The neuropsychiatry of dementia: psychometrics, clinical implications and outcome

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Long-term cognitive outcome of delirium in elderly hip-surgery patients.
A 2.5 year prospective matched controlled study

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ABSTRACT

OBJECTIVE: To study outcome from delirium in elderly hip-surgery patients. Design: Prospective matched controlled cohort study. Hip-surgery patients (n=112) aged 70 and older who participated in a controlled clinical trial of haloperidol prophylaxis for delirium, were followed for an average of 30 months after discharge. Patients with a diagnosis of dementia or mild cognitive impairment (MCI) were identified based on psychiatric interviews. Proportions of patients with dementia/MCI were compared across patients who had postoperative delirium and selected control patients matched for preoperatively assessed risk factors who had not developed delirium during index hospitalization. Other outcomes were mortality rate and rate of institutionalization. RESULTS: During the follow-up period 54.9% of delirium patients had died compared to 34.1% controls (relative risk = 1.6, CI: 1.0-2.6). Dementia or MCI was diagnosed in 77.8% of the surviving patients with postoperative delirium and in 40.9% of control patients (relative risk = 1.9, 95% CI = 1.1-3.3). Half the patients with delirium were institutionalized at follow-up compared to 28.6% controls (relative risk = 1.8, 95% CI = 0.9-3.4).

CONCLUSION: The risk of dementia or MCI at follow-up is almost doubled in elderly hip-surgery patients with postoperative delirium compared with at risk patients without delirium. Delirium may indicate underlying dementia.

Keywords: Delirium, Follow-up, Dementia, Mild Cognitive Impairment, Mortality
INTRODUCTION

Delirium is highly prevalent in elderly patients and it is associated with high morbidity and mortality, increased length of hospital stay and institutionalization following discharge.\(^1\)\(^-\)\(^8\) Estimated incidence rates for delirium after orthopedic hip-surgery vary from 5 to 45%.\(^9\)\(^-\)\(^16\) While several studies report high prevalence of cognitive impairment after delirium in heterogeneous patient samples,\(^4\)\(^,\)\(^6\)\(^,\)\(^17\)\(^-\)\(^21\) few studies examined the risk of dementia associated with delirium in elderly hip-surgery patients after one year or more.

Two studies including general medical patients showed that in hospital delirium is associated with cognitive decline at follow-up,\(^17\)\(^,\)\(^18\) whereas another study failed to show a similar association.\(^22\) Medical illness, when it is associated with delirium, can significantly contribute to deterioration in cognitive performance.\(^20\) Prevalence of incident dementia is higher at 2-3 year follow-up in medical patients with delirium on admission compared to patients without delirium.\(^4\)\(^,\)\(^19\) Incident Vascular dementia at follow-up was significantly associated with baseline delirium in a study by Rahkonen et al. that included a population based cohort of 199 non-demented elderly aged 85+.\(^21\) Dolan et al. studied geriatric patients with hip fractures excluding those with a medical chart diagnosis of dementia: Patients with delirium were twice as likely to have cognitive impairment at 2-year follow-up.\(^19\) However, none of these studies examined the relative risk of dementia associated with delirium in a relatively homogeneous hip-surgery patient sample after controlling for important preoperatively assessed delirium risk factors. Also, few if any studies included independent baseline and follow-up clinical interviews by a geriatrician or old-age psychiatrist.

The aims of this study were to evaluate the effects of postoperative delirium on follow-up cognitive function in elderly hip-surgery patients; to evaluate the long-term effect of delirium on mortality and dependency, i.e. independent living or institutionalization; and to evaluate the MMSE as a delirium risk factor measure. To the best of our knowledge this is the first study that controlled for baseline differences in patient characteristics prior to the onset of delirium.
CHAPTER 6

METHODS

Ethical Considerations
The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. All patients or their relatives gave fully informed written consent.

