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A comparison between the use of single-bed rooms and multiple-bed rooms as predictors of delirium and falls in hospitalized geriatric patients

PhD dissertation

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Preface and acknowledgements

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List of abbreviations

ADL	Activities of Daily Living
AUH	Aarhus University Hospital, Denmark
BMI	Body Mass Index
CAM	Confusion Assessment Method
CCI	Charlson Comorbidity Index
CDT	Clock Drawing Test
DSM	Diagnostic and Statistical Manual of Mental Disorders
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems
ICU	Intensive Care Unit
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile Range
MBI	Barthel-100 Index
MMSE	Mini Mental State Examination
NICE	British National Institute for Health and Care Excellence
NR	Not Reported
OP	Operative
OR	Odds Ratio
PV+	Positive Predictive Value
PV-	Negative Predictive Value
REDCap	Research Electronic Data Capture
ROC	Receiver Operating Characteristic
RR	Relative Risk
SIRS	Systemic Inflammatory Response Syndrome
SPMSQ	Short Portable Mental Status Questionnaire
SNRI	Serotonin-Noradrenalin Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressants

List of Papers

Paper I **Single-bed rooms in a geriatric ward prevent delirium in older patients.**
Blandfort S, Gregersen M, Rahbek K, Juul S, Damsgaard EM.
Aging Clinical and Experimental research. 2020;32(1) 141-147. doi: 10.1007/s40520-019-01173-y.

Paper II **Analgesic and psychoactive medications and the risk of falls in relation to delirium in single-bed rooms compared to multiple-bed rooms in geriatric inpatients.**
Blandfort S, Gregersen M, Rahbek K, Juul S, Damsgaard EM.
Aging Clinical and Experimental research, 2019 Aug. doi: 10.1007/s40520-019-01335-y. [Epub ahead of print]

Paper III **The short IQCODE as a predictor for delirium in hospitalized geriatric patients.**
Blandfort S, Gregersen M, Rahbek K, Juul S, Damsgaard EM.
Aging Clinical and Experimental research, 2019 Nov. doi: 10.1007/s40520-019-01412-2. [Epub ahead of print]

1. Introduction

The proportion of older people in Denmark is increasing. In 2018, 8% of the Danish population was 75 years or older, and the percentage is expected to reach about 14% in 2050 (1). Figure I1 shows the projections for Denmark (1, 2).

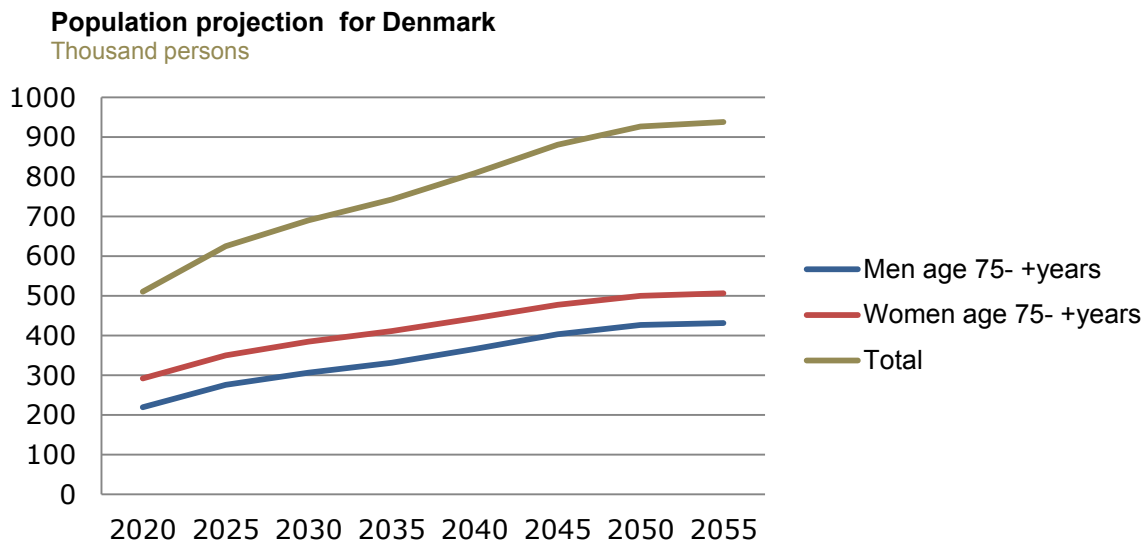

Figure I1 Population projections for Denmark, from Statistics Denmark (1).

Approximately 23% of all hospital admissions in 2018 in Denmark were of patients 75 years or older (2). Despite improved health status among older people, the increasing elderly population will cause the number of hospital admission among older patients to increase in the future.

Plans developed by a government expert panel recommended that the Danish Regions[1] reduce the number of hospital beds by 20% and increase outpatient treatments by 50% from 2007 to 2020 (3). As a part of the modernization, the regions are building 16 hospitals, hereof seven as new hospitals. The last new hospital is planned to be commissioned in 2025. The new hospitals include only single-bed rooms with own bathroom. Typical single-bed rooms have an area of 33 to 35 m^2 and are furnished with an

[1] Denmark is divided into five Regions, with health service as their main responsibility.

extra bed so that relatives can stay with the patient overnight. Single-bed rooms allow more treatments to take place in the room, so that functions can be moved to the patient. This means less need for examining rooms, rehabilitation facilities, and common rooms (4).

2. Background

2.1 The geriatric patients

Geriatric patients are characterized by multimorbidity, cognitive impairment, physical disability, malnutrition, falls, polypharmacy, iatrogenic complications, and dependence on personal assistance. Many patients are frail which can be considered a syndrome in which the body's ability to withstand stress is impaired, and small influences (e.g., minor surgery, pain, medication side effects) may have major health consequences (5, 6). The frailty increases the risk of delirium (7, 8).

2.2 Delirium

2.2.1 Description

Delirium is characterized by the acute onset of fluctuations in the mental state and a reduced ability to maintain attention. The patients become incoherent in thinking and speech and have impaired memory and a changed level of consciousness, moving from a wakeful state to drowsiness, or becoming unresponsive (7, 9).

Three different subtypes of delirium are distinguished. The hyperactive subtype is characterized by increased psychomotor activity, restless behavior as well as loud shouting, while the hypoactive type is characterized by lack of initiative, slow responses, and drowsiness. The hypoactive subtype is the most common type among older hospitalized patients (10, 11). There is a risk of hypoactive delirium being overlooked or misdiagnosed as depression. The third subtype appears as mixed delirium, with fluctuating hypoactive and hyperactive periods (10, 12). In a study by Lundström et al., it is shown that patients with dementia more often have hyperactive or mixed delirium (13). Morandi et al. showed that patients with dementia are more affected by mixed delirium (14).

2.2.2 Diagnosis of delirium

The syndrome was first described in the literature 2,500 years ago by Hippocrates (15). Throughout history, the syndrome has had many different names. It was not until 1987 that specific diagnostic criteria for the disorder were established and that delirium was recorded in the USA diagnostic list DSM-III and most recently specified in DSM-5[2] (2013). In ICD-10[3] from 1992, delirium was registered with the diagnostic code F05 (16, 17). Diagnostic instruments have been developed for use in clinical work and research, and today there are numerous screening tools validated for the assessment of delirium (18, 19). Table B1 shows a selection of screening tools based on the criteria in DSM-III to DSM-IV. The tools are validated to be usable among older patients including patients with dementia.

[2] Diagnostic and Statistical Manual of Mental Disorders
[3] International Statistical Classification of Diseases and Related Health Problems (WHO)

Table B1 Screening tools validated for assessment of delirium in demented inpatients

Delirium screening tool	Rating by	Sensitivity (%)[1]	Specificity (%)[1]	Danish version
Confusion Assessment Method (CAM) (20-25)	Trained nurses, researchers, and clinicians	(46)[2] (94-100)	(63)[2] (90-100)	Yes
Delirium Rating Scale (DRS) (26, 27)	Clinicians with psychiatry experience	82-94 (depends on cut-point)	82-94 (depends on cut-point)	No
Delirium Rating Scale, Revised (DRS-R-98) (28-30)	Clinician with psychiatry experience	56-92 (depends on cut-point)	67-93 (depends on cut-point)	No
Digit Span Test (DST) (31, 32)	Nurses	34-81	63-90	No
Single Question in Delirium (SQiD) (33)	Clinicians	77	51	No
Inter-RAI Acute Care Assessment System (four items pertaining to delirium) (34)	Trained research nurses	82-90	69-91	No
Simple Question for Easy Evaluation of Consciousness (SQUEEC) (33)	Clinicians	83	59 (dementia)-81 (the whole group)	No
Short Portable Mental Status Questionnaire (SPMSQ) (35)	NR	17-73 (depends on errors for dementia and delirium)	89-100 (depends on errors for dementia and for delirium)	No
The 4As Test (4AT) (36-41)	No special training is required	83-100	65-94	Yes (42)

[1] Range of the sensitivity and the specificity measured across studies.
[2] From untrained nurses and researchers

A systematic review in 2012 by Morandi et al. found that the CAM has the best possibilities for diagnosing delirium superimposed on dementia (43).The Confusion Assessment Method (CAM) was developed in 1990 in the USA by Sharon Inouye. It is comprised of nine criteria derived from the DSM-III-R (44). So far, CAM is the most commonly used tool (18, 19). A German study of frail elderly patients showed a sensitivity of 0.77, a specificity of 0.96 to 1.00, and a Cohen's kappa coefficient of 0.95 (20). Similarly, an American systematic review found a sensitivity of 0.94 and a specificity of 0.89 (25).

Trained healthcare professionals can diagnose delirium using CAM. The Danish edition from 2013 was translated by Nicolaj Bang Foss, DMSc. It is recommended by the Centre

for Clinical Guidelines, see Appendix 1. The clinical guideline recommends using the Danish version of the training manual and coding guide for CAM (45).

It is recommended by the British National Institute for Health and Care Excellence (NICE) to use CAM for diagnosing delirium (46). The screening tool can be used for patients undergoing surgical, medical, geriatric, and palliative-care treatment. It is based on observations by healthcare professionals. It is illustrated in Table B2.

Table B2. Description of Confusion Assessment Method criteria

Criteria	Observations
1:	**Acute onset and a fluctuating course.** Is there evidence of an acute change in the patient's mental state compared to the habitual state? Does the abnormal behavior vary during the day? The questions can be answered based on information from caregivers or family.
2:	**Inattention.** Is the patient easy to distract and has difficulty keeping track of what is said?
3:	**Disorganized thinking.** Does the patient seem incoherent, with rambling and irrelevant speech, unclear thoughts, and switching from subject to subject?
4:	**Altered level of consciousness.** Has the patient's level of consciousness changed, so the patient appears hyperactive, lethargic, or inaccessible?

A delirium diagnosis requires the presence of criteria 1 and 2, and at least one of criteria 3 and 4 (44, 46).

Subsyndromal delirium has been described by different scientists (47-49). There is no standard definition of subsyndromal delirium in the specific diagnostic criteria, but it is described as a condition where some of the symptoms of delirium according to the DSM-5 criteria and CAM are present (48, 49). Meagher et al. argue that inattention should be contained in the description of subsyndromal delirium (50).

2.2.3 Occurrence

Delirium occurs frequently in older hospitalized patients, with prevalence at admission from 10% to 35% (7, 51-53). In old medical inpatients, delirium occurs in up to 36% (30, 54, 55). In frail older inpatients, prevalence varies from 31% to 60% (7, 8, 51, 56). In hip fracture patients, the incidence of preoperative delirium has been reported from 14% to 44%, whereas the incidence of postoperative delirium varies from 13% to 73% (57-65). Among hip fracture patients with dementia, the incidence of delirium rises dramatically to preoperatively 69% and postoperatively 96% (60, 66). After cardiac surgery, the postoperative incidence is reported up to 56% in patients 70 years or older (67-69). In intensive care units, the reported occurrence of delirium varies from 16% to 89% (7, 70, 71). The estimated prevalence and incidence rates of delirium in older inpatients vary, depending on setting and study methodology.

2.2.4 Causes of delirium

The pathophysiology of delirium is still poorly known. There are several explanatory models, e.g. hypotheses regarding chemical and inflammatory changes in the brain and hypotheses regarding effects of stress in the brain (12, 72-74). Until now, no biomarker has been found (75, 76). The causes of delirium are thought to be multifactorial, dependent on a complex interplay of predisposing factors such as high age, sensory impairment and pre-existing cognitive impairment and precipitating factors such as infection, severe medical illness and medications. A robust person can withstand more noxious exposures before developing delirium than can a frail person. On the other hand, a frail person with many predisposing risk factors can develop delirium after less intense exposures, such as a single dose of sedatives (77-80). The influence of predisposing and precipitating risk factors is illustrated in Figure B1. Examples of predisposing and precipitating risk factors that have been identified in the clinical studies among geriatric and medical patients and patients with hip fracture are described in Table B3. However, the findings in different studies vary. Many of the risk factors are incorporated into multicomponent intervention programs for preventing delirium. A Cochrane review of preventing delirium in inpatients (not-ICU patients) from 2016 found evidence that

multicomponent non-pharmacologic interventions are effective in preventing delirium during hospitalization, but less robust to reduce the severity and duration of delirium (78). Delirium affects health adversely in terms of increased morbidity, poor rehabilitation outcomes, prolonged hospitalization, increased institutionalization and mortality (54, 61, 81-86), and sequela with serious adverse implications and high health care costs (7, 87).

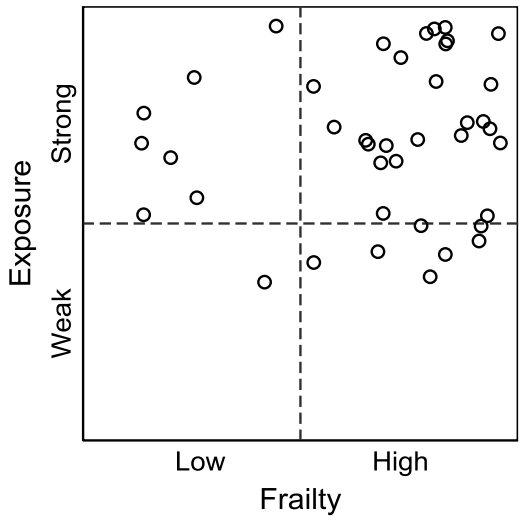

Figure B1 Interplay of frailty and precipitating factors for delirium.

Table B3. Examples of predisposing and precipitating risk factors of delirium in geriatric patients, medical patients, and patients with hip-fracture.

Predisposing risk factors	Precipitating risk factors
High age (7, 52, 54, 56, 63, 74, 88)	Critical illness or sepsis (54, 74)
Gender male (52, 74)	Fever (≥38° C) (52, 55)
Cognitive impairment (7)	Pain (89)
Dementia (7, 88, 90)	Poly-pharmacy (7, 65)
Hearing impairment (52)	Anticholinergic medication (88)
Visual impairment (52)	Psychotropic drug and SSRI (54, 63)
Depression (63, 88-90)	Use of a bladder catheter (52, 55, 79, 90)
Previous delirium (52)	Urinary tract infections (63, 90)
Functional impairment (30, 54)	Constipation (63, 90)
Dependency (79)	Malnutrition, low serum albumin or BMI<20 kg/m^2 (57, 63, 79, 91)
Alcohol misuse (7)	Sleeping disturbance postop. (63, 92)

2.3 Hospital settings

Noise in a hospital environment from alarms, telephones, medical equipment and fellow patients, together with different personnel rotating between fellow patients and patient rooms, patients who experience multiple transfers from one room to another, and missing control over lighting level can all contribute to sensory overstimulation and sleep disruption, which may lead to confusion and occurrence of delirium in older inpatients. In a case-control study by Goldberg et al., transfer of older patients was associated with an increased risk of delirium (93). It seems to be the same risk for frail patients (94). Furthermore, in a general community hospital, McCusker et al. found that the severity of delirium became exacerbated by room change (95). In a study by Evensen et al. of geriatric patients, they found no association between ward-transfers and delirium, but they found nighttime investigations associated with incident delirium (96). Sleeping

disturbances also seems associated with delirium (63). In a cohort study by Fitzgerald et al., they found that sleep disruptions were associated with delirium irrespective of the presence of dementia (92).

2.4 Single-bed rooms' impact on delirium

It is expected that noise and disturbances can be reduced in a single-bed room. In a study with geriatric inpatients, sleep-disturbing factors were assessed before and after moving from an old hospital with multiple-bed rooms to a new hospital with single-bed rooms, patients in single-bed rooms had a better sleep during night with an experience of fewer disruptions (97).

The single-bed rooms in new Danish hospitals are designed to allow many treatments to take place in the room. The rooms have their own bathroom (4). This will reduce transfers of patients admitted to single-bed rooms compared to patients admitted to multiple-bed rooms. But the association between ward design and the risk of delirium in older patients has received little research attention.

No studies among older inpatients and only a few among younger patients have investigated the effect of shift from multiple-bed rooms to single-bed rooms. In a prospective study from an intensive care unit, Zaal et al. did not find a significant difference in the risk of delirium. Among patients who stayed in single-bed rooms the incidence was 45% versus 51% among patients in multiple-bed rooms. However, the duration of delirium was reduced in the single-bed rooms ($p=0.04$) (98). In another retrospective study from an intensive care unit, Caruso et al. found a difference in the incidence of delirium. Patients who stayed in single-bed rooms had a lower risk of developing delirium than patients hospitalized for the same reasons but stayed in multiple-bed rooms, 6.8% vs. 15.1%; $p<0.01$. The authors did not find any difference in the duration of delirium or subtypes of delirium (99). In the study by Zaal et al., the incidence of delirium was much higher than in the study by Caruso et al. No studies including older inpatients admitted to a geriatric, medical, or orthopedic department were identified in the literature search.

2.5 Falls

Upon aging, muscle strength and the function of the sensory organs are reduced, and the risk of falls increases. Dizziness and balance problems are frequent causes of falls in the older patients. In geriatrics, we all know stories like this:

“An older patient using a wheelchair who wanted to use the toilet but wasn't able to call out for help. As a result, the patient fell out of the chair when he was trying to get to the toilet.”

According to the reporting of known incidents in Danish hospitals, falls during hospitalization in 2018 accounted for approximately 1 fall per 700 admissions among inpatients 65 years or older (2, 100). In the Geriatric Department, Aarhus University Hospital, Aarhus, Denmark, 1 fall per 40 admissions was reported in 2018 (100, 101).

