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Relationship between postoperative delirium, postoperative neurocognitive disorders, and dementia in older surgical patients

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2023

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Artigo de revisão bibliográfica

Dissertação de candidatura ao grau de Mestre em Medicina submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

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Porto, maio de 2023

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Maio de 2023

Agradecimentos

Ao meu Orientador, Professor Doutor Humberto Machado, por aceitar orientar esta revisão e pelo seu total apoio e disponibilidade, que foram imprescindíveis para a realização deste trabalho.

À minha Coorientadora, Professora Doutora Maria João Susano, pela sua disponibilidade e dedicação, por todos os conselhos e conhecimentos que me transmitiu e pela confiança que depositou em mim.

Resumo

Introdução:

Face à expectativa do número crescente de idosos submetidos a cirurgias e anestesia, estima-se que as complicações neurocognitivas no pós-operatório aumentem. Estas incluem o delirium pós-operatório, a complicação mais frequente nos doentes cirúrgicos idosos, e o distúrbio neurocognitivo pós-operatório, previamente denominado de disfunção cognitiva pós-operatória. Ambas as complicações cognitivas são prevalentes na população idosa, possuem fatores de risco em comum e foram associadas a desfechos clínicos adversos, nomeadamente diminuição da qualidade de vida, aumento da mortalidade e declínio cognitivo a longo-prazo. Em linha com observações anteriores, foi proposto que o delirium e o distúrbio neurocognitivo pós-operatório possam fazer parte do mesmo espetro de complicações cognitivas pós-operatórias. Adicionalmente, há preocupação crescente de que estas alterações poderão, em último caso, levar a demência. O objetivo deste artigo é analisar a relação entre o delirium pós-operatório, distúrbio neurocognitivo pós-operatório e demência.

Métodos:

Foi realizada uma pesquisa entre setembro de 2022 e abril de 2023 nas plataformas PubMed e Google Scholar. Após aplicação dos critérios de inclusão e exclusão, foi realizada uma seleção manual para garantir apenas a inclusão de artigos relevantes. Um total de 23 artigos foram incluídos nesta revisão.

Resultados:

A evidência sugere que o delirium pós-operatório aumenta o risco de declínio cognitivo no primeiro mês após a cirurgia ("recuperação neurocognitiva tardia"), mas esta associação parece não se manter ao fim de 1 ano de seguimento. Estas observações sugerem que o delirium pós-operatório e o distúrbio neurocognitivo pós-operatório poderão não fazer parte do mesmo espetro de alterações cognitivas. No entanto, tal não contradiz a evidência recente de que o delirium pós-operatório poderá precipitar uma trajetória de declínio cognitivo. Múltiplos estudos corroboram uma associação epidemiológica entre o delirium pós-operatório e a demência. Adicionalmente, alguns resultados sugerem uma relação dose-resposta entre a duração e magnitude do delirium e a demência, sugerindo um possível papel causal do delirium pós-operatório no desenvolvimento de demência. O distúrbio neurocognitivo pós-operatório, no entanto, não parece estar associado ao desenvolvimento de demência.

Conclusão:

A literatura sugere que o delirium pós-operatório poderá ser um fator de risco potencialmente modificável para demência. No entanto, é ainda incerto se este induz diretamente dano neuronal permanente ou se revela indivíduos cognitivamente suscetíveis. Uma vez que 40% dos casos de delirium são passíveis de prevenção, ensaios multicêntricos e randomizados de grandes dimensões são necessários para compreender a influência da prevenção do delirium na incidência e progressão da demência.

Palavras-chave: “Complicações Cognitivas Pós-operatórias”, “Disfunção cognitiva pós-operatória”, “Delirium pós-operatório”, “Demência”

Abstract

Introduction:

Postoperative cognitive complications are estimated to increase in the face of a growing number of older patients undergoing surgery and anesthesia. Neurocognitive disorders include postoperative delirium, the most frequent complication in older surgical patients, and postoperative neurocognitive disorder, previously referred to as postoperative cognitive dysfunction. Postoperative delirium and postoperative neurocognitive disorder are prevalent in older patients, have overlapping risk factors, and have been linked to unfavorable outcomes, namely increased mortality, decreased quality of life, and long-term cognitive decline. In light of prior observations, it has been proposed that postoperative delirium and postoperative neurocognitive disorder may be part of the same *continuum* of postoperative neurocognitive impairment. Furthermore, there is growing concern that postoperative cognitive complications might ultimately lead to dementia. This review article aims to analyze the relationship between postoperative delirium, postoperative neurocognitive disorder, and dementia.

Methods:

A comprehensive online search was conducted between September 2022 and April 2023 using PubMed and Google Scholar. After applying inclusion and exclusion criteria, a manual selection was made to ensure that only relevant articles were added. A total of 23 articles were included in this review.

Results:

Evidence suggests that postoperative delirium increases the risk of cognitive decline in the 30 days following surgery (delayed neurocognitive recovery). Still, this association does not hold up to 1 year of follow-up. Such observations suggest these entities may not be part of the same *continuum*. Regardless, this does not contradict recent evidence that POD might precipitate a trajectory of cognitive decline. Several studies provide epidemiologic evidence that supports an association between postoperative delirium and dementia. Furthermore, some results suggest a “dose-response” relationship between the extent and severity of delirium episodes and incident dementia, suggesting a possible causal role of postoperative delirium in developing dementia. Postoperative neurocognitive disorder, however, does not seem to be associated with dementia.

Conclusion:

Current evidence suggests that postoperative delirium might be a manageable risk factor for dementia. However, whether delirium induces permanent neuronal damage or unmasks vulnerable individuals with low cognitive reserve is still unclear. As 40% of cases of delirium are preventable, large, randomized, and multicenter trials are needed to explore if preventing postoperative delirium impacts the number of new incident dementia diagnoses and its trajectory of cognitive decline.

