Editor’s key points

- Postoperative cognitive dysfunction (POCD) has been proposed as a risk factor for the development of dementia.
- This study followed 686 Danish patients previously enrolled in the ISPOCD 1 and 2 studies for several years after surgery.
- There was no association between POCD at 1 week or 3 months and a later diagnosis of dementia or depression.
- POCD seems to be largely reversible, but further studies of its long-term effects are needed.

Background. Postoperative cognitive dysfunction (POCD) is a common complication in elderly patients after major surgery. An association between POCD and the development of dementia has been suspected. In this study, we assessed if POCD was a risk factor for the occurrence of dementia.

Methods. Danish patients enrolled between November 1994 and October 2000 in the two International Studies of Postoperative Cognitive Dysfunction (ISPOCD 1 and 2) were followed until July 1, 2011. Cognitive performance was assessed at three time points: before operation, at 1 week, and 3 months after surgery, using a neuropsychological test battery. The time of (first) occurrence of dementia after surgery was assessed using the National Patient Register and the Psychiatric Central Research Register. Recorded dementia diagnoses (ICD-8 and ICD-10) were: Alzheimer’s disease, vascular dementia, frontotemporal dementia, or dementia without specification. The risk of dementia according to POCD was assessed in the Cox regression models.

Results. A total of 686 patients with a median age of 67 [inter-quartile range (IQR) 61–74] yr were followed for a median of 11.1 (IQR 5.2–12.6) yr. Only 32 patients developed dementia during follow-up. The hazard ratio (95% CI) for any dementia diagnoses in patients with POCD at 1 week (n=118) and POCD at 3 months (n=57) after surgery compared with those without POCD was 1.16 (0.48–2.78), P=0.74, and 1.50 (0.51–4.44); P=0.47, respectively.

Conclusions. POCD was not significantly associated with registered dementia over a median follow-up of 11 yr.

Keywords: dementia; postoperative cognitive dysfunction; postoperative complications

Accepted for publication: 2 October 2012

Postoperative cognitive dysfunction (POCD) is a common complication among the elderly after major surgery. Age is an important risk factor for both the development of POCD and the appearance of dementia, and because of the population ageing, the number of elderly patients undergoing surgery is likely to grow in the future. At the same time, dementia represents a large burden to the healthcare system. It has been shown that POCD has long-term consequences in terms of increased all-cause mortality, risk of leaving the labour market prematurely, and dependency on social subsidy. Furthermore, it has been proposed that there is an association between POCD and the development of dementia due to a common pathological mechanism through the anaesthetic effect on amyloid β peptide oligomerization and deposition. However, some clinicians have questioned whether surgery or major illness can cause cognitive decline at all, and if at all POCD exists as a clinical entity.

Hence, it remains uncertain whether POCD can be a precursor of dementia.

We aimed to assess a possible association between POCD and the occurrence of dementia. Furthermore, we wanted to explore if POCD was related to the development of depression, organic amnesic syndrome, or mild cognitive disorder.

Methods

Ethics

The ISPOCD studies were approved by the research ethics committees for all of the Danish centres, and patients were enrolled after giving written informed consent. The processing of personal follow-up data was approved by The Danish Data Protection Agency (Datatilsynet, Copenhagen, Denmark; journal number 2010-41-5167).
The cohort and databases

Patients were enrolled in both International Studies of Post-operative Cognitive Dysfunction (ISPOCD 1 and 2) in the USA and in Europe. Patients were aged 40 yr or above and presented for major or minor non-cardiac surgery in regional or general anaesthesia.6–10 We excluded patients already diagnosed in the databases with dementia at any time point before enrolment, scored ≤23 on the Mini-Mental State Examination (MMSE) test, had disease in the central nervous system, were abusing drugs, alcohol or taking antidepressants, had previously been admitted for cardiac or neurological surgery or already performed a neuropsychological test, were unable to comprehend the test language, had visual disorder, or hearing impairment. In Denmark, we recruited from four centres between November 1994 and May 1996 in the ISPOCD1 study and between October 1998 and October 2000 in the ISPOCD2 study.3 For the present study, we conducted a long-term follow-up of the Danish patients from surgery (years 1994–6 and 1998–2000) until July 1, 2011, using the unique national personal identification (CPR) number assigned by the Danish Civil registration system to all 5.6 million residents of Denmark at birth or immigration.11 The Danish Civil registration system contains data on date of birth, sex, home address, immigration, emigration, and date of death.