The well-known risk factors for falls in the older patients are loss of consciousness, impaired balance, decreased muscle strength, dizziness, vision impairment, polypharmacy, alcohol, cognitive impairment and dementia (102, 103). A fall for older can have significant consequences for their health, such as fractures, concussions and mortality (104). Furthermore, a fall can also trigger a fear of falling again, which can cause the older to become less active and participate less in social activities (103). A history of falls increases the risk of inpatient geriatric fall (105). Bedrooms and in some cases also bathrooms are reported as particularly risky places (102, 105-107). Delirium often causes restlessness, gait disturbance, blurred vision, dizziness, and muscle weakness, thereby increasing the risk of falls (102, 105, 106, 108). In a prospective study, Stenvall et al. found among patients admitted with femoral neck fracture that inpatients falls were associated with male, post-operative delirium day seven and sleeping disturbance (106).

2.6 Analgesics and psychoactive drugs

The proportion of users of analgesics and psychoactive drugs increases with age (109, 110). In older people, the pharmacokinetics change due to decreased degradation of drugs in the intestinal mucosa and decreased liver metabolism and renal function. Psychoactive drugs include antipsychotics, anxiolytics, hypnotics and antidepressants, and

anti-dementia drugs. The first-generation antipsychotic drugs have been used for treatment of psychotic symptoms for over 60 years. The second-generation drugs were developed in the 1990s and are characterized by more tolerable side effects but still with metabolic side effects. Anxiolytics are used in acute situational anxiety and as an acute treatment or supplementary treatment for anxiety disorders, psychoses, and depression. Hypnotics and sedatives are mostly used to treat sleep disturbances. Selective serotonin reuptake inhibitors (SSRI) are the most commonly used antidepressants in Denmark, but there are other types, such as serotonin-noradrenalin reuptake inhibitors (SNRI) and the older tricyclic antidepressants (TCA) (111). Anti-dementia drugs are used in Alzheimer's disease, Lewy body dementia, and dementia in Parkinson's disease. Table B4 shows the number of users who redeemed prescriptions in 2008 and 2018 for analgesics and psychoactive drugs (112).

Table B4. Number of persons redeeming prescriptions for psychoactive drugs and opioids in 2008 and 2018

Drug type	*Number of users per 1,000 inhabitants*			
	All		80+ years old	
	2008	2018	2008	2018
Natural opium alkaloids (opioids) (N02AA)	16	29	77	139
Other opioids (N02AX)	45	37	156	113
Antipsychotics (N05A)	21	23	61	52
Anxiolytics (N05B)	44	22	147	69
Hypnotics and sedatives (N05C)	53	40	214	158
Antidepressants (N06A)	77	72	229	195
Anti-dementia drugs (N06D)	3	4	41	59

Despite a slight decrease in the last 10 years in the use of opioids and psychoactive drugs, except anti-dementia drugs, consumption is still significantly higher among old people than among the rest of the population (112).

The consumption is highest in nursing homes, where 41% of all residents have used prescription analgesics, and almost 40% of residents with dementia have used antipsychotic drugs during a 1-year period (113, 114).

Pharmacological interventions for prevention and treatment of delirium have been investigated in a Cochrane review from 2018. The authors found no clear evidence that antipsychotic medication reduces the incidence, severity or duration of delirium (115). This is in accordance with another systematic review from 2019 including 16 randomized clinical trials (RCT) and 10 observational studies. Nikooie et al. could not recommend routine use of haloperidol or second-generation antipsychotics for treating delirium (116). This was further confirmed in an RCT from 2018, where Boogaard et al. did not find, that prophylactic haloperidol compared to placebo reduced the incidence or duration of delirium (117). The usefulness of antipsychotics as treatment for delirium is beyond the scope of this dissertation.

2.7 Use of analgesics and psychoactive drugs and occurrence of delirium or falls during hospitalization

Several clinical studies have investigated the association between use of analgesics or psychoactive drugs and delirium. No association between postoperative delirium and use of opioids has been found (118-120), but tramadol (other opioids, N02AX) has been associated with delirium after elective major abdominal surgery (121). Severe pain after surgery, including undertreated pain, has also been associated with postoperative delirium (122).

Few psychotropic drugs have been associated with the development of delirium. In a case-control study, Marcantonio et al. found that postoperative delirium was associated with both long-acting and short-acting benzodiazepines (118). This is in accordance with a cohort study by Neerland et al., however, the association was only found in cognitively impaired patients with hip fracture receiving intravenous benzodiazepines perioperatively. No association was found in patients who were cognitively intact (65). In geriatric patients, no association between use of benzodiazepines and delirium was found. Instead, the authors found an association between antidepressant and neuroleptics consumption and delirium (123). In another study by Edlund et al., the authors found that the use of

neuroleptics on the day of admission was also associated with delirium in older inpatients. But the authors did not find any association between delirium and use of antidepressants (52). Use of SSRI and psychotropic drugs prior to admission was in medical inpatients associated with delirium (54). It seems that the studies are heterogeneous, and an association between delirium and drugs for mental illness or dementia in older patients is inconsistent.

Use of drugs for mental illness or opioids has been suspected to increase the risk of falls in older patients. In a case-control study of older inpatients (mean age 82) admitted for surgical or medical reasons, the study showed no association between falls and use of opioids (124). In two reviews, there was no convincing association between consumption of opioids and falls (125, 126).

In a prospective study, Mazur et al. found that use of neuroleptics during hospitalization in a sub-acute geriatric ward was associated with falls (OR: 4.3, 95% CI 1.9-9.6) (105). This result was confirmed in a case-control study, where patients (mean age 82) were admitted to mixed surgical and internal medicine departments. The authors found an association between falls and long-acting benzodiazepines, SNRI, and Z drugs[4](127). They did not find any association between falls and consumption of short-acting benzodiazepines or mirtazapine (124). In a prospective study, Stenvall et al. did not find any association between use of benzodiazepines, antidepressants, or neuroleptic drugs and falls in patients admitted with femoral neck fracture in orthopedic wards (106). In a meta-analysis, Bloch et al. found, among persons 80 years or older, that falls in daily life were associated with consumption of psychotropic drugs, antidepressants, benzodiazepines, hypnotic drugs, and neuroleptics (128).

In another systematic review by Hartikainen et al., benzodiazepines, antidepressants, and antipsychotics were associated with falls (126). A post-hoc RCT among patients with dementia in residential-care found a dose-dependent association between risperidone and falls (129).

[4] Zolpidem and zopiclone are referred to as Z drugs. They are short-acting hypnosedatives but are not benzodiazepine drugs (127).

Throughout the studies there is heterogeneity among populations, settings, medications and dosages, and definitions of falls.

2.8 Instruments to assess prehospital cognitive impairment and risk of delirium

It is important to know which patients are at high risk of developing delirium – whether in multiple-bed rooms or single-bed rooms. Delirium is more common in older patients who also suffer from dementia (7, 78, 119, 121-123, 130-132), and it is a challenge to diagnose delirium superimposed on dementia. Therefore, it is important to know the prehospital cognitive functions of the patients to be able to handle these patients according to their risk of developing delirium after admission to hospital. Assessment of cognitive functions in acute settings is important, as most dementia is not previously diagnosed (133). However, in some patients it can be difficult to perform due to underling medical illnesses, which may affect the level of consciousness and in some cases the ability to communicate. In older patients with acute medical illness and underlying cognitive impairment, it can be a challenge to distinguish between manifestations of delirium and dementia, especially if the patient´s history is not available. Instruments which have been used for assessment of cognitive impairment and for identifying delirium include among others: the Mini Mental State Examination, Clock Drawing Test, Digit Span Test and Short Portable Mental Status Questionnaire. They require the patient's attention and ability to cooperate and they all show a picture of the cognitive function at the testing time. Studies have found that they have limited usefulness for identify delirium in acute setting (31, 32, 35, 41, 134-137).

In Denmark, 6% of older people aged 75 years or older have a dementia-related diagnosis (138). Based on international population surveys, the Danish Health and Medicines Authority considers that dementia is under-diagnosed in Denmark (138, 139). Accordingly, it is necessary to find an easy tool to assess prehospital cognitive impairment in acutely admitted patients and thereby predict the risk of delirium.

2.9 Identifying patients at high risk of delirium with IQCODE screening

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a sensitive tool for detecting dementia (140, 141). It depends on reports from the relatives, but not from the patient, and it may be used in cognitively impaired and delirious patients. The score ranges from 1 to 5, high scores being unfavorable. In a systematic review, it was found that an IQCODE cut-point of 3.3 had a sensitivity of 91% and a specificity of 66% to detect undifferentiated dementia in adult hospitalized patients (142).

Table B5 shows a number of studies that have found a high IQCODE score is associated with delirium.

Table B5. Studies showing association on high IQCODE and delirium during hospitalization

Author, year	Population	Results
Juliebø et al., 2009 (57)	Hip fracture	A score of 3.6 or higher was associated with pre and post op. delirium.
Witlox et al., 2011 (143)	Hip fracture	A score of 3.6 or higher was associated with delirium.
Watne et al., 2014 (144)	Hip fracture	A score higher then 3.44 was associated with delirium.
Krogseth et al., 2016 (145)	Hip fracture	Pt with delirium had median (IQR) 4.8 (4.1-5.0) and no delirium median (IQR) 4.1 (3.6-4.9), p<0.001.
Miu et al., 2016 (131)	Post acute care	A cutoff of 3.42 was associated with delirium.
Han et al., 2017 (146)	Emergency department	Pt with delirium had median (IQR) 4.06 (3.38-4.69) and no delirium median (IQR) 3.19 (3.00-3.56)
Neerland et al., 2017 (65)	Hip fracture	A cutoff on 3.44 or higher was associated delirium.

One study investigated the predictive value of short IQCODE for delirium during hospitalization. Priner et al. demonstrated that an IQCODE score >3.125 could predict

postoperative delirium in older patients undergoing elective surgery, with a sensitivity of 80% and a specificity of 66% (147). We expect the prevalence of cognitive impairment to be moderate in the geriatric population, but we do not know whether IQCODE is able to predict delirium in patients admitted to a geriatric department.

2.10 Literature review

I aimed to review the literature systematically to assess:

1) The effect of single-bed rooms on the risk of delirium during hospitalization.
2) The effect of single-bed rooms on the risk of falls during hospitalization.
3) The use of analgesics and psychoactive drugs as risk factors for delirium.
4) The use of analgesics and psychoactive drugs as risk factors for falls.
5) IQCODE as a risk-tool to predict delirium during hospitalization.

The PICO framework (148) format was used to structure the systematic review, and standard methods were followed. The search strategy was divided into 3 different searches structured according to the hypotheses, which are presented later. Search strategy number 2 contains the three hypotheses number 2 to 4, see page 27. For the different searches, the following items were selected;

1) Geriatric inpatients, single-bed room, multiple-bed room, and delirium.
2) Geriatric inpatients, single-bed room, multiple-bed room, analgesic, psychoactive drug, delirium, and falls.
3) Geriatric inpatients, delirium and IQCODE.

The last systematic literature search for the present thesis was conducted in October 2019, where relevant articles were selected. This search included PubMed, Embase, CINAHL and The Cochrane Library databases. Furthermore, an Internet search was done in Google Scholar, and browser and reference searches were done on all included articles. The search strategies are illustrated in Appendix 2.

In Appendix 3, an overview of studies and systematic reviews are presented in Table L1 and L2. Table L1 are showing 14 studies and 4 systematic reviews from the first and

second search strategy. Table L2 shows the third search strategy; here I focused on prognostic studies, and one study was included.

The evidence level was assessed according to the Oxford Centre for Evidence-based Medicine-Levels of Evidence (149).

2.11 Background summary and research questions

Geriatric patients represent a most vulnerable group of older patients. Their risk of delirium is high. Few studies have investigated the impact of the design of the patient's rooms in the hospitals and if it influences the risk for developing delirium. In the literature review, we found two studies from intensive care units examining the incidence of delirium. I In one study, the authors found that the incidence of delirium was reduced in single-bed rooms compared to multiple-bed rooms (99), however this was not confirmed in the other study (98). I found no studies which investigated the impact of single-bed rooms compared to multiple-bed rooms on the risk of delirium in geriatric or medical patients or in patients with hip fracture.

In the literature review, we searched for studies which examined if analgesics and psychoactive drug can be risk factors for delirium and falls during hospitalization.
In a post hoc RCT, an association between risperidone dosages and the risk of falls was found. But different cohort and case-control studies had inconsistent results. It seems that these diverging results can be related not only to varying methods of delirium assessment, but also to the different kinds of patients and variations in choice of drugs and dosage.

There is a strong evidence that dementia is associated with delirium. Therefore, it is of interest to explore whether a screening tool for baseline cognitive impairment can predict delirium. IQCODE may be a tool that can be used in hospitals when patients are admitted acutely. Some studies have shown an association between the result of IQCODE and delirium, and one study has concluded that IQCODE could predict the risk of delirium in elderly patients after elective surgery. Therefore, it is of interest to investigate whether the IQCODE has the same predictive value in acutely admitted geriatric patients.

3. Aims and Hypotheses

3.1 Opportunities

In March 2017, our geriatric department moved from old hospital buildings with multiple-bed rooms to a new hospital with single-bed rooms. There were no changes in uptake area, staff, and admission criteria. This gave us an outstanding opportunity to study the effect of single-bed rooms compared with multiple-bed rooms on the incidence of delirium, consumption of analgesics and psychoactive drugs, and the risk of falls. Furthermore, we used the opportunity to test the short IQCODE as a tool to predict delirium during hospitalization.

3.2 Aims

- To examine the risk of incidence of delirium among patients admitted to a geriatric department in relation to single-bed rooms vs. multiple-bed rooms
- To examine if a decreased incidence of delirium in single-bed rooms was associated with a simultaneous change in consumption of analgesics and psychoactive drugs
- To investigate if relocation of the geriatric wards to a new modern hospital had affected the incidence of falls both among patients with delirium and patients without delirium
- To investigate if use of analgesics and psychoactive medications is associated with the incidence of delirium and falls among patients in a geriatric ward
- Finally, to investigate the usefulness of the short IQCODE in predicting delirium in patients admitted to a geriatric ward.

3.3 Hypotheses

In a study population of patients aged 75 years or older and admitted to geriatric wards, the following hypotheses were tested:

1. Single-bed rooms reduce the incidence of delirium compared to multiple-bed rooms in geriatric inpatients.
2. A reduced incidence of delirium in single-bed rooms is associated with a simultaneous change in use of analgesics and psychoactive drugs.
3. The relocation from multiple-bed rooms to single-bed rooms affects the incidence of falls.
4. Use of analgesics and psychoactive medications is associated with the risk of delirium and falls.
5. The short IQCODE questionnaire can predict delirium during hospitalization of patients in a geriatric ward.

4. Methods

4.1 Design

The PhD dissertation includes two studies: an observational prospective study and a prognostic study, see Figure M1.

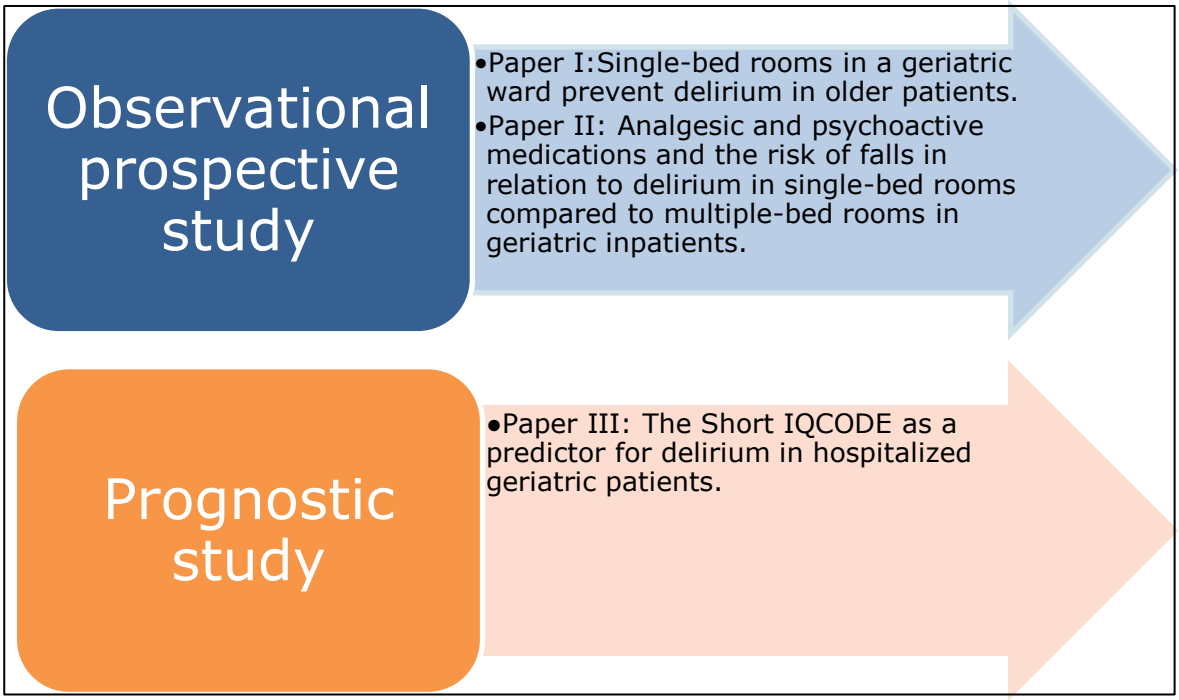

Figure M1. Description of studies and Papers

4.2 Study population

4.2.1 Paper I and Paper II

In March 2017, the Geriatric Department at Aarhus University Hospital, Denmark, was moved from old hospital buildings with multiple-bed rooms (old wards) to a new hospital with single-bed rooms (new wards).

Patients were consecutively recruited when they were admitted to the geriatric wards. Figure M2 illustrates where patients came from before admission to the geriatric wards. From September 15, 2016 to March 19, 2017, patients were admitted to the old wards and between March 20 and December 19, 2017 to the new wards.

4.2.2 Paper III

From March 20 to December 19, 2017, patients were recruited from the Emergency Department at Aarhus University Hospital by the geriatric team when it was decided that the patient should be transferred to the geriatric wards, see Figure M2.