Keywords: “Postoperative Cognitive Complications”, “Postoperative Cognitive Dysfunction”, “Postoperative delirium”, “Dementia”

List of Abbreviations

Aß42 – Amyloid ß 42

AD – Alzheimer's Disease

ApoE – Apolipoprotein E

ASA – American Society of Anesthesiologists

CABG - Coronary Artery Bypass Graft

CAM – Confusion Assessment Method

CAM-ICU – Confusion Assessment Method - Intensive Care Unit

CSF – Cerebrospinal fluid

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

GCP – General Cognitive Performance

ICD-11 – International Classification of Diseases, 11th Revision

ISPOCD – International Study of Post-Operative Cognitive Dysfunction

MCI – Mild Cognitive Impairment

MMSE – Mini-Mental State Examination

NCD – Neurocognitive Disorder

NfL – Neurofilament light

NIA-AA – National Institute for Aging and the Alzheimer Association

PACU – Post-Anesthesia Care Unit

POCD – Postoperative Cognitive Dysfunction

POD – Postoperative Delirium

PreCI – Preoperative Cognitive Impairment

P-Tau – Phosphorylated tau

T-Tau – Total tau

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Introduction

Since the 20th century, it has been clear that some patients undergoing surgery and anesthesia, particularly older patients, may experience cognitive changes. Bedford was the first to approach this matter through a case series in 1955.[1,2] Patients undergoing surgery and anesthesia, especially those over 65, may experience postoperative cognitive impairment even if previously cognitively healthy.[3] The number of older patients receiving surgical and anesthetic surgeries has increased and is estimated to rise, making this a concern as the population ages. Postoperative neurocognitive complications are estimated to increase.[4,5]

Postoperative neurocognitive complications include postoperative delirium (POD) and postoperative neurocognitive disorder (NCD), previously known as postoperative cognitive dysfunction (POCD).[4]

POD is the most frequent complication in elderly surgical patients.[6,7] It is a confusional state that develops in the hospital and lasts until one week after surgery or until discharge, characterized by a sudden onset and a fluctuating course of impaired cognition, attention, and consciousness.[4,8] Sleep-wake cycle abnormalities are also frequently present.[5,7,9,10] The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states that delirium can manifest as hyperactive (predominantly characterized by agitation, refusal to cooperate, or aggressiveness), hypoactive (characterized by slow movement, slow speech, or lethargy), or mixed subtypes (characterized by an oscillation between hyperactive and hypoactive poles).[2,6,10] The hypoactive variant is more common in older patients and is frequently mistaken for depression or dementia.[6,7,10]

POD prevalence depends on the patient population, the type of surgical procedure, and the evaluation methods employed.[5,11] DSM-5 states that 15% to 53% of elderly surgical patients may experience POD, but these rates may increase to 65% after particular procedures, such as hip fracture surgery, cardiac surgery, and emergency surgery.[10,12] The combined effect of an individual's predisposing factors and a precipitating event, such as surgery and anesthesia, determine the risk of developing delirium.[4,5,8] The main predisposing factors for POD are advanced age (> 65 years old) and pre-existing cognitive impairment, including dementia. Frailty, low educational level, concurrent comorbidities, vision and hearing impairment, history of alcohol abuse, and depression are further recognized risk factors.[8,13] Acute postoperative pain and inflammation may also potentiate delirium.[14,15]

The gold standard method to diagnose delirium, according to DSM-5 criteria, is through a formal psychiatric interview.[16] However, less time-consuming, straightforward, and reliable bedside diagnostic methods, such as the Confusion Assessment Method (CAM), are often preferred in the pragmatic medical setting. This screening test relies on four criteria: degree of awareness, inattention, disordered thinking, and acute onset and variable course.[8]

POD is consistently associated with unfavorable outcomes, including increased mortality, prolonged hospitalization, and faster cognitive decline with ultimate long-term deterioration. Research suggests that POD is preventable in 30 to 40% of patients.[13,17–19] According to several studies, even non-demented surgical patients who develop POD are susceptible to long-term impairment.[15,18,20] There is a 40% chance that patients with POD will never regain their preoperative cognitive level.[12]

Research into cognitive complications in the postoperative period intensified during the 1980s after clinical reports of cognitive decline following cardiac surgery.[1,4] By then, multiple researchers introduced pre- and postoperative neuropsychological tests to assess for cognitive change after coronary artery surgery. POCD emerged in this context as an objective measure of decline in cognition after surgery and anesthesia detected by a difference in performance on a battery of neuropsychological tests.[1,4,21] The debate on POCD was extensive in the literature on cardiac surgery. However, subsequent research showed that this complication also involved non-cardiac surgical patients.[1,12]

The International Study of Postoperative Cognitive Dysfunction (ISPOCD)'s investigators carried out a paradigmatic multicenter experiment on 1218 individuals aged 60 and over, following major noncardiac surgery in 1998.[22] The results revealed that about 10% of the patients developed cognitive decline at three months postoperatively.[1,22] This data is consistent with that of subsequent studies, namely a recent systematic review demonstrating an overall incidence of 11.7% of POCD three months after noncardiac surgery.[23] Discovering POCD also occurred following noncardiac surgery contradicted the widely accepted belief that postoperative cognitive decline was a direct consequence of cardiac surgery.[1] The cognitive decline following surgery was repeatedly associated with perioperative cerebral hypoperfusion and hypoxemia. The ISPOCD, on the other hand, demonstrated that POCD developed in the absence of these conditions by monitoring perioperative blood pressure and oxygenation.[1,22,24]

