

The Fallacy of Persistent Postoperative Cognitive Decline

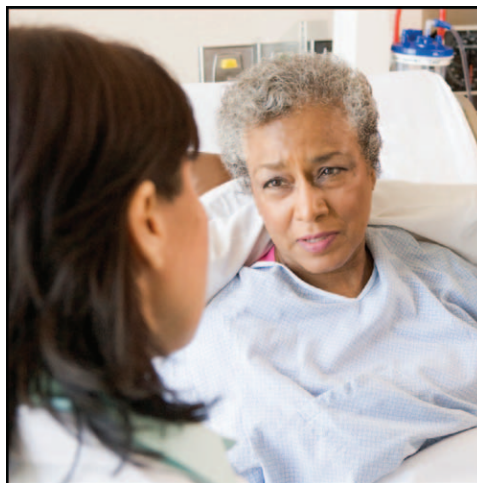
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THERE is a widespread belief in the medical community and lay public that anesthesia and surgery pose a substantial risk of producing long-term cognitive damage in elderly patients. This view endures despite a growing body of clinical research data showing that major surgery and general anesthesia are unlikely to cause persistent postoperative cognitive decline (POCD) or incident dementia. Viewing the studies in an evidential pyramid illustrates that the weight of clinical evidence is heavily tilted against persistent POCD attributable to surgery or anesthesia in older surgical patients (fig. 1 and Supplemental Digital Content 1, online appendix, <http://links.lww.com/ALN/B226>). The study by Dokkedal *et al.*¹ in this issue of ANESTHESIOLOGY reinforces this perspective by using a powerful methodological approach.

Dokkedal *et al.*¹ examine the association between exposure to surgery and long-term cognition in a Danish cohort of 8,503 middle-aged and elderly twins. Their findings substantiate the current evidence of no clinically relevant persistent POCD attributable to surgery or anesthesia, whereas preoperative cognitive trajectory and coexisting disease burden are likely to be strongly predictive of long-term postoperative cognitive trajectory.¹ The large number of patients and the use of rigorous longitudinal cognitive testing in this study increased the reliability



“... older patients should today be reassured that surgery and anesthesia are [not] implicated in causing persistent cognitive decline or incident dementia.”

orientation 6 months after surgery. These changes can persist years after surgery and in many cases are probably irreversible.”³ Hawthorne⁴ wrote for the British Broadcasting Corporation, “When you go into hospital for heart surgery you do not expect to get brain damage. But that is exactly what is happening to thousands of people a year in Britain.”

Despite the lack of proof regarding either the cognitive cost or the culpability of the machine, off-pump cardiac surgery was invented and prematurely promoted in an attempt to avoid the hypothetical public health crisis

of the findings and echoed the results of another twin study that followed World War II veteran twin pairs between 1990 and 2002 and found no negative cognitive effects on the twin who underwent heart surgery.²

Historically, some of the landmark studies regarding persistent POCD were in cardiac surgery, which was also included in the study by Dokkedal *et al.*¹ It was generally believed, although without compelling evidence, that heart surgery was frequently associated with a cognitive cost and that this was largely attributable to the cardiopulmonary bypass machine. Importantly, such beliefs were reflected in reputable, mainstream media and have impacted public consciousness to this day. In the New York Times, Jauhar wrote, “Studies suggest that anywhere from 10 to 50% or more of bypass patients do poorly on tests of memory, language, and spatial

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Corresponding article on page 312. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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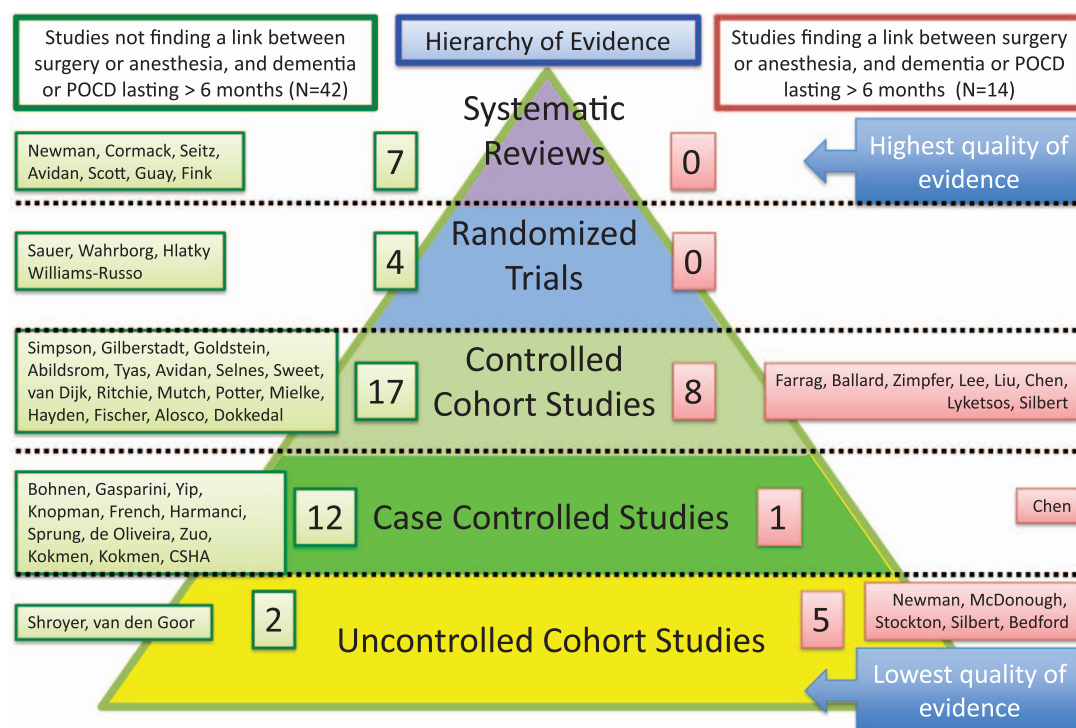


Fig. 1. Hierarchy of evidence pyramid showing studies that have and have not found a link between surgery or anesthesia and dementia or postoperative cognitive decline (POCD) lasting greater than 6 months (more details are provided in Supplemental Digital Content 1, online appendix, <http://links.lww.com/ALN/B226>). CSHA = Canadian Study on Health and Aging.

of brain damage after cardiac surgery with cardiopulmonary bypass, colloquially referred to as “pump-head.”⁵ It has now been established beyond reasonable doubt that there is no difference in intermediate-term (greater than 6 months) cognitive outcomes regardless of whether cardiopulmonary bypass is used.^{6,7} The misguided solution of off-pump cardiac surgery was ultimately revealed to pertain to a nonexistent problem. It proved financially costly and importantly was associated with inferior surgical outcomes.⁶ A recent landmark randomized controlled trial by Sauër *et al.*⁸ upended perceived wisdom in finding that patients who underwent heart surgery had better cognitive performance after 7.5 yr than patients who had undergone percutaneous coronary intervention, without any surgery or anesthesia. In his editorial contextualizing this trial, Selnes⁹ stated, “This study by Sauër *et al.* adds to a long list of previous studies that by now have convincingly demonstrated that surgical interventions for coronary artery disease are not associated with a higher risk of late cognitive decline or Alzheimer’s disease than medical or nonsurgical interventions.” In a systematic review focused on patients older than 65 yr, Fink *et al.*¹⁰ summarized, “persistent cognitive impairment after the studied cardiovascular procedures may be uncommon or reflect cognitive impairment that was present before the procedure.” Specifically, they found that “CABG [coronary artery bypass grafting] may have little persistent adverse cognitive effect in older adults.”¹⁰