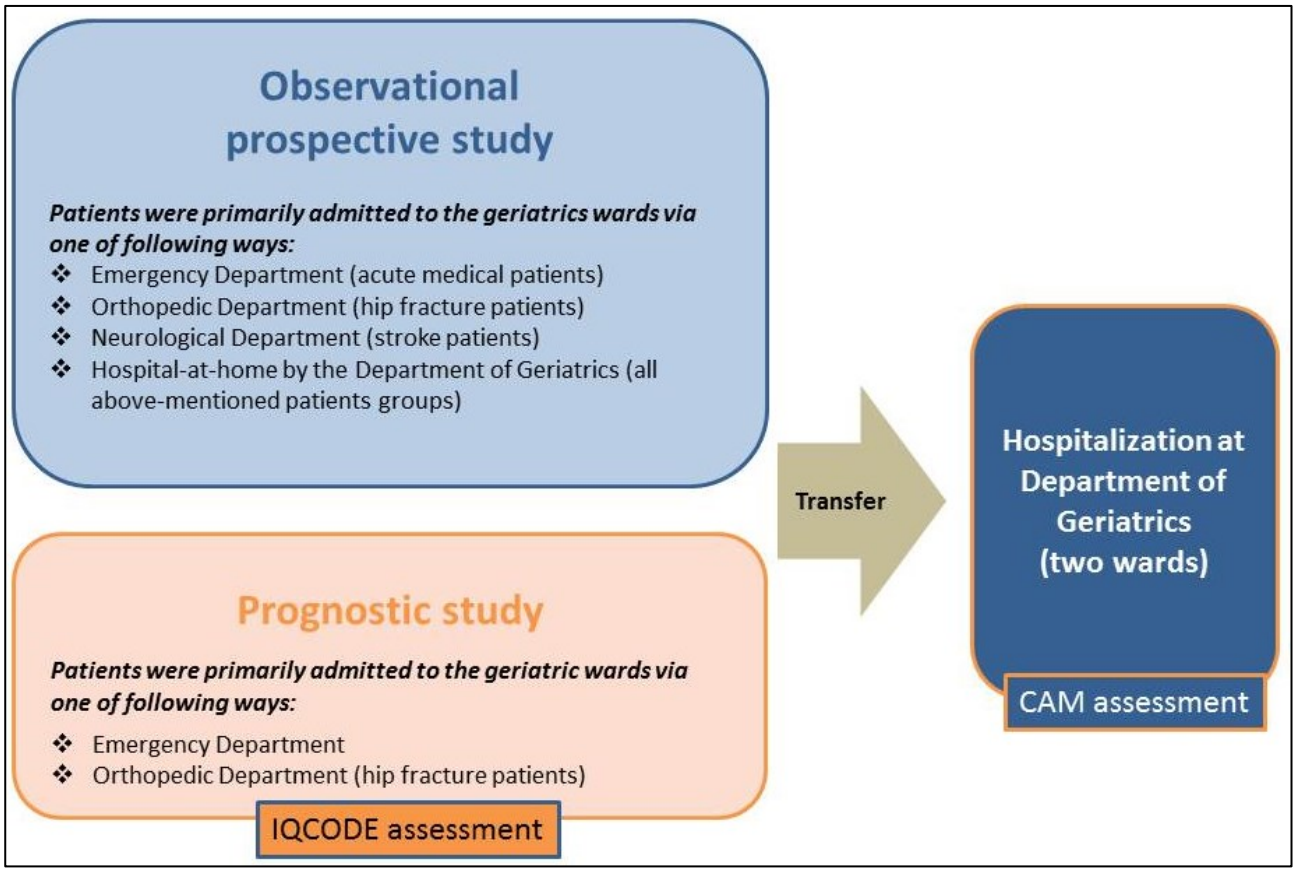

Figure M2 Showing where patients were before admission to Geriatric wards and where the cognitive assessment was made.

4.2.3 Inclusion criteria

1. Patients aged 75 years or older and admitted to geriatric wards

*For **Paper III**, there was a further inclusion criterion:*

2. Patient referred from Emergency or Orthopedic Department

4.2.4 Exclusion criteria

Patients were excluded if they:

1. had already been included once after a prior admission to the same hospital
2. were dying or somnolent at the time of admission, as assessed by a specialist in geriatrics
3. were unable to communicate for different reasons, e.g. aphasia, dementia, or deaf-mute
4. were unable to understand or speak Danish
5. were hospitalized during Christmas and New Year's Holiday 2016 (1 week), Easter 2017 (1 week) and summer holiday 2017 (4 weeks) when the wards had holiday staffing
6. were admitted to the new wards less than 30 days after discharge from the old wards.

*For **Paper III**, there was a further exclusion criterion:*

7. Delirium was assessed using the Confusion Assessment Method (CAM), and patients who had no CAM assessments during hospital stay were excluded from the analysis.

4.3 Exposure and outcomes

4.3.1 Paper I

Exposure:

- Admitted to the old wards or to the new wards
- Length of stay

Outcome:

- Development of delirium during hospitalization assessed by the Confusion Assessment Method (CAM)
- Duration of delirium

4.3.2 Paper II

Exposure:

- Admitted to the old wards or to the new wards
- Development of delirium during hospitalization assessed by CAM
- Consumption of psychoactive drugs and analgesics

Outcome (See Figure M3):

- Consumption of psychoactive drugs and analgesics
- Falls during hospitalization
- Development of delirium during hospitalization assessed by CAM

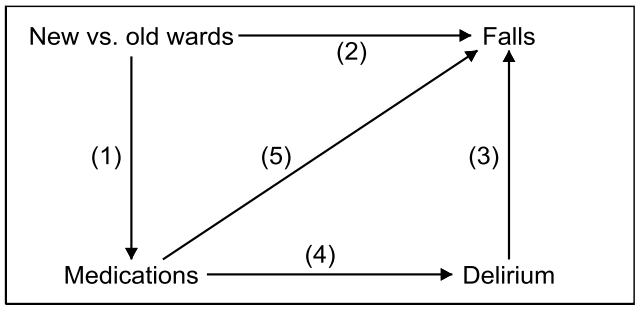

Figure M3 Associations analyzed in Paper II
Numbers are explained in the statistical analyses.

4.3.3 Paper III

Predictor:

- Result of screening by the short IQCODE questionnaire

Outcome:

- Development of delirium during hospitalization assessed by CAM

An overview of the data collection in the different papers is illustrated in Table M1.

Table M1. Overview of data collection

	Hospitals wards	Delirium (CAM)	Analgesics and psychoactive drugs	Falls during hospitalization	IQCODE	Baseline characteristics	SIRS
Paper I	√	√				√	√
Paper II	√	√	√	√		√	√
Paper III		√			√	√	

4.4 Setting

The old wards consisted of two geriatric wards located at different addresses. There were five 3-bed rooms, eleven 2-bed rooms, and two single-bed rooms with 13 shared bathrooms. A 2-bed room is illustrated in Figure M4. The rooms had one or two windows at the end of the room next to one of the beds. The geriatric wards constituted a total area of approximately 1,550 square meters. Visiting time was unrestricted within the limits of consideration for other patients in the room.

The two geriatric wards in the new hospital are located on two different floors in the same building. In total, there are 32 single-bed rooms with large windows and own bathrooms and a total area of roughly 2,350 square meters, see Figure M5. Visiting time is unrestricted, and a relative can stay overnight in the room, which was very inconvenient in the old wards.

Figure M4 A two-bed room in the old wards.

Figure M5 A single-bed room in the new wards.

4.5 Measurements

4.5.1 Confusion Assessment Method

The Confusion Assessment Method (CAM) criteria and how to use it is described in section 2.2.2 (Diagnosis of delirium).

CAM was the only screening tool which was translated to Danish by the beginning of the study. It is suitable for use in a geriatric ward and has excellent sensitivity and specificity when used by trained staff.

At admission, all enrolled patients were examined for delirium by the geriatric staff using a Danish translation of the Confusion Assessment Method (CAM) (45). Every day at 8 a.m. (±2 H) and at 8 p.m. (±3 H) until discharge, the patients were assessed with CAM or in few cases by a physician diagnosing delirium by the ICD-10 code F05. All CAM measurements were registered in the electronic patient record and subsequently copied to the research database by the author. If CAM was missing in the electronic patient record, the relevant staff member was immediately contacted to complete the assessment.

Delirium present at admission was defined as a positive CAM score or by a diagnosis of delirium at the first scheduled screening, which typically took place within the first 10 hours after admission. Cases of delirium diagnosed after the first scheduled screening were defined as new cases. An episode of delirium was considered ceased after 24 hours of negative CAM screenings. Patients with subsyndromal delirium do not have a positive CAM, and therefore they were not diagnosed with delirium.

As preparation for the present study, the geriatric staff members, comprising nurses, nurse assistants, occupational therapists, and physiotherapists completed a course on delirium and its treatment in geriatric patients, including the Danish version of the training manual and coding guide for CAM, followed by a test (45). This preparation took place before inclusion of the first patients. New staff attended the same course before performing CAM screenings. The course lasted one and a half hour, where following themes were included: description and definition of delirium, incidence and prevalence, predisposing and precipitating risk factors, non-pharmacological and pharmacological interventions and assessment of delirium by CAM with the focus on how to use CAM on patients with

dementia or chronic cognitive impairment. The lectures were performed by a research assistant (specialized in CAM and delirium) and did not differ from time to time.

In a PubMed search, no studies were found that examined the Danish translation, validity, and inter-rater reliability in a Danish geriatric population. Therefore, in the 4-week period between the first seminar and inclusion, we conducted a reliability study that included 52 patients admitted to the geriatric ward. Staff members and a research assistant (expert in CAM and delirium) independently conducted a CAM screening of a patient with an interval of no more than 1 hour between screenings. The results were blinded to both observers. The inter-rater agreement was measured by Cohen's kappa. We found 98% agreement and after adjusting for the random agreement the agreement was 85% (κ 0.85). We did not make a new inter-rater reliability test during the study period.

4.5.2 Analgesics and psychoactive drugs

From the medical records, the information regarding the following medications was extracted, see Table M2. We recorded the use (yes/no) at any time from admission to an event of delirium or to discharge.

Table M2. ATC-codes and pharmacological groups presented in this study (150)

ATC codes	Pharmacological groups
N02AA	natural opium alkaloids (e.g. morphine, opioids, oxycodone)
N02AX	other opioids (e.g. tramadol)
N05A	antipsychotics (e.g. olanzapine, risperidone, haloperidol)
N05B	anxiolytics (e.g. apozepam, diazepam, oxazepam)
N05C	hypnotics and sedatives (e.g. zolpidem, zopiclone)
N06A	antidepressants (e.g. SSRI, SNRI, TCA)
N06D	anti-dementia drugs (e.g. rivastigmin, galantamin)

As Risperidone is used for treatment of delirium in our department, we analyzed the dosage of Risperidone as recorded at the date of first use of the medication. We did not include dosage or treatment duration for other medications in the analysis.

4.5.3. Falls

Falls were defined as fall from chair or bed or from standing or walking, and as episodes where the staff found the patient lying or sitting on the floor. It is mandatory to report falls as accidental events to The Danish Patient Safety Authority Register and in the electronic patient records. Time from admission to the first fall was recorded. The number of falls per patient was not included in the analysis.

4.5.4 IQCODE

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a sensitive tool for detecting clinical dementia. The original IQCODE questionnaire includes 26 items. It was developed at the end of the 1980s as a tool for assessing a change from previous to current levels of cognitive function (141). In 1994, a validated short form IQCODE with 16 items gave similar results (140-142). The IQCODE asks about changes in the patient's cognitive performance over the last 10 years. The informant must assess the patient's ability in regard to each question on a 5-point Likert scale; 1) much improved, 2) a bit improved, 3) not much changed, 4) a bit worse, 5) much worse. The IQCODE score is calculated as the mean of item responses, with a possible range of 1 to 5, low scores being favorable, and 3 corresponding to no overall change in cognitive performance. The questions concern various everyday situations where the patient needs memory and intellect, for example, remembering recent things, learning new things, handling money by purchasing, etc. (140). The geriatric team was introduced to using the IQCODE (Danish version) by a research assistant and peer-to-peer training, see Appendix 3 (151).

Patients were included by the geriatric team after asking for consent to contact a member of the patient's family or a close friend in order to complete the IQCODE questionnaire. After consent was obtained, the geriatric team phoned and interviewed the relative. In a

few cases, the interview was completed face to face. No matter what method was used, the interview was conducted in the same way. An interview lasted about 10 minutes. The introductory wording to the relatives or friends was "We want you to remember what your relative (or friend) was like 10 years ago and then compare it with how he (or she) was before the illness that brought him (or her) to this admission." In some cases, it was not possible to get in touch with the relatives before the transfer. The interview was then performed as soon as possible.

4.6 Baseline Characteristics

From the patient records, the following baseline characteristics were extracted: age, gender, housing conditions (nursing home, sheltered home or own home), prior diagnosis of dementia, main hospitalization diagnosis, body mass index (BMI), comorbidity, physical functional ability, body temperature[5], pulse[5] and respiratory rates[5], and blood samples: hemoglobin, sodium, creatinine, albumin, white cell count, and C-reactive protein.

Dementia was identified by:

- Using the International Classification of Diseases 10th Revision (ICD-10) codes Dementia in Alzheimer's disease (F00 and G30.1), Vascular dementia (F01), Dementia in other diseases (F02), Unspecified dementia (F03), and Delirium superimposed on dementia (F05.1) (152).

Comorbidity was estimated by:

- Charlson Comorbidity Index (CCI) evaluates the burden of comorbidity conditions. (153). It is a frequently used and generally recognized measure of co-morbidity (154). CCI has been found to be capable of predicting short-term mortality and risk of hospitalization among residents in nursing homes (155). It was calculated based on all diagnoses recorded in the patient journal for the current admission made by a physician (152).

[5] Temperature, pulse and respiratory rates were used to calculate The Systemic Inflammatory Response Syndrome (SIRS)

Physical functional ability was assessed by:

- The Barthel-100 Index (MBI) measures the basic self-care ADL. It ranges from 0 to 100 points and assesses 10 items: transferring, walking, managing stairs, eating, personal care, toiletry, bathing, dressing, bowel control, and bladder control. MBI is classified as follows: 100-80 points: independent or little dependent, 79-50 points: moderately dependent, 49-25 points: substantially dependent, and 24-0 points: completely dependent (156, 157). The Barthel-100 was assessed and recorded in the patient's journal for the current admission made by the geriatric staff.

Sepsis was assessed by:

- The Systemic Inflammatory Response Syndrome (SIRS). It is defined as temperature >38°C or <36°C, pulse >90 bpm, respiratory rate >20 breaths per minute and white cell count >12 x 10^9/L or <4 x 10^9/L with at least two positive criteria for the definition of sepsis (158).

4.7 Ethics

The studies include observations and processing of register data, but no interventions, and they are exempted from notification to the regional Ethics Committee according to the Danish Act on Research Ethics Review of Health Research Projects § 14, stk. 2. The Confusion Assessment Method (CAM) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) are recognized methods for assessing cognitive status (139), and they are not perceived as a burden to patients. The study protocol was approved by the Danish Data Protection Agency, case no. 1-16-02-254-16. Data were stored according to good research practice in Research Electronic Data Capture (REDCap) hosted at Aarhus University, Denmark (159). For Papers I and II, the study was registered at ClinicalTrials.gov (Identifier NCT03199768) and for Paper III (Identifier NCT03175276).

4.8 Statistical considerations

The statistical analyses were performed with Stata software, version 15.1 or 16.0 (StataCorp, LLC, College Station, Texas, USA). We used 95% confidence intervals (CI). P-values less than 0.05 were considered statistically significant.

4.8.1 Power calculations in Paper I and Paper II

The power calculation was based on an observational study by Caruso et al. In an intensive care department, the incidence of delirium in single rooms was 6.8% versus 15.1% in multiple-bed rooms (99). Expecting a similar difference, we needed 320 patients in each group to obtain a power of 90% with a significance level of 5%. (As described in section 4.8.4, a revised power calculation for Paper III led to an extension of the study period, and we actually included close to 1,000 patients in the analyses in Papers I and II).

4.8.2 Statistical analyses in Paper I and Paper II

Patients' baseline characteristics were compared by Student's t-test or Wilcoxon's rank sum test for continuous variables, and Pearson's chi-squared test or Fisher's exact test for categorical variables.

The incidence of delirium during hospital stay was compared between the old and the new wards using a Cox regression model adjusted for potential confounders: age, comorbidity, housing conditions, prior diagnosis of dementia, SIRS, and main diagnosis (infection, fracture, other). Time at risk began at admission and ended at the first delirium episode or with censoring at the date of discharge or death. Patients with delirium present on admission were excluded from the incidence analysis. Some patients were admitted both once to the old and once to the new ward, and to adjust for this clustering, we used robust variance estimates.

A comparison of time to recovery from a patient's first delirium episode was performed using Cox regression with censoring at discharge and adjusted for Charlson's comorbidity index. It included patients with delirium present at admission, but in a secondary analysis

these patients were excluded. For these analyses, the duration of a delirium period was defined by consecutive, positive results of the twice-daily CAM assessments after these modifications: a missing assessment was substituted by the result of a non-missing neighbor assessment with positive neighbor assessments taking precedence over negative assessments. If one or two negative assessments were surrounded by positive assessments, they were substituted by positive assessments.

In Paper II, Cox regression was used to compare the following:: (1) the use of medications, (2) the risk of falls in the old and the new wards, (3) the risk of falls in relation to delirium, (4) the risk of delirium in relation to medications, and (5) the risk of falls in relation to medications see Figure M3 page 31. The analyses were validated by a test of the proportional hazard's assumption. Some patients were admitted once to both the old and to the new wards. To adjust for this clustering, we used robust variance estimates.

All Cox regression analyses were validated by a test of the proportional hazard assumption and with inspection of "log minus log" plots.

4.8.3 Power calculation in Paper III

For the power calculation, we used an IQCODE score cut-point of 3.125, as suggested by Priner et al. (147). In a pilot study in the old wards, the risk difference of delirium was 23.1% between patients with low and high IQCODE scores. Assuming this risk difference, we calculated a need of 47 patients in the smaller of the two IQCODE groups to obtain a power of 90% with a significance level of 5%. However, the incidence of delirium turned out to be much reduced in the new wards, and to obtain a power of 90%, we revised the estimated number of patients needed to 76 in the smaller IQCODE group, and this extended the study period by 8 months.

4.8.4 Statistical analyses in Paper III

To compare delirious and non-delirious patients, we used Student's t-test or Wilcoxon's rank sum test for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables.

A receiver operating characteristic (ROC) curve was prepared, and the area under the curve was calculated. Sensitivity, specificity, the positive predictive value (PV+), and the negative predictive value (PV-) were calculated at selected cut-points. The association between IQCODE score and the occurrence of delirium was examined by logistic regression to estimate the independent predictive contribution of IQCODE.