The absence of a uniform definition and standardized measurement methods caused the POCD definition to be highly heterogeneous. Over time, investigators have used different kinds and numbers of tests, calculation methods, statistical thresholds, and variable time intervals after surgery to assess for POCD.[1,4] For example, the incidence of POCD at three months may range from approximately 10-16% to 40%, depending on the thresholds used to define cognitive decline compared to baseline.[16] Furthermore, there is no acknowledged definition of POCD in the International Classification of Diseases, 11th Revision (ICD-11), and no precise diagnostic criteria in the DSM-5, which has turned POCD into a research construct with limited clinical applicability.[1,9,25,26]

The research on POCD in anesthesiology and surgery literature is isolated from cognitive studies in the general population.[1] Several studies, however, demonstrate a persistent correlation of POCD with increasing age and fewer years of education, two factors also associated with cognitive decline in the general community.[1,16,22,23] Despite its limitations, this construct showed that even subtle postoperative cognitive impairment might have significant clinical outcomes, such as higher 1-year mortality after noncardiac and cardiac surgery.[1,9,21] Furthermore, there is growing concern that postoperative cognitive deterioration will eventually lead to dementia.[21]

The growing awareness of the convergence between cognitive deterioration in the general population and the postoperative period and the need for uniformization for research purposes recently encouraged some nomenclature changes to set it accordingly with DSM-5.[1,4] The definition of POCD now follows the DSM-5 diagnostic criteria for neurocognitive disorders requiring a subjective cognitive concern (noticeable by the individual or a third party), an objective measurement of cognitive decline, and maintenance of functional independence (mild NCD) or not (major NCD, or dementia).[4,10]

The experts also proposed modifying the term POCD into “delayed neurocognitive recovery” and “postoperative mild or major NCD”, depending on the onset and severity of cognitive changes.[4] Up to 30 days after a surgical and anesthetic procedure, any form of cognitive decline that meets DSM-5 diagnostic criteria for mild or major NCD is considered “delayed neurocognitive recovery”. Pharmacological effects, pain, emotional distress from hospitalization, and potential postoperative complications are all relevant factors that may hinder cognition during this time. Following those 30 days of expected recovery up to 12 months following the surgery, cognitive deterioration meeting DSM-5 criteria for mild or major NCD will classify as "postoperative" mild or major NCD.[1,4,27] Any form of cognitive decline diagnosed beyond 12 months postoperatively is termed NCD.[4]

A significant cognitive decline from baseline in one or more cognitive domains that interferes with independence in daily life activities corresponds to major NCD or dementia.[13,28] The estimates of the prevalence of dementia in older adults from higher-income countries are 5-10%, and it doubles every five years after 65 years. Increasing age is the dominant risk factor for major NCD, but lower education levels are also a consistently reported risk factor. The risk of dementia increases with concurrent cardiovascular disease, depression, and inflammation.[28]

The most common etiology of major NCD in older adults (aged ≥ 65 years) is Alzheimer's disease (AD), accounting for 60 to 90% of cases.[10,29] AD is an insidious neurodegenerative disease marked by an early impairment in learning and memory areas.[29,30] According to DSM-5, the diagnosis is likely if there is a classic amnestic presentation, a progressive and persistent deterioration in cognition, and no indication of a mixed etiology.[10,28] Pathophysiological alterations, such as amyloid deposition in the brain (detected by Positron Emission Tomography) or reduced levels of amyloid ß42 (Aß42) and elevated levels of phosphorylated tau (P-Tau) and total tau (T-tau) in the cerebrospinal fluid (CSF), begin years before clinical presentation.[28–30] The second most common etiology is vascular dementia, mainly associated with cerebrovascular disease. In many situations, vascular dementia coexists with AD (a condition known as mixed dementia). Although clinical presentation may vary, there is usually a history of a stroke or transient ischemic attack with cognitive deficits or neurological sequelae from earlier cerebrovascular events.[28,30]

Pre-existing NCD is a widely recognized risk factor for POD. Evidence in non-surgical patients has shown that delirium contributes independently to increasing the risk of dementia development.[13,31] Despite POD not being linked definitively to long-term cognitive decline or dementia, multiple studies have suggested that non-demented surgical patients who develop POD are at risk for long-term cognitive impairment, including dementia.[15,18,20,32,33] Whether delirium unravels a brain's susceptibility to dementia or causes direct and permanent neuronal harm leading to dementia is yet unknown.[13] A common underlying pathogenesis has been proposed in light of prior observations that POD and postoperative NCD (-POCD) were frequent in older patients and held overlapping risk factors. These observations elicit the question of whether POD and postoperative NCD are part of a neuropathologic *continuum*.[34]

As a result, it seems fair to query if POD and postoperative NCD might be somehow related to each other and, eventually, connected to dementia development. Might POD and postoperative NCD be part of a *continuum* leading to dementia? We will review the current evidence concerning the potential relationship between these entities.

Methods

A comprehensive online search was conducted between September 2022 and April 2023 using PubMed and Google Scholar. Combinations of the following search terms were used: “postoperative delirium”, “postoperative cognitive dysfunction”, “perioperative neurocognitive disorders”, “mild neurocognitive disorder”, “major neurocognitive disorder” and “dementia”.

Inclusion criteria comprised cohort studies, case-control studies, and randomized controlled trials published between 2012 and 2022 in English. Also, only patients aged 65 years or older were included. Exclusion criteria encompassed animal subjects and some study designs, such as editorials, case series, and case reports. After applying inclusion and exclusion criteria, a total of 93 articles remained. Afterward, a manual selection was made, and other articles from reference lists were added. As a result, 23 articles were considered relevant (Figure 1).

Is Postoperative Delirium Associated with Postoperative Neurocognitive Disorder?