It is interesting to consider why the perceptions of persistent POCD and dementia attributable to surgery endure despite the refutation studies. It is likely that persistent POCD is a powerful example of a post hoc ergo propter hoc (after this, therefore because of this) misattribution fallacy. Anecdotes can be very compelling and one often hears about people whose cognitive abilities were permanently diminished after their surgery. It might, therefore, be assumed that the surgery or the anesthesia *caused* the cognitive change. However, the first-time detection of cognitive decline or dementia after surgery is to be expected for several reasons. First, cognitive decline and dementia are common with aging, especially when there are coexisting diseases such as diabetes mellitus, depression, chronic obstructive pulmonary disease, heart failure, and vascular disease. Similarly, approximately half of people older than 60 yr undergo a major surgical procedure. Therefore, it is predictable that in some older adults, cognitive decline or dementia will be initially detected after surgery. Second, the preoperative cognitive trajectory of surgical patients is not currently assessed. It is likely that many older surgical patients are already experiencing subclinical or unappreciated cognitive decline. When they undergo major surgery, they are sometimes not seen by friends and colleagues for a few months. In this intervening period, they would continue to decline along their predicted trajectory, but with the time gap, cognitive decline becomes apparent (fig. 2). Third, it is now appreciated that rapid-onset dementia can occur over a period of weeks to

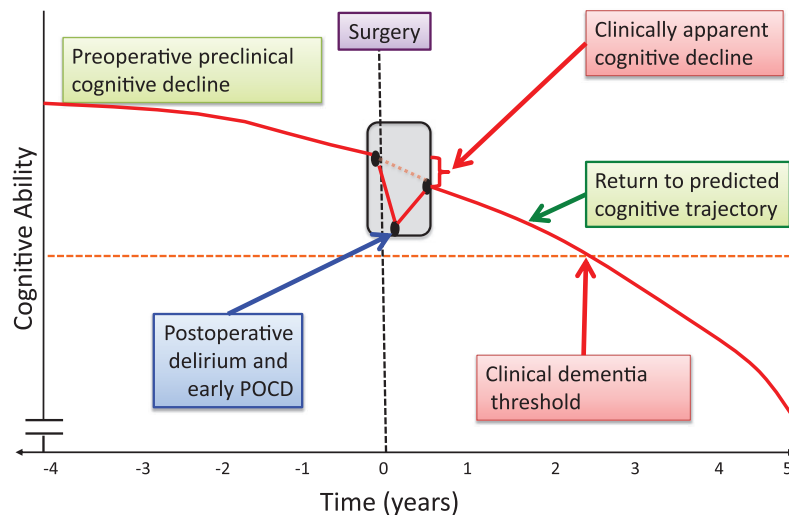


Fig. 2. Hypothetical preoperative and postoperative cognitive trajectory. POCD = postoperative cognitive decline.

months.¹¹ Unsurprisingly, this will manifest in some people in the postoperative period. Finally, despite evidential dissonance, it is difficult to change a firmly entrenched belief among many researchers, clinicians, and the general public. For all these reasons, when elderly people become demented or experience persistent cognitive decline after a surgical procedure, we suggest that the surgery is usually a coincidence masquerading as the cause.

It is important that we do not “throw out the baby with the bath water.” Although dementia and persistent cognitive decline are unlikely to be caused by surgery, the brain is vulnerable in the perioperative period, and it is important to mitigate the indisputable neurological consequences of major surgery, including delirium, early POCD, overt stroke, and covert stroke. Postoperative delirium is a pathophysiologically obscure, reversible condition characterized by acute onset inattention and disorganized thinking.¹² Early POCD is a reversible cognitive decline that occurs within days to weeks after surgery.¹³ Delirium and early POCD are distressing for patients and family members and are associated with worse outcomes.^{12,13} Perioperative covert stroke is an understudied, underappreciated, and potentially preventable complication.¹⁴ As such, it is important for researchers to focus attention on the strategies to prevent postoperative delirium, early POCD, and perioperative stroke.

It is tragic when parents choose not to vaccinate their children against measles because of the persistent fallacy that there is a causal link between vaccination and autism. It is similarly tragic when adults older than 50 yr forego quality of life-enhancing surgery based largely on hypothesis-generating cohort studies and a *post hoc ergo propter hoc* fallacy dating to a 1955 report by Bedford in the Lancet, which suggested that persistent POCD was a concern following complaints from patients and their families regarding problems with cognitive function after surgery.¹⁵ On the basis of a growing body of evidence, of

which the study by Dokkedal *et al.*¹ is emblematic, older patients should today be reassured that surgery and anesthesia are unlikely to be implicated in causing persistent cognitive decline or incident dementia. At the same time, we must energetically seek to alter the dominant narrative on the platform of public opinion and ensure that reputable media sources correct the misconceptions that they have previously promulgated.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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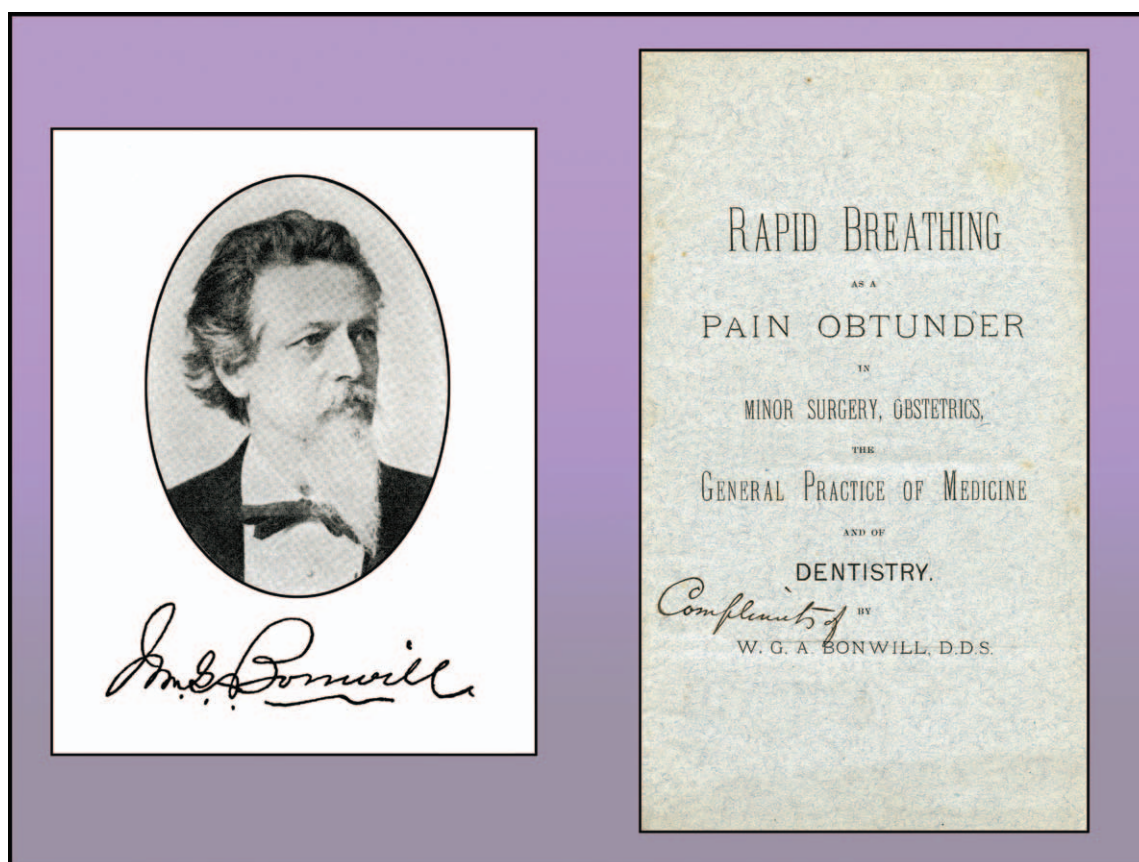
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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Before the Lamaze Method: Bonwill “Rapid Breathing”