To investigate the outcomes of interest, we used the National Patient Register12 and the Psychiatric Central Research Register.13 These national databases contain data on a daily basis on all inpatient or outpatient hospital contacts to somatic hospital departments since 1977 and psychiatric hospital departments since 1969, respectively. ICD-8 codes were used until 1993, and since January 1994 ICD-10 codes have been used in both databases, and in 1995, data on outpatients were included in both registers. ISPOCD data were linked to the Danish Civil Registration System, the National Patient Register, and the Psychiatric Central Research Register by the CPR number. Hence, it is possible with great certainty to establish whether a Danish ISPOCD patient has been admitted to a Danish hospital (as inpatient or outpatient), irrespective of changes in the patient’s name, or address.

Neuropsychological assessment and criteria for POCD

There is no consensus definition of POCD in the medical community. As previously described, the cognitive performances were assessed at three time points:6 before surgery (usually 1 day before operation), at 1 week (or at hospital discharge if earlier), and at 3 months after surgery using a battery of neuropsychological tests. We used data from the four following tests: the Visual Verbal Learning test, the Concept Shifting test, the Stroop Colour Word Interference test, and the Letter Digit Coding test. We used seven variables in the calculation of the endpoint of POCD: (i) cumulative number of words recalled in three trials and at (ii) delayed recall from the Visual Verbal Learning test; (iii) time and (iv) number of errors in part C from the Concept Shifting test; (v) time and (vi) error scores from the Stroop Colour Word Interference test, part three; and (vii) number of correct answers from the Letter Digit Coding test. We adjusted for learning effects by the use of normative data obtained from 352 healthy age-matched controls (not undergoing hospitalization or surgery) who performed the same tests at the same time interval as the patients. We defined the learning effect as the mean change (in controls) from baseline in each test. A patient was considered to have POCD if the Z-score (at least two Z-scores in individual tests, or the composite Z-score of all seven variables) of the difference with the preoperative cognitive assessment, using the mean and standard deviation from the control group, was larger than 1.96.6

Primary outcome measure

The primary outcome was time to (first) diagnosis of dementia given at an inpatient or outpatient hospital contact; hence, only physicians (of all specialties) at a hospital could diagnose the patients. Risk estimates for any (of the several possible) dementia diagnoses in patients with POCD were compared with those without POCD at both 1 week and 3 months after surgery. Registered International Classification of Diseases (ICD) dementia diagnoses are: Alzheimer’s disease (ICD-10: F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9), vascular dementia (ICD-10: F01.0, F01.1, F01.2, F01.3, F01.8, F01.9), frontotemporal dementia (ICD-10: F02.0), and dementia without specification (ICD-10: F03.9).

The diagnosis of the different subtypes of dementia was made at the discretion of the physician treating the patient. We assessed dementia as a single non-specific term using the ICD-8 codes 290-290.10 and 290.18-290.19 and ICD-10 codes F 00.0-01.9, F03.9, and G30-30.9.14 We used ICD-8 codes (before January 1994) to exclude patients diagnosed with dementia before the operation.

Secondary outcome measures

Furthermore, we wanted to explore secondary outcome measures that were either co-existent or predictors of dementia. Hence, we sought for a possible association between POCD at both time points and the development of depression (ICD-10: F32–F33.31),15 ‘Organic amnesic syndrome, not induced by alcohol and other psychoactive substances’ (ICD-10: F 04), or ‘Mild cognitive disorder’ (ICD-10: F06.7).

Covariates

The analyses were adjusted for sex, age, education, and a history of co-morbidity. We defined co-morbidity as being present if one or several of the following conditions were recorded before operation: heart disease, pulmonary disease, diabetes, or cancer.
Statistics
The associations of POCD at 1 week and 3 months with the covariates were tested with Pearson’s χ² test for categorical, and Wilcoxon signed-rank test for continuous covariates. The impact of POCD on the outcomes was assessed as a hazard ratio (HR) in Cox proportional hazard regression models on time to the first occurrence of the outcome (e.g. first dementia diagnosis) or censoring (death, lost to follow-up or July 1, 2011) whichever came first. For the impact of POCD at 1 week, the time-origin was 1 week after surgery, while for POCD at 3 months, the time-origin was at 3 months after surgery. Patients for whom the outcome occurred before the time-origin were excluded from the analysis. We estimated 95% confidence intervals (CI) of the incidence rates assuming a Poisson distribution for the number of events. P<0.05 was considered significant. All analyses were performed using the commercial statistical software package SAS (SAS Institute Inc., Cary, NC, USA).