POD and postoperative NCD are depicted as distinct entities, assessed with different tools at distinct timings.[16] However, they are both frequent in older surgical patients, share risk factors, and frequently co-exist.[16,34] Furthermore, both entities seem to be associated with decreased quality of life, increased mortality, and long-term cognitive decline.[1,16] This raises whether they are separate disorders or part of the same *continuum* of postoperative neurocognitive impairment.[16,34]

Epidemiologic evidence

Saczynski and colleagues investigated the cognitive trajectory of 225 patients throughout the first year after heart surgery in a longitudinal cohort study.[15] The investigators used the Mini-Mental State Examination (MMSE) preoperatively and two days, 1, 6, and 12 months after surgery to assess cognitive function. They found that individuals with POD had worse cognitive performance at one month and one year postoperatively than those who did not have POD. They also found that POD patients were less likely to regain baseline cognitive function at six months than the non-POD group. However, after controlling for baseline differences, including preoperative cognitive function, the mean MMSE score was not statistically significant 12 months after surgery.[15] Nevertheless, the generalizability of the results might be limited by the use of MMSE as a tool for detecting cognitive impairment as it may be insensitive to subtle cognitive decline and is by some considered inadequate for the assessment of postoperative cognitive decline.[1,15,16] Comparably, Lingehall et al. showed that older patients undergoing cardiac surgery who developed POD recovered their prior baseline cognitive abilities at 1-year follow-up.[35]

Sauër et al. found that 30 days after cardiac surgery, cognitive decline was more substantial in patients who had developed POD than those who did not.[32] Yet, one year following surgery, both groups demonstrated cognitive improvement compared to baseline.[32] These findings corroborate previous findings of Saczynski et al. and are consistent with those of Brown and colleagues.[15,36] The latter found that in a group of 142 cardiac surgery patients, those who developed POD had a significantly lower cognitive performance at 1-month follow-up.[36] They also found that POD had the most detrimental impact on psychomotor processing speed and visuoconstruction in the first month following surgery. After the 1-year follow-up, those with POD had a lower processing speed than those without POD, but they found no difference in the composite measure of cognitive function.[36] Nevertheless, patients who later developed POD had lower baseline cognitive performance scores than those without POD. Still, the lack of adjustment for baseline cognitive performance makes it difficult to determine how much of this cognitive impairment is due to POD *per se*.[37]

Franck et al. conducted a secondary analysis of a randomized clinical trial (RCT) of 850 non-cardiac surgical patients.[38] They explored the relationship between postoperative NCD and different combinations of delirium, namely delirium that occurred up to 60 minutes after surgery or Post-Anesthesia Care Unit (PACU) delirium and POD. Those who developed PACU delirium and POD had worse cognitive outcomes at 1-week follow-up. However, after multivariable analysis, they found no overall association between POD and postoperative NCD at 1-week and 3-month follow-ups.[38] Nevertheless, there are some limitations inherent to secondary data analysis. Loss of follow-up might have contributed to inadequate power to identify an association between POD and POCD. Out of 1175 patients analyzed in the clinical trial, only 479 patients (40.8%) were screened for POCD at 1 week and 3 months postoperatively.[36,38] Additionally, recent evidence indicates that cognitive trajectory following POD may be biphasic.[18] Therefore, a three-month follow-up period may be insufficient to capture this nonlinear trend.[18,38]

Daiello and colleagues based their findings on data from an observational study of cognitive outcomes from 551 patients following major noncardiac surgery to test for the association between POD and POCD at 1, 2, and 6 months postoperatively.[34] Orthopedic surgeries were the most frequent surgical procedure (81%), and the most common anesthesia type was general anesthesia (85%). They found that POD enhanced the likelihood of cognitive impairment within 30 days after surgery. However, contrary to the hypothesized association, they found that the relationship between these entities did not hold at 2 and 6 months after surgery. Also, postoperative NCD became more frequent at each follow-up in patients who had not developed POD.[34] Interestingly, these results may contradict the theory that both entities are part of the same neuropathologic *continuum*. During the first month after surgery, cognitive outcomes might be influenced by remaining anesthetic effects, pain, sleep dysregulation, and the influence of sedative and analgesic medication. Accordingly, the latest terminology defines this timeframe as “delayed neurocognitive recovery”.[4,34]

Sprung et al. conducted a large cohort study that explored the development of mild or major NCD among 1667 older surgical patients with normal baseline cognition.[20] Among these, 1152 (69%) returned nine months later for their first postoperative visit. Patients who had experienced POD had a greater prevalence of mild or major NCD at the first follow-up visit when compared to those who did not develop POD (33.3% versus 9%, $P < 0.001$). This association persisted after controlling for other confounding variables. These results align with the hypothesized association between POD and postoperative NCD in surgical patients with normal baseline cognitive function.[20]

Is Postoperative Delirium Associated with Dementia?

Dementia or pre-existing cognitive impairment is an important predisposing factor for delirium development.[13] However, it is still controversial whether delirium unravels previous low cognitive reserve and neurological vulnerability or whether it can directly cause dementia through irreversible neuronal damage.[13,17] Increasing evidence from the general population shows that a delirium episode might lead to permanent cognitive decline and incident dementia, ranging from epidemiologic[17,39] to neuropathological evidence[39]. For example, a population-based cohort study conducted by Davis et al., the Vantaa 85+, explored delirium as a risk factor for dementia in 553 individuals aged 85 and older.[39] Over a decade, the participants underwent several cognitive assessments, and the establishment of previous delirium episodes was determined retrospectively based on information from participants verified by medical reports. They found that a delirium history correlated to an increased likelihood of new dementia diagnosis at the subsequent follow-up and a faster deterioration in MMSE scoring. Yet, the retrospective delirium evaluation based on information from participants and informants may have compromised the data's reliability by adding recall bias.[39]