5. Results

5.1 Patients comprising the study population

5.1.1 Paper I and Paper II (160, 161)

In Papers I and II, 1,014 admissions of 964 different patients were included; 50 patients were admitted to both the old and the new ward. See flowchart in Figure R1 and patient characteristics in Table R1, page 43.

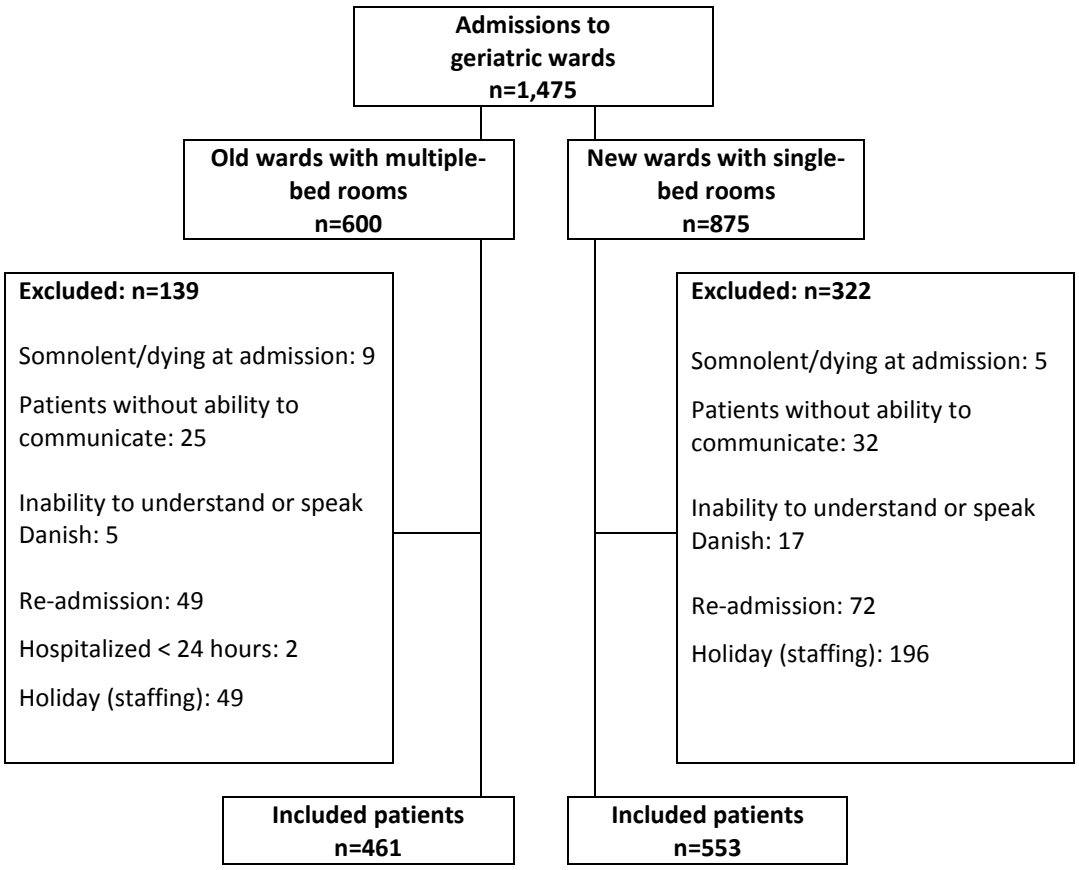

Figure R1 Flowchart for inclusion in Paper I and Paper II (160, 161)}

Table R1. Patients characteristics in all three Papers (160-162)

	Paper I and Paper II		Paper III	
	Old ward with multiple-bed rooms. Number (%) or median (IQR[1])	**New ward with single-bed rooms. Number (%) or median (IQR[1])**	**Patients without delirium Number (%) or median (IQR[1])**	**Patients with delirium Number (%) or median (IQR[1])**
N	461 (100%)	553 (100%)	248 (100%)	58 (100%)
Age	87 (82-91)	86 (81-90)	86 (82-89)[2]	88 (83-93)[2]
Gender				
Male	169 (36%)	232 (42%)	94 (38%)	27 (47%)
Female	292 (64%)	321 (58%)	154(62%)	31 (53%)
Living arrangements				
Own home	434 (94%)	504 (91%)	221 (89%)	53 (91%)
Nursing homes	27 (6%)	49 (9%)	27 (11%)	5 (8%)
Medical history				
Prior diagnosis of dementia	40 (9%)	49 (9%)	14 (6%)[2]	8 (14%)[2]
Falls	50 (11%)	51 (9%)	29 (12%)	5 (9%)
Charlson comorbidity index				
0 (none)	151 (33%)	183 (33%)	92(37%)	22(38%)
1-2 (low)	216 (47%)	274 (49%)	117 (47%)	31(53%)
3-5 (moderate)	81 (18%)	81 (15%)	33 (13%)	5(9%)
6-12 (severe)	13 (3 %)	15 (3%)	6 (2 %)	0
Physical ability (Barthel-100)[3]				
Minor (100-80)	54 (12%)	76 (14%)	35 (14%)[2]	2 (4%)[2]
Slight (79-50)	143 (31%)	161 (29%)	88 (36%)[2]	11 (19%)[2]
Moderate (49-26)	134 (29%)	162 (30%)	78 (32%)[2]	14 (25%)[2]
Severe (25-0)	127 (28%)	150 (27%)	46 (19%)[2]	30 (53%)[2]
Body Mass Index (BMI)[4]				
Underweight[5]	44(10%)	50 (9%)	21 (9%)[2]	8 (15%)[2]
Normal weight[6]	218 (50%)	290 (54%)	121 (50%)[2]	38 (70%)[2]
Overweight[7]	178 (40%)	201 (37%)	102 (42%)[2]	8 (15%)[2]

[1] Interquartile range, i.e. 25% and 75% percentiles.
[2] Statistically significant differences
[3] Barthel Index-100. Missing: 7 in Papers 1 & 2 and 2 in Paper 3
[4] Missing: 33 in Papers 1 & 2 and 9 in Paper 3
[5] Defined as BMI <18.5,
[6] Defined as BMI 18.5-24.9
[7] Defined as BMI ≥25

Table R2. Characteristics at hospitalization (Paper I and Paper II (160, 161))

Characteristics	Old ward with multiple-bed rooms. Number (%) or median (IQR[1])	New ward with single-bed rooms. Number (%) or median (IQR[1])	*p* value
N	461	553	
Delirium at admission	48 (10%)	57 (10%)	0.96
Diagnosis at hospitalization			
Infection	135 (29%)	183 (33%)	0.19
Cardiac	35 (8%)	32 (6%)	0.25
Stroke	44 (10%)	55 (10%)	0.92
Fracture[2]	97 (21%)	108 (20%)	0.58
Other	150 (33%)	175 (32%)	0.76
SIRS≥2[3]	94 (20%)	114 (21%)	0.94
Blood samples			
Hemoglobin, mmol/L[4]	7.4 (6.6-8.2)	7.4 (6.5-8.2)	0.82
Sodium, mmol/L[5]	139 (136-142)	139 (136-141)	0.18
Creatinine, µmol/L[5]	83.3 (64-117.5)	80.0 (61.3-116)	0.23
Albumin, g/L[5]	28.0 (25.0-32.3)	28.0 (25-32)	0.42
White blood cells, 10^9/L[6]	9.7 (7.8-12.4)	9.5 (7.5-12.3)	0.19
C-reactive protein, mg/L[6]	56.3 (20.3-103.8)	57.8 (17.5-124.6)	0.37

[1] Interquartile range, i.e. 25% and 75% percentiles.
[2] >70% were hip-fracture
[3] Systemic Inflammatory Response Syndrome (SIRS) (Missing: 5)
[4] Hemoglobin (Missing: 2) taken in the period: 4 days before or 3 days after admission.
[5] Sodium (Missing 2), creatinine (Missing 2), albumin (Missing 3) taken in the period up to 4 days before admission.
[6] White blood cells (Missing: 3) and C-reactive protein (Missing 4) taken in the period: 4 days before to 2 days after admission

Baseline patient characteristics and characteristics by hospitalization were well balanced between the old and the new wards. In 105 patients (10%), delirium was present at the first CAM screening after admission, with no statistically significant differences between the old wards and the new wards. Among patients with delirium at first screening, 21% had a prior diagnosis of dementia, and among patients without delirium at first screening, 7% had a prior diagnosis of dementia.

Median length of stay (LOS) was 7 days in the old wards and 6 days in the new wards, with no statistically significant difference.

> "LOS ranged from 1 to 24 days in the old wards, and 15 patients (4%) had a LOS of 14 days or more. In the new wards, LOS ranged from 1 to 36 days, and 5 patients (1%) had a LOS of 14 days or more" (*Direct quotation from Paper I (161)*).

During hospitalization 54 patients died: 29 patients (6%) in the old wards and 25 patients (5%) in the new wards, with no statistically significant difference between old and new wards.

> "In the old wards, 35 patients (8%) stayed in single-bed rooms throughout the hospital stay; of these, 13 patients had delirium at admission, and 4 patients developed delirium during hospital stay" (*Direct quotation from Paper I (161)*).

5.1.2. Paper III (162)

In Paper III, 353 patients were eligible. Thirteen percent did not participate for different reasons, and 306 patients participated in the study, see flowchart in Figure R2, page 46. Almost a third of the non-participants families or friends were not able to answer some of the items or to complete the IQCODE questionnaire. Between participants and non-participants, there were no differences in gender, age, living arrangements, a prior diagnosis of dementia, comorbidity, physical ability, development of delirium or length of stay.

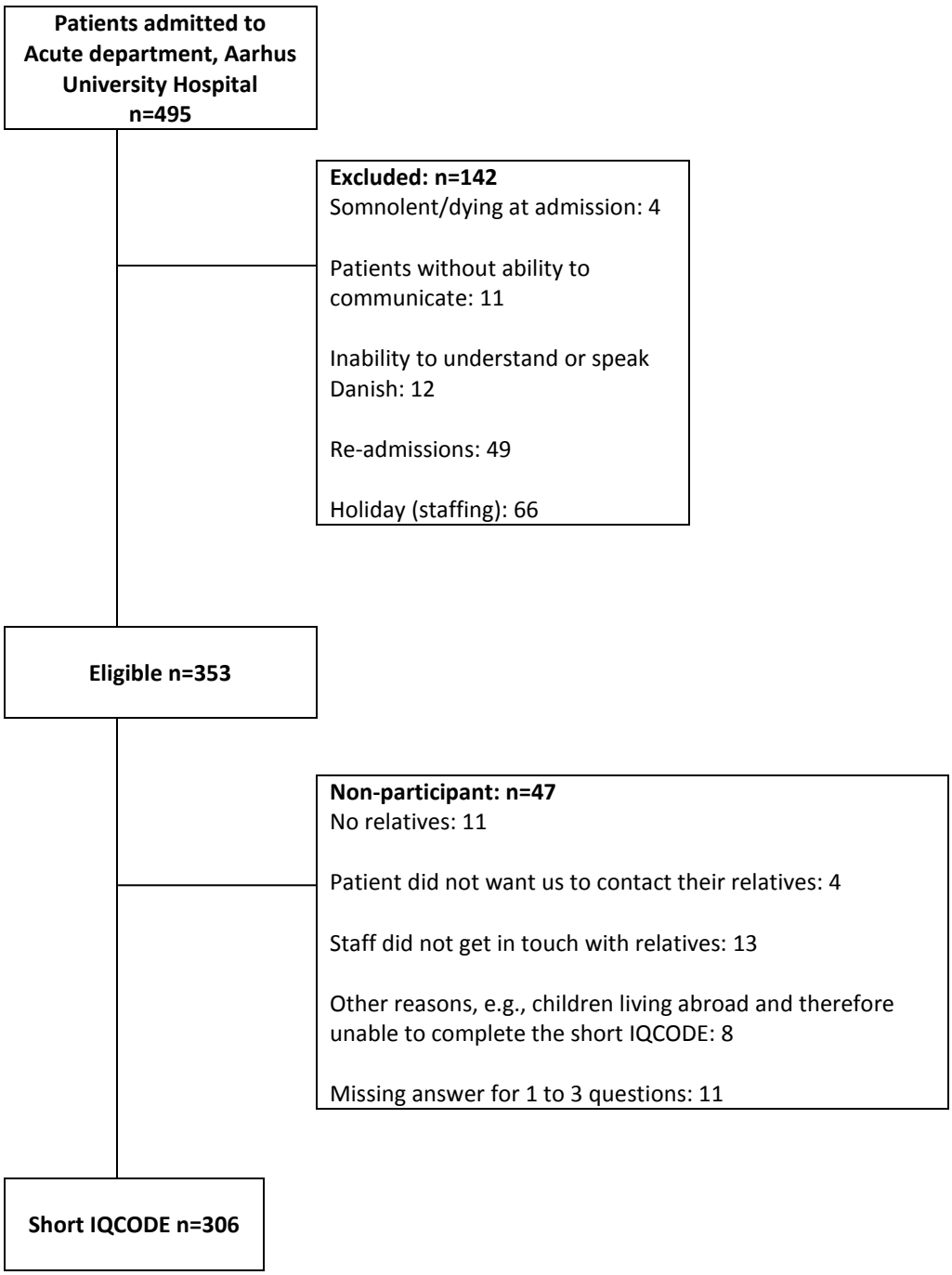

Figure R2. Included and excluded patients, Flowchart: (Paper III (162))

Table R1 on page 43 shows baseline characteristics in patients with and without delirium during hospitalization. Patients with delirium were significantly older, had a prior diagnosis of dementia, low physical ability, and a lower body mass index (BMI) than patients without delirium. At hospitalization, patients with delirium had a significantly higher IQCODE score than patients without delirium, see Table R3.

Table R3. Characteristics at hospitalization in Paper III (162)

Characteristics	Patients without delirium Number (%) or median (IQR[1])	Patients with delirium Number (%) or median (IQR[1])	*p* value
N	248	58	
Short IQCODE	3.5 (3.1-4.1)	4.3 (3.6-4.8)	<0.001
Diagnosis at hospitalization			
Infection	88 (35%)	23 (40%)	0.56
Fracture	54 (22%)	13 (22%)	0.92
SIRS≥2[2]	56 (23%)	13 (22%)	0.98
Blood samples			
Hemoglobin, mmol/L[3]	7.4 (6.4-8.2)	7.3 (6.5-8.1)	0.53
Sodium, mmol/L[4]	139 (136-142)	139 (137-142)	0.78
Creatinine, µmol/L[4]	80 (61-116)	81.0 (62-119)	0.91
Albumin, g/L[4]	28 (25-31)	28 (24-31)	0.42
White blood cells, 10^9/L[5]	9.9 (7.7-12.8)	9.2 (7.7-11.9)	0.47
C-reactive protein, mg/L[5]	72 (26-140)	69 (26-117)	0.99

[1] Interquartile range, i.e. 25% and 75% percentiles.
[2] Systemic Inflammatory Response Syndrome (SIRS)
[3] Hemoglobin taken in the period: 4 days before or 3 days after admission.
[4] Sodium, creatinine, albumin (Missing 1) taken in the period up to 4 days before admission.
[5] White blood cells and C-reactive protein taken in the period: 4 days before to 2 days after admission

Median length of stay (LOS) was 7 days (IQR 5-8) in the old wards and 7 days (IQR 5-9) in the new wards, with no statistically significant difference.

At the first CAM screening after admission, 28 patients had delirium, and during hospital stay, 30 patients developed delirium, in total 58 patients (19%).

5.2 The incidence of delirium in single-bed rooms and multiple-bed rooms (Paper I (161))

The 1,014 included patients were, according to the plan, CAM-screened twice a day during hospitalization, and of the 14,246 planned examinations, 13,923 (98%) were actually completed.

In total, 105 patients (10%) had delirium at the first screening after admission to the geriatric wards, and there was no significant difference between the old and the new wards. For the remaining 909 inpatients, 140 (15%) experienced delirium during the hospital stay, and there was a significant difference between the ward types, p=0.01. Table R4 shows a distribution between the two ward types.

Table R4. Distribution of delirium in the old and new wards

	Old ward with multiple-bed rooms. Number (%)	New ward with single-bed rooms. Number (%)
N	461	553
Delirium at admission	48 (10%)	57 (10%)
No delirium at admission	413	496
Delirium during hospital stay	77 (19%)	63 (13%)

> "During the first 14 days of hospital stay, the cumulative incidence of delirium was 29% in patients admitted to the old wards and 16% in patients admitted to the new wards. The patients in the new wards had a significantly reduced risk of delirium compared with the patients in the old wards (HR: 0.66, 95% CI 0.47-0.92, p<0.02), adjusted for age, comorbidity, housing conditions, prior diagnosis of dementia, SIRS, and main diagnosis. Figure 2 [Figure R3 in this thesis] shows the cumulative incidence of delirium among patients in the old and the new wards." (*Direct quotation from Paper I (161)*)

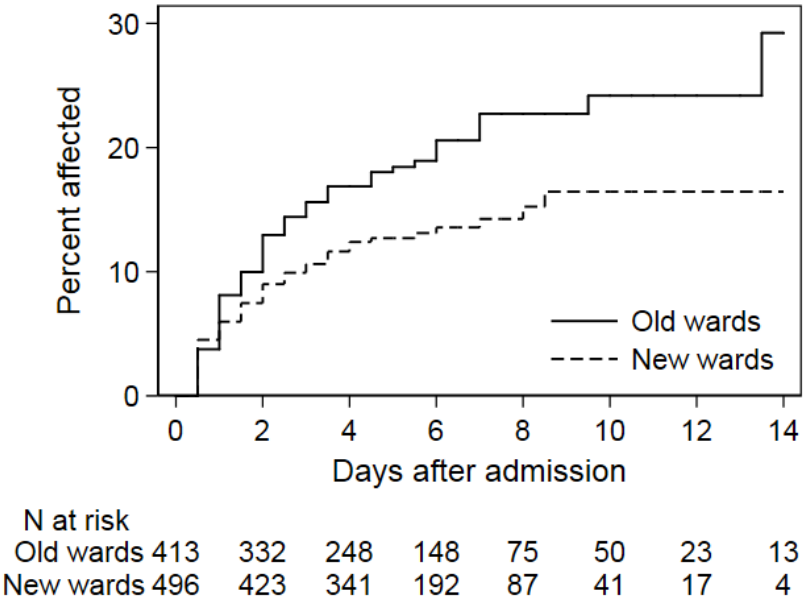

Figure R3 Cumulative incidence of delirium (105 patients with delirium at admission not included) (161)

Development of delirium while in hospital was associated with age (HR per 10 years: 1.58, 95% CI: 1.18-2.11, p=0.002), with a prior diagnosis of dementia (HR: 1.74, 95% CI: 1.02-2.98, p=0.04) and with severe to moderate physical disability (HR: 2.24, 95%CI 1.52-3.29) (161). It was not associated with SIRS, Charlson comorbidity index, or living arrangement.

