

Long-term Consequences of Postoperative Cognitive Dysfunction

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Background: Postoperative cognitive dysfunction (POCD) is common in elderly patients after noncardiac surgery, but the consequences are unknown. The authors' aim was to determine the effects of POCD on long-term prognosis.

Methods: This was an observational study of Danish patients enrolled in two multicenter studies of POCD between November 1994 and October 2000. The cohort was followed up from the date of surgery until August 2007. Cognitive function was assessed by a neuropsychological test battery at three time points: before, at 1 week after, and at 3 months after noncardiac surgery. Data on survival, labor market attachment, and social transfer payments were obtained from administrative databases. The Cox proportional hazards regression model was used to compute relative risk estimates for mortality and disability, and the relative prevalence of time on social transfer payments was assessed by Poisson regression.

Results: A total of 701 patients were followed up for a median of 8.5 yr (interquartile range, 5.3–11.4 yr). POCD at 3 months, but not at 1 week, was associated with increased mortality (hazard ratio, 1.63 [95% confidence interval, 1.11–2.38]; $P = 0.01$, adjusted for sex, age, and cancer). The risk of leaving the labor market prematurely because of disability or voluntary early retirement was higher among patients with 1-week POCD (hazard ratio, 2.26 [1.24–4.12]; $P = 0.01$). Patients with POCD at 1 week received social transfer payments for a longer proportion of observation time (prevalence ratio, 1.45 [1.03–2.04]; $P = 0.03$).

Conclusions: Cognitive dysfunction after noncardiac surgery was associated with increased mortality, risk of leaving the labor market prematurely, and dependency on social transfer payments.

POSTOPERATIVE cognitive dysfunction (POCD) is a common and well-known complication after surgery. Although primarily described after cardiac surgery, it is also known as a consequence of noncardiac surgery. The elderly population, in particular, is at risk of cognitive deterioration after surgery. Impairment of neurocogni-

tive function after cardiac surgery can be persistent and diminish quality of life.^{1–3} A recent study has suggested an association between 1-yr mortality and POCD after noncardiac surgery, but the relation of cognitive dysfunction to mortality longer than 1 yr after surgery is unknown.⁴ Nonetheless, from the patient's perspective, cognitive decline is a major concern, and anecdotal reports suggest that the symptoms of cognitive decline may persist long after the operation.^{5,6} At least 1 yr after noncardiac surgery, some patients still exhibit impaired cognitive function.⁷ However, some clinicians have challenged the importance of POCD because the cognitive decline seems to be elusive and the long-term effects are uncertain.⁸

The first and second International Study of Post-Operative Cognitive Dysfunction (ISPOCD1 and 2) undertook the two largest studies of POCD after noncardiac surgery to date.^{9–13} Both were international multicenter studies with more than 2,500 patients enrolled from 25 centers in 12 countries. One-third of the patients were enrolled in Denmark. Our aim was to estimate the effects of POCD on mortality, withdrawal from the labor market, need for social transfer payments, and nursing home placement in the Danish patients.

Materials and Methods

Ethics

The research ethics committees for all of the centers (now merged into one: De Videnskabsetiske Komitéer for Region Hovedstaden, Hillerød, Denmark) approved the study, and patients were enrolled after giving written informed consent. The processing of personal follow-up data were approved by the Danish Data Protection Agency (Datatilsynet, Copenhagen, Denmark; journal number 2007-41-0460).

ISPOCD Studies

The ISPOCD1 and 2 studies included men and women aged 40 yr or older presenting for major or minor noncardiac surgery during regional or general anesthesia.^{9–13} A total of 2,536 patients were enrolled in Europe and in the United States of America. In Denmark, patients were recruited from four centers between November 1994 and May 1996 in the ISPOCD1 study and between October 1998 and October 2000 in the ISPOCD2 study.