In 1875 a paper titled “The Air an Anaesthetic” was read at Philadelphia’s Franklin Institute. The author, William Gibson Arlington Bonwill, D.D.S., M.D. (1833 to 1899; *left*), had apprenticed in dentistry in New Jersey and Maryland before practicing dentistry in Delaware and then Pennsylvania. In 1880 Dr. Bonwill published (*right*) “Rapid Breathing as a Pain Obtunder in Minor Surgery, Obstetrics, the General Practice of Medicine and of Dentistry.” In 1894 Dr. Bonwill reported to other dentists and surgeons that “in an experience of twenty years [of dentistry] I have not used an anesthetic in my office.... My opinion is that if I could have introduced rapid breathing as a pain obtunder before nitrous oxide came out, you would all be using it.” Note that Dr. Bonwill demonstrated his “rapid breathing” techniques in Russia in 1897—54 years before Dr. Fernand Lamaze’s 1951 introduction in France of obstetrical breathing techniques that Lamaze had observed in Russia. (Copyright © the American Society of Anesthesiologists, Inc.)

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Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins

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ABSTRACT

Background: Postoperative cognitive dysfunction is common, but it remains unclear whether there are long-term adverse cognitive effects of surgery combined with anesthesia. The authors examined the association between exposure to surgery and level of cognitive functioning in a sample of 8,503 middle-aged and elderly twins.

Methods: Results from five cognitive tests were compared in twins exposed to surgery, classified as major, minor, hip and knee replacement, or other, with those of a reference group without surgery using linear regression adjusted for sex and age. Genetic and shared environmental confounding was addressed in intrapair analyses of 87 monozygotic and 124 dizygotic same-sexed twin pairs in whom one had a history of major surgery and the other did not.

Results: Statistically significantly lower composite cognitive score was found in twins with at least one major surgery compared with the reference group (mean difference, -0.27 ; 95% CI, -0.48 to -0.06), corresponding to one tenth of an SD, that is, a negligible effect size. In the intrapair analysis, the surgery-exposed co-twin had the lower cognitive score in 49% (95% CI, 42 to 56%) of the pairs. None of the other groups differed from the reference group except the knee and hip replacement group that tended to have higher cognitive scores (mean difference, 0.35 ; 95% CI, -0.18 to 0.87).

Conclusions: A history of major surgery was associated with a negligibly lower level of cognitive functioning. The supplementary analyses suggest that preoperative cognitive functioning and underlying diseases were more important for cognitive functioning in mid- and late life than surgery and anesthesia. (ANESTHESIOLOGY 2016; 124:312-21)

COGNITIVE impairment is a well-known complication after surgery with delirium and postoperative cognitive dysfunction (POCD) as the most common disorders.¹ Early (7 days) POCD occurs in adult surgical patients of all ages, but elderly patients are at higher risk, and at 3 months after surgery, cognitive impairment is still detectable in patients older than 60 yr.²⁻⁵ POCD may be present for longer than 6 months in some patients⁶ with potential long-term implications for the patient including impaired quality of life,^{7,8} increased mortality risk,^{3,9} higher prevalence of time receiving welfare benefits, and increased risk of leaving the labor market prematurely.⁹

In recent years, POCD has received increasing attention in the literature, and several pathophysiologic factors and pathways have been suggested, including anesthetics and inflammatory response to the surgical trauma.¹⁰ Animal

What We Already Know about This Topic

- Postoperative cognitive dysfunction is common in the elderly, but the contributions of surgery, anesthesia, preexisting conditions, and other factors are unclear
- A large Danish registry of middle-aged and elderly twins provides a powerful approach to detect subtle effects of surgery and anesthesia on cognitive functioning by minimizing environmental and genetic confounding

What This Article Tells Us That Is New

- In a study of 8,503 twins, a negligible but statistically significant decrease in a sensitive composite cognitive score was present in twins with at least one major surgery, but there was no difference by intrapair analysis
- There was no clinically significant association of major surgery and anesthesia with long-term cognitive dysfunction, suggesting that factors other than surgery and anesthesia are more important

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 255. This work has been presented as an oral contribution at the 22nd Nordic Congress of Gerontology, May 26–28, 2014, Gothenburg, Sweden, and as a poster contribution at the 15th Congress of the International Society for Twin Studies, November 16–19, 2014, Budapest, Hungary.

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studies suggest that general anesthetics are a possible pathogenic factor of POCD as brain cell damages, apoptosis, and decrease in cognitive skills are seen in animals after prolonged exposure.^{11–15} On the basis of the evidence from the human studies, type of surgery is suggested as a risk factor of POCD as the incidence of early POCD after minor surgery was significantly lower than after major surgery.¹⁶ Several explanations for this finding have been proposed including non-resolution of the inflammatory response after surgery.^{10,17} Moreover, the disease prompting the surgery may be responsible for the cognitive impairment as two very common diseases among the elderly, namely cardiac disease and cancer, are found to be associated with cognitive impairment.^{18–20} A longitudinal study has shown that patients with coronary artery disease showed significant declines in different cognitive domains after 6 yr of follow-up, regardless of whether they had on-pump coronary artery bypass graft surgery, off-pump coronary artery bypass graft surgery, or no surgery.¹⁹ Furthermore, the incidence of cognitive impairment in colorectal cancer patients before chemotherapy is more than three times that of aged-matched healthy controls.²⁰ No differences were found by disease stage or between patients pre- and postoperatively, indicating that factors other than surgery and anesthesia were responsible for the higher proportion of cognitive impairment in these patients at baseline.