We found no difference between the old and the new wards in the duration of first delirium episode (HR: 1.06, 95% CI 0.86-1.32, p=0.57); see Figure R4 (161). This was also the case for the 140 patients who developed delirium during hospital stay.

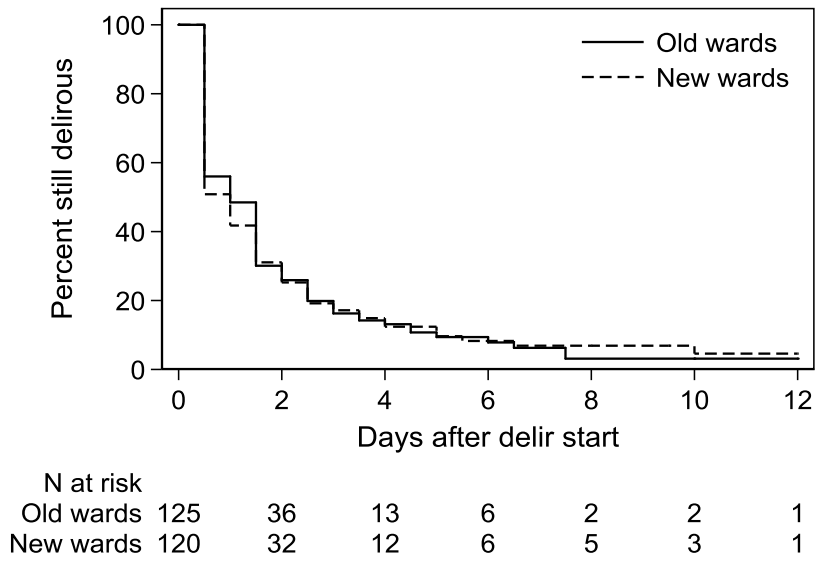

Figure R4 Time from diagnosis to recovery of the first period of delirium (161).

5.3 Complications of delirium after discharge

(Complementary results from study I)

During the first 30 days after discharge, we observed that patients with delirium had a higher probability to be admitted to a 24-hour care center or to a nursing home, to visit the emergency department after a traumatic fall, and to die, compared to patients who did not develop delirium, see Table R5.

Table R5. Follow-up 30 days after discharge for patients with and without delirium

	Patient without delirium n (%)	Patients with delirium n (%)	RR (95% CI)	P-value
N	769	245		
24-hour care center[1]	202 (26%)	115 (47%)	1.79 (1.50-2.14)	<0.0001
Nursing Home[2]	41(5%)	21(9%)	1.61 (0.97-2.67)	0.07
Re-admission	114 (15%)	32(13%)	0.88 (0.61-1.27)	0.49
Traumatic falls[3]	10(1%)	8(3%)	2.51 (1.00-6.29)	0.04
Death	58(8%)	41 (17%)	2.22 (1.53-3.22)	<0.0001

[1]Discharged to a 24-hour care center
[2]Moved to nursing home in the first 30 days after discharge
[3]Admitted to emergency department after a traumatic fall

Among patients who had developed delirium during hospitalization, the 30-days risk to die, to be moved to a nursing home or a 24-hour care center, or to suffer a traumatic fall after discharge was significantly increased compered to patients who had not developed delirium.

5.4 Use of analgesics and psychoactive drugs (Paper II (160))

Table R6 shows the use of analgesics and psychoactive drugs among inpatients.

Table R6. Use of analgesics and psychoactive drugs during hospitalization

	Old wards with multiple-bed rooms. n (%)	New wards with single-bed rooms. n (%)
Natural opium alkaloids (opioids) (N02AA)	228 (49%)	268 (48%)
Other opioids (N02AX)	27(6%)	39 (7%)
Antipsychotics (N05A)	25 (5%)	35 (6%)
Anxiolytics (N05B)	21 (5%)	21 (4%)
Hypnotics and sedatives (N05C)	94 (20%)	106 (19%)
Antidepressants (N06A)	135 (29%)	155 (28%)
Anti-dementia drugs (N06D)	19 (4%)	20 (4%)

There were no significant differences in the use of analgesics and psychoactive drugs between the two wards, see Figure R5.

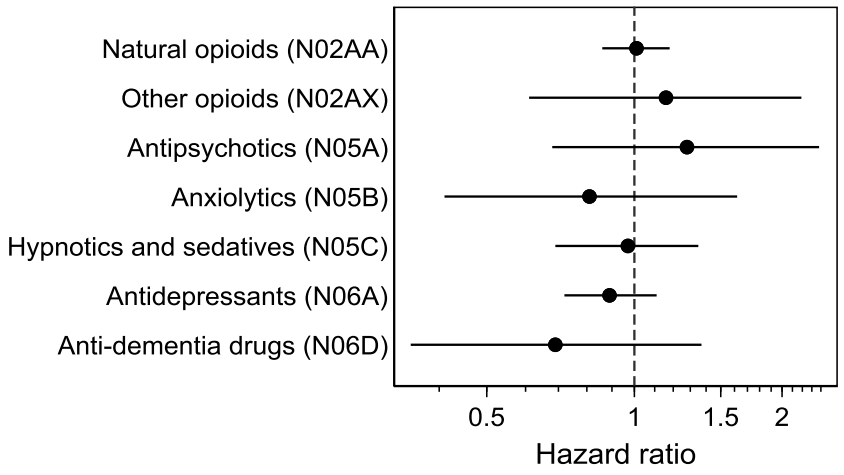

Figure R5 Use of medications in the new vs. old wards during hospitalization.

Thirty-six patients (4%) received risperidone during hospitalization; 24 of these received it as a new ordination during hospitalization. Five patients from the old wards and seven from the new wards received risperidone at admission for causes other than delirium. The median dose for risperidone was 1.5 mg (IQR 0.5 mg-5 mg) in the old wards and in the new wards 2.5 mg (IQR 1 mg-5.5 mg), p=0.40 (160, 161).

5.5 Falls in relation to delirium in the old and new wards (Paper II (160))

"In the old wards, 26 (6%) patients and in the new wards 23 (4%) had experienced one or more falls during hospitalization; the difference was insignificant, HR=0.81 (95%CI 0.46-1.42). Patients with delirium had an increased risk of falls, HR=4.68 (95% CI: 2.58-8.46, p<0.001). There was however, a significant interaction between ward type and delirium on the risk of falls, p=0.008. As illustrated in Figure 3 [Figure R6 in this thesis], the contrast in the incidence of falls between patients with and without delirium was modest in the old wards, while there was a strong contrast in the new wards." (*Direct quotation from Paper II* (160)).

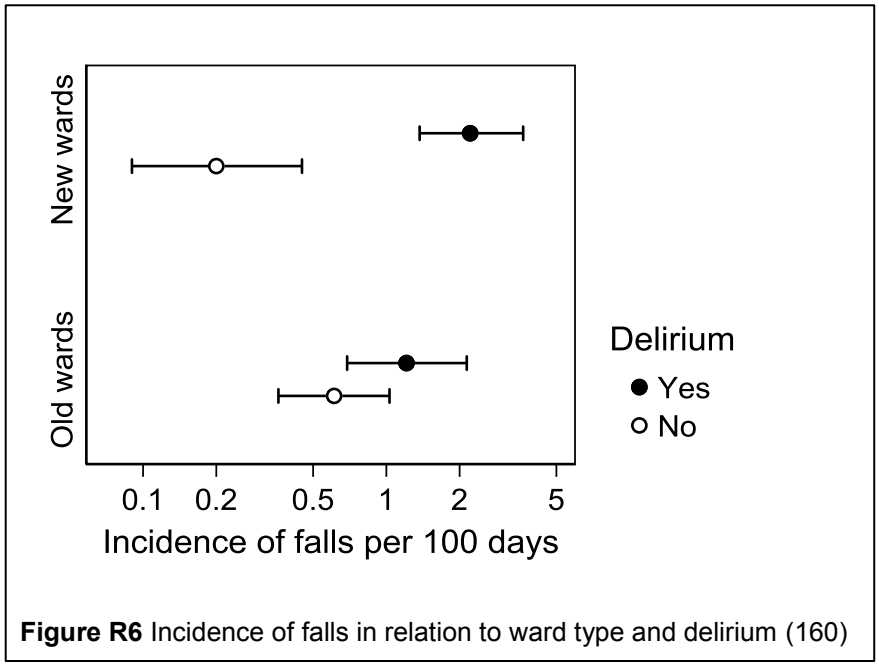

Figure R6 Incidence of falls in relation to ward type and delirium (160)

5.6 Use of analgesics and psychoactive drugs and risk of falls (Paper II (160))

The incidence of falls among inpatients receiving a particular analgesic or psychoactive drug is shown in Table R7. We found an insignificantly higher risk of falls among patients using antipsychotics and anti-dementia drugs (160).

Table R7. The risk of falls in relation to use of analgesic and psychoactive drugs (160)

Medication exposure	Number exposed n (%)	Patients with falls n (%)	Risk ratio (95% CI)[1]
Regardless of exposure	1,014(100%)	49 (5%)	-
Natural opium alkaloids (opioids) (N02AA)	496 (49%)	23 (5%)	0.92 (0.53-1.60)
Other opioids (N02AX)	66 (7%)	2 (3%)	0.61 (0.15-2.46)
Antipsychotics (N05A)	60 (6%)	6 (10%)	2.22 (0.98-5.00)
Anxiolytics (N05B)	42 (4%)	1 (2%)	0.48 (0.07-3.41)
Hypnotics and sedatives (N05C)	200 (20%)	10 (5%)	1.04 (0.53-2.05)
Antidepressants (N06A)	290 (29%)	19 (7%)	1.58 (0.90-2.76)
Anti-dementia drugs (N06D)	39 (4%)	4 (10%)	2.22 (0.84-5.87)

[1] The risk ratio compares users and non-users of the medication.

5.7 Use of analgesic and psychoactive drugs and risk of delirium (Paper II (160))

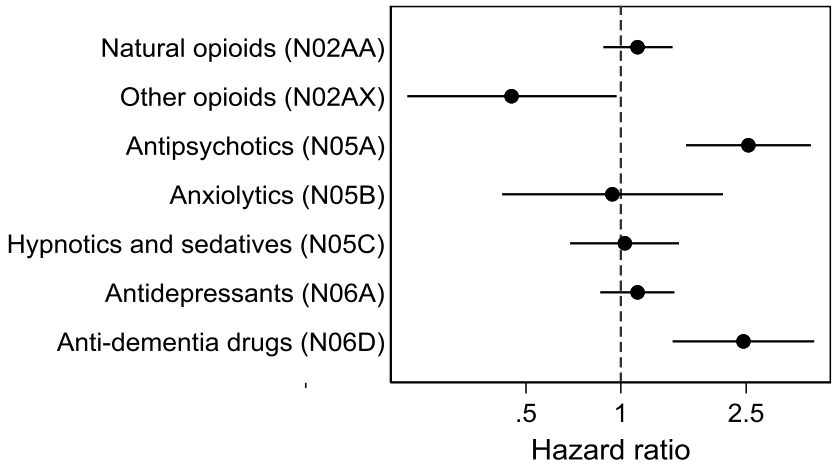

Figure R7 Hazard ratio (95% CI) for delirium after use of various medications vs. no prior medication

Figure R7 illustrates hazard ratios (HR) for delirium in relation to use of prior medications. Users of other opioids had a decreased risk to develop delirium (HR: 0.45, 95% CI 0.21-0.97), while patients using anti-dementia (HR: 2.45, 95% CI 1.46-4.11) or antipsychotic drugs (HR: 2.54, 95% CI 1.61-4.01) had a higher risk (160).

5.8 Identifying high-risk patients with IQCODE screening (Paper III (162))

> "In Table 2 [Table R8 in this thesis], a crude analysis shows associations between the risk of delirium and high IQCODE score, high age, a prior diagnosis of dementia, and impaired physical ability, while overweight appeared to protect against delirium. In an analysis with mutual adjustment for the other risk factors, the IQCODE score retained its predictive value while a prior diagnosis of dementia did not contribute further to prediction once the IQCODE score was known." ((*Direct quotation from Paper III (162)*).

Table R8. Risk factors for development of delirium (162)

	Crude Odds Ratio (95% CI)	*p-value*	Mutually adjusted Odds Ratio (95% CI)	*p-value*
IQCODE per unit	3.53 (2.22-5.60)	<0.001	2.64 (1.54-4.53)	<0.001
Age per 10 years	1.92 (1.15-3.20)	0.01	1.89 (1.05-3.39)	0.03
Prior diagnosis of dementia	2.67 (1.06-6.72)	0.04	1.14 (0.36-3.58)	0.82
Severe to moderate physical disability	3.36 (1.72-6.54)	<0.001	1.97 (0.94-4.12)	0.07
BMI < 18.5	1.21 (0.50-2.97)	0.67	0.91 (0.33-2.52)	0.86
18.5 ≤BMI ≤25	1 (reference)			
BMI > 25	0.25 (0.11-0.58)	<0.001	0.29 (0.12-0.67)	<0.01

Table R9 shows the association between different IQCODE score levels and the risk of delirium.

Table R9. IQCODE score and risk of delirium (162)

IQCODE score	All patients	Patients with delirium
<3.0	1	1 (100%)
3.0 - <3.3	110	6 (5%)
3.3 - <3.5	23	5 (22%)
3.5 - <4.0	62	8 (13%)
4.0 - <4.5	48	12 (25%)
4.5 – 5.0	62	26 (42%)
Total	306	58 (19%)

Figure R8 and Table R10 show the ability of IQCODE to discriminate between patients developing and not developing delirium at different cut-points.

Table R10. Sensitivity, specificity, and predictive values at selected IQCODE cut-points (162)

IQCODE cut-point	Sensitivity	Specificity	PV+	PV–	OR
≥ 3.0	0.98	0	0.19	0	0
≥ 3.3	0.88	0.42	0.26	0.94	5.3 (2.3-12.1)
≥ 3.5	0.79	0.49	0.27	0.91	3.7 (1.9-8.0)
≥ 4.0	0.66	0.71	0.35	0.90	4.6 (2.5-8.5)

"The ROC area was 0.72, and choosing an IQCODE cut-point of 3.3, a third of the patients would be in a low-risk group, with a risk of 6% of developing delirium, and two-thirds would be in a high-risk group, with a risk of 26%. It would predict 51 (88%) of the 58 patients with delirium at a cost of 144 false-positive predictions. Increasing the cut-point would reduce the number of false-positive predictions, but also reduce the number of true-positive predictions" ((*Direct quotation from Paper III* (162))

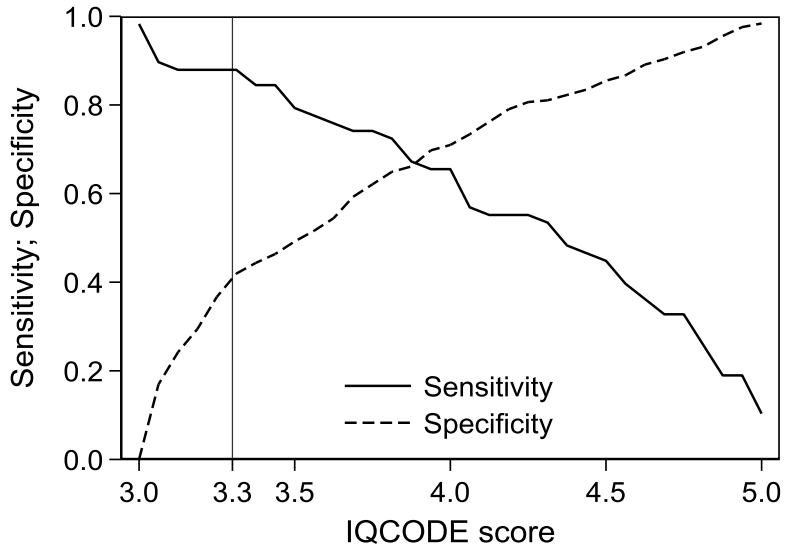

Figure R8 Sensitivity and specificity in relation to the IQCODE score's ability to predict delirium during hospitalization (162)

The above analyses included all patients, also patients who had delirium at the first CAM test after admission, and some of these may have had delirium before admission. In a supplementary analysis, the patients with delirium at first screening were excluded. The crude associations between the risk of delirium and high IQCODE score, high age, and impaired physical ability are shown in Table R11. IQCODE score and age retained their predictive values in the mutually adjusted analysis for the other risk factors,

Table R11. Risk factors for development of delirium among patients who did not have delirium at first screening after admission; n=278

	Crude Odds Ratio (95% CI)	***p-value***	**Mutually adjusted Odds Ratio (95% CI)**	***p-value***
IQCODE, per unit	5.31 (2.75-10.29)	<0.001	5.68 (2.54-12.69))	<0.001
Age, per 10 years	3.42 (1.64-7.11)	0.001	3.90 (1.60-9.53)	0.003
Prior diagnosis of dementia	0.58 (1.06-6.72)	0.60	0.25 (0.02-4.48)	0.23
Severe to moderate physical disability	3.12 (1.28-7.56)	<0.02	1.31 (0.49-3.64)	0.61
BMI < 18.5	1.69 (0.56-5.12)	0.34	1.33 (0.34-5.13)	0.68
18.5 ≤ BMI ≤ 25	1 (reference)			
BMI > 25	0.35 (0.12-1.00)	0.04	0.38 (0.12-1.17)	0.09

6. Discussion

6.1 Summary of key findings

The key findings of the studies included in this thesis are

1. The risk of geriatric hospitalized patients developing delirium was lower in new wards with single-bed rooms than in the old wards with multiple-bed rooms.
2. In the new wards, patients developing delirium had a significantly higher risk of falls compared with patients who did not develop delirium during hospitalization.
3. The use of analgesics and psychoactive drugs was similar in the two wards. The risk of falls was insignificantly associated with the use of these drugs.
4. Patients using antipsychotics and anti-dementia drugs had an increased risk of delirium.
5. Patients admitted to geriatric wards are at high risk of having cognitive impairment, and IQCODE is a tool that can contribute to identifying patients at high risk of delirium.