A recent case-control study nested in a prospective population-based cohort published in 2021 showed that delirium in older adults is an independent risk factor for cognitive decline estimated at 1.8 MMSE points (95% CI -3.5 to -0.2).[40] Furthermore, an episode of delirium leads to a more significant chance of a new dementia diagnosis following 12 months (OR 8.8, 95% CI 1.9 to 41.4), independently of age, disease severity, comorbid illnesses, frailty, and baseline cognitive function.[40] Furthermore, they found that longer duration, greater frequency, and severity of delirium episodes predicted worse cognitive outcomes.[40] These data add robustness to the hypothesized association between delirium and long-term cognitive outcomes. Additionally, a linear correlation between the extent and severity of delirium exposure and new dementia diagnosis raises the possibility of a causal relationship, making delirium a potentially modifiable risk factor for dementia.[40,41]

Epidemiologic evidence

Several studies have examined POD's influence on cognitive function following the first postoperative year. However, many have explored the link between POD and longer-term cognitive decline instead of a dementia diagnosis *per se*.[42] Neufeld et al. conducted a prospective cohort to assess the outcome of POD *versus* non-POD patients after elective or emergent surgery under general anesthesia.[43] The study included 91 patients, and 45% of them developed POD. At the 18-month follow-up, there was no statistically significant difference in long-term survival and cognitive and physical ability between the patients who developed POD and those who did not. However, the reliability of these data is hindered by limited sample size, potentially leading to low statistical power.[43] Furthermore, they used a single measurement in time to assess POD, which may have led to an inaccurate diagnosis given that POD is an acute and fluctuating disorder.[44] An examination throughout an extended timeframe or at different time points would aid in determining the presence of POD.[44]

Inouye et al. conducted prospective cohort research, the "Successful AGing after Elective Surgery" (SAGES), that revealed novel insights into the relationship between POD and long-term cognitive decline.[18] They explored the cognitive decline in the short-term and long-term in non-demented and high-functioning patients after developing POD by extending the follow-up up to 36 months following major elective noncardiac surgery. They combined all 11-test battery scores into a weighted composite measure, the General Cognitive Performance (GCP) score. The group with POD exhibited a remarkable decrease in GCP score one month following surgery compared to the group without POD. In the second month of follow-up, there was a recovery above baseline with no statistically significant difference between groups, followed by a gradual decline to below baseline at 12-36 months. From the 2nd to the 36th month of follow-up, the GCP score declined significantly more in the POD group than in the non-POD group. These results suggest that POD may affect cognitive performance in a biphasic pattern but also that POD may increase 2.8-fold the rate of one's cognitive decline. Although the POD group had a lower baseline cognitive score, both groups were above the mean estimated for cognitive performance in an older population. Notably, this suggests that POD might induce permanent changes in cognitive trajectory even in patients with cognition above the mean.[18] Furthermore, demonstrating a linear correlation between delirium severity after surgery and the rate of long-term cognitive decline is paramount to understanding the relationship between POD and long-term cognitive decline.[45] A prospective cohort study of 560 patients without dementia conducted by Vasunilashorn et al. assessed the relationship between delirium severity and the rate of cognitive decline within 36 months following major elective surgery.[45] This study showed that participants with more severe forms of POD experienced a more significant rate of cognitive decline in the longer term, exceeding that already observed for patients with dementia.[40,45]

Several studies in patients undergoing hip surgery have suggested an association between delirium following surgery and dementia.[46] Olofsson et al. conducted a prospective cohort study on 135 patients and no history of dementia exploring POD as a potential risk factor for incident dementia up to 36 months following surgery.[42] The researchers concluded that 3 years following surgery, about 32% (43 of 135) of patients had been diagnosed with dementia; of those, 91% had

had POD before discharge. They also observed that the dementia group had a longer POD duration. In contrast, only 39% of participants in the no dementia group had developed POD. The analysis accounted for other features, such as sensory impairment, cardiovascular disease, diabetes mellitus, depression, and postoperative disturbances, such as urinary retention, urinary tract infection, and sleeping disruptions. After applying logistic regression, the investigators concluded that POD is an independent risk factor for dementia development within the three years following surgery.[42] However, an important limitation of this study is the absence of preoperative cognitive serial testing. A single-point cognitive assessment will not accurately represent an individual's cognitive trajectory.[14] Additionally, this is a small-sized sample, limiting the generalizability of these results.[46] Thus, a recent and unique meta-analysis of six prospective cohort studies assessed the hypothesis of POD increasing the risk of subsequent dementia development after an emergency or elective hip surgery in individuals without previous dementia.[46] Of the 844 participants who underwent a hip operation, about 265 (31.4%) developed POD, and 101 (11.9%) patients with POD were diagnosed with dementia. Their results showed that after elective and emergency hip surgery, POD increases the risk of incident dementia development in the subsequent 6 months up to 5 years postoperatively.[46]

In the cardiac surgery setting, Lingehall et al. conducted a prospective cohort study to investigate whether POD was related to and increased the risk of dementia up to 5 years after elective cardiac surgery with cardiopulmonary bypass in 114 non-demented older individuals aged 70 years and older.[35] About 64 patients (56.1%) developed POD and 30 out of 114 developed dementia (26.3%). Around 26 out of the 30 people (86.7%) who developed dementia had POD. Although participants diagnosed with dementia were older, results indicate that the decline in the mean MMSE score was significantly steeper in POD patients. Also, POD increased the risk of dementia development by about seven-fold, suggesting that cognitive decline is not due to aging alone. They also observed that a lower baseline MMSE score was substantially related to dementia development within five years of surgery. However, there was no significant interaction between the MMSE score and POD, suggesting an independent association with dementia development. These findings support the hypothesis that the risk of dementia increases in patients who develop POD after cardiac surgery. Nonetheless, it would be relevant to determine whether this outcome limits to the cardiac surgery population or if it applies to non-cardiac patients too.[35] In another prospective cohort study, the investigators explored the cognitive outcomes of patients who developed delirium in the PACU compared to those who did not.[43] Contrary to the hypothesized association, they found no link between POD and cognitive decline up to 18 months postoperatively. Nonetheless, this study had a limited sample size (91 patients) which might have led to a lack of statistical power. Again, baseline and 18-month follow-up cognitive assessment was conducted via telephone, limiting the sensitivity and accuracy of cognitive decline detection.[43]