Results
A total of 2536 patients were enrolled in the ISPOCD 1 and 2 studies; of which, 720 were Danish patients. We were able to identify a valid CPR number and surgical date in 686 (95.3%) of these patients, who had a median age of 67 [inter-quartile range (IQR) 61–74] yr (Table 1). They were followed for a median of 11.1 (IQR 5.2–12.6) yr, 421 (60.5%) died during follow-up, and one was censored due to emigration. Thirty-two patients (4.6%) developed dementia during follow-up (Figs 1 and 2). The HR (95% CI) for any diagnosis of dementia in patients with POCD at 1 week and POCD at 3 months after surgery compared with those without POCD was 1.16 (0.48–2.78), P=0.74, and 1.50 (0.51–4.44), P=0.47, respectively (Table 2). None of the 19 (3.4%) patients with POCD at both 1 week and at 3 months (of the 559 patients tested at both time points) had dementia or depression. The median time intervals from surgery until the dementia diagnosis were 6.5 (IQR 3.6–11.1) and 8.8 (IQR 4.7–12.0) yr for patients with or without POCD at 1 week, respectively (P=0.31). For POCD at 3 months, the corresponding median time intervals were 4.5 (IQR 2.9–6.8) and 8.6 (IQR 4.5–11.6) yr (P=0.11). The preoperative MMSE was significantly lower in those diagnosed with dementia (median 28 (IQR 27–29) vs 29 (IQR 27–29); P=0.04). The type of surgery performed was not significantly different according to dementia (abdominal 53%, orthopaedic 10%, and other type 37% in the dementia group vs abdominal 42%, orthopaedic 18%, and other type 40%; P=0.22).

A total of 24 patients were diagnosed depressive during follow-up, and the occurrence of depression was not associated with POCD at 1 week or 3 months; HR 0.72 (0.21–2.45), P=0.60, and 1.11 (0.25–4.85), P=0.87, respectively (Table 2). No patients were diagnosed with organic amnesic syndrome and only three patients had mild cognitive disorder.

Table 1
Patient characteristics. Characteristics of patients assessed for POCD or not at 1 week or 3 months after surgery. Pearson’s χ² test used for categorical, and Wilcoxon signed-rank test for continuous variables. Patients with or without POCD at 3 months had significant differences in age* (P=0.0006) and cancer† (P=0.04)

<table>
<thead>
<tr>
<th></th>
<th>Patients assessed at 1 week (n=597)</th>
<th>Patients assessed at 3 months (n=577)</th>
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<tbody>
<tr>
<td></td>
<td>No POCD (n=479)</td>
<td>POCD (n=118)</td>
</tr>
<tr>
<td>Age [median (IQR)]</td>
<td>66 (61–74)</td>
<td>69 (62–74)</td>
</tr>
<tr>
<td>Male sex [n (%)]</td>
<td>198 (41.3)</td>
<td>59 (50.0)</td>
</tr>
<tr>
<td>Level of education [n (%)]</td>
<td></td>
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<tr>
<td>Below high school</td>
<td>351 (73.3)</td>
<td>97 (82.2)</td>
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<tr>
<td>High school</td>
<td>48 (10.0)</td>
<td>11 (9.3)</td>
</tr>
<tr>
<td>Above high school</td>
<td>80 (16.7)</td>
<td>10 (8.5)</td>
</tr>
<tr>
<td>History of heart disease [n (%)]</td>
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<tr>
<td>History of pulmonary disease [n (%)]</td>
<td></td>
<td></td>
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<tr>
<td>Diagnosed diabetes [n (%)]</td>
<td>21 (4.4)</td>
<td>6 (5.1)</td>
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<tr>
<td>Diagnosed cancer [n (%)]</td>
<td>144 (30.3); n=476</td>
<td>35 (29.7)</td>
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</table>
Discussion

We were unable to show a significant association between POCD and dementia in this long-term follow-up of nearly 700 Danish surgical patients. Likewise, there was no significant relationship between POCD and depression. The recorded incidence of organic amnesic syndrome and mild cognitive disorder was very low in this cohort and no detailed analysis could be performed of these conditions.

To our knowledge, this is the first study to address whether patients with POCD are at increased risk of developing dementia—an association we were not able to establish.

The follow-up information is extensive (11 yr), and of high quality, as data on all inpatient or outpatient hospital contacts (somatic and psychiatric) in Denmark are collected prospectively on a routine basis for registration in administrative databases as part of the official health survey—independent of specific research purposes.