In the following, these findings will be discussed; see also Papers I, II, and III for further details.

6.2 Geriatric patients

Patients admitted to Geriatric department are characterized by a high degree of frailty, a high risk of physical disabilities and cognitive impairment, and a high use of analgesic and psychoactive drugs, also when compared to old people in general. They are all characterized by a high risk of developing delirium.

6.3 The incidence of delirium in single-bed rooms and multiple-bed rooms

In the present study of geriatric patients, we found a considerably decreased incidence of delirium, also after the adjustment, among patients staying in single-bed rooms compared with patients staying in multiple-bed rooms (161). Limited attention has been given to the impact of single-bed vs. multiple-bed rooms on the risk of delirium, and only clinical studies in intensive care units has examined this subject (98, 99). Caruso et al. found similar to our results, that use of single-bed rooms could reduce the risk of delirium in an intensive care unit (99)., whereas Zaal et al. found no significant difference in the risk of developing delirium in single-bed rooms compared to multiple-bed rooms. Instead, Zaal et al. found a reduced duration of delirium in single-bed rooms compared to multiple-bed room (98). We did not find any difference in the duration of delirium between the wards. This is in accord with the results from Caruso et al. (99, 161).

There may be several reasons why single-bed rooms contribute to a lower incidence of delirium. Single-bed rooms allow patients to have relatives with them during the hospitalization. Clinical studies show that family may have an important role in preventing and reducing delirium in older inpatients (163-165). In addition, single-bed rooms allow for better night-time sleep with fewer disruptions (97), and a previous study has shown that nocturnal disturbances may increase the risk of postoperative delirium (166). Another possible explanation for a reduced incidence of delirium in single-bed rooms is the possibility to let examinations and conversations take place in a room with privacy, and this means less relocation of the patients. A clinical study by Goldberg et al. found the frequency of relocations of old patients to be associated with the risk of delirium (93). The total area is up to 50% larger in the new wards compared to the old wards, and the windows extend from floor to ceiling. We did not investigate the influence of space and light on the risk of developing delirium. Zaal et al. found that the light intensity was significantly lower in multiple-bed rooms compared to single-bed rooms, and this may have contributed to the different incidences (98).

6.4 Complications of delirium after discharge

We found that high age, a prior diagnosis of dementia, and severe to moderate physical disability were associated with the development of delirium during hospitalization. A state of delirium contributed to a higher risk of discharge to a 24-hour care center after hospitalization, moving to a nursing home, and incidence of traumatic falls and deaths in the first month after discharge. This pattern is in line with other studies (51, 54, 55, 82, 85, 167, 168).

6.5 Use of analgesics and psychoactive drugs in single-bed rooms vs. multiple-bed rooms

We found no difference in the consumption of analgesics and psychoactive drugs between the old and the new wards. An earlier study by Gade Holdensen et al. explored the consumption of haloperidol in older inpatients during a change from multiple-bed rooms to single-bed rooms and found that the consumption was reduced by 50% (169). In our department, we rarely treat delirium with antipsychotics, and in these cases, we use risperidone rather than haloperidol. There were no differences in the number treated nor the dosage between the old and the new wards.

In an RCT by Agar et al., the efficacy of risperidone and haloperidol were compared to placebo. The authors found that patients receiving haloperidol or risperidone had higher delirium symptom scores than patients in the placebo arm (170).

6.6 Falls in relation to delirium in single-bed rooms and multiple-bed rooms

Falls among older patients are well known, and the incidence is high in geriatric wards compared to other hospital wards. Geriatric patients frequently suffer cognitive impairment, physical disability, balance deficit, polypharmacy, and visual impairment, all characteristics which are related to the risk of falls (102, 105, 171). Patients who suffered from delirium

during hospitalization had a higher risk of falls than patients without delirium. This result is in agreement with other clinical studies (102, 105, 106, 172).

There was no overall difference in the risk of falls in the two wards. In the new ward, the risk of falls was reduced among non-delirious patients compared to the old wards, whereas patients with delirium had a higher risk of falls in the new wards. One explanation may be that patients who developed delirium despite the favourable environment in the new wards were especially vulnerable and therefore at higher risk of falling. It is also possible that a larger proportion of delirious patients in the new wards had hyperactive delirium with an increased risk of falling. This was seen in a study by O´Keeffe et al. (173). However, the subtype of delirium was not recorded in our study, so this possibility cannot be determined. Another explanation could be that fellow patients in the old wards had a preventive effect by alerting the staff if there was a risk of falls in a delirious patient.

6.7 Use of analgesics and psychoactive drugs and risk of delirium or falls during hospitalization

The use of opioids (N02AA) was not associated with delirium. Our observation is in accordance with other studies (118-121). For patients who took other opioids (N02AX), the incidence of delirium was reduced. This differs from previous studies that found tramadol to be a precipitating factor for delirium (121, 174) We believe that the contrast between these findings is caused by an increased awareness of tramadol as a risk factor for delirium, and we have seen a recent decrease in the number of persons redeeming prescriptions for other opioids in Denmark (160).

The incidence of delirium was high among patients using antipsychotics. The underlying mental illness probably escalates both the risk of delirium and the effect of the consumption of antipsychotics, but a direct side-effect of the medication on the risk of delirium can neither be confirmed nor ruled out in the present observational study.

The risk of delirium was also higher for patients who had a consumption of anti-dementia drugs. There is strong evidence that the risk of delirium is associated with dementia (7, 10, 55, 78, 119, 121-123, 130-132) and this probably explains the observed association

between anti-dementia drugs and delirium. However, the study cannot determine whether there is a direct positive or negative effect of anti-dementia drugs on the risk of delirium.

We found no association between the use of analgesics and psychoactive drugs and the risk of falls. Due to time and cost considerations, we abstained from examining dosage and duration of treatments. In a post hoc analysis of an RCT among nursing home residents with dementia, Katz et al. found a dose of risperidone 1 mg/day to be associated with a decreased risk of falls, but the effects of lower and higher doses were uncertain. (129). Three reviews documented different results in different studies (125, 126, 128).

6.8 Identifying high-risk patients with IQCODE screening

We found that a higher IQCODE score at admission was associated with the risk of delirium during hospitalization. This is in line with the findings of other studies (65, 131, 143-145, 147). Priner et al. investigated the predictive potential of IQCODE and found it a useful tool to predict the risk of postoperative delirium (147). The geriatric patients in the studies in this thesis were a high-risk group with a high risk of developing delirium during hospitalization.

An assessment of the risk of developing delirium could help direct attention and allocate resources to high-risk patients in order to prevent delirium during hospitalization.

> "The relevant interventions could be frequent screenings, e.g. by CAM, multi-component non-pharmacological risk reduction as single-bed rooms, promotion of sleep hygiene and early mobilization, ensuring that patients have their glasses and hearing aids, optimizing hydration, nutrition, and bladder and bowel function, and, if needed, provision of supplementary oxygen" (*Direct quotation from Paper III* (162)).

In the present study, an IQCODE cut-point of 3.3 classified two-thirds of older patients with a relatively high risk of delirium of approximately 26% and the remaining one-third with a lower risk of approximately 6%. After adjustment for a number of known risk factors for delirium, IQCODE retained its predictive value, both for patients with delirium at admission and for patients who developed delirium during hospitalization.

"Although it is possible to categorize patients into a larger high-risk group and a smaller lower-risk group, patients in the lower-risk group still had a risk of approximately 6% of developing delirium during hospitalization. This reflects the fact that patients admitted to a geriatric department are in general quite vulnerable, typically with significant physical and mental impairments and multiple diseases.

For these patients, we do not suggest the use of IQCODE as a strict screening tool with a fixed cut-point to decide which patients require special attention and care. First, even patients in the low-risk group have a considerable risk to develop delirium. Second, IQCODE does not make other information about risk factors unimportant. The IQCODE score and the individual responses can be a useful supplement to other clinical information." (*Direct quotation from Paper III* (162)).

Different multicomponent tools predicting delirium during hospitalization have been developed and many of them include cognitive impairment with predisposing or precipitating risk factors, i.e., sensory impairment, increasing age, functional ability, illness severity and infection (175, 176). Generally, the different tools have a high sensitivity, but like in our study of IQCODE, specificity is relatively low, and the positive predictive values do not differ from our study when considering the rate of delirium (176).

It is a challenge to diagnose delirium in patients suffering from dementia or other cognitive impairment. For Alzheimer dementia, vascular dementia and dementia with Lewy bodies there is some overlap with DSM-5 and ICD-10 diagnosis of delirium. Fluctuating cognition is seen in Alzheimer dementia and vascular dementia, and Lewy bodies symptoms of hallucinations and delusions are described (10). The IQCODE can be a useful supplement to CAM in identifying delirium in patients suffering from Alzheimer dementia, vascular dementia and patients with cognitive impairment, as these patients may also fulfil the acute onset and fluctuating course criteria in CAM.

6.9 Dementia among the older inpatients

In the present studies, the prevalence of a prior diagnosis of dementia ranged from 7% to 9%. However, approximately two-thirds of patients in the predictive study had an IQCODE score of 3.3 or higher, giving rise to a suspicion of dementia. It seems that there is an

under-diagnosis of dementia in these inpatients which corresponds to estimates of the Danish Health Authority (138, 139).

The information from the IQCODE provides practical insight into the impact of cognitive impairment from the perspective of relatives. Some older people complain of memory loss, but according to a study by Derouesné et al., many older people do not realize their cognitive deficit and the impact it has on their daily life (177).

6.10 Methodological considerations

6.10.1 Selection problems

For Papers I and II, a large population of geriatric patients was included. During the study period, admission criteria, uptake area, and staff composition remained stable, and hence the patient populations in the old and the new wards can be considered comparable, and so can the patient-related prognosis for delirium and falls. The patients in the two ward types were quite similar, and adjustment for age, comorbidity, physical disability, a prior diagnosis of dementia, and acute illness did not change the results.

The exclusion of approximately 6% of patients who were dying or were unable to communicate was inevitable. This happened in both ward types. It hardly affected the main results.

For Paper III, the study was conducted in the new ward, where the settings and participants remained the same during the data collection. It is a normal procedure in our department to invite the patient's family or a close friend to set goals for the hospitalization and to plan the discharge, unless the patient refuses involvement of relatives. In total, 87% of invited patients participated, and there were no major differences between participating and non-participating patients.

We did not store data on the patients who were excluded. For patients who were excluded during holiday periods, there are no reasons to believe that they differed from the included population, as the uptake area and the admission criteria were the same during the whole

period. For the patients unable to understand or speak Danish, there are no doubt socio-economic and cultural differences from the included population

6.10.2 Information problems

CAM is a validated and robust method of assessing delirium (20, 22, 25). To identify delirium, a CAM score was collected prospectively by trained geriatric staff morning and evening during the whole hospitalization. All involved staff completed the same course before using CAM. During the data collection the clinical guidelines for delirium did not change. The staff composition and the usual staff replacement did not change in relation to the relocation of the department. Moreover, delirium fluctuates, and screening the patients morning and evening during the hospital stay reduced the risk of missing episodes of delirium.

Another strength of the studies is that tests for delirium were carried out in almost all patients. Just 2% of all planned CAM screenings were missing. One percent of the patients were not in the wards at the time the examinations were conducted, or the patients were somnolent. For 0.9%, the CAM score was missing for unknown reasons.

Before the study was performed, a test of a sample of 52 patients found a satisfactory inter-rater agreement between two observers using CAM. The survey was conducted only on a small group of approximately 15 to 20 employees who were at work during those days. We did not repeat an examination of the reliability during the study period, and we can only presume that the reliability remained satisfactory. We cannot exclude misclassifications, but we see no reason to believe that they should differ in the two types of wards. Thus, any misclassifications would reduce rather than increase the observed contrast between ward types. Approximately 80 staff members were involved in CAM examinations during the study period.

CAM does not measure the severity or subtypes of delirium. We could have chosen to use an instrument measuring this, e.g. the Memorial Delirium Assessment Scale or Delirium Rating Scale, but the staff was accustomed to CAM. Furthermore, these instruments were not translated into Danish.

In Paper II, we were able to determine whether a medication was given before or after delirium started or before or after the first fall. However, we did not have information on the use of medications prior to the admission, and this may have influenced the results. We chose to compare the dosages of risperidone, but not other medications, and we may have overlooked differences in the dosage of other medications between the two wards.
In the geriatric wards it has been a tradition to focus on reporting falls among older patients. Also, few geriatric patients can get up from the floor without assistance after a fall, and therefore there were few, if any, missed falls among patients.

The IQCODE interviews in Paper III were conducted by trained geriatric staff, and staff members had completed the same course before using IQCODE.

The IQCODE interview does not involve the patients; relatives or friends were informants. The information from relatives or friends may be affected by recall problems.
Some studies have shown that responding to IQCODE is not influenced by the duration or quality of the relationship between the patient and the informant (140, 178), whereas another study shows that the relationship between patient and informant is important (179). In the present project, the relatives in eight cases did not feel able to answer the questions regarding comparison of the present situation with that 10 years ago. The period of 10 years was chosen by Jorm et al. because it is a practical reference point for the relatives (180). It is a long period during which patients may have had other cerebral diseases affecting cognitive functions such as stroke. This makes the answer and interpretation of IQCODE more difficult. It is expected that cognitive function decreases with age because of a higher number of comorbidities. Thus, it is presumed that a 10-year observation period may yield a less clear picture in an elderly person than in a younger one. An age-differentiated interpretation of IQCODE would be helpful.

6.10.3 Confounding

The size of both studies and the number of episodes of delirium allowed us to adjust for potential confounders. In paper I, the patients in the old and new wards were quite similar, and adjustments for potential confounders did not change the results substantially. In theory, the optimal way to study the effects of such factors would be an RCT, allocating

patients randomly to various ward arrangements, but this is obviously not feasible, for ethical, political, and economic reasons.

In the present study, we had the opportunity to utilize the relocation of the geriatric department as a so-called "natural experiment". This is a less-than-perfect alternative to an RCT, and it is important to realize that the difference between wards in the risk of delirium may depend on more factors than single-bed rooms vs. multiple-bed rooms; there are many other differences between the old and the new wards. The results must, therefore, be interpreted with caution.

In Paper II, we met a confounding-by-indication problem as we could not distinguish whether the use of antipsychotics and anti-dementia drugs were a main cause of delirium and falls, or the cause was the mental health problems generating the indication for subscribing the drugs.

In the predictive study in paper III, confounding is less of an issue, because the study does not imply a causal hypothesis, the main question being whether IQCODE is useful in predicting the risk of delirium. This was confirmed, and IQCODE retained its predictive value after adjustment for competing predictors.

6.10.4 Generalizability

In these studies, the geriatric population is a selected group of quite vulnerable older patients with a high risk of cognitive impairment, falls, and physical disability. The patient mix in other countries and even in other Danish geriatric departments may be different, but we believe that our results in principle are valid for geriatric patients elsewhere.

For the CAM assessments, we had to exclude patients who were dying or somnolent at the time of admission, and patients who were unable to communicate for various reasons. These patients are also at risk of delirium, but there is no reason to assume that the main results of our studies are irrelevant for them.

In our geriatric department, there is a regular cooperation with relatives or friends. In other wards where this is not done, it might be difficult to recruit a relative or friend, and this may affect the utility of informant tools as IQCODE in practice (181).

7. Conclusion

We found evidence that the risk of delirium for patients in geriatric wards is reduced in single-bed rooms compared with multiple-bed rooms. In single-bed rooms, patients with delirium had a higher risk of falls compared to other patients. The associations between mental frailty, the use of psychoactive drugs, and the risk of delirium and falls reflect a complex causal pattern that cannot be completely disentangled.

Patients admitted to geriatric wards are frail and at high risk of having acute and chronic cognitive impairment. IQCODE is a useful tool which can contribute to identifying patients at high risk of delirium and patients who may benefit from dementia-friendly treatment and care.

7.1 Perspectives

The consequences of having delirium during hospitalization are serious for geriatric patients and their relatives, and an extra burden on the health care system. Development of preventive interventions is needed.

This thesis shows a substantially reduced risk of delirium among geriatric patients in single-bed rooms compared to multiple-bed rooms. We therefore recommend that hospital facilities are developed to allow all geriatric patients to be admitted to single-bed rooms during hospitalization. Today, we have 21 acute hospitals in Denmark. Seven are new-built or are going to be new-built with single-bed rooms only. Nine are going to be renovated as up-to-date hospitals. This modernization of the Danish hospitals will make it possible to admit the geriatric patients to single-bed rooms in 16 of the acute hospitals.

Because geriatric patients are at high risk of developing delirium, the staff in the hospitals should be educated in prevention, detection, and treatment of delirium. Especially the detection of patients with hypoactive delirium is a challenge. In patients with delirium, there should be increased attention to the risk of falls, especially for patients in single-bed rooms. A program for prevention of falls among delirious patients is needed.

Many geriatric patients have cognitive problems, but many cases of dementia in this population are not recognized. There is a need to strengthen the professional competence of the hospital staff to detect patients with cognitive problems, and thus those with a high risk of developing delirium. The IQCODE questionnaire is a useful screening tool for this purpose.

Little is known about medication and risk factors for delirium. The effect of various medications is especially difficult to study because of problems with disentangling the effect of medications from the effect of the diseases and ailments providing the indication for the medication. Further studies should investigate the drug level in the plasma and the risk of delirium.

It is still necessary to develop and test screening instruments that can be used in emergency admissions to identify patients at high risk of developing delirium during hospitalization. These instruments should contain information on premorbid cognitive functions and other assessments of the fragile patient such as illnesses and use of medications.

8. Summary in English

Delirium is a severe complication which occurs frequently in elderly inpatients and especially in patients with pre-existing cognitive impairment. In March 2017, a geriatric department was moved from old hospital buildings with multiple-bed rooms (old wards) to a new hospital with single-bed rooms (new wards), with no changes regarding uptake area, staff, and admission criteria.

The aims of this thesis are as follows: 1. to investigate the risk of delirium among patients in single-bed rooms compared with multiple-bed rooms 2. to investigate the risk of delirium, change in medication use, and the incidence of falls among patients in single-bed rooms compared with multiple-bed rooms. 3. to investigate whether the use of analgesics and psychoactive medications was associated with the risk of delirium and falls. 4. to assess the usefulness of the IQCODE questionnaire in predicting delirium during hospitalization in elderly inpatients.

The PhD dissertation includes two studies: an observational prospective study and a prognostic in the Geriatric Department at Aarhus University Hospital, Denmark.