Most existing research focuses on a particular surgical population, commonly subdivided into cardiac and non-cardiac surgical patients. Recent retrospective cohort research conducted by Mohanty et al. investigated whether POD led to an increased incidence of dementia at 12 months following major surgery.[47] They included 39,665 patients aged approximately 66 years old who underwent a major surgery of a wide range of specialties, predominantly general or orthopedic surgery, cardiothoracic, neurosurgery, urologic and gynecologic, and vascular surgeries. There were 3327 (8.4%) participants developing POD, and they were more likely to be older (median age of 71), have more comorbidities, and have undergone vascular and cardiothoracic procedures. The rate of incident dementia diagnosis in the first year following a surgical intervention was significantly higher in the participants who had had an episode of POD (23.6% *versus* 1.5%), even after adjusting for confounding variables such as age, sex, the severity of comorbid disease, mild cognitive impairment (MCI), American Society of Anesthesiologists (ASA) class, surgical specialty and complexity, and emergency status. Thus, these results add to the hypothesis that even individuals with a normal baseline cognition who develop POD are at increased of new dementia diagnosis one year following discharge, independently of surgery type. This research has significant strengths that overcome the restrictions of several previously cited studies, such as a large sample size encompassing a wide range of distinct specialties.[47] Nevertheless, this study is not without its limitations. The researchers obtained their data based on a medical record system and assessed for delirium based on ICD diagnosis codes without performing any clinical assessment, which might have led to the underdiagnosis of POD.[47]

Neuropathological and biomarker evidence

Multiple researchers acknowledge the intricate interconnection between these two entities and speculate about their pathophysiologic relationship. Most of the debate is about whether delirium is a marker of neurological vulnerability and a predictor of future dementia, unmasks unrecognized dementia, or whether it directly causes permanent neuronal damage, ultimately leading to dementia.[13,14,17,19,48]

Several studies have suggested an epidemiologic link between POD and dementia. However, the evidence supporting the direct role of delirium on dementia development via neuronal damage is still scarce.[19,48] The Vantaa 85+ research, a previously cited cohort study based on a population sample, examined whether an episode of delirium carried a higher load of neuropathologic dementia markers.[39] Their data suggested that in participants with dementia and no previous delirium episode, there was a strong association with AD, vascular, and Lewy body neuropathology. On the contrary, demented participants with a record of delirium episodes had no association with these biomarkers.[39] Even though these findings were insufficiently powered to be conclusive, the hypothesis of delirium inducing a different type of pathogenic pathway emerges.[13]

Other investigators proposed determining if POD is linked to direct neuronal injury by analyzing contemporaneous biomarkers of neuronal damage, such as Neurofilament Light (NfL), a marker for neuronal injury and degeneration.[19,48] For example, Casey et al. conducted a prospective biomarker cohort analysis to explore the link between delirium and neuronal damage in 108 non-cardiac surgical patients.[19] They took blood samples preoperatively up to 4 days postoperatively to analyze for changes in NfL and a panel of 10 cytokines. Concurrently, they also assessed for delirium and its severity. The incidence of POD was 36.1%, and these patients had undergone higher-risk procedures in general. They found that NfL levels gradually increased in both delirious and non-delirious groups after surgery, but the rise was statistically more prominent in the delirium group. They also showed that IL-8, a marker of inflammation, and NfL correlated with delirium severity postoperatively. Yet, NfL's contribution to delirium severity was independent of inflammation, suggesting that POD might be associated with neuronal damage. Although it is not possible to establish causality due to the observational nature of this study, it has a significant strength. The authors analyzed the preoperative change in NfL and its association with delirium instead of measuring postoperative NfL values. This would have led to a less accurate reflection of acute degeneration.[19] However, the small sample size and the strong association between IL-8 and NfL, which raises the possibility that systemic inflammation induced by surgery may also contribute to neuronal damage, acting as a confounding variable, limits the reliability of these results.[19,27]

Fong et al. conducted a matched nested case-control study from a cohort of 108 older non-demented adults submitted to a major elective procedure.[49] They found that the patients with the highest preoperative NfL values had a significantly greater risk of developing POD and were more likely to experience severe delirium. These results support the theory that POD might be a marker of neurological vulnerability and pre-existing neuronal damage. The investigators also identified that NfL values increased more prominently in the delirium group 2 days postoperatively and that higher NfL levels were associated with POD development.[49] These findings suggest that delirium may lead to neuronal damage. However, whether POD directly causes neuronal injury or solely its precipitants, namely surgery, is still unclear. Another finding from this study is that POD patients with the NfL values in the highest quartile at 1-month postoperatively had a more significant decline in their GCP scores by that time.[49] These results suggest that for some patients, POD might have a long-term effect on cognitive function and that neuronal damage may persist beyond the acute insult (i.e., surgery). However, there are some limitations to this research, namely the small sample size and the short-term follow-up, as within 30 days postoperatively, the potential for recovery from the surgical insult may still exist.[4,49]