Mild cognitive impairment with memory deficits has been shown to associate with subsequent dementia, particularly Alzheimer's disease (AD),²¹ and it has further been suggested that POCD and dementia share some of the perioperative risk factors, including anesthetics.²² However, a meta-analysis²³ including 15 case-control studies found that a history of exposure to general anesthesia was not associated with an increased risk of AD, and also in a recent cohort study, it was not possible to ascertain an association between POCD and dementia.²⁴

Our aim was to examine the association between exposure to surgery and subsequent level of cognitive functioning in a very large population of middle-aged and elderly twins with almost complete records of surgeries since 1977, hereby enabling us to test for more subtle differences in cognitive functioning. The use of a twin design further enabled us to address the potential confounding from shared environmental and genetic factors as an approach to adjust for preoperative cognitive functioning.

Materials and Methods

The current study was based on the linkage of the intake examination data of the Longitudinal Study of Middle-Aged Danish Twins (MADT) and the Longitudinal Study of Aging Danish Twins (LSADT) with the Danish National Patient Register (NPR) in Copenhagen. Both studies included an assessment of cognitive functioning and have previously been described in detail elsewhere.^{25–27} In brief, participants in the MADT and the LSADT were ascertained through the Danish Twin Registry comprising twin pairs born in 1870 to 2004 and considered

representative of the general population in Denmark.^{28,29} The MADT represented a random sample of 120 intact twin pairs from each birth cohort from 1931 to 1952. The LSADT was initiated in 1995 and included Danish twins aged 75 yr or older and residing in Denmark by January 1995. Further cohorts aged at least 70 yr were added in 1997, 1999, and 2001.

The MADT and the LSADT included a questionnaire on sociodemographic factors, health and diseases, and life style factors along with physical and cognitive tests. We excluded patients who had undergone neurosurgery.

Register Linkage

Since 1968, all Danish citizens have been assigned a unique 10-digit identifier, the central personal register number (the CPR number), which is the key to individual information in all official registries covering the Danish population.³⁰ Within Statistics Denmark, the central personal register enables the linkage between Danish registries, including the Danish NPR. The Danish NPR comprises data on surgeries performed in Danish hospitals since 1977 along with data on diagnoses. Until 1996, the Danish National Board of Health's Classification of Surgeries was used to classify surgeries, and from 1996, the Nordic Classification of Surgical Procedures was used. Data on outpatients and emergency patients were added in 1995.³¹ Thus, the register has nationwide coverage and is considered to have high validity, especially with regard to surgical procedures.³²

Exposure Assessment

The exposure group encompassed twins who had at least one surgical procedure within 18 to 24 yr before intake cognitive examination. The exposure group was separated into four groups by type of surgical procedure taking into account the severity of the underlying disease: (1) major surgeries, including cardiac, thoracic, laparotomy, central and peripheral vascular, and major fracture surgeries, (2) knee and hip replacement surgeries, (3) minor surgeries, and (4) other surgeries. Minor surgeries included all-day only procedures, surgeries followed by less than 2 days of hospitalization, and, independently of the first two criteria, surgery codes representing eye, skin, endoscopic procedures along with biopsies and other small surgical procedures. The classification was performed by two experienced anesthesiologists (T.G.H. and L.S.R.), who, independently of one another, went through the records of surgery codes in the study sample for the period from 1977 and until intake examination (details can be found in the appendix).

Twins who had more than one surgical procedure were assigned to the groups using the following algorithm: (1) major surgery if any, (2) knee and hip replacement surgery if any, but no major surgery, and (3) other surgeries if any, but neither major nor knee and hip replacement surgery. The reference group in all analyses comprised twins with no surgical procedures from 1977 and until intake examination. The exposure was reassessed by using three more narrow time frames to assess whether time since surgery modified the association

between exposure to surgery and cognitive performance: (1) 2 yr (2) 1 yr, and (3) 3 months preceding intake examination. Also the effect of cumulative exposures was investigated based on the type of surgical procedures carried out from 1977 and until cognitive examination. Five exposure groups were defined according to both the type and number of surgeries performed: (1) minor surgeries, (2) one major/other surgery, (3) two major/other surgeries, (4) three major/other surgeries, and (5) more than three major/other surgeries.

Outcome Measurement

The outcome was cognitive functioning assessed by a five-component test battery. The specific tasks included in the test battery were (1) a category fluency task, in which individuals were asked to name as many animals as they could during a 1-min interval, (2) forward and (3) backward digit span, and (4) immediate and (5) delayed recall of a 12-item list. An overall composite measure of cognitive functioning was computed by adding the five standardized scores (using mean and SD from participants aged 45 to 49 yr) of each of the five-component tasks.³³ The composite cognitive score has been used in a series of previous studies. It has been shown to be a valid, reliable, and very age-sensitive measure of cognitive functioning although moderately stable over a 2-yr interval (0.60), and it has a high internal consistency reliability (0.75).^{33–36}

Covariates

Potential confounders were identified in other similar studies,^{5,37} including sex, age, and educational attainment. However, as the effect sizes were similar regardless of whether educational attainment was included in the statistical model, this covariate was omitted in the analyses.

Intrapair Analyses

To address genetic and shared environmental confounding and to take preoperative cognition into account, intrapair analyses were performed. The 8,503 twins in the study population consisted of 1,065 monozygotic pairs and 1,179 dizygotic, same-sexed twin pairs, as well as 4,015 twin individuals from opposite-sexed pairs and “single twins,” that is twins who had a co-twin who was either deceased or a nonparticipant. To avoid confounding by sex, the intrapair analyses only included same-sexed pairs. To obtain the biggest contrast in exposure, the intrapair analyses only included pairs in whom one had a history of major surgery and the other no surgery. Among the 1,065 monozygotic pairs, a total of 87 such pairs were identified, whereas the corresponding number for dizygotic twins was 124 among 1,179 pairs. Consequently, 211 exposure-discordant pairs were included in the intrapair analyses.

Statistical Analyses

Descriptive statistics were expressed as means and SDs for continuous variables and as numbers and proportions for categories. The comparisons of composite cognitive scores

between twins exposed for at least one surgery (major, minor surgery, knee and hip replacement surgery, and other surgeries) before examination of cognitive functioning and twins not exposed were performed using multivariate linear regression models adjusting for sex and age at examination. The within-pair dependency of twin individuals was considered by estimating the standard errors using the cluster option of STATA (release 13; STATA Corp., USA). Model assumptions were checked by residual plots and quantile-quantile plots of residuals.

In the intrapair analyses, the proportion of pairs in which the co-twin who had been exposed to anesthesia and major surgery also had the lower composite cognitive score was calculated including the 95% CI using the binomial distribution.

Results

A total of 8,527 Danish twins with a valid cognitive score were included: 4,309 of 4,314 from the MADT (younger than 70 yr) and 4,218 of 4,731 from the LSADT (70 yr or older).

Of these participants, 65% had at least one surgery preceding intake examination. We excluded 24 twins with neurosurgery from the study: 10 from the MADT and 14 from the LSADT, reducing the sample sizes to 4,299 and 4,204, respectively (table 1).

Major surgery was slightly more common in twins aged 70 yr and older compared with twins younger than 70 yr (20 vs. 17%). The unadjusted mean cognitive scores varied slightly between exposure groups, whereas the cognitive scores were substantially lower for older compared with younger participants, as expected. However, twins aged 70 yr and older with knee and hip replacement surgery had the highest cognitive score (1.68) of surgery groups (ranging from 0.88 to 1.68) and even higher than the reference group (1.24).