The first study included patients aged ≥75 years admitted between September 2016 and December 2017. Every morning and evening, a nurse, a nurse assistant, an occupational therapist, or a physiotherapist trained to detect delirium assessed the presence of delirium using the confusion assessment method (CAM). Data on the consumption of analgesic and psychoactive medications and on falls during hospitalization were extracted from medical records.

The prognostic study enrolled consecutive patients during March to December 2017. In agreement with the patient, the staff interviewed a family member or a friend by phone using the IQCODE questionnaire. The power of IQCODE to predict delirium was examined.

In the observational study, 461 admissions to the old wards and 553 admissions to the new wards were included. Patients' characteristics were similar between patients admitted to the old wards and to the new wards. In 105 patients, delirium was present at admission, with no significant difference between the old and new wards. Patients admitted to the new

wards had a significantly reduced incidence of delirium during hospital stay compared with patients admitted to the old wards, hazard ratio 0.66 (95% CI: 0.48-0.93, p<0.02). There was no difference between the old and the new wards in the duration of the first delirium episode. There was no difference in the consumptions of analgesic and psychoactive medications between the wards. In the new wards, patients who had delirium had an increased risk of falls compared to patients without delirium, while in the old wards this contrast was smaller. Among patients who received antipsychotic drugs and anti-dementia drugs, the incidence of delirium was increased, and patients who received these drugs had an insignificantly higher risk of falls.

In the prognostic study, 353 patients were eligible, and 306 completed the IQCODE questionnaire. The incidence of delirium during hospitalization was 19%. The IQCODE score was associated with the incidence of delirium, with an area under a receiver operating characteristic (ROC) curve of 0.72. A cut-point of 3.3 could split the inpatients into a large group with a risk of almost 26% to develop delirium and a small group with a risk of almost 6%.

We conclude that the risk of delirium is reduced in single-bed rooms compared with multiple-bed rooms. Use of analgesics and psychoactive drugs was identical in the old and new wards. In single-bed rooms, but not in multiple-bed rooms, there was an increased risk of falls among patients with delirium compared to other patients. The use of antipsychotics and anti-dementia drugs during hospitalization was associated with an increased risk of delirium and an insignificantly higher risk of falls.

IQCODE is a useful tool to detect pre-existing cognitive impairment in older inpatients but should not be the only tool used to predict delirium.

Based on these results, we strongly recommend that geriatric inpatients be admitted to single-bed rooms. It is important to identify patients with delirium, and the geriatric staff should receive an education in prevention and treatment of delirium. Furthermore, as patients with delirium are at high risk of falls during hospitalization, a program for prevention is needed. Among geriatric patients, there are many patients with pre-existing cognitive impairment. There is a need to strengthen the professional competence in the hospital staff to be able to detect dementia and provide care to patients with dementia. The

IQCODE questionnaire can be used to advantage in a geriatric department, however this instrument should be refined and tested in new studies.

9. Summary in Danish/Dansk resumé

Delirium er en alvorlig komplikation, der ofte forekommer hos ældre patienter med allerede eksisterende kognitiv svækkelse. I marts 2017 blev en geriatrisk afdeling flyttet fra gamle hospitalsbygninger med flersengsstuer (gamle afdelinger) til et nyt hospital med enestuer (nye afdelinger) uden ændringer med hensyn til optagelsesområde, personale og indlæggelseskriterier.

Formålet med denne afhandling er; 1. at undersøge risikoen for delirium blandt patienter på enestuer sammenlignet med flersengsstuer; 2. at undersøge risikoen for delirium, ændring i brug af medicin og incidensen af fald blandt patienter på enestuer sammenlignet med flersengsstuer; 3. at undersøge, om brugen af smertestillende midler og psykoaktive medikamenter var forbundet med risikoen for delirium og fald; 4. at vurdere om IQCODE-spørgeskemaet kan prædiktere delirium under hospitalsindlæggelse hos gamle patienter.

Ph.d.-afhandlingen bygger på to studier; en observationel prospektiv undersøgelse og en prognostisk undersøgelse på Geriatrisk afdeling på Aarhus Universitetshospital, Danmark.

Det første studie omfatter patienter i alderen ≥75 år indlagt mellem september 2016 og december 2017. Delirium blev vurderet af delirium-uddannede sygeplejersker, social og sundhedsassistenter, ergoterapeuter og fysioterapeuter hver morgen og aften ved hjælp af Confusion Assessment Method (CAM). Data om medicinforbrug og fald under indlæggelse blev trukket fra patientjournalerne.

Det prognostiske studie inkluderede konsekutive patienter fra marts til december 2017. Efter aftale med patienten interviewede personalet en pårørende telefonisk ved hjælp af IQCODE-spørgeskemaet. IQCODE's evne til at forudsige delirium blev undersøgt.

I det observationelle studie blev 461 indlæggelser inkluderede på de gamle afdelinger og 553 inkluderede på de nye afdelinger. Patienternes karakteristika var ens for patienter indlagt på de gamle og de nye afdelinger. Delirium var til stede ved indlæggelsen hos 105 patienter, uden nogen signifikant forskel mellem de gamle og nye afdelinger. Patienter i de nye afdelinger havde en markant reduceret forekomst af delirium under opholdet på hospitalet sammenlignet med patienter i de gamle afdelinger; hazard ratio 0,66 (95% CI: 0,48-0,93, p<0,02). Der blev ikke observeret nogen forskel mellem de gamle og de nye

afdelinger i varigheden af den første delirium-episode. Der var ingen forskel i brug af medikamenter mellem afdelingerne. I de nye afdelinger havde patienter, der havde oplevet delirium, en meget højere risiko for fald end patienter uden delirium; i de gamle afdelinger var denne kontrast lille. Risikoen for delirium var øget blandt patienter, der anvendte antipsykotika og antidemensmedicin, og patienter, der modtog disse medikamenter havde en ikke-signifikant øget risiko for fald.

I det prognostiske studie var 353 patienter egnet til inklusion, og 306 gennemførte IQCODE. Forekomsten af delirium under indlæggelse var 19%. IQCODE var associeret med risikoen for delirium, og ROC-kurvens areal var 0,72. Et skærepunkt på 3,3 kunne adskille patienterne i en større gruppe med en risiko på cirka 26% for at udvikle delirium og en mindre gruppe med en risiko på cirka 6%.

Vi konkluderer, at risikoen for delirium er reduceret på enestuer sammenlignet med flersengsstuer. Analgetika og psykoaktive stoffer var ens i de gamle og nye afdelinger. På enestuer, men ikke på flersengsstuer, var der en højere risiko for fald blandt patienter, der udviklede delirium end blandt patienter som ikke udviklede delirium. Brug af antipsykotika og antidemensmedicin under indlæggelse var forbundet med en øget risiko for delirium og en ikke-signifikant højere risiko for fald.

IQCODE er et nyttigt værktøj til ældre patienter til at opdage allerede eksisterende kognitiv svækkelse, men kan ikke alene prædiktere delirium.

På baggrund af projektets resultater anbefaler vi, at geriatriske patienter bliver indlagt i enestuer. Det er vigtigt at identificere patienter i delirium, og en uddannelse i forebyggelse og behandling af delirium anbefales. Eftersom patienter i delirium er i høj risiko for fald under indlæggelse, er der behov for et program til forebyggelse. Blandt geriatriske patienter er der større risiko for allerede eksisterende kognitiv svækkelse. Det er nødvendigt at styrke de faglige kompetencer hos hospitalets personale for at være i stand til at opdage demens og give pleje til patienter med demens. IQCODE-spørgeskemaet kan med fordel bruges i en geriatrisk afdeling. Hvor instrumentet med fordel forbedres og testes i nye undersøgelser.

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Appendix 1: CAM – Danish version

Kendetegn	**Ikke tilstede**	**Tilstede**
1. Akut indsættende og fluktuerende forløb: *Oplysninger om dette kendetegn fås normalt fra familie eller plejepersonale.* Er der tegn på en akut ændring i patientens mentale tilstand i forhold til den habituelle? Varierer den abnorme adfærd i løbet af døgnet, dvs. kommer og går den eller bliver den mere eller mindre alvorlig?		
2. Uopmærksomhed: *Dette kendetegn viser sig ved et positivt svar på følgende spørgsmål:* Har patienten svært ved at fastholde opmærksomhed, er let at distrahere, har svært ved at holde styr på det der blev sagt?		
3. Uorganiseret tankegang: *Dette kendetegn viser sig ved et positivt svar på følgende spørgsmål:* Er patientens tankegang uorganiseret og usammenhængende med vrøvlende og irrelevant tale, uklare og ulogiske tanker eller uforudsigelig skift fra et emne til et andet?		
4. Ændret bevidsthedsniveau: *Dette kendetegn viser sig ved et positivt svar på følgende spørgsmål:* Er patientens bevidsthedsniveau ændret, således at patienten er: • På vagt (overopmærksom) • Sløv (søvnig) • Som i en døs (vanskeligt at få opmærksomhed) • Ukontaktbar		

For at stille diagnosen delirium skal kendetegn 1 og 2 og enten 3 eller 4 være tilstede (182).

Appendix 2: Search Protocol

PICO is structured according to the search strategy and the hypotheses explained in section 2.9 Literature review.

Table S1. PICO with free text word and number of studies included

Hypothesis	Search strategy	Patient	Exposure	Comparison	Outcomes	Studies included
1	1	Older, frail elderly geriatric inpatients, hospitalization	Single rooms	Multiple-bed rooms	Delirium	2 studies (from ICU), see Table L1 in Appendix 3
2-4	2	Older, frail elderly geriatric inpatients, hospitalization	Single rooms	Multiple-bed rooms	Analgesic and Psychoactive drugs	14 studies or systematic reviews, see Table L1 in Appendix 3
			Analgesic and psychoactive drugs	No use of analgesic and psychoactive drugs	Falls Delirium	
			Delirium	No delirium	Falls	
5	3	Older, frail elderly, geriatric inpatients, hospitalization	Cognitive decline assessed by IQCODE	No cognitive decline	Delirium	1 study with prognostic value, see Table L2 in Appendix 3

Table S2. Selection criteria

Inclusions	Exclusions
❖ Older patients admitted to geriatric-, medical- or orthopaedic department. If no studies from these departments exist other hospitals department can bee included. ❖ In search strategy 3 only prognostic studies are included. ❖ Papers in English, Danish, Norwegian and Swedish. ❖ Published after 1987. ❖ Papers with estimated high level of evidence.	❖ Papers where the method is not described or insufficient evidence. ❖ Papers on patients with organ transplantation, multi-traumatized, alcohol abuse or psychiatric illness. ❖ Papers dealing with patients from very different cultures and communities. ❖ Papers from the Primary sector. ❖ Papers in which the presence of delirium in the patient is decided retrospectively.

Database search

Search strategi: 1	Search Term	Total hits
PubMed	(("Aged"[Mesh]) OR elderly patients) AND ((((Patients' Rooms[MeSH Terms]) OR (((Single room) OR Private ward) OR Side room))) AND ((delirium) OR delirium[MeSH Terms]))	41
Embase	'aged'/exp AND ('single room' OR 'private ward') AND 'delirium'/de	4
Cochrane library	'older people' AND ('single room' OR 'private ward') AND delirium	0
CINAHL	(MH "Aged") AND (MH "Delirium") AND (MH "Inpatients") AND "single room hospital" (MH "Delirium") AND "single room hospital"	0 1
Fit inclusion		0

Search strategi: 2	Search Term	Total hits
PubMed	(((((((Older) OR Elderly) OR Frail Elderly[MeSH Terms] OR ("Aged"[Mesh]))) AND ((hospitalization) OR hospitalization[MeSH Terms])) AND ((delirium) OR delirium[MeSH Terms])))))) AND (((((((((((((((((("Accidental Falls"[Mesh]) OR "Analgesics, Opioid"[Mesh]) OR "Antipsychotic Agents"[Mesh]) OR ("Hypnotics and Sedatives"[Mesh])) OR "Antidepressive Agents"[Mesh]) OR antidepressant drugs*) OR Anti-dementia drugs*) OR "Nootropic Agents"[Mesh]) OR "Risperidone"[Mesh]) OR "Benzodiazepines"[Mesh]) OR benzodiazepine) OR "Psychotropic Drugs"[Mesh]) OR psychotropic drugs)) *combined with* ((((Patients' Rooms[MeSH Terms]) OR (((Single room) OR Private ward) OR Side room)))	371 4
Embase	('aged'/exp OR 'aged' AND 'delirium'/de AND ('hospital patient'/exp OR 'hospitalization'/exp))AND 'geriatrics'/exp/mj OR ('psychotropic agent'/exp OR 'hypnotic sedative agent'/exp OR 'benzodiazepine derivative'/exp OR 'risperidone'/exp OR 'nootropic agent'/exp OR ('anti dementia' AND drugs*) OR (antidepressant AND drugs*) OR 'antidepressant agent'/exp OR 'opioid induced hyperalgesia'/exp ('accidental falls' OR 'falling'/exp/mj)	64
Cochrane library	'older people' AND delirium AND hospitalization AND (psychotropic drugs OR Falls)	37
CINAHL	(MH "Aged") AND (MH "Delirium") AND (MH "Inpatients") AND ((MH "Psychotropic Drugs") OR (MH "Hypnotics and Sedatives") OR (MH "Antianxiety Agents, Benzodiazepine") OR (MH "Risperidone") OR 'anti dementia drugs*' OR (MH "Antidepressive Agents") OR (MH "Accidental Falls"))	31
Fit inclusion		14

Search strategi: 3	Search Term	Total hits
PubMed:	(((((((((Older) OR Elderly) OR Aged[MeSH Terms])) AND ((hospitalization) OR hospitalization[MeSH Terms])) AND ((delirium) OR delirium[MeSH Terms])))))) AND ”Informant Questionnaire on Cognitive Decline in the Elderly”	19
Embase	('informant questionnaire on cognitive decline in the elderly'/exp OR 'informant questionnaire on cognitive decline in the elderly') AND 'delirium'/exp AND 'hospital patient'/exp OR 'hospitalization'/exp	19
Cochrane library	"Informant Questionnaire on Cognitive Decline in the Elderly" AND delirium AND hospitalization	0
CINAHL	"Informant Questionnaire on Cognitive Decline in the Elderly" AND (MH "Delirium") AND hospitalization (MH "Inpatients")	3
Fit inclusion		1

Appendix 3: Tables of the literature

Table L1: Clinical studies and systematic reviews concerning use of patient rooms, analgesics and psychoactive drugs and risk of delirium and fall

Table L2: Prognostic study concerning IQCODE's ability to predict delirium during hospitalization.

Table L1. Clinical studies and systematic reviews concerning use of patient rooms, analgesics and psychoactive drugs and risk of delirium and fall in chronological order (1/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Marcantonio, 1994 (118)	Nested case-control study within prospective cohort study. 91 cases and 154 controls.	245 patients admitted to general and orthopedic surgery and gynecology services. Mean age 73 years.	Use of psychoactive medication (meperidine, morphine, fentanyl, oxycodone, codeine, benzodiazepine, and anticholinergic drugs) 24 h before delirium developed.	Delirium was assessed by CAM once daily. Benzodiazepines (OR, 3.0; 95% CI, 1.3 to 6.8, p<0.01). Meperidine (OR, 2.7; 95% CI, 1.3 to 5.5. Narcotics (OR, 1.4; 95% CI, 0.5 to 4.3, p>0.05). Anticholinergic drugs: p>0.05.	NR	Benzodiazepines increase the risk of postoperative delirium. Comments: Dose unclear. Evidence: 3b.
Morrison, 2003 (122)	Prospective cohort study.	541 patients with hip-fracture were admitted to orthopedic surgery. Mean age above 60 years. Patients with delirium by admission excluded.	Patients received pr. day< 10 mg of parenteral morphine sulphate equivalents compared to patients who received more.	Delirium assessed by CAM once daily. Incidence 16%. Patients using less opioids: RR for delirium 5.4, 95% CI 2.4-12.3. Use of meperidine: RR 2.4; 95% CI 1.3-4.5.	NR	Avoiding or using low dose opioids increases the risk of postoperative delirium. Comments: Dose unclear of meperidine. Evidence: 2b.

Table L1 (continued 2/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Katz, 2004 (129)	Post hoc RCT Double-blind, placebo-controlled clinical trial.	537 Residential-care dementia patients.	Intervention: 4 groups: 1: placebo 2: Risperidone 0.5 mg /day 3: Risperidone 1 mg/day 4: Risperidone 2 mg/day.	NR	166 falls events Groups and falls (%) 1: falls 22.3% 2: falls18% 3: falls 12.7% 4: falls 27.3%. Risperidone 1 mg/day HR 0.53 (95% CI 0.26-0.88, p<0.05). Risperidone 0.5 mg/day HR 0.74 (95% CI 0.44-1.27, p=0.38). Risperidone 2 mg/day day HR 1.31 (95% CI 0.81-2.10, p=0.37).	Risperidone 1 mg/day associated with decrease risk of falls also after adjusted for wandering. Comments: No history of falls. Evidence: 1b
Stenvall, 2006, (106)	Prospective study. .	97 patients admitted with femoral neck fracture to an orthopedic department. Mean age 82 years.	Delirium was assessed by Organic Brain Syndrome Scale (OBS-scale). First screening was 8 hours after surgery.	Delirium postop.: 75%, and delirium after day 7: 52%.	An inpatient fall was defined as an incident, when the patient unintentionally came to rest on the floor. Fallers: 26/97. The post op. fall rate was 16.3/1000 Days (95% CI 12.2-20.4). Delirium after Day 7, HR 4.6 (95% CI 1.2-16.4) adjusted.	High incidence of delirium. Inpatient falls were independently associated with post op. delirium, males, and sleeping disturbances. Evidence: 2b

Table L1 (continued 3/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Hartikainen, 2007 (126)	Systematic review. Studies published 1996-2004: 1 RCT, 19 cohort studies, 9 case- control studies.	Population-based, community-dwellers, residential care settings, nursing home residents, geriatric care settings. Participant aged >60 years.	Use of medication from medical record and patients reporting. Medication; benzodiazepines, antidepressants, antipsychotics, opioids.	NR	Benzodiazepines: Increased risk; p<0.05 in 17 studies. Antidepressants: Increased risk for TCA and SSRI in 12 studies; p<0.05. Antipsychotics: Increased risk in 6 studies; p<0.05. One RCT-study shows dose-dependency for Risperidone and 3 studies found no association. Opioids: 1 study had p<0.05 and 1 study had p>0.05.	Psychotropic drug seems to be associated with increased risk of falls. Heterogeneity between studies, population definition of falls. Medication defined inadequately >50% did not systematic classified medications. Comments: Unknown number of studies at the various medical groups Evidence 3a↓.
Bo, 2009 (123)	Prospective study	253 acute patients admitted to geriatric ward or general medical ward. Mean age 82 years. Patient admitted with delirium were excluded.	Medicine collected: neuroleptics, antidepressants, benzodiazepines.	Delirium assessed by to qualified senior psychiatrist. Short Portable Mental Status Questionnaire (SPMSQ) by ≥3 errors, or if nurses note symptoms of delirium then CAM was used. Antidepressant (p=0.03), neuroleptics (p<0.01), benzodiazepines (p=0.92).	NR	Use of neuroleptics and antidepressant are associated with delirium, and benzodiazepines are not associated to delirium. Comments: The chosen analysis does not show the tendency of the association Evidence: 2b↓.