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Neuropsychological Testing and Criteria for POCD

Patients completed the following neuropsychological tests at entry into the study (usually the day before surgery), 1 week after surgery (or at discharge from the hospital if discharged within 1 week), and 3 months after surgery: the Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Color Word Interference Test, and the Letter Digit Coding Test.^{9,14-18} In the Visual Verbal Learning Test, 15 words are individually presented over a series of three consecutive presentations. Each word is presented visually for 2 s. The participant is asked to recall as many words as possible after each trial as well as after 20 min (delayed recall). The Visual Verbal Learning Test is used to assess learning and memory abilities. The Concept Shifting Test is a trail-making test where the participant is required to alternate between letters and digits to assess processing speed. In the Stroop Color Word Interference Test, words spelling out a color are printed in contrasting ink colors (e.g., green printed with red ink) and the participant is asked to tell the printed color of the word rather than the actual meaning of the word. This test estimates the patient's ability to concentrate and ignore distracting stimuli. In the Letter Digit Coding Test, the participant is asked to match letters with digits. Mental processing speed and concentration are assessed with this test.

Seven variables were used in the calculation of the endpoint of POCD: cumulative number of words recalled (1) in three trials and (2) at delayed recall from the Visual Verbal Learning Test; (3) time and (4) number of errors in Part C from the Concept Shifting Test; (5) time and (6) error scores from the Stroop Color Word Interference Test, Part 3; and (7) number of correct answers from the Letter Digit Coding Test. To correct for learning effects, normative data were obtained from 352 healthy age-matched controls (not undergoing surgery or hospitalization) who performed the same tests at the same time interval as the patients. Learning effect was defined as the mean changes in controls from baseline in each test. We calculated the change in each individual patient's test scores from baseline (preoperatively) to the tests at 1 week and at 3 months after the operation and subtracted the learning effect. The resulting differences were divided by the SD of the corresponding changes in the controls to obtain a Z score for each test. Patients were defined as having cognitive dysfunction when at least two Z scores in individual tests or the composite Z score (of all seven variables) was greater than 1.96, as previously described.⁹

Data Sources

All Danish residents are assigned a 10-digit unique identifier (Danish Civil Registration System number) at birth or immigration. The Danish Civil Registration System** con-

tains information on birth date, sex, address, immigration, emigration, and date of death.¹⁹ The DREAM database (a Danish acronym for the Register-based Evaluation of Marginalization) is a national register of social transfer payments. It has tracked weekly information from 1991 onward on all citizens in Denmark ever receiving financial support—e.g., disability pension or unemployment compensation—and thus covers our study period from 1994 until end of follow-up in 2007.^{20,21} ISPOCD data were linked to the Danish Civil Registration System and the DREAM database through the Danish Civil Registration System number. Early withdrawal from the labor market was defined as either receiving early retirement pension (intentional) or receiving disability pension (unintentional). Disability pension (also called involuntary retirement compensation) is granted by the municipal authorities based on an assessment of health and work ability: The individual's work ability has to be permanently reduced to a degree where it is impossible to return to work. By law, it is possible for the recipient to work part time while receiving disability pension, and also to return to work over time. It is possible to actively reject a retirement pension. However, these options are rarely used, and consequently such persons would not be included in our analysis. We defined persons as receiving social transfer payments if they were registered in the DREAM database as a recipient of a financial compensation for not being completely integrated into the labor market. Financial compensation included payment related to sickness absence, disability pension, unemployment, and rehabilitation. We used current address registered in the Danish Civil Registration System to determine whether the person was a nursing home resident as previously described.²²

Statistical Analysis

We calculated time from surgery until the outcome of interest (death, withdrawal from the labor market, or nursing home placement). In the analysis of mortality, we censored individuals at time of emigration or August 1, 2007, whichever came first. In the analysis of withdrawal from the labor market or nursing home placement, individuals were censored at the time of death, emigration, or August 1, 2007. In Denmark, the conventional age of retirement was 67 yr, but in 2004 the official age of retirement changed from 67 to 65 yr. Only persons aged 60–65 yr can benefit from the voluntary retirement system; therefore, only individuals not already retired and aged 65 yr or less at the time of the operation were included in the analysis of withdrawal from the labor market. It is possible to work beyond age 67 yr, but we chose to focus on the premature withdrawal to identify the vulnerable patients. In the analysis of social transfer payments, we calculated the total proportion of weeks the patients received social transfer payments from the time of operation until death, emi-

** Available at: www.cpr.dk. Accessed September 29, 2008.

gration, or age 70 yr. The cutoff point of 70 yr was chosen because it is possible to continue to work until age 70 yr, regardless of pension possibilities, and thus be eligible for various social transfer payments. After age 70 yr, most persons in Denmark receive retirement pension.