Our study has several limitations. First, there is a limited power in our analysis, and we may therefore have overlooked an association. The total number of events was rather small (32 demented patients), and with only seven and four incident events over 11 yr in the two POCD groups, the risk is negligible from a clinical point of view, even though the HRs for developing dementia were around 1.16 and 1.50 in patients with POCD at 1 week and 3 months, respectively. It is likely that our cohort represents a subgroup with a higher level of cognitive functioning at baseline as patients should obtain a score above 23 in the MMSE test before inclusion in the ISPOCD studies. Hence a high level of baseline cognitive function in our participants limited the study’s ability to detect an association between POCD and dementia since an increased cognitive reserve is protective for dementia.16 The incidence rate of dementia in our study (Table 2) does not differ from that in the general Danish population, and it is comparable with 44.5 per 10 000 person-years found in another Danish study, taking into consideration that patients were somewhat younger in that cohort; median: 52.7 IQR (42–68) compared with 67 (IQR 61–74) in our study.17 It is estimated that at least two-thirds of patients with dementia in Denmark will be diagnosed on contact with secondary hospital healthcare.18 Nevertheless, it should be noted that general practitioners or private practicing specialists in psychiatry or neurology might diagnose persons with dementia without this being recorded in the

Table 2 Risk factors. Risk of experiencing dementia or depression according to the presence of POCD or not, at 1 week, or 3 months after surgery. We adjusted for sex, age, education, and co-morbidity. None of the HRs was statistically significant (all P>0.05)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Time at risk (patient-years)</th>
<th>Number of events</th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>Mean incidence per 10 000 person-years (95% CI)</th>
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<tr>
<td>Dementia</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>POCD at 1 week</td>
<td>117</td>
<td>1193</td>
<td>7</td>
<td>1.06 (0.46–2.46)</td>
<td>1.16 (0.48–2.78)</td>
<td>59 (24–121)</td>
</tr>
<tr>
<td>No POCD at 1 week</td>
<td>479</td>
<td>4605</td>
<td>25</td>
<td>1.00</td>
<td>1.00</td>
<td>54 (35–80)</td>
</tr>
<tr>
<td>POCD at 3 months</td>
<td>57</td>
<td>476</td>
<td>4</td>
<td>1.66 (0.58–4.75)</td>
<td>1.50 (0.51–4.44)</td>
<td>84 (23–215)</td>
</tr>
<tr>
<td>No POCD at 3 months</td>
<td>518</td>
<td>5103</td>
<td>27</td>
<td>1.00</td>
<td>1.00</td>
<td>53 (35–77)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
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<tr>
<td>POCD at 1 week</td>
<td>118</td>
<td>1208</td>
<td>3</td>
<td>0.54 (0.16–1.81)</td>
<td>0.72 (0.21–2.45)</td>
<td>25 (5–73)</td>
</tr>
<tr>
<td>No POCD at 1 week</td>
<td>473</td>
<td>4510</td>
<td>21</td>
<td>1.00</td>
<td>1.00</td>
<td>47 (29–71)</td>
</tr>
<tr>
<td>POCD at 3 months</td>
<td>56</td>
<td>466</td>
<td>2</td>
<td>1.03 (0.24–4.38)</td>
<td>1.11 (0.25–4.85)</td>
<td>43 (5–155)</td>
</tr>
<tr>
<td>No POCD at 3 months</td>
<td>514</td>
<td>5045</td>
<td>21</td>
<td>1.00</td>
<td>1.00</td>
<td>42 (26–64)</td>
</tr>
</tbody>
</table>
registers. In this way, it is most likely that only patients with the more severe forms of dementia are recorded in the registers. The Danish database is exhaustive so that all hospital contacts are registered; if a person does not feature in the database, the person has not had any contact with a hospital. In Denmark, all medical treatment in-hospital is free for all residents, so it seems unlikely that patients would remain at home without being hospitalized if relatives should consider that person to have significant dementia. Obviously, dementia could be overlooked, but an underestimation of the incidence of dementia would be a problem in both groups (with or without POCD). A power analysis revealed that we were able to detect an HR of 2.8 for POCD at 1 week, and an HR of 3.2 at 3 months with a power of 80% at the 5% level of significance. More than 8600 patients are needed to detect an HR of 1.5—a number that is unlikely to be included in any long-term follow-up study. The ISPOCD studies are the largest studies of POCD to date, and they included 2500 patients. Since dementia is an infrequent outcome (in our sample about 50 per 10 000 person-years), a clinically relevant HR should necessarily be high, for example, HR > 3. Since we did not find an effect of this order of magnitude, this strengthens the conclusion that POCD is not associated with future dementia. While patients with POCD at 3 months have a higher mortality, this does not bias the results from the survival analyses as the HR indicates a ratio of dementia incidence rate for the living; the cognitive concern is not considered clinically relevant if patients die before they experience dementia. Furthermore, the preoperative MMSE was significantly lower in the later diagnosed demented group, which suggests that the process of cognitive deterioration was already initiated before surgery.

