognition tests compared with those who had not undergone any intervention; however, the authors consider the difference as an effect of negligible size. Intra-pair analysis showed that the twin exposed to surgery had lower scores on cognitive tests in 49% of the pairs. Twins aged 70 and older who underwent hip and knee arthroplasty scored higher on cognitive tests, even higher than those who had not undergone any intervention. The study suggests that underlying diseases may be an important risk factor for slight variations in cognitive function between surgical and non-surgical groups and preoperative cognitive function may be a more important determinant of cognitive functioning at later ages than surgery and anesthesia.

Another prospective cohort study evaluating the association between anesthesia and dementia or Alzheimer disease included patients aged 65 years or older without dementia ( $n=3988$ ) who were followed up to the onset of dementia, death, or abandonment. At the beginning of the study, information was collected on previous surgical procedures under general or neuraxial anesthesia and new interventions were reported every two years.<sup>48</sup> A comparison was made between patients undergoing high-risk surgeries under general anesthesia, other surgeries under general anesthesia, other surgeries under neuraxial anesthesia and patients not undergoing surgical intervention and anesthesia. During the follow-up period, 946 (24%) subjects were diagnosed with dementia, 752 (19%) had Alzheimer's disease, and 42% of those involved reached the end of the study without any diagnosis of dementia. Adjusted risk of dementia was not higher in the group of subjects with high-risk surgeries under general anesthesia compared to the group without history of anesthesia (HR=0.86, 95% CI 0.58–1.28); the same was true for Alzheimer disease (HR=0.95, 95% CI 0.61–1.49). The authors concluded that there was no association between exposure to anesthesia and development of dementia/Alzheimer disease in older adults.

In 2016, the Mayo Clinic researchers published a new population-based prospective cohort study assessing the association between general anesthesia exposure after 40 years of age and incidence of mild cognitive impairment in the elderly. Subjects aged between 70 and 89 years ( $n=19,731$ ) undergoing various neuropsychological assessments at baseline and at 15 months were selected, and data on exposure to anesthesia after the age of 40 were also collected.<sup>49</sup> Of the 1731 participants, 536 (31%) developed mild cognitive impairment. Exposure to anesthesia, number of exposures, and total time of cumulative exposure were not associated with mild cognitive impairment. However, on a secondary sensory analysis, they found an association between anesthesia after the age of 60 and incidence of mild cognitive impairment (adjusted HR = 1.25, 95%

CI 1.02–1.55,  $p=0.04$ ). The authors do not exclude the possibility that exposure to anesthetic agents at an advanced stage of life may be associated with increased incidence of mild cognitive impairment. However, they concluded that there was no significant association between cumulative exposure to anesthesia after the age of 40 and this cognitive change.

## Conclusion

The prevalence of Alzheimer disease is expected to increase as the population ages. More and more elderly people undergo surgery and general anesthesia, so it is pertinent to assess their association with the development of dementia. Animal studies suggest that surgery and anesthetics may accelerate Alzheimer's disease, with cognitive changes such as postoperative cognitive dysfunction being common. Clinical evidence linking the adverse effects of anesthesia to cognitive impairment and exacerbation of neurodegeneration in susceptible individuals is worthy of attention. In most situations, it is difficult to discriminate whether cognitive changes are due to surgery or anesthesia, inflammation or natural course of aging. The results of observational studies in humans assessing the relationship between anesthesia, surgery, and dementia have been inconsistent. Several factors should be taken into consideration in future study designs, such as selection of a sufficient sample, appropriate control groups (non-surgical and without anesthesia), preoperative assessment of cognitive function through standardized psychological tests, and the use of biomarkers and neuroimaging to determine the existence of Alzheimer disease and amyloid burden. Moreover, it would be interesting to develop hypotheses for future studies based on the relationship between anesthesia and Alzheimer disease and the neurobiological process underlying the disease.

More prospective cohort studies or randomized clinical trials, ideally with biomarkers and/or neuroimaging, are required to understand the relationship between anesthesia and Alzheimer's disease. Until then, an effort should be made to improve the perioperative care of older adults who may be at risk for postoperative cognitive changes, and the choice of anesthetic technique should be based on the surgical procedure and other clinical factors regarding either the patient or the technique involved.

## Conflicts of interest

The authors declare no conflicts of interest.

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