Cox proportional hazard models were used to compute hazard ratios and 95% confidence intervals quantifying the impact of POCD on mortality, labor market withdrawal, and nursing home placement, respectively. The analysis of mortality was controlled for sex, age, level of education (stratified by below, at, or above high school), and the presence of cancer at baseline. Analysis of mortality in patients with or without POCD at 1 week was assessed with time baseline defined at surgery, whereas the survival analysis of patients with or without POCD at 3 months were assessed with time baseline defined at 3 months after surgery. Analysis of labor market withdrawal was controlled for sex and age.

We estimated prevalence ratios of social transfer payments with 95% confidence intervals using Poisson regression analysis. The analysis was controlled for sex and age. A scale parameter was added to the Poisson regression model to account for overdispersion, and the logarithm of the time at risk was entered into the model as an

offset. We considered *P* values less than 0.05 to be statistically significant, and *P* values for all analysis were two-sided. Data analysis and statistical evaluation were performed using a commercial statistical package (SAS Institute Inc., Cary, NC).

Results

Out of the 720 Danish patients enrolled in the IS-POCD1 and 2 studies, we identified 701 patients (97.3%). Patients with POCD at 1 week, as well as at 3 months, were significantly older ($P = 0.01$ and $P = 0.0009$, respectively) than patients without cognitive impairment (table 1), and not all patients performed the neuropsychological tests at both sessions 1 week and 3 months after surgery (fig. 1). The date of surgery was known in 683 patients (94.9%) having a median age of 67 yr (interquartile range, 61–74 yr), and data were collected with a median follow-up time of 8.5 yr (interquartile range, 5.3–11.4 yr). **POCD was identified in 119 patients (19.5% of 683) after 1 week and 57 (9.6%) after 3 months.**

We found no association between POCD 1 week after surgery and mortality. In contrast, patients with POCD at 3 months had a significantly increased mortality (ad-

Table 1. Preoperative Characteristics and Neuropsychological Test Results

	Patients Assessed at 1 Week, n = 625		Patients Assessed at 3 Months, n = 603	
	No POCD n = 501	POCD n = 124	No POCD n = 543	POCD n = 60
Age	65.7 (10.3)	68.0 (8.1)	65.7 (10.0)	70.2 (8.3)
Male sex	207 (41.3%)	60 (48.4%)	230 (42.4%)	26 (43.3%)
Diagnosed cancer	146 (29.3%) n = 498	37 (29.8%)	160 (30.3%) n = 528	11 (18.6%) n = 59
Level of education				
Below high school	364 (72.6%)	100 (81.3%)	401 (73.9%)	43 (71.7%)
High school	52 (10.4%)	12 (9.8%)	56 (10.3%)	6 (10.0%)
Above high school	85 (17.0%)	11 (8.9%) n = 123	86 (15.8%)	11 (18.3%)
Type of operation				
Upper abdominal	176 (35.1%)	60 (48.4%)	205 (37.8%)	22 (36.7%)
Lower abdominal	94 (18.8%)	21 (16.9%)	102 (18.8%)	11 (18.3%)
Orthopedic	105 (21.0%)	20 (16.1%)	105 (19.3%)	15 (25.0%)
Other	126 (25.1%)	23 (18.6%)	131 (24.1%)	12 (20.0%)
Concept Shifting Test Part C				
Time, s	46.8 (21.5)	48.5 (19.7)	46.9 (20.8)	47.0 (19.7)
Number of errors	0.8 (1.5) n = 491	0.9 (1.8) n = 122	0.8 (1.6) n = 533	0.7 (1.5)
Letter Digit Coding score	26.8 (8.0) n = 496	25.0 (7.6) n = 123	26.8 (7.9) n = 537	24.2 (8.2)
Stroop Color Word Test Part 3				
Time, s	54.0 (17.7)	57.6 (19.1)	54.4 (17.6)	54.9 (17.6)
Number of errors	1.3 (2.7) n = 481	1.6 (3.2) n = 123	1.3 (2.6) n = 527	1.5 (2.7) n = 58
Visual Verbal Learning, number of words				
Cumulative recall	25.5 (6.0)	25.8 (5.7)	25.7 (6.0)	25.4 (6.4)
Delayed recall	8.5 (3.0) n = 492	8.5 (3.0) n = 122	8.5 (3.0) n = 533	8.8 (2.9)

Danish patients undergoing surgery (n = 720) tested at 1 week and at 3 months after noncardiac surgery for having postoperative cognitive dysfunction (POCD) or not. Data are mean (SD) or number (%).