Compared with the reference group, twins with major surgery preceding intake examination had slightly lower cognitive scores when adjusted for sex and age (mean difference, -0.27 ; 95% CI, -0.48 to -0.06) (table 2), which is equivalent to about one tenth of an SD (table 1), that is, negligible effect size.³⁸ In contrast, we found that those with knee and hip replacement surgery had higher cognitive score at intake (mean difference, 0.35 ; 95% CI, -0.18 to 0.87) although the difference did not reach significance. For twins with minor or other surgical procedures, no differences were found in cognitive score in comparison with the reference group. Analyses stratified on overall age (younger than 70 yr and 70 yr or older) yielded similar estimates.

To further illustrate the effect size associated with major surgery (0.1 SD), we analyzed separately one of the cognitive tests included in the cognitive composite score, namely the animal fluency test (*i.e.*, mention as many animals as possible in 1 min). Here, one tenth of an SD corresponds to 0.7 named animal. In the MADT, the mean number of animals

Table 1. Characteristics and Summary Statistics for Composite Cognitive Scores among Participants from the Study of Middle-aged Danish Twins (< 70 Yr) and the Longitudinal Study of Aging Danish Twins (≥ 70 Yr), in Totals and by Type of Surgical Procedure

Characteristics	Totals	Surgical Procedure Groups				
		Major Surgery*	Minor Surgery	Knee and Hip Replacement	Other Surgery	Without Surgery
n (%)						
All	8,503 (100)	1,546 (18)	1,729 (20)	171 (2)	2,092 (25)	2,965 (35)
< 70 yr	4,299 (100)	732 (17)	1,004 (23)	38 (1)	1,043 (24)	1,482 (35)
≥ 70 yr	4,204 (100)	814 (20)	725 (17)	133 (3)	1,049 (25)	1,483 (35)
Female sex, n (%)						
All	4,560 (54)	1,011 (65)	837 (48)	112 (66)	1,144 (55)	1,456 (49)
< 70 yr	2,106 (49)	561 (77)	430 (43)	13 (34)	567 (54)	535 (36)
≥ 70 yr	2,454 (58)	450 (55)	407 (56)	99 (74)	577 (55)	921 (62)
Age, yr, mean (SD)						
All	67 (12)	68 (12)	65 (12)	74 (8)	67 (12)	67 (11)
< 70 yr	57 (6)	57 (6)	57 (6)	61 (5)	56 (6)	57 (6)
≥ 70 yr	77 (5)	77 (5)	77 (5)	77 (5)	77 (5)	77 (5)
Cognitive score, mean (SD)						
All	2.89 (3.95)	2.58 (4.02)	3.17 (4.05)	2.26 (3.78)	2.94 (4.01)	2.89 (3.79)
< 70 yr	4.59 (3.50)	4.47 (3.63)	4.62 (3.70)	4.26 (3.61)	4.73 (3.45)	4.54 (3.33)
≥ 70 yr	1.15 (3.60)	0.88 (3.58)	1.17 (3.63)	1.68 (3.65)	1.17 (3.74)	1.24 (3.49)

* Including cardiac, thoracic, laparotomy, central and peripheral vascular, and fracture surgeries.

Table 2. Mean Differences in Composite Cognitive Scores between Twins with Major, Minor, Knee and Hip Replacement, or Other Surgical Procedures and the Reference Group

Surgical Procedure Groups	Total		< 70 yr		≥ 70 yr	
	n	Differences in Cognitive Scores (95 % CI)*	n	Differences in Cognitive Scores (95 % CI)*	n	Differences in Cognitive Scores (95 % CI)*
Major†	1,546	−0.27 (−0.48 to −0.06)	732	−0.27 (−0.59 to 0.04)	814	−0.30 (−0.59 to −0.01)
Minor	1,729	−0.06 (−0.27 to 0.14)	1,004	−0.03 (−0.30 to 0.25)	725	−0.09 (−0.39 to 0.20)
Knee and hip replacement	171	0.35 (−0.18 to 0.87)	38	0.16 (−1.05 to 1.36)	133	0.35 (−0.23 to 0.92)
Other	2,092	−0.08 (−0.27 to 0.10)	1,043	−0.06 (−0.33 to 0.20)	1,049	−0.04 (−0.30 to 0.23)
Without surgery	2,965	Reference	1,482	Reference	1,483	Reference

* Multiple linear regression analysis adjusted for sex and age at intake examination. † Including cardiac, thoracic, laparotomy, central and peripheral vascular, and fracture surgeries.

named in 1 min is 24.2, and this means that a one tenth of an SD lower score corresponds to 23.5, which represents a difference that must be considered clinically unimportant. In comparison, the difference in cognitive score between the group younger than 70 yr and that older than 70 yr is about a 0.9 SD (table 1), which in the animal fluency test would correspond to a six-word difference.

We also analyzed the data according to those who had undergone surgery up to 2 yr (n = 1,738), 1 yr (n = 1,109), or 3 months (n = 391), respectively, preceding intake examination (fig. 1). Overall, the mean differences in cognitive scores in the surgery groups compared with those without surgery in the same periods were similar across strata. Although the majority of estimates did not reveal statistical significance, the results indicated no interaction of time since surgery with the association between surgery and cognitive score at intake examination. When we stratified on overall age (younger than 70 yr and 70 yr or older), the analyses yielded similar estimates in each of the age groups.

In addition, analyses were stratified on the type and number of surgical procedures to investigate the dose–response pattern of cumulative exposure to surgery and anesthesia on cognitive impairment (table 3). We found that exposure to three or more surgeries was associated with significantly lower score, about one fifth of an SD.

The intrapair analysis of twin pairs in whom one had a history of major surgery and the other had no surgery was included to further adjust for genetic and shared environmental factors. In the analysis of all 211 discordant pairs, we found that the surgery-exposed twin had a lower cognitive score than the co-twin in 49% (95% CI, 42 to 56%) of the pairs (fig. 2), suggesting that it was as common to have the higher cognitive score when exposed to surgery as it was to have the lower cognitive score. When twin pairs were restricted according to the magnitude of the intrapair differences in cognitive score to the top 75, 50, and 25%, respectively, the analyses yielded similar results. This was