Given the consistent epidemiologic association between POD and dementia, biomarkers of AD are being studied as predictors of POD.[48,50] For example, Cunningham et al. conducted a cohort study on 282 older patients without clinical dementia undergoing elective hip or knee arthroplasty.[50] The study explored if neurological vulnerability quantified through assessing the AD signature biomarkers would independently predict the risk of POD development. The investigators found amyloid ß 42 (Aß42) concentrations in the cerebrospinal fluid (CSF) to be the strongest independent predictor of POD in this surgical population. Considering that the decline of CSF Aß42 levels is thought to occur a decade or more before clinically evident dementia, these results support the hypothesis that POD may unmask dementia in individuals with AD pathology features.[50]

The hypothesis that POD and AD might share the same pathophysiologic process led to the investigation of the role of the apolipoprotein E (ApoE) ε4 allele as a potential predictor of POD by Vasunilashorn and colleagues.[51] These investigators conducted a study on 557 patients without clinical dementia submitted to major non-cardiac surgical procedures. After adjustment for confounding factors, such as age, sex, surgical procedure, and baseline cognitive function, they found that ApoE ε4 had no association with increased POD incidence, severity, or duration.[51] These results are in line with those from the Vantaa 85+ study, suggesting that in non-demented patients, POD may not merely be a marker of preclinical AD and that these entities may not share the same pathophysiological process.[13,51]

Exposure to delirium seems to accelerate the rate of cognitive decline. However, it is still unknown whether this occurs through acknowledged dementia neuropathology or a distinct mechanism.[52] Davis et al. explored this association by analyzing data from 3 population-based studies with a sample of nearly 990 brain donors.[7,39] The assessment of the participant's change in cognitive performance in MMSE points occurred throughout a 6-year follow-up before death. They found that cognitive decline due to delirium was -0.37 MMSE points per year (95% CI, -0.60 to -0.13, $P < 0.001$) and decline attributable to dementia-related neuropathology was -0.39 MMSE points per year (95% CI, -0.57 to -0.22, $P < 0.001$). Nevertheless, the interaction of both events involved an additional yearly decline of 0.16 MMSE points (95% CI, -0.29 to -0.03, $P = 0.01$), resulting in the highest cognitive decline. Comparatively, the effect of age alone on the rate of MMSE score change was 0.01 points per year. These results show that previous delirium exposure in the presence of dementia-related neuropathologic burden holds cognitive decline higher than expected for each process separately. This data is in line with prior findings from the Vantaa85+

study, further suggesting that delirium contributes to long-term cognitive decline in an independent but interrelated fashion.[39,52]

Is Postoperative Neurocognitive Disorder Associated with Dementia?

Postoperative NCD, previously POCD, has been proposed as a risk factor for dementia. Increasing age and lower educational levels are risk factors for postoperative cognitive decline and cognitive decline in the community.[53] Evidence indicates that POCD harbors meaningful long-term consequences, such as increased all-cause mortality, risk of premature work withdrawal, and reliance on social contributions.[9,26,53] However, it is still unknown whether postoperative NCD is a harbinger of dementia.[9,26]

Epidemiologic evidence

Steinmetz and colleagues conducted a long-term follow-up (11 years) cohort study of 686 patients (median age of 67 years) without dementia undergoing major or minor non-cardiac procedures to assess a potential association between postoperative NCD and dementia development.[26] The investigators did not identify any association between dementia and a prior diagnosis of POCD at both 1-week and 3-month follow-ups.[26] These results support the view that postoperative NCD probably is self-limiting and reversible.[3,26] Nevertheless, the detection of an association may have been limited by the relatively low number of events, as only 32 patients (4.6%) developed dementia.[26]

Evered et al. performed a prospective longitudinal analysis on 326 patients submitted to an elective coronary artery bypass graft (CABG) surgery to explore the long-term effect of POCD.[21] The authors determined dementia's prevalence at 7.5 years following CABG surgery and correlated it with POCD's occurrence. The results showed a higher prevalence of dementia at 7.5 years after CABG surgery than expected for a population of comparable age groups.[21] However, they found no association between POCD at 3 or 12 months and dementia at 7.5 years. Furthermore, they detected an incomplete overlap between these two entities, as only 44% of demented patients had POCD at 7.5 years. Also, POCD at 3 or 12 months predicted long-term cognitive decline, but not dementia.[21] These results suggest that everyday functionality seems preserved, despite the objectively detected cognitive decline. They also identified preoperative cognitive impairment (PreCI) and peripheral vascular disease to be relevant predictors of dementia at 7.5 years following CABG surgery.[21] Thus, the elevated prevalence of dementia after CABG seems to be mainly impacted by pre-existent cognitive impairment or cardiovascular disease rather than postoperative

NCD (-POCD). Choosing a nonsurgical control group with cardiovascular disease for future research would help determine their involvement in dementia development after CABG surgery.[21]

Neuropathological and biomarker evidence

The 2011 National Institute for Aging and the Alzheimer Association (NIA-AA) criteria underscore that AD pathology is detectable through standardized biomarkers several years before clinically evident dementia.[29,54] Thus, Evered et al. hypothesized that older surgical patients with CSF biomarkers diagnostic of AD pathology would have an increased risk of POCD.[54] Their results showed a significant association between low baseline CSF Aß42 levels and POCD three months following surgery. These results must be interpreted cautiously, as the sample was small-sized (59 participants). Nevertheless, these data raise the hypothesis that individuals with preclinical AD are more susceptible to cognitive decline in the postoperative period. Interestingly, there was no association between low baseline CSF Aß42 levels and baseline cognition, suggesting a hypothetic role of anesthesia and surgery in aggravating or inducing a cognitive decline in susceptible patients.[54]

Conclusion

Several researchers have addressed a possible association between postoperative neurocognitive complications and dementia. In the face of a growing number of elderly patients undergoing surgery and anesthesia, the clinical significance of this discussion relies on the possibility that preventing POD might also prevent postoperative NCD and, in the long term, dementia.[2,7]