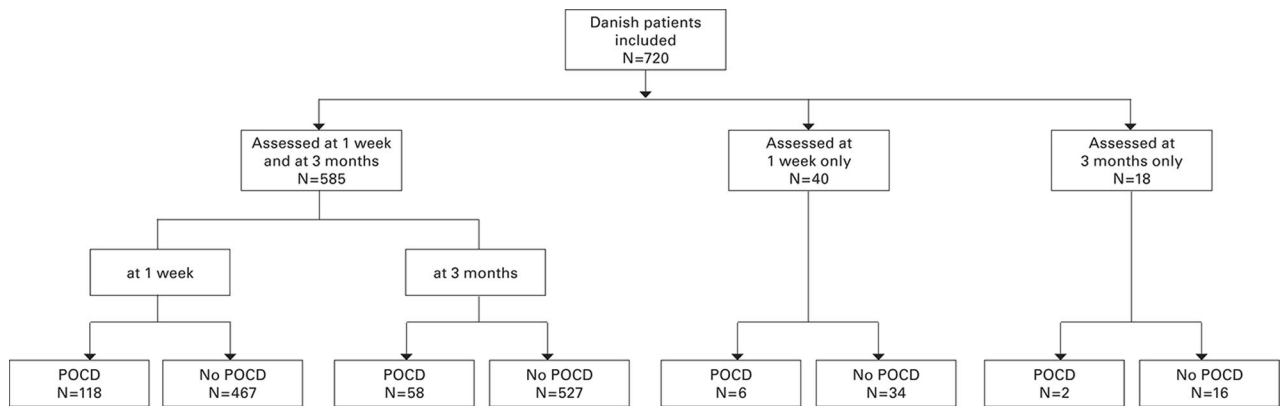


Fig. 1. Assessment of postoperative cognitive dysfunction (POCD) at 1 week and/or 3 months after surgery among Danish patients.

justed hazard ratio, 1.63 [95% confidence interval, 1.11–2.38]; $P = 0.01$) (table 2 and fig. 2) (unadjusted hazard ratio, 1.64 [1.13–2.38]; $P = 0.009$). If in addition adjusted for educational level, the hazard ratio was 1.64 (95% confidence interval, 1.12–2.41; $P = 0.01$). The risk of mortality in patients with POCD at both 1 week and 3 months ($n = 19$) compared with patients without POCD at any test ($n = 428$) was 1.89 (1.05–3.40; $P = 0.03$) if unadjusted and 1.60 (0.88–2.90; $P = 0.12$) if adjusted for sex, age, and cancer.

The risk of leaving the labor market prematurely because of disability or voluntary early retirement was higher among patients with POCD at 1 week (hazard ratio, 2.26 [1.24–4.12]; $P = 0.01$) (table 2 and fig. 3) (unadjusted, 3.18 [1.77–5.71]; $P = 0.0001$). Stratified by intentional (voluntary early retirement) or unintentional (disability) premature leave, the unadjusted hazard ratios were 2.66 (1.35–5.22; $P = 0.005$) and 2.39 (0.76–7.54; $P = 0.14$), respectively, and the hazard ratios adjusted for sex and age were 1.80 (0.91–3.57; $P = 0.09$) and 3.07 (0.93–10.2; $P = 0.07$), respectively.

Patients with POCD at 1 week received social transfer payments for a higher proportion of time (60.0% vs. 41.2%; prevalence ratio, 1.45 [1.03–2.04]; $P = 0.03$) (table 3). The risk of admission to a nursing home was not significantly associated with POCD (table 2).

Discussion

Under the conditions of this prospective multicenter cohort study, we found that the presence of cognitive dysfunction 3 months after noncardiac surgery was associated with an increased mortality. Furthermore, we found that patients with cognitive decline at 1 week had an increased risk of leaving the labor market prematurely and a higher prevalence of time receiving social transfer payments.