Study Design and Objectives
This was a case-control study evaluating the long term outcome of post-operative delirium on cognitive decline in elderly hip-surgery patients. All study data were collected as part of a randomized trial to test whether low-dose haloperidol prophylactic treatment could prevent delirium after hip-surgery. Briefly stated, the primary outcome of the clinical trial was delirium (DSM-IV and Confusion Assessment Method criteria) occurring within a period of five postoperative days. No effect was found on incident delirium, but there was a beneficial effect both on severity and duration of delirium. Risk classification in the clinical trial was based on the presence of one or more predictive baseline risk factors as described by Inouye et al.: Visual impairment, defined as binocular near vision worse than 20/70 after correction, Severe illness, measured by the Apache II (Acute Physiology Age and Chronicle Health Examination, scale of 0 to 70), with a cut-off score of > 16 indicating increased severity, Cognitive impairment Mini Mental Status Examination (MMSE score of <24 on a scale of 0 to 30) and Dehydration (ratio of blood urea nitrogen to creatinine of ≥18). Only 5/132 patients who were at low risk (=0 risk points) developed post-operative delirium compared to 69/471 who were at intermediate (=1-2 risk points) or high risk (=3-4 risk points), supporting validity of the medical risk factor model in a hip-surgery patient sample.

In the present study follow-up data on cognitive function and functional status were searched for and compared to incident delirium during hospital stay, predefined baseline risk factors used in the randomized clinical trial, and other potential risk factors.

Participants
The original study sample (n=603) has been described elsewhere. All patients with post-operative delirium (n=74) including those without risk factors for delirium and who had not been randomized to receive study medication, were eligible to participate as cases in the follow-up part of the study. Also eligible to participate were control patients without delirium who had a similar risk factor profile as those with delirium (see patient Flow Chart). The risk factor profile has established predictive validity in hip-surgery patients. A hierarchical method was used to match delirium cases and control. Age
and MMSE scores had the highest priority (max. age difference ± 2 years: a maximum difference of 2 points on the MMSE was accepted unless it meant that a patient with a score of less than 24 was matched to a control patient with a score higher than 24. Secondary priority was given to the APACHE score (a maximum of ± 2 points difference). Finally, the measure of Dehydration and gender had least priority.

_Patient Flow Chart_

603 RCT patients
Kalisvaart et al., 2005

74 with delirium

3 lost to follow-up

71 eligible follow-up study
- 41 with matched control
- 30 without

- 1 lost to follow-up
- 4 refusals
- 39 deaths

27 interviewed

529 no delirium

41 matched controls follow-up study

- 5 refusals
- 14 deaths

22 interviewed
Measurements and Procedures

Follow-up data on cognitive impairment and institutionalization of all participating patients were searched for. Eligible patients and a knowledgeable informant (spouse, other caregivers) were interviewed at follow-up by an experienced old-age psychiatrist (MK) who was blind to baseline diagnosis of delirium, risk factors and study medication. A research nurse (RV) who had been involved in baseline in-hospital patient assessments independently assessed cognition. Patients and informants filled out a depression rating scale and neuropsychiatric symptoms checklist.

Mortality data were retrieved from the Alkmaar hospital database. The hospital serves the region were all participating patients lived and any deaths to occur are reported back regularly. Data were checked by writing to the patients' general practitioners (GP) and requesting for any relevant information. If necessary, the GP was contacted directly by telephone.

Patient interviews were scheduled February 2003 – May 2004: the average post surgery follow-up period was 30 months (range 2-3 years) and interviews with delirium and control patients were evenly distributed over this time period. Available resources did not allow us to interview all 603 patients. Therefore, we invited all patients with post-operative delirium surviving the follow-up period to participate as well as the selected matched controls.

Follow-up assessments included standard clinical psychiatric interviews with the patient and (if possible) a knowledgeable informant, preferentially a spouse. The research nurse (RV) who was uninformed about psychiatric interview outcomes independently assessed cognitive/behavioral symptoms using the standardized MMSE (score range 0-30), modified Digit Span test of attention (score range 0-42),28 the 15-items version of the Geriatric Depression Scale29 (GDS-15, 0-15) and the Neuropsychiatric Inventory Questionnaire (NPI-Q, 0-36) a 12 item informant based screen for neuropsychiatric symptoms.30,31 On average, interviews took 45 minutes per patient. Diagnosis of dementia or another mental disorder were defined based on the DSM-IV criteria: for MCI the Peterson criteria were used.33 The Cognitive Impairment Rating Scale (CIRS)34 was used to clinically characterize the MCI type. The CIRS was constructed for the clinical and neuropsychological diagnosis of different cognitive impairments in MCI. It is a patient interview based global clinical impression of major cognitive domains (executive functions, memory, language, praxis). In this study the CIRS clinical diagnosis part was used only and no comprehensive neuropsychological test battery was used at follow-up. Predefined MCI categories were MCI amnestic, non-amnestic and multiple domain.