Most analyzed studies indicate that POD increases the probability of a cognitive decline in the 30 days following surgery (delayed neurocognitive recovery). Still, this association does not hold up to 1 year of follow-up, suggesting that POD and postoperative NCD may not be part of the same neuropathological *continuum*.[15,32,34–36,38] Nevertheless, the apparent absence of an association between these entities does not contradict recent evidence that POD might precipitate a trajectory of cognitive decline.[34]

Most of these studies have only investigated the effect of POD on cognitive function during the first year following surgery. However, recent evidence suggests POD is associated with long-term decline and an accelerated rate of cognitive decline similar to mild NCD or MCI over a three-year follow-up period, even in individuals with normal baseline cognitive function.[18,20]

Despite multiple studies investigating the association between POD and longer-term cognitive decline instead of a dementia diagnosis *per se*, numerous analyzed studies have provided epidemiologic data to support the hypothesis that POD increases the risk of dementia.[18,20,42,43,46,47] Recent evidence indicates that an episode of POD in patients with normal baseline cognitive function is strongly linked with increased incident dementia diagnosis after major surgery, even after adjusting for potential confounders such as surgery type and complexity.[47] Furthermore, evidence suggests a linear correlation between the extent and severity of POD and the diagnosis of new dementia. The possibility of a “dose-response” association between POD and incident dementia has important clinical implications, as delirium might be preventable in up to 40% of cases.[40,41] These observations also raise the possibility of a causal relationship. However, further investigation is necessary to understand if POD induces a cascade of neuronal damage that ultimately leads to dementia or whether it unmasks susceptible individuals with a low cognitive reserve not detectable at baseline, even with careful screening, or both.[18,55] Either way, evidence suggests POD might be a potentially modifiable risk factor for dementia, as it signals a group of individuals with a higher risk of cognitive decline.[18,40]

Most research concerning the relationship between POD and dementia does not characterize dementia according to its etiology. If POD has a stronger association with a particular dementia etiology, this is not yet understood.[51] The emerging evidence regarding this relationship's pathophysiology is still scarce and conflicting.[48] Further exploring this matter is critical to developing targeted prevention strategies.[36]

Although it is now acknowledged that mild NCD or MCI is a harbinger of subsequent cognitive decline in the general population, the included studies do not seem to support the hypothesis that postoperative NCD is associated with or predisposes to dementia. So far, very few studies have explored this association according to the latest nomenclature.[21,26,54,56] However, the unification and standardization of nomenclature according to the general community will be necessary for future longitudinal studies to understand if postoperative cognitive decline follows the same pattern as in the general population.[1] Recent evidence showing an increase in biomarkers of neuronal injury raised the possibility that anesthesia and surgery might set off or exacerbate the cognitive decline in vulnerable individuals.[1,54] Further research is necessary to understand the etiologic role of anesthesia and surgery in this field, as it would provide the possibility of targeted and tailored surgical and anesthetic care.[1]

Because 40% of cases of delirium are thought to be preventable, large, randomized, and multicenter trials are needed to explore if preventing postoperative delirium impacts the number of new incident dementia diagnoses and its trajectory of cognitive decline.[41] Trials respecting the latest terminology recommendations for perioperative NCD are also vital to enable the generalization of findings and investigation of preventive strategies with clinical applicability.[57]

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Appendix

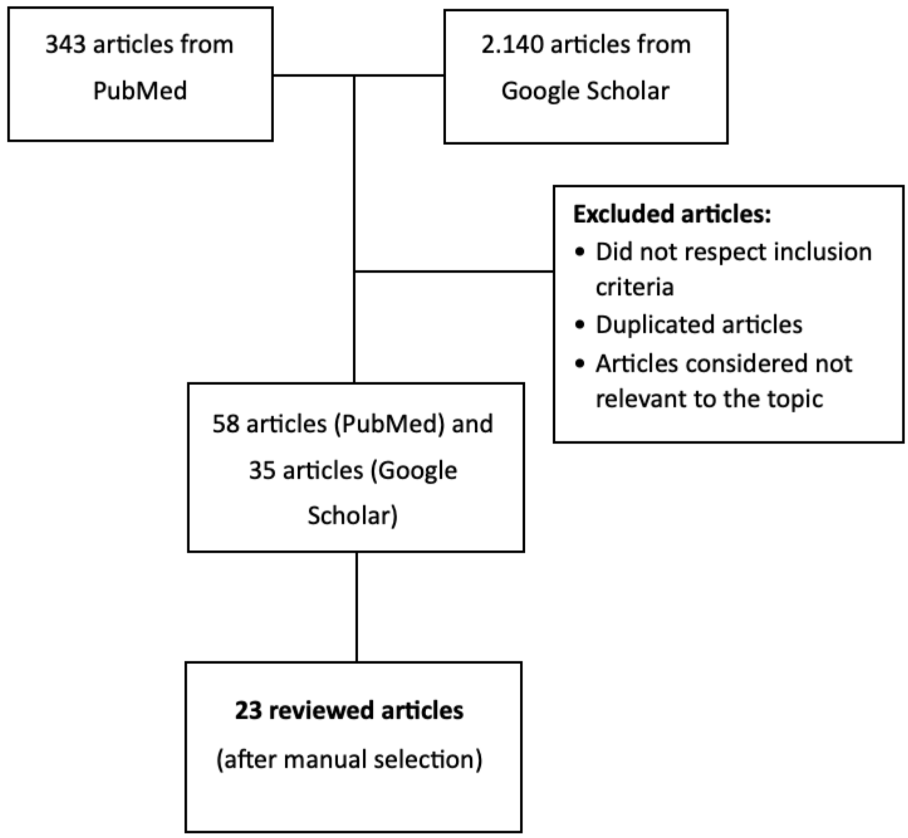

Figure 1. Research methodology flowchart.

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