No other studies have assessed the effect of cognitive dysfunction on long-term prognosis beyond 1 yr after noncardiac surgery. We studied only a subset of Danish patients, but we believe that the clinical implications of our results are broad because the ISPOCD studies cov-

Table 2. Consequences of Postoperative Cognitive Dysfunction

	n	Time at Risk, Patient Years	Number of Events	Hazard Ratio (95% CI)	P Value
All-cause mortality*					
POCD at 1 week	119	1,029	54	0.91 (0.68–1.23)	0.55
No POCD at 1 week	492	3,867	206	1.00	
POCD at 3 months	57	412	32	1.63 (1.11–2.38)	0.01
No POCD at 3 months	539	4,449	217	1.00	
Labor market withdrawal†					
POCD at 1 week	29	100	16	2.26 (1.24–4.12)	0.01
No POCD at 1 week	169	791	40	1.00	
POCD at 3 months	11	41	4	1.17 (0.42–3.28)	0.76
No POCD at 3 months	183	849	51	1.00	
Nursing home placement					
POCD at 1 week	119	1,008	5	0.61 (0.24–1.58)	0.31
No POCD at 1 week	492	3,815	29	1.00	
POCD at 3 months	57	404	4	1.45 (0.51–4.10)	0.49
No POCD at 3 months	539	4,377	31	1.00	

Postoperative cognitive dysfunction (POCD) assessed at 1 week and at 3 months after noncardiac surgery ($n = 683$). Time at risk is the cumulative number of years the patients are followed up in each category.

Hazard ratios are adjusted for * sex, age, and cancer or for † sex and age.

CI = confidence interval.

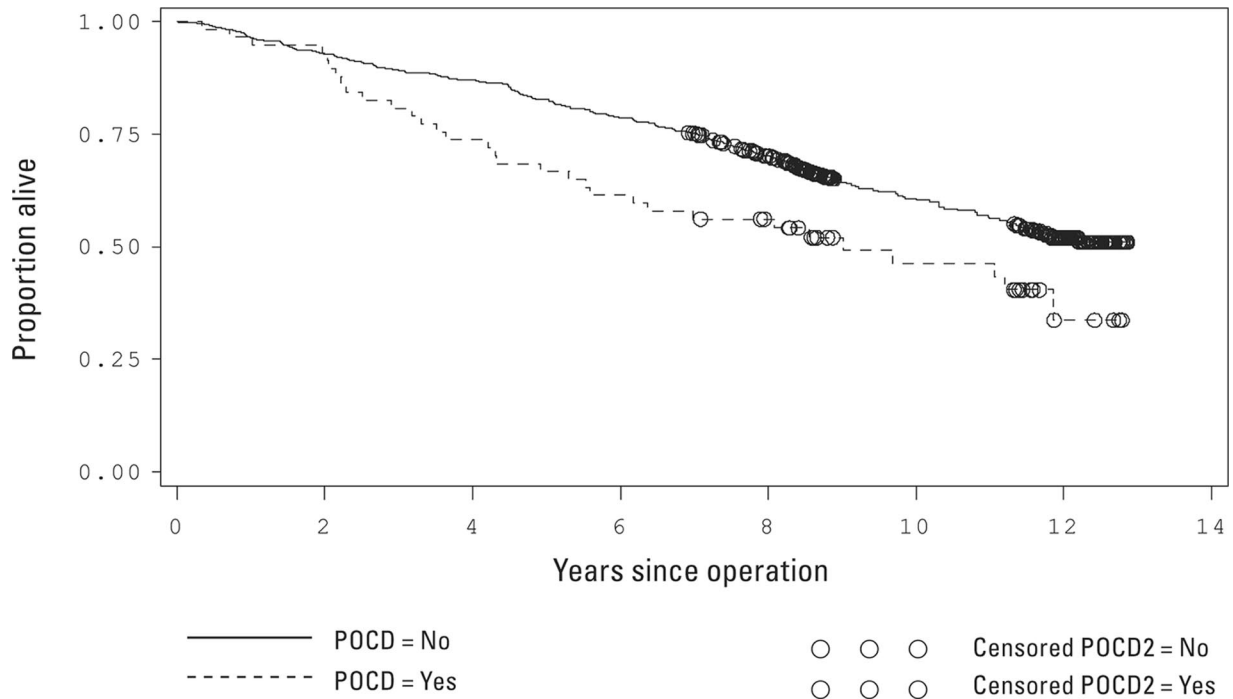


Fig. 2. Survival of patients (n = 596) according to the presence of postoperative cognitive dysfunction (POCD) or not as assessed 3 months after noncardiac surgery. Circles are censored observations.