Care was taken to facilitate patient participation in the study. If patients were unable
to come to the hospital at follow-up they were visited at home by the two members of the research team (MK and RV). If patients had died during the follow-up period a family member and the patient’s general practitioner were interviewed in order to gather demographic and medical information.

Outcomes
The primary outcome was the diagnosis of dementia or MCI. Secondary outcomes were mortality and institutionalization.

Statistical analysis
Means or proportions were used to describe demographic and clinical characteristics of the study sample at baseline and at follow-up. Relative risk of cognitive disorders, mortality and institutionalization associated with delirium was estimated using univariate analysis. Two-tailed p values of <0.05 were considered to indicate statistical significance. Subsequently, a logistic regression analysis approach was used to examine the association between baseline patient/clinical characteristics, delirium and primary outcome. Presence of delirium and potential other independent predictors that were significant in univariate analysis were entered in the regression model to calculate the odds (backward elimination) (p <.10). Statistical calculations were performed using SPSS for Windows, version 14 (SPSS, Inc. Chicago, IL).
RESULTS

Matching procedure
The planned analysis of primary and secondary outcomes is based on data of 71/74 patients with postoperative delirium: three delirium patients who had not been eligible for randomization to haloperidol or placebo in the RCT\textsuperscript{15} were lost early to follow-up. The baseline risk factor profile of patients with delirium was considerably worse than that of the patients without. Of all 529 patients without delirium only 41 had a risk profile similar to that of patients with delirium. So, for 30/71 delirium patients no control patient was included.

Table 1: Average scores, mean ranks and average risk points at baseline for delirium (n=71) and control patients (n=41)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Delirium (n= 71)</th>
<th>No delirium (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>82.8 (SD 6.5)</td>
<td>82.6 (SD 6.9)</td>
</tr>
<tr>
<td>Male/female</td>
<td>23/48</td>
<td>7/34</td>
</tr>
<tr>
<td>Acute/elective</td>
<td>36/35</td>
<td>11/30</td>
</tr>
<tr>
<td>Placebo/Haloperidol/no medication</td>
<td>36/32/3</td>
<td>27/12/2</td>
</tr>
<tr>
<td>MMSE</td>
<td>21.2 (4.6)</td>
<td>22.6 (4.5)</td>
</tr>
<tr>
<td>APACHE score</td>
<td>15.1 (3.9)</td>
<td>14.2 (3.2)</td>
</tr>
<tr>
<td>Dehydration index</td>
<td>12.1 (3.9)</td>
<td>13.1 (3.4)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>0.34 (0.14)</td>
<td>0.37 (0.17)</td>
</tr>
<tr>
<td>Total risk (1-4)</td>
<td>Mean=2.1 (.98)</td>
<td>Mean=1.9 (1.04)</td>
</tr>
<tr>
<td>GDS</td>
<td>1.5 (1.5)</td>
<td>1.0 (1.4)</td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>13.8 (3.4)</td>
<td>14.8 (3.3)</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>6.5 (2.7)</td>
<td>7.2 (2.2)</td>
</tr>
</tbody>
</table>

\(M = \text{mean raw score (SD). p-value 2-sided; *: chi-square calculated for randomized patients only}\)
Matched delirium patients did better on the MMSE than unmatched delirium patients (p=.01). No other significant baseline differences between groups were demonstrated.

At baseline, there were no significant differences in age, sex and the four predefined risk factors between delirium patients and controls (table 1). Patients with delirium were more often acutely admitted to hospital than patients without delirium (p=.03). Also, their depression scores were somewhat higher, but average GDS scores were very low and not in the range of clinical depression. A larger proportion of patients with delirium had been assigned to haloperidol prophylaxis treatment condition than controls, although this difference did not reach statistical significance (p=.07).

**Primary outcome**

A total of 39/71 patients with postoperative delirium had died during the follow-up period. Twenty-seven survivors consented to be interviewed. The other patients refused (n=4) or were lost to follow for other reasons (n=1). A total of 22/41 control patients were interviewed: 14 had died and 5 refused. Baseline characteristics of remaining patients with or without delirium actually interviewed (n=22, n=27) were not significantly different, except for a significantly higher total number of risk points in delirium patients compared to No delirium patients: mean=1.9 (SD 1), vs mean=1.3 (SD .72), Z=2.2, p=.03; and higher number of acute admissions in the delirium group compared to No delirium: 9/27 vs 2/22, Chi² 4.1, p=.04.