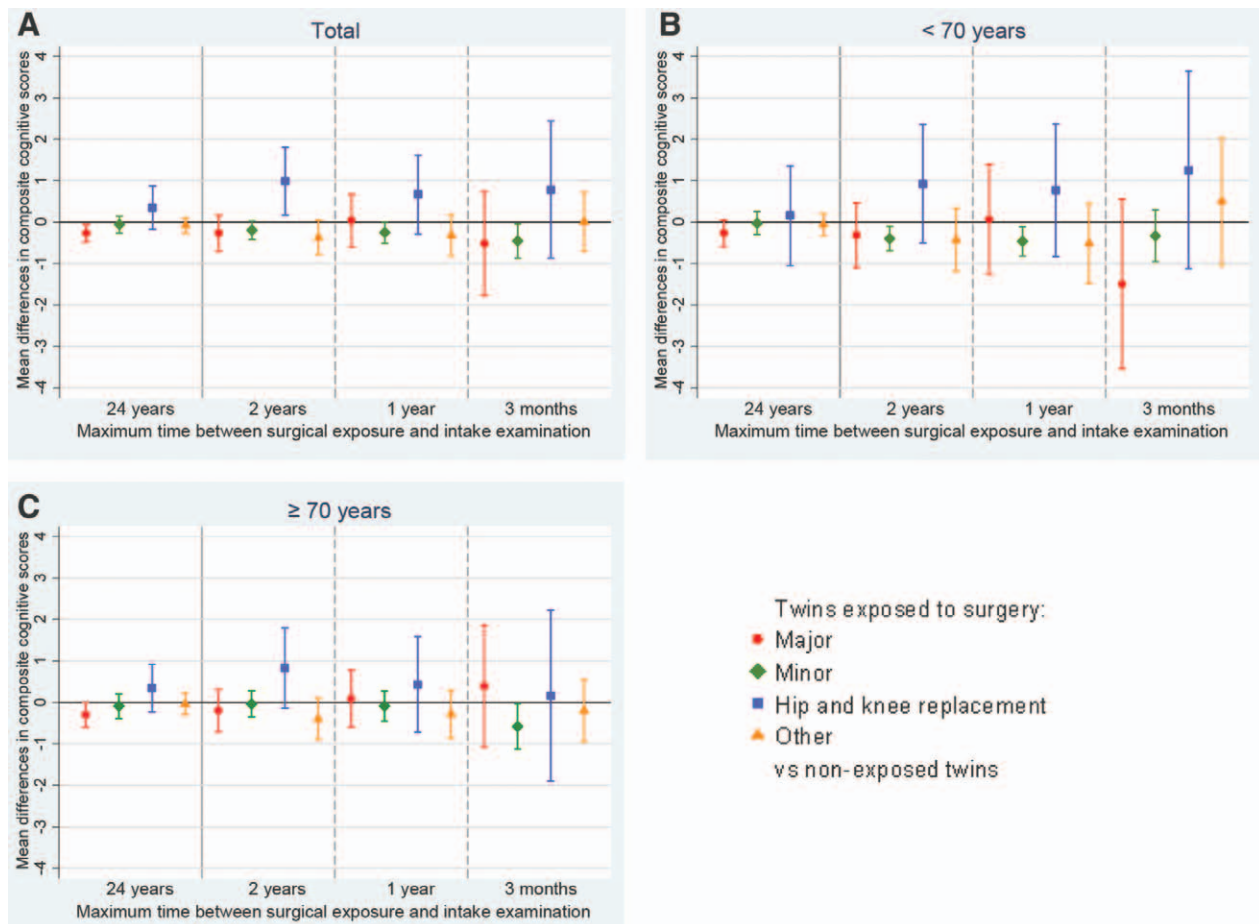


Fig. 1. Mean differences in composite cognitive scores between twins who had undergone major, minor, knee and hip replacement, or other surgical procedures up to 24 yr ($n = 5,538$), 2 yr ($n = 1,738$), 1 yr ($n = 1,109$), or 3 months ($n = 391$) preceding intake examination and the nonexposed group; (A) all participants; (B) participants aged < 70 yr; (C) participants aged ≥ 70 yr.

Table 3. Mean Differences in Composite Cognitive Scores between Twins with Minor Surgery, One Major/Other Surgery, Two Major/Other Surgeries, Three Major/Other Surgeries or More Than Three Major/Other Surgeries and the Group without Surgery Preceding Intake Examination

	Total		< 70 yr		≥ 70 yr	
Number/Type of Surgical Procedures	n	Differences in Cognitive Scores (95 % CI)*	n	Differences in Cognitive Scores (95 % CI)*	n	Differences in Cognitive Scores (95 % CI)*
> 3 major/other	478	-0.50 (-0.84 to -0.15)	225	-0.67 (-1.19 to -0.15)	253	-0.33 (-0.79 to 0.13)
3 major/other	437	-0.47 (-0.79 to -0.16)	203	-0.17 (-0.64 to 0.30)	234	-0.70 (-1.13 to -0.26)
2 major/other	948	0.04 (-0.21 to 0.29)	424	-0.10 (-0.46 to 0.26)	524	0.16 (-0.18 to 0.50)
1 major/other	1,946	-0.07 (-0.26 to 0.12)	961	-0.03 (-0.30 to 0.24)	985	-0.07 (-0.34 to 0.19)
Minor	1,729	-0.06 (-0.26 to 0.14)	1,004	-0.03 (-0.30 to 0.25)	725	-0.09 (-0.39 to 0.20)
No surgery	2,965	Reference	1,482	Reference	1,483	Reference

* Multiple linear regression analysis adjusted for sex and age at intake examination.

also the case when the twins were stratified by zygosity (data not shown).

Discussion

In this study comprising 8,503 twins, major surgery was associated with a negligibly lower level of cognitive functioning. Thus, the study provides evidence against a clinically relevant

association between exposure to surgical procedures and anesthesia and subsequent cognition in mid- and late life.

Twins who had undergone major surgery had slightly lower cognitive scores, corresponding to one tenth of an SD, compared with the reference group, but in the intra-pair analysis where genetic and shared environmental factors were adjusted for by design, no association was observed.

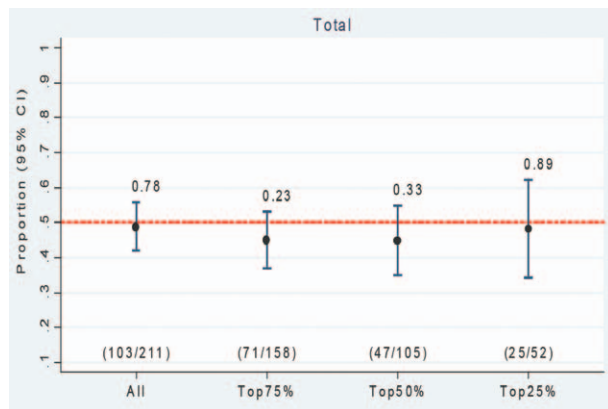


Fig. 2. Proportion of twin pairs in which the twin exposed to major surgery had a lower composite cognitive score for all twin pairs and stratified according to the magnitude of intra-pair difference in cognitive score. Above each line is the *P* value from the binomial test, which tests whether the proportion equals to 0.5.

Twins who had undergone hip or knee replacement had slightly higher cognitive scores, although not significantly so, whereas no differences were found in the minor or other surgery group when compared with the reference group.

The time interval between surgery and cognitive examination had no impact on effect sizes, and no dose–response pattern for number of surgeries was found although having had three or more major/other surgeries was significantly associated with a lower cognitive score corresponding to one fifth of an SD.