ered multiple types of surgery, patients, and anesthesia techniques. Focusing on one country probably facilitates the determination of possible social consequences, and it certainly provides a high quality of data related to death registration, status on the labor market, and registration of social transfer payments; in addition, a minimal

number of participants were lost to follow-up. However, some limitations related to this study need to be addressed. First, our data are inconsistent because a higher mortality in patients with POCD was detected only at 3 months even though patients with POCD at 1 week seem to be more at risk of labor market withdrawal and

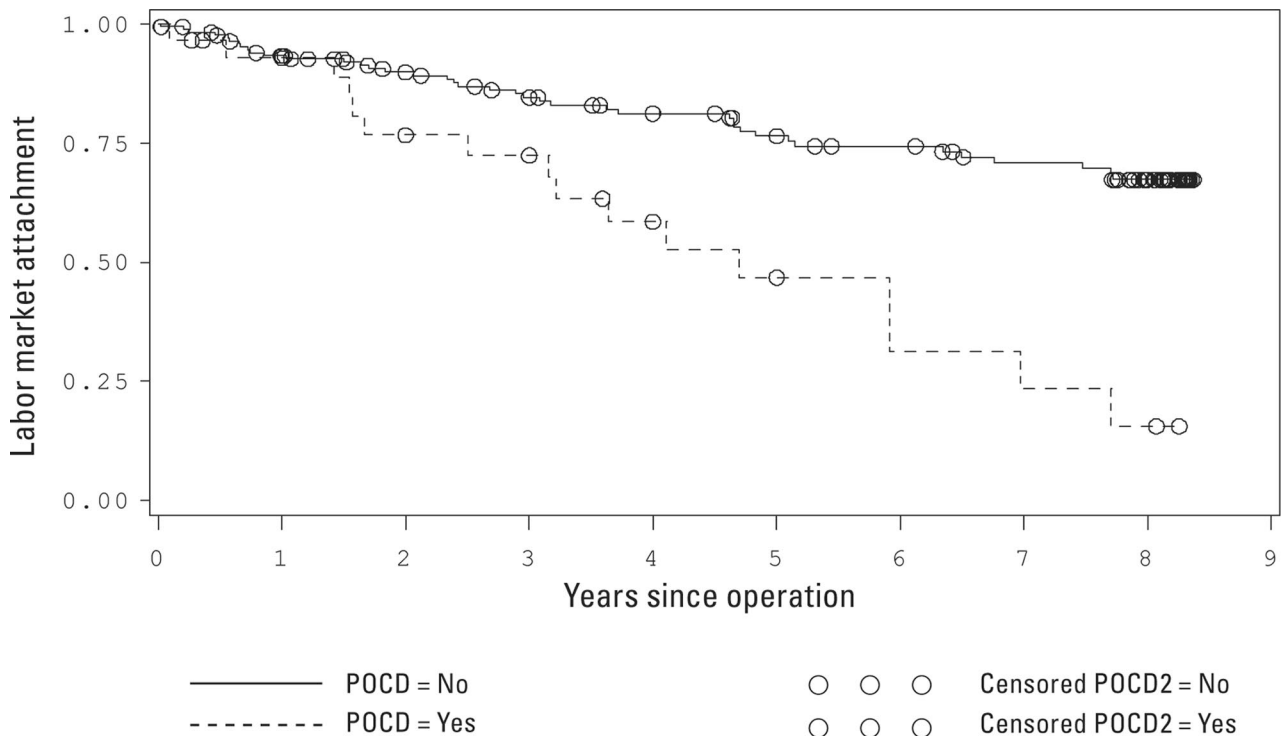


Fig. 3. Labor market attachment of patients (n = 198) according to the presence of postoperative cognitive dysfunction (POCD) or not as assessed 1 week after noncardiac surgery. Circles are censored observations.