Postoperative delirium was associated with an increased risk of cognitive disorders at follow-up (table 2). Alzheimer dementia (AD) was diagnosed in 10/27 patients with postoperative delirium, 6/27 had Vascular dementia (VaD) or mixed VaD-AD, 4/27 had MCI amnestic type and 1/27 had MCI multi-domain type. Alzheimer dementia was diagnosed in 1/22 patients without postoperative delirium, 1/22 presented with the clinical picture of Frontotemporal dementia and 7/22 had MCI multi-domain type. No mood disorder was diagnosed in any of the patients.

An intermediate analysis including 28 patients with baseline MMSE >23 only, showed postoperative delirium was not associated with an increased risk of cognitive disorders at follow-up (RR=1.8, CI: 0.8-3.9), possibly due to the small number of patients included.

At follow-up, no group differences were found for self-rated depression, attention deficits (Digit span) and neuropsychiatric symptoms. There was a trend showing greater informant rated cognitive decline in patients with post-operative delirium than in those without (p=.06). At follow-up, patients with delirium had lower MMSE scores than those without (p=.02).

Notably, no effect was found for treatment condition on primary outcome; 11/17
haloperidol treated patients had dementia or MCI compared to 18/29 patients receiving placebo treatment (p=.86).

Multivariate analysis showed that delirium predicted dementia/MCI at follow-up and that baseline characteristics (i.e. type of admission) did not (Wald: 6.5, p=.011).

**Secondary outcomes**

Postoperative delirium was associated with an increased risk of death at follow-up (table 2). There was a trend showing higher institutionalization in patients with postoperative delirium than in those without. No effect was found for treatment condition (haloperidol - placebo) on secondary outcomes: 22/45 patients in the haloperidol treatment condition had died during the follow-up period and 30/62 patients in the placebo treatment condition (p=.95), and 7/22 were institutionalized, compared to 18/39 in the placebo group (p=.27).

Postoperative delirium was associated with an increased risk of death or dementia (i.e. combined primary and secondary outcomes cognitive status and mortality): 60/71 patients with postoperative delirium had died or had dementia/MCI compared to 23/41 controls, (RR=1.5, CI: 1.1-2.0).
Table 2. Cognitive status, mortality and institutionalization at follow-up for delirium and control patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Delirium</th>
<th>No delirium</th>
<th>N</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No cognitive impairment</td>
<td>6</td>
<td>21 (5-16)</td>
<td>13</td>
<td>RR=1.9 (CI: 1.1-3.3)*</td>
</tr>
<tr>
<td>- MCI-dementia</td>
<td></td>
<td>15 (3-12)</td>
<td>9 (7-2)</td>
<td>RR=1.8 (CI: 1.05-3.2)**</td>
</tr>
<tr>
<td>Alive / deceased</td>
<td>32/39</td>
<td>21/20</td>
<td>27/14</td>
<td>RR=1.6 (CI: 1.01-2.6)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR=1.4 (CI: 0.8-2.4)**</td>
</tr>
<tr>
<td>Independent living/</td>
<td>19/19</td>
<td>12/13</td>
<td>20/8</td>
<td>RR=1.8 (CI: 0.9-3.4)*</td>
</tr>
<tr>
<td>institutionalized</td>
<td></td>
<td></td>
<td></td>
<td>RR=1.8 (CI: 0.9-3.7)**</td>
</tr>
<tr>
<td>ICQODE</td>
<td>3.8 (.97)</td>
<td>3.9 (.83)</td>
<td>3.3 (.58)</td>
<td>t-test 2.2, p=.03*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test 2.3, p=.03**</td>
</tr>
<tr>
<td>GDS</td>
<td>2.2 (2.7)</td>
<td>2.4 (2.9)</td>
<td>1.2 (1.6)</td>
<td>t-test 1.5, p=.13*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test 1.6, p=.13**</td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>15.3 (4.1)</td>
<td>15.4 (4.4)</td>
<td>16.1 (2.6)</td>
<td>t-test .7, p=.46*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test .6, p=.56**</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>7.4 (4.0)</td>
<td>8.1 (4.3)</td>
<td>8.7 (3.6)</td>
<td>t-test 1.1, p=.27*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test .49, p=.63</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.6 (6.5)</td>
<td>22.8 (6.8)</td>
<td>26.2 (3.9)</td>
<td>t-test 2.4, p=.02*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test 2.0, p=.06**</td>
</tr>
<tr>
<td>NPI-Q total</td>
<td>5.7 (6.5)</td>
<td>6.4 (7.1)</td>
<td>4.1 (5.2)</td>
<td>t-test .9, p=.37*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test 1.2, p=.25**</td>
</tr>
<tr>
<td>NPI-Q distress</td>
<td>5.9 (7.3)</td>
<td>6.6 (8.0)</td>
<td>4.6 (6.5)</td>
<td>t-test .6, p=.54*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t-test .9, p=.38**</td>
</tr>
</tbody>
</table>