Our results are reassuring in relation to long-term adverse cognitive effects of exposure to major surgery and anesthesia in adulthood for two reasons: First, effect sizes of one tenth to one fifth of an SD are very subtle and may be clinically irrelevant; second, our large sample size ensures estimates with high confidence. Cognitive impairment is a feared aspect of aging,³⁹ and thus, our finding of a subtle yet persistent cognitive impairment after surgery and anesthesia may be a concern. However, the results from the intrapair analysis and across surgical procedures suggest that factors other than surgery and anesthesia are important. In the intrapair analysis, the association between major surgery/anesthesia and cognitive score disappeared, and along with evidence of high correlation in cognitive scores among twins,⁴⁰ this suggest that long-term postoperative cognitive functioning is primarily determined by the preoperative cognitive functioning. The severity of the underlying diseases across surgery groups is diverse with the more severe diseases in twins belonging to the major surgery group (*e.g.*, cardiac and vascular surgeries and laparotomies) than to the minor (*e.g.*, eye and laparoscopic surgeries) and knee and hip replacement surgery groups. Thus, the observations of a lower cognitive score in the major surgery group, no difference in the minor and other surgery groups, and even a higher score in the hip and knee replacement group in comparison with the reference group indicate that the underlying disease is a major determining factor.

There was a tendency to better cognitive scores in the hip and knee replacement group compared with all other groups including the reference group. This is most likely due to the fact that the best functioning individuals are offered hip and knee replacements. Furthermore, it could also be explained by reduction in pain and increased mobility after successful joint replacements and subsequent improvement in level of functioning.

Comparisons with other studies are hampered by differences in methodology, including differences in design, endpoints, and length of follow-up. The current study reports mean differences in composite cognitive score, whereas most other studies report dichotomous outcomes, primarily incidence of POCD. Moreover, the current study has longer follow-up (up to 24 yr) than other studies.⁴¹

Despite the methodological differences, our findings across surgical procedures and in the intrapair analyses are to a large extent in line with other studies that assessed cognition more than 6 months postoperatively.^{16,37,42} Still, a recent cohort study⁴³ (*n* = 192) found an increased incidence of POCD in surgical patients older than 60 yr compared with age- and sex-matched controls at 1 yr postoperatively, and a meta-analysis of 17 studies⁴⁴ concluded that no impairment in cognitive performance could be documented at 3 to 6 months after hip and knee replacement. However, only two small studies that included control groups assessed cognitive functioning at 3 months of follow-up in this meta-analysis and that conclusion may, therefore, not be justified. Another study of 270 elderly patients undergoing elective orthopedic surgery found improvements in some verbal cognitive tasks including immediate and delayed verbal recall and either deterioration or no differences in other tasks at follow-up at approximately 1 yr.⁴⁵ Hence, our findings of a tendency to a slightly higher composite cognitive score in the hip or knee replacement group could be considered to be in agreement with these findings. However, caution in this interpretation is warranted as the effect size in our study is small and nonsignificant. In addition, even if surgery successfully treats chronic pain and restores both physical and cognitive functioning in this patient group,^{46,47} the recovery may take time and is only registered by longer follow-up.

Our finding of no effect of time interval between surgery and cognitive examination on effect sizes does not support the current evidence of a gradual resolution of POCD between 3 months and 1 to 2 yr,^{6,37} but the CIs are quite wide.

Exposure to three or more surgeries seemed to be a risk factor but may be explained by underlying disease(s) or complications after surgery. Interestingly, a cross-sectional study⁴⁸ found no association between number of general anesthetic exposures and cognitive deficits in 606 participants aged 75 yr or older. Likewise, a case–control study of 1,010 participants found no association between cumulative number of exposures of general anesthesia and AD.⁴⁹

Major strengths of the current study are the use of study samples from population-based surveys retrieved from the

Danish Twin Registry²⁸ and the completeness of the Danish NPR,^{31,32} which minimized the risk for selection bias. The Danish National Health Care System with no out-of-pocket expenses further minimizes the bias from different access to health care depending on the educational and socioeconomic factors that are known to be strongly associated with cognitive performance. However, the study is performed in a relatively homogeneous Northern European population and thus the results should be replicated in other settings.

The large sample size of more than 8,500 twins is another strength as this enabled us to detect even very subtle cognitive score differences with high accuracy. In the literature, there is a compelling body of evidence that twins are similar to the general population with regard to health and survival^{50–54} and in recent cohorts also with regard to cognitive functioning.⁵⁵ An observed, slightly lower cognitive functioning in older cohorts⁵⁶ should not affect the associations in this study as the comparisons are conducted within a twin population. In addition, we have no reason to believe that the effect of surgery and anesthesia differs between twins and singletons and so our findings are likely generalizable to the nontwin population.

The use of the co-twin design has a number of strengths. First, it is statistically powerful, reflected in the narrow CI on the effect measure (proportion of pairs in which the major surgery-exposed twin had the lowest score: 49%; 95% CI, 42 to 56%) despite that only 211 pairs were included. Furthermore, the design controls for childhood socioeconomic status and genetic endowment, both known to be strongly associated with cognitive functioning in mid- and late life.^{34,57} Finally, due to the high correlation in cognitive performance within twin pairs, especially within monozygotic twin pairs, the co-twin is the best matched control.

Even though we argued that the risk of selection bias is small in this study, selection bias due to mortality and nonattendance should be considered when interpreting the results. The nonattendance of 518 twins (6%) in the cognitive examination may be explained by severe cognitive or physical impairments.³⁶ An explorative data analysis (not shown) revealed that nonattendees had 1.3 times higher odds of having had any surgery than attendees. Hence, it cannot be ruled out that a small fraction of surgery-exposed twins may be particularly susceptible to surgery and anesthesia or disadvantaged in other ways.

The cross-sectional design of this study did not allow us to consider selective mortality, that is, those with cognitive decline may have less chance of surviving to the study intake. Results were similar when restricting the analyses to surgeries performed less than 3 months before intake and hence minimizing the risk of survival bias. We did not assess cognition preceding surgery/anesthesia. However, in the intrainpair analysis, preoperative cognition was taken into account to some degree as the intrainpair similarity of intelligence is high.⁴⁰

Unmeasured comorbidity is likely to represent an important factor for cognitive performance. If the operated

participants have less comorbidity than the nonoperated (which may be anticipated among the oldest in the cohort because surgery is often not performed among those who are very frail), the surgery–cognition association will be underestimated. However, if the operated participants have more comorbidity (which may be anticipated among middle-aged and younger elderly), the association will be overestimated. We see no such age dependence in our study (table 2). A limitation of the exposure measure is that information about outpatient procedures performed before 1995 is not available. This could mean inclusion of exposed cohort members in the unexposed group and tend to bias the results toward null. However, major surgery very rarely took place in an outpatient setting before 1995.

Finally, alternative explanations related to the cognitive measure used in this study should be considered in the interpretation of our findings. Low sensitivity may be associated with an inability to detect cognitive deficits that may have been picked up by other cognitive test batteries. It is noteworthy that the composite cognitive score used is shown to be very age sensitive with a difference of 2.5 SD from age 45 to 90 yr.³³ Although the composite cognitive score does not capture exactly the same cognitive domains as the psychometric test batteries used to detect POCD, it reflects elements that are pivotal for daily living, including working memory.

In conclusion, exposure to major surgery and anesthesia was associated with a negligible reduction in cognitive functioning among middle-aged and elderly twins. This finding substantiates the current evidence of no long-term major adverse cognitive effect of surgery and anesthesia as the very large sample size along with the sensitive cognitive measure allow us to detect very subtle effect sizes.

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Competing Interests

The authors declare no competing interests.