Table 3. Number of Weeks on Social Transfer Payments According to Postoperative Cognitive Dysfunction or Not

	Total Weeks Followed Up	Total Compensated Weeks	Crude Rate, %	Prevalence Ratio (95% CI)	P Value
POCD at 1 week, n = 42	9,413	5,653	60.0	1.45 (1.03–2.04)	0.03
No POCD at 1 week, n = 219	54,659	22,509	41.2	1.00	
POCD at 3 months, n = 15	3,186	1,381	43.3	0.97 (0.51–1.84)	0.93
No POCD at 3 months, n = 243	61,070	26,987	44.2	1.00	

Postoperative cognitive dysfunction (POCD) assessed at 1 week and at 3 months after noncardiac surgery. Prevalence ratios with 95% confidence intervals (CIs) adjusted for sex and age.

receipt of social transfer payments. However, only 15 patients younger than 70 yr with POCD at 3 months were included in the social transfer payments analysis, making the estimates imprecise. The same applies to the labor market group aged younger than 65 yr, in which we identified only four patients who withdrew from the labor market among those with POCD at 3 months. Both confidence intervals surrounding the two point estimates of 0.97 and 1.17 are wide, and conclusions based on those intervals seem meaningless.

Second, not all patients were assessed for POCD at 1 week and at 3 months. Patients who experienced deterioration in their cognitive ability may have been more prone to decline participation in the subsequent neurocognitive testing, because POCD at 1 week was more common in patients who missed the assessment at 3 months.²³

We believe that the association of cognitive dysfunction 3 months after surgery with increased all-cause mortality could be mediated through inability to seek and follow up on medical treatment and care, thereby reducing the preservation of physical health. We do not know why the mortality was persistently higher after 2 yr in patients who did not recover after 3 months, as shown by the separation of the two mortality curves in figure 2. Therefore, the cause of death might not be explained solely by the surgery itself. As previously mentioned, our data are inconsistent in some places with the nonsignificant risk estimates pointing away from an increased risk of mortality and nursing home placement for patients with POCD at 1 week. We do not have an explanation for this inconsistency, but patients with POCD at 3 months may have been more severely cognitively injured during surgery, initiating a different life trajectory. Neurocognitive impairment in general is a well-known predictor of mortality in older adults.^{24–26} The association between 1-yr mortality and POCD has been demonstrated in a recent study.⁴ Although the primary focus was to identify predictors of POCD, the authors found an increased 1-yr mortality in the patients who had POCD at both hospital discharge as well as at 3 months. The authors' findings of increased 1-yr mortality could very well be confounded by comorbidity and age, because patients with POCD were older and had a higher comorbidity score.⁴ However, no difference in 1-yr mortality was found if the patients had cognitive

impairment only at hospital discharge or at 3 months, and the analysis was unadjusted. This is in accord with our study, because patients with POCD at both time points had a higher mortality when the analysis was unadjusted. However, if adjusted for sex, age, and cancer the association was not present. Only 19 patients had POCD at both postoperative tests. Furthermore, we found the adjusted mortality in patients with POCD only at 3 months to be significantly higher after 2 yr (fig. 2). Patients with cognitive dysfunction after surgery report memory deficits and a decreased ability to concentrate.⁶ Memory and concentration are necessary to function in most jobs, and neurocognitive deficits can therefore have devastating consequences for a patient's ability to stay on the labor market and remain independent of social transfer payments, e.g., financial compensation given for absence because of sickness. Our results support this assumption. We did not distinguish between intentional and unintentional labor market withdrawal, because the reasons for retirement are not always obvious—even for the persons themselves. A person may experience the workload and challenges as increasing, and even though the job can be managed it may seem a substantial burden. In Denmark, the process of applying for disability pension (involuntary) is time-consuming, and the difference in economic compensation as compared with early retirement pension (voluntary) is negligible. As a consequence, the person frequently withdraws voluntarily from the labor market, even though involuntary entitled. The risk estimates stratified for intentional or unintentional premature leave all pointed in the same direction as the combined measure, but lacked the power to be statistically significant. The two curves in figure 3 separate after 2 yr, which we believe is explained by the patient's ability to compensate for the cognitive impairment the first period after the operation.