Delirium: Total delirium sample at follow-up including matched and unmatched delirium patients.
*: Total Delirium sample vs. Control comparisons,
**: Matched delirium – Control comparisons IQCODE p=.03, MMSE p=.06.
RR = Relative risk, CI = Confidence Interval. IQCODE, GDS, Digit Span, MMSE and NPI: mean (SD)
This study examined cognitive disorders at follow-up associated with postoperative delirium in elderly hip-surgery patients. Patients who developed delirium after surgery during hospital stay had a 170% increased risk of dementia or MCI in the 30 months follow-up period. Baseline differences between delirium patients and controls did not account for the effects found implying that delirium independently predicted long-term adverse outcome. Secondly, significant higher proportions of patients with postoperative delirium had died at follow-up compared to those without delirium and institutionalization was similar for both groups.

The increased risk of cognitive disorders or death after delirium is impressive and our findings may have important prognostic implications for elderly patients who are at risk for postoperative delirium. Such high rates of cognitive impairment and mortality raises concern, particularly when one considers that delirium is often under-diagnosed and in many instances preventable.

Four previous studies found an increased dementia risk associated with delirium at follow-up. Koponen followed-up 33 delirium patients of whom 29 were diagnosed with dementia at baseline and found significant decline in MMSE scores. Rockwood et al. studied geriatric patients from a general medical service over a 3-year period. They found that 60% of patients with delirium on admission but no dementia were diagnosed with dementia at follow-up (n=15) compared to only 18.5% of patients without delirium. In a study by Rahkonen et al. acutely admitted older patients with delirium were included and followed-up for a 2-year period. During follow-up 55% of patients were diagnosed as being demented. In another study by Rahkonen et al. an epidemiological cohort of 199 non-demented elderly aged 85+ were followed-up during a 3-years period. Incident delirium in the follow-up period was retrospectively diagnosed in 20/199 patients. At the end of the follow-up period dementia was diagnosed in 13/20 cases with delirium and in 46/133 controls (p=.001). The relative risk of cognitive disorders found in our sample is comparable to those found in the earlier studies. However, none of these studies examined the relative risk of dementia associated with delirium in a homogeneous hip-surgery patient sample after controlling for important preoperatively assessed delirium risk factors or they did not include independent follow-up clinical assessments. The strengths of this study are the primary outcome data set; inclusion of a homogeneous hip-surgery patient sample; use of standardized and validated methods for diagnosing delirium based on clinical patient interviews; pre surgery and pre delirium measures of predefined baseline risk factors; psychiatric assessment at follow-up; and sub typing of cognitive outcome.
The underlying mechanism for the apparent association between delirium and cognitive decline is still largely unclear. It has been suggested that delirium and dementia share the same underlying pathology: delirium may serve as a marker of a subclinical dementing process. Alternatively, it can be hypothesized that delirium itself triggers a whole range of metabolic and autonomic dysregulations and neurotransmitter changes that have neurotoxic effects on the brain and may ultimately lead to dementia. Yet another explanation may be that in some patients the somatic condition underlying delirium may not have fully remitted at the time of discharge from hospital. In turn, that may increase the risk of future dementia, especially in frail elderly patients. This hypothesis would be consistent with findings that delirium and its symptoms often persist for months after onset. So, which hypothesis is supported by our data? To test the hypothesis that delirium exerts a toxic effect on the brain would at least have required a non demented patient sample at baseline. Absence of dementia prior to surgery was not ascertained in this study and no conclusions on causality can be drawn from that. As this study includes an orthopedic patient sample and delirium duration was carefully monitored in the RCT part of the project results do not support the hypothesis that delirium symptoms persisted after discharge from hospital and perhaps confounded follow-up diagnosis of dementia. In this study care was taken no major cognitive differences existed between patients with delirium and controls prior to surgery. Nevertheless, we could not match 30/71 delirium patients to controls because of differences in the risk factor profile at baseline. Unmatched delirium patients did worse on the MMSE than matched delirium patients indicating more impairment. Moreover, a wide score range was observed for the MMSE (10–29). So, it is rather clear some patients already had dementia or MCI before entering the study. Although no conclusions on causality can be drawn from this study it further reinforces the finding that underlying dementia may be a contributor to inpatient delirium and that identification of underlying cognitive impairment may not be made until after an inciting event such as major orthopedic surgery.