Secondly, several subtypes of dementia exist, but we chose to focus only on the diagnosis as a single non-specific term rather than specifically. It could be interesting to analyse the subtypes in order to suggest pathophysiological mechanisms, but the total number of demented subjects was low, and from the patient’s point of view, the major concern is not aetiology, but whether postoperative cognitive deterioration results in dementia. Numerous studies have failed to show that POCD depends on the type, dosage, and metabolism of specific anaesthetics, and so far, the aetiology of POCD is unknown. A registered diagnosis of dementia was found to be correct in 85% of cases according to ICD-10 or DSM-IV criteria for dementia. Hence, we were able to establish with great certainty whether a Danish ISPOCD patient has been admitted to a Danish hospital and given a dementia diagnosis of rather good validity. However, the classification into specific subtypes of dementia diagnoses was less valid.

The risk of depression was not significantly associated with POCD. Consequently, there is no evidence of POCD as a risk factor for depression, but the number of events was low, similar to the number in the dementia analysis, and a similar risk of overlooking cases not recorded in the databases exists. The number of patients with organic amnesic syndrome and mild cognitive disorder was even smaller, and therefore, it was pointless to estimate any HRs. Even though patients with poor preoperative performance are difficult to identify using the ISPOCD neuropsychological test battery as a result of floor effects in the tests, a further deterioration relative to the perioperative performance would probably be detected in the national patient registry if the cognitive decline had clinical implications. Thus, organic amnesic syndrome and mild cognitive disorder are not common concerns in the present cohort.

Population studies have found mild cognitive deficits to be a strong predictor of subsequent dementia several years later, and a study of 2364 elderly persons found that subjects with mild cognitive impairment at the initial examination were 2.8 times more likely to experience Alzheimer’s disease 18–24 months later than normal elderly individuals. Although POCD is a condition of subtle cognitive changes, it is not similar to mild cognitive impairment. A POCD patient does not necessarily have a cognitive complaint, which typically is the case with mild cognitive impairment, usually presented as a decline in memory.

When considering a possible impact of anaesthesia on the development of dementia, the evidence is sparse. Bohnen and colleagues reported an inverse relationship between the age of onset for Alzheimer’s disease and the cumulative exposure to anaesthesia before the age of 50, but the CI of the odds ratios were rather large, and most other studies have not been able to establish an association between anaesthesia and dementia. One of the problems in several studies is the lack of accurate information about the timing of surgery and the development of dementia. A recent study did not detect accelerated cognitive decline in subjects undergoing surgery, but the relationship between time of surgery and cognitive testing was not well controlled and many surgical procedures were minor. The study did not determine the presence (or absence) of POCD. The ISPOCD studies provide data on the patients’ cognitive ability before surgery, and also 1 week and 3 months after operation. The neuropsychological deterioration in the perioperative period is reversible for the most part, but before this study, it was uncertain whether these subtle cognitive changes could be a precursor of long-term dementia. This study cannot elucidate whether anaesthesia and surgery per se is associated with a risk of dementia.

Even though cognitive decline is an important concern due to an increased risk of mortality, withdrawal from the labour market, and social subsidy, this study supports the current view that postoperative cognitive decline is largely reversible; the clinician should be able to reassure the patient (or their relatives) that there is no good evidence that long-term cognitive decline may be caused by surgery.

However, POCD is a condition that requires a better understanding, especially in terms of aetiological factors in order to prevent the cognitive complications due to surgery. Larger studies of long-term effects of POCD are needed.

In conclusion, POCD did not seem to be associated with the development of dementia.
Declaration of interest
L.S.R. is Editor-in-Chief of Acta Anaesthesiologica Scandinavica. J.S. has received a Consultant fee for The Medicines Company as a member of the steering committee and national investigator for the EUROMAX trial.

Funding
This work was supported by departmental funding only.

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Handling editor: J. P. Thompson