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Appendix: Surgery Codes According to the Danish National Board of Health's Classification of Surgeries and Treatments and the Nordic Classification of Surgical Procedures That Are Included in the Specified Surgery Groups: Major Surgery, Minor Surgery, Knee and Hip Replacement Surgery, and Other Surgeries

Major surgeries

Cardiac surgeries, included codes

Danish National Board of Health's Classification of Surgeries and Treatments: 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30119, 30120, 30149, 30200, 30240, 30241, 30350, 30354, 30700, 30780, 31020, 31119, 31130, 31268, 31269, 31699, 32400, 32920, 32940, 32960

Nordic Classification of Surgical Procedures: KFKD00, KFMD00, KFMD10, KFNA00, KFNA20, KFNC10, KFNC30, KFNC40, KFNC50, KFNE96, KFNG96, KFXB96

Thoracic surgeries, included codes

Danish National Board of Health's Classification of Surgeries and Treatments: 34100, 34140, 34260, 34420, 34960, 35080, 35160, 35180, 35300, 35340, 35380, 35740, 40540, 40549

Nordic Classification of Surgical Procedures: KGAB10, KGAB13, KGAC50, KGDB11, KGDC00, KJCC10

Central and peripheral vascular surgeries, included codes

Danish National Board of Health's Classification of Surgeries and Treatments: 86080, 86300, 86550, 86552, 86560, 86570, 86585, 86670, 86700, 86740, 86760, 86772, 86875, 86911, 86912, 86920, 86950, 86951, 86952, 86963, 86970, 86971, 86972, 87000, 87015, 87020, 87050, 87052, 87055, 87064, 87070, 87072, 87073, 87074, 87075, 87076, 87163

Nordic Classification of Surgical Procedures: KPAF21, KPBH10, KPFD30, KPDG10, KPDG24, KPDH24, KPEG10, KPEH10, KPEH20, KPEH30, KPFH22, KPFH26, KPFH27

Laparotomies, included codes

Danish National Board of Health's Classification of Surgeries and Treatments: 40190, 40220, 40350, 40400, 40450, 40480, 40510, 40560, 40569, 40600, 40680, 40960, 41120, 41300, 41500, 41720, 41740, 41760, 41800, 41880, 41890, 41980, 42000, 42100, 42140, 42180, 42240, 42260, 42280, 42330, 42340, 42380, 42620, 42680, 42720, 42740, 42749, 43120, 43140, 43380, 43420, 43440, 43460, 43540, 43660, 43680, 43700, 43740, 43780, 43787, 43800, 43820, 43840, 43860, 43880, 43900, 44020, 44060, 44120, 44150, 44160, 44200, 44400, 44480, 44600, 44790, 44840, 44860, 44900, 44920, 44940, 44960, 44980, 45020, 45060, 45080, 45100, 45120, 45160, 45180, 45200, 45240, 45320, 45340, 45480, 45560, 45680, 45780, 45800, 45840, 45860, 45880, 46020, 46060, 47020, 47089, 47280, 47340, 47360, 47365, 47580, 47640, 47740, 47960, 48140, 48420, 48550, 48700, 48880, 48900, 48960, 48980, 49000, 50400, 50440, 50480, 50660, 50700, 50740, 50800, 51340, 51360, 51440, 51680, 51760, 52440, 52660, 52680, 52760, 54060, 55150, 57480, 58040, 58060, 58100, 58700, 60020, 60040, 60060, 60100, 60120, 60140, 60180, 60200, 60240, 60280, 60300, 60320, 60340, 60360, 60380, 60400, 60420, 60460, 60480, 60500, 60520, 60560, 60580, 60700, 60940, 60960, 61000, 61020, 61100, 61380, 61400, 61440, 61520, 61540, 61549, 62400

Nordic Classification of Surgical Procedures: KJAH00, KJAL30, KJDA00, KJDB00, KJDE00, KJEA10, KJFB00, KJFB60, KJFC00, KJFC30, KJFF10, KJFF13, KJFF23, KJFF27, KJFG00, KJFG10, KJFH10, KJFK10, KJFL10, KJGB00, KJGB10, KJGB20, KJGB30, KJJB00, KJKA20, KJKA21, KJWD00, KJWW96, KKAC00, KKAC20, KKBA10, KKBj10, KKBj60, KKCA00, KKCC10, KKCD10, KKKB10, KLAE10, KLAF00, KLBE00, KLCC10, KLCD00, KLCD11

Major fracture surgeries, included codes

Danish National Board of Health's Classification of Surgeries and Treatments: 73700, 75109, 75119, 75201, 75203, 75204, 75205, 75209, 75210, 75211, 75212, 75213, 75230, 75231, 75232, 75234, 75241, 75242, 75243, 75244, 75245, 75249, 75250, 75252, 75253, 75255, 75259, 75279, 75319, 75329, 75339, 75349, 75379, 75389, 75636, 75637, 75638, 75660, 76640, 82271, 82275, 82375, 82377

ICD-10: KNAG30, KNAG42, KNBJ51, KNBJ71, KNBJ81, KNFJ61, KNFJ80, KNFJ82, KNFJ83, KNFJ84, KNFJ85, KNGJ22, KNGJ40, KNGJ53, KNHJ40, KNHJ60, KNHJ62, KNHJ63, KNHJ70, KNHJ71, KNHJ72, KNHJ77

Minor surgeries

Included all day-only procedures, surgeries followed by less than 2 days of hospitalization,* and irrespective of the first two criteria surgery codes that are compatible with eye surgery, endoscopic and biopsy procedures, skin surgery, and other small surgeries.

Danish National Board of Health's Classification of Surgeries and Treatments

Eye surgeries, included codes 10000–1990

Endoscopic and biopsy procedures, included codes 90900–93190

Skin surgeries, included codes 89520–90860

Nordic Classification of Surgical Procedures:

Eye surgeries, included codes CA, CB, CD, CE, CF, CG, CH, CJ, CK, CW

Endoscopic and biopsy procedures, included codes UD, UE, UG, UJ, UK, UL

Skin surgeries, included codes QA, QB, QC, QD, QW, QX

Other small surgery procedures, included codes TA, TB, TC, TD, TE, TF, TG, TH, TJ, TK, TL, TM, TN, TP, TQ

Knee and hip replacement surgeries, included codes

Danish National Board of Health's Classification of Surgeries and Treatments: 70030, 70031, 70032, 70033, 70034, 70039, 70041, 70042, 70043, 70044, 70131, 70132, 70133, 70134, 70142, 70143, 70144, 70232, 70332, 70340, 70342, 70343, 70431, 70439, 70540, 70939, 70949, 71239,

Nordic Classification of Surgical Procedures: KNFB30, KNFB40, KNFC01, KNFC12, KNFC20, KNFC21, KNFC40, KNGB13, KNGB20, KNGB30, KNGB40, KNGC13, KNGC21, KNGC43

Other surgeries

Danish National Board of Health's Classification of Surgeries and Treatments and Nordic Classification of Surgical Procedures: Surgery codes that are not included in major, minor, or knee and hip replacement surgeries

* Due to unavailability of the exact date of surgery in the National Patient Register before 1996, the date was considered to be the date of hospital admission plus 1 day. From 1996 onward, the date of surgery was available in the Danish National Patient Register and therefore accordingly used.