Baseline MMSE was 22.5 in the no delirium group while follow-up MMSE was 26.2. What could account for this apparent transient cognitive impairment? Note that baseline and follow-up groups are not identical and healthy and cognitive intact patients may have survived the follow-up period while others did not. An intermediate paired observations analysis showed MMSE improved 1.2 points in the No Delirium group (n=22) (t-test: 2.2, p=.04), but no change was observed in the total group and in the delirium group. Dementia prevalence was higher in patients who had post-operative delirium as compared to those who did not. Though findings are based on relatively small numbers of patients and may be coincidental, we hypothesize that the (psychological) stress
associated with hospital admission may have caused some individuals to underachieve during baseline cognitive testing. During follow-up cognitive function may have returned to pre admission levels in patients without MCI or dementia. These findings imply that the MMSE not only measures stable or ‘trait dependent’ aspects of cognition, e.g. underlying dementia, but temporary or ‘state dependent’ changes as well. Therefore, cognitive dysfunction as measured with the MMSE in newly admitted hospital patients should be interpreted cautiously, as it may not be a symptom exclusively related to underlying dementia.

Treatment condition did not affect the long run outcome. Patients randomized to haloperidol or placebo had died or were cognitively impaired much the same way at follow-up. So, low-dose haloperidol prophylaxis at baseline did not protect against increased risk of mortality and cognitive decline. Vice versa, it did not have a negative effect on primary outcome. It would seem to us that where short term effects may be expected, the duration and dosage of the prophylactic treatment were too short or too low to really make a difference 2.5 years later.

Weaknesses of this study that need to be discussed are: 1. Baseline evaluations were aimed at excluding delirium, and not at diagnosing different neuropsychiatric syndromes. Delirium is associated with cognitive impairment. When evaluating the long term effects of delirium it is important to control for premorbid cognitive disorders. In this study patients were matched based on four risk factors, including the MMSE. No detailed neuropsychiatric assessment was used at baseline. A cognitive screening test does not provide the same diagnostic information as a clinical interview and cases with underlying cognitive disorders may have gone undetected. 2. The study is underpowered to evaluate the long term effects of postoperative delirium. Power calculations were based on the original intervention study. In the present follow-up study all delirium patients were included and a control sample. The baseline risk factor distribution did not permit us to sample any more control patients. 3. Patients were followed-up after 2.5 years. No intermediate assessments took place. Possible confounders of results occurring during this time interval may have gone undetected. Ideally, follow-up diagnosis and multiple assessments would have been preferred for all participating patients. These are preliminary findings on cognitive outcome from delirium. Future studies could focus on pre delirium clinical assessments, rigorous screening for pre delirium cognitive impairment, and repeated mid term and long term follow-up cognitive testing.

This controlled study evaluated the long term effects of postoperative delirium. It underlines the major impact of this neuropsychiatric syndrome on the well-being of elderly hip-surgery patients. More than half the patients with post operative delirium
die during 2 to 3 years after hospitalization; the vast majority of those surviving have a cognitive disorder. Although delirium is independently associated with cognitive impairment at follow-up, some patients with delirium may already have underlying dementia. Outcome from delirium is poor particularly for patients with dementia.37 Our findings point to the imperative to screen for underlying impairment, since delirium may ensue and therefore, increase risk of morbidity and mortality. Monitoring at risk patients, not only during hospitalization but also following discharge, should be combined with delirium prevention strategies.
Reference List

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