The degree of cognitive impairment in patients with dementia has been shown to be a predictor for nursing home placement.²⁷ In general, the patients in our study had a better cognitive ability at baseline; they did not have an established cognitive impairment before the operation. In Denmark, several programs are instituted to assist the elderly to keep them at home, whereas nursing home placement only affects the most severely injured or demented people. Because POCD is a more subtle condition, the patients in our study were in better

cognitive shape than demented, and could probably remain in their homes with domestic support—a condition we were unable to detect in our study.

Higher educational level has traditionally been associated with better life expectancy due to a healthier lifestyle,²⁸ but the risk of mortality in patients with POCD at 3 months remained the same when we adjusted for level of education. Cognitive dysfunction after surgery affects multiple domains, and some domains are more vulnerable than others, varying the impact of cognitive impairment among patients.^{29–31} Some subjective measures, such as quality of life, have repeatedly been shown to be associated with cognitive dysfunction after cardiac surgery.^{1–3} Withdrawal from the labor market and dependency of social transfer payments are objective measures, emphasizing the importance of neurocognitive impairment after surgery as a complication worth attention. Therefore, cognitive deficits detected as early as 1 week after surgery can be a harbinger of later complications and can be clinically important. With this evidence of the possible consequences of POCD, future research should focus on its etiology to reduce the manifestation of the condition.

Bedford concluded in 1955 that “Precautions in relation to operations on the elderly are suggested.”⁶ The possible long-term consequences of surgery should be kept in mind in making decisions about treatment.

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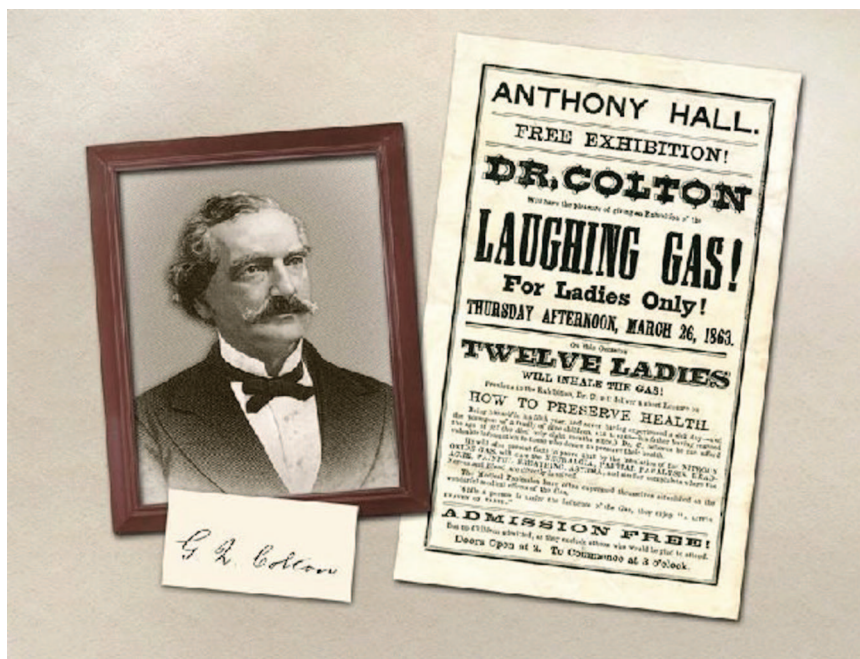
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ANESTHESIOLOGY REFLECTIONS

Colton's Laughing Gas Broadsheet



In Schenectady, New York, by mid-March of 1863, broadsides advertised a free "Exhibition of the LAUGHING GAS" scheduled for the afternoon of March 26, 1863. A traveling showman named "Doctor" Gardner Quincy Colton (1814–1898) promised to gas 12 women recreationally with nitrous oxide, the same gas that he had provided as a dental anesthetic in 1844 for Horace Wells. One of these broadsides was removed, folded in half twice, and inserted as a bookmark into an 1841 edition of Rev. Richard Baxter's *The Saints' Everlasting Rest*. As the bookmark settled between the pages, the book moved with its family some 155 miles northwest to Pulaski, New York, just east of Lake Ontario. Generations passed, and the book was purchased at an estate sale and sold by Internet auction in 2004 to the Wood Library-Museum of Anesthesiology. Note that by mid-1863, Colton had revived dentists' asphyxial use of 100% nitrous oxide, which resulted in sporadic "crazed" and "apoplectic" cases of postoperative cognitive deficit. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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