Table L1 (continued 4/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Corsinovi, 2009 (102)	Longitudinal observational study	620 patients consecutively admitted to Acute Geriatric Ward. Mean age 79 years.	Delirium and polypharmacy.	NR	Incidence of fall was 6/1000 patient-days. Delirium (RR=3.6; 95% CI 1.1-11.7). Polypharmacy (RR=1.2; 95% CI 1.1-1.3)	Multiple factors cause falls in older inpatients. Comments: Polypharmacy not described Evidence: 2b.
Brouquet, 2010 (121)	Prospective study	118 older patients admitted for elective major abdominal surgery. Mean age 81.	Use of analgesic: Intravenous tramadol. Daily dose of 300 mg.	When nurses observed an acute confusion state, the geriatricians assessed CAM twice a day until complete cognitive recovery. Incidence postop. 23.7%. Tramadol: (adjusted HR 7.1, 95% CI 2.2-22.5 p=0.0009).	NR	Tramadol, ASA status 3-4 and impaired preoperative mobility increases the risk of post. op. delirium. Evidence: 2b.

Table L1 (continued 5/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Bloch, 2011 (128)	Meta-analysis The search period was 1981-2007. Studies included: 32 cohorts and 15 case-controls, 24 cross-sectionals studies.	Elderly people pertaining to falls in daily life. Participant aged >60 years.	Psychotropic drugs, antidepressants, benzodiazepines, hypnotic drugs, neuroleptic.	NR	Pooled OR on drugs (No. of Studies). Psychotropic drugs (15): (OR: 1.78, 95% CI 1.57-2.01). Antidepressants (27): (OR: 1.59, 95% CI 1.46-1.73). Benzodiazepines (14): (OR: 1.39, 95% CI 1.24-1.54). Hypnotic drugs (23): (OR: 1.54, 95% CI 1.40-1.69). Neuroleptic (15): (OR: 1.50, 95% CI 1.32-1.71).	Use of psychotropic drugs is associated with falls in older people. The methods to identify falls differ. Evidence: 3a↓(cross-sectional studies included).
Sieber, 2011 (119)	Prospective study	236 patients admitted with hip fracture to an Orthopedic Department. Mean age 82 years. Patients with delirium at admission were excluded.	Patients were assessed for pain, and use of opioid. Opioid was PCA morphine intravenously Bolus 1-2 mg of morphine, 500-1000 mg acetaminophen every 8 h. 2.5-10 mg oxycodone every 4 h.	Postop. day 2 CAM was assessed. Not statistically significant associated with use of any post op. opioid.	NR	Postop delirium is not associated with the use of opioids. Comments. Assessed by trained staff. But only the second post op. day. Evidence: 2b.

Table L1 (continued 6/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Zaal, 2013, (98)	Cohort study	55 patients admitted to multiple-bed rooms and 75 patients admitted to single-bed rooms in intensive care unit. Mean age 59 years.	Multiple -bed rooms compared with single -bed rooms. Light intensity was measured.	Delirium assessed by CAM-ICU. 51% in multiple-bed rooms vs. 45% in single-bed rooms. Incidence of delirium in single-bed rooms OR 0.6 (95% CI 0.3-1.6, p=0.53) compared to multiple-bed rooms. Mean days with delirium reduced with 0.4 days in single-bed rooms compared to multiple-bed rooms, p=0.0005.	NR	No difference in incidence of delirium between single-bed rooms and multiple-bed rooms. Number of days with delirium reduced in single-bed rooms compared to multiple-bed rooms. Light intensity was lower in multiple-bed rooms compared to single-bed rooms p<0.001. Comments: Unknown if patients with delirium at admission were excluded Evidence: 2b.
Caruso, 2014, CCMJ (99)	Retrospective study	1,253 patients admitted to intensive care unit. Mean age 59 years.	Single-bed rooms compared to multiple-bed rooms.	Delirium assessed by CAM-ICU twice a day. Incidence of delirium 13%. 6.8% in single-bed rooms vs. 15.1% in multiple-bed rooms. Incidence delirium in multiple-bed rooms: OR 4.0 (95% CI 2.1-7.6, p<0.05) compared to single-bed rooms.	NR	Low incidence of delirium among ICU-patients. Pt. in single-bed rooms have a lower risk of delirium than ICU-patients in multiple-bed rooms Comments: Unknown if patients with delirium by admission are excluded. Evidence: 2b.

Table L1 (continued 7/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Park, 2015 (125)	Systematic Review The search period was 2008-2013. Studies included: 3 RCT, 17 cohort studies, 8 case-control studies, and 8 cross-sectional	Total participants: 223,659. Community-dwelling, inpatients, outpatients, facility or nursing home residents or healthcare data from databases. Included age >60 years.	Medication use and multiple risk factors for falls.	NR	Fall defined by "Prevention of Falls network European", Kellogg's and Tinnetti's working groups (No. of studies) Psychotropic medication (10): 5 studies p<0.05. Antipsychotics (neuroleptics) (11): 1 study p<0.05. Sedative and hypnotics or anxiolytics/hypnotics (11): 5 studies p<0.05. 1 study: *Chronic use* of sedatives or antipsychotic increased risk of fall and *acute use* reduce risk of fall. Antidepressants (16): 7 studies p<0.05. 3 studies: SNRI higher risk of fall compared to TCA and SSRI. Benzodiazepines (6): 1 Study p<0.05 with benzodiazepines≥ 1mg/day. Z DRUGS (3): 2 Studies p<0.05 (Zolpidem). Medications for dementia (3): No association. Opioids (5): 3 studies p<0.05.	The authors concluded use of sedative and hypnotics, antidepressants is related to risk of falls. Heterogeneity between studies (study design, participant, fall def., and doses). Evidence: 3a↓(heterogeneity and cross-sectional studies included).

Table L1 (continued 8/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Mazur, 2016 (105)	Prospective observational study	788 patients admitted to a sub-acute geriatric ward. Mean age 80 years.	Patients classified in groups of risk of falls. Use of neuroleptics before and after admission.	CAM was used to assess delirium – unknown how often. Incidence of delirium among fallers 30.8% and Non-fallers 3.8%, p<0.001.	Incidence: 26(3%). Delirium: OR 9.8 (95% CI 4.0-24.2) Use of neuroleptic during hospitalization: OR 4.3 (95% CI 1.9-9.6).	Risk factor for falls: delirium, history of falls and high age. Evidence: 2b
Neerland, 2017 (65)	Prospective follow-up study.	696 hip fracture patients. Pre-fracture cognitive function assessed by IQCODE. Cognitive impairment defined by a score 3.44 or higher	Use of Benzodiazepine.	Patients were assessed for delirium pre- and post op. by CAM. Preop. delirium: 28%, postop. delirium: 32%. Patients with cognitive impairment and delirium had more often received benzodiazepine IV periop. (OR 2.5, 95% CI 1.3-4.7). No difference in cognitively intact patients.	NR	Risk factors for incident delirium differ in according to baseline cognitive status. Evidence: 2b

Table L1 (continued 9/9)

First author, year	Study design	Population, setting, age	Exposure	Outcomes		Conclusion/comments
				Delirium	Falls	
Wedmann, 2019 (124)	Matched case-control study	Patient admitted to mixed surgical department and internal medicine. Cases 481 (falls), controls 481.. Mean age 82 years.	The use of medicine 24 h prior to the fall Dose-dependent effect was examined.		Falls was collected by fall protocols. Defined in 3 groups depending on trauma. Incidence rate 4.36/1000 pt. days Long-acting benzodiazepines (OR 3.5, 95% CI 1.2-10.5) SNRI (OR 2.6, 95% CI 1.2-5.1), Low-potency neuroleptics (OR 1.9 95% CI 1.1-3.2), Z drugs (OR 2.3 95% CI 1.4-3.6). Short-acting benzodiazepines, mirtazapine or opioids were not associated with falls.	Long-acting benzodiazepines, SNRI, neuroleptics and Z drugs are associated with inpatients falls. Dose dependent effect was examined. Evidence: 3b

Table L2. Prognostic study concerning IQCODE's ability to predict delirium during hospitalization

First author, year	Study design	Population, setting, age	Predictors	Outcomes	Conclusion/comments
				Delirium	
Priner, 2008 (147)	Prospective study	101 patients admitted to elective surgery for hip and knee prosthesis. Mean age 74 years.	IQCODE before operation, after postop. 24 h .	CAM was used by nurses. Incidence delirium (14.8%) IQCODE score>50 (3.125): 34% (without delirium), 80% (with delirium). IQCODE score>50 (OR 12.7, 95% CI 1.4-115.5). IQCODE score>50: sensitivity 0.80, specificity 0.66,	IQCODE can predict the risk of postop. delirium in elective surgery for hip and knee prosthesis. Evidence:2b

95% CI = 95% confidence interval
ICU=Intensive care unit
NR=not reported
OP=operative
OR=Odds ratio
RR=relative risk
SNRI=Serotonin-noradrenalin reuptake inhibitor
SSRI=Selective Serotonin Reuptake Inhibitor
TCA= Tricyclic antidepressive agents

Appendix 4: IQCODE – Danish version

Informant Questionnaire on Cognitive Decline in the Elderly

The Short Form (16 items)

Når De besvarer spørgsmålene skal De tænke på hvordan Deres pårørende var for 10 år siden sammenlignet med hvordan han/hun er nu.

Nedenfor er der angivet nogle situationer hvor man skal bruge sin hukommelse og intellekt. Vurder om det har været bedre, uændret, eller forværret i løbet af de sidste 10 år.

Det er vigtigt at sammenligne hans/hendes nuværende præstation i forhold til for 10 år siden. For eksempel, hvis din pårørende for 10 år siden altid glemte hvor han / hun havde lagt ting henne, og han / hun stadigvæk gør det, så vil det korrekte svar være "uændret". Angiv venligst de forandringer du har observeret ved at sætte en cirkel omkring det svar, som De mener passer bedst.

Hvordan fungerer Deres pårørende sammenlignet med for 10 år siden med hensyn til:

	1	2	3	4	5
1. Huske ting i forhold til familie og venner for eks. arbejde, fødselsdag, adresse	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
2. Huske ting som er sket for nylig	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
3. Huske indholdet af samtaler der foregik nogle dage tidligere	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
4. Huske sin egen adresse og sit eget Telefonnummer	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
5. Huske hvilken dato og måned det er	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
6. Huske hvor ting normalt er opbevaret	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
7. Huske hvor ting ligger selvom de ikke er lagt på deres vanlige sted	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
8. Vide hvordan man anvender forskellige elektriske apparater i hjemmet (f.eks. kaffemaskine, brødrister, fjernsyn, stereoanlæg, husholdningsapparater)	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
9. Lære at bruge et nyt redskab eller apparat i hjemmet	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
10. Lære nye ting	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
11. Følge handlinger i en bog eller i Fjernsynet	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
12. Træffe beslutninger i hverdagen	Meget	Lidt bedre	Uændret	Lidt værre	Meget værre

	bedre				
13. Håndtere penge ved indkøb	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
14. Tage hånd om personlig økonomi (f.eks. pension, bank)	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
15. Regnefærdigheder i dagligdagen (for eks. hvor meget mad der skal købes ind, hvor lang tid der er gået mellem familie eller venner har aflagt besøg)	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre
16. Evne til at forstå hvad der sker og resonere fornuftigt.	Meget bedre	Lidt bedre	Uændret	Lidt værre	Meget værre

-

Appendix 5: Paper I

Aging Clinical and Experimental Research
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ORIGINAL ARTICLE

Single-bed rooms in a geriatric ward prevent delirium in older patients

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Abstract

Background Few studies have investigated treatment environment risk factors for delirium in geriatric patients. In March 2017, a geriatric department was moved from old hospital buildings with multiple-bed rooms (old wards) to a new hospital with single-bed rooms (new wards), with no changes regarding uptake area, staff and admission criteria.

Aims The aim of this study was to investigate the risk of delirium among patients in single-bed rooms compared with multiple-bed rooms.

Methods An observational prospective study included patients aged ≥ 75 years admitted between 15 September 2016 and 19 March 2017 to the old wards and between 20 March and 19 December 2017 to the new wards. Exclusion criteria were terminal illness, somnolence at admission and inability to communicate in Danish. Delirium was assessed by trained nurses, nurse assistants, occupational therapists and physiotherapists every morning and evening using the Confusion Assessment Method (CAM).

Results We included 1014 patients. Patients' characteristics were similar between patients admitted to the old wards and to the new wards. Delirium was present at admission in 105 patients, with no significant difference between the old and new wards. Patients in the new wards had a significantly reduced incidence of delirium during hospital stay compared with patients in the old wards; hazard ratio 0.66 (95% CI 0.48–0.93, $p < 0.02$). No difference between the old and the new wards was observed in the duration of the first delirium episode.

Conclusion We found evidence that the risk of delirium is reduced in single-bed rooms compared with multiple-bed rooms in geriatric wards.

Keywords Delirium · Geriatric · Hospital design · Single-bed room

Background

Delirium occurs frequently in older hospitalized patients with a prevalence at admission of 18–35% and an incidence during hospitalization of 11–56% [1].

Delirium is a disorder of brain function characterized by acute onset of mental state fluctuations. A main clinical feature is reduced ability to maintain attention. Moreover, patients become incoherent in thinking and speech and have impaired memory and altered level of consciousness, moving from a wakeful state to drowsiness, or becoming unresponsive [2]. Many old patients are predisposed to delirium due to cognitive impairment [1].

Previous studies have demonstrated an association between the development of delirium and an increased risk of morbidity and mortality, poor rehabilitation outcomes, prolonged hospitalization and increased institutionalization [3–10].

The influence of hospital ward design on the risk of delirium in older patients has received little research attention. One study in an intensive care unit found that patients (mean age 59 years) staying in single-bed rooms had a lower risk of developing delirium than patients staying in multiple-bed rooms, 6.8% vs. 15.1%; $p < 0.01$ [11]. To our knowledge, no study has investigated the influence of single-bed rooms as opposed to multiple-bed rooms on delirium in geriatric patients.

The aim of the present study was to investigate the risk of delirium among patients 75 years or older admitted to a

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geriatric department in relation to the architecture of the ward, especially single-bed rooms vs. multiple-bed rooms. We had the opportunity to perform the study because a geriatric department was moved from an old hospital building with multiple-bed rooms to a new hospital with single-bed rooms, without any changes in uptake area, staff or admission criteria.

Patients and methods

Study design and patients

The project was conducted as an observational, prospective cohort study as part of a quality development project by the Geriatric Department at Aarhus University Hospital, Denmark. The study population was patients 75 years or older, admitted to the old hospital with multiple-bed rooms (old wards) in the period from 15 September 2016 to 19 March 2017, and to the new hospital with single-bed rooms (new wards) from 20 March to 19 December 2017. Patients were excluded if they (1) had already been included once after a prior admission to the same hospital; (2) were dying or somnolent at the time of admission, as assessed by a specialist in geriatrics; (3) were unable to communicate for different reasons, e.g., aphasia, dementia or deaf-mute; (4) were unable to understand or speak Danish; (5) were hospitalized during Easter 2017 (1 week) and summer holiday 2017 (4 weeks) when the new wards had holiday staffing; (6) were admitted to the new wards less than 30 days after discharge from the old wards.

Differences between the old and new wards

The old wards consisted of two geriatric wards located at different addresses. There were 5 three-bed rooms, 11 two-bed rooms and two single-bed rooms with 13 shared bathrooms. The rooms had one or two windows at the end of the room next to one of the beds. The geriatric wards constituted a total area of approximately 1550 m^2. Visiting time was unrestricted within the limits of consideration for other patients in the room.

The two geriatric wards in the new hospital are located on two different floors in the same building. In total, there are 32 single-bed rooms with large windows and with own bathrooms and a total area of roughly 2350 m^2. Visiting time is unrestricted, and a relative can stay overnight in the room, which was very inconvenient in the old wards.

Measurements of delirium

At admission, all enrolled patients were examined for delirium by the geriatric staff using a Danish translation of the Confusion Assessment Method (CAM), originally developed by Inouye [12]. Every day at 8 a.m. (± 2 h) and at 8 p.m. (± 3 h) until discharge, the patients were assessed with CAM or in few cases by a physician diagnosing delirium (ICD-10 code F05). All CAM measurements were registered in the electronic patient record and subsequently copied to the research database by one of the authors (SB). If CAM was missing in the electronic patient record, the relevant staff member was immediately contacted for completion.

Delirium present at admission was defined as a positive CAM score or by a diagnosis of delirium at the first scheduled screening, which typically took place within the first 10 h after admission. Cases of delirium diagnosed after the first scheduled screening were defined as new cases.

The British National Institute for Health and Care Excellence (NICE) recommends CAM for diagnosing delirium. The method is an easy-to-use screening tool for patients undergoing surgical, medical, geriatric, and palliative-care treatment. It includes four criteria: (1) an acute beginning and a fluctuating course, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness. A delirium diagnosis requires the presence of criteria 1 and 2, and at least one of criteria 3 and 4 [13, 14].

A German study of frail elderly patients showed a sensitivity of 0.77, a specificity of 0.96–1.00 and a Cohen's kappa coefficient of 0.95 [15]. Similarly, an American systematic review found a sensitivity of 0.94 and a specificity of 0.89 [16]. A Danish clinical guideline recommends using the Danish version of the training manual and coding guide for CAM [12, 17, 18].

As preparation for the present study, the geriatric staff members, comprising nurses, nurse assistants, occupational therapists and physiotherapists completed a course on delirium and treatment in geriatric patients, including the Danish version of the training manual and coding guide for CAM followed by a test [17]. This preparation took place before inclusion of the first patients, and new staff tended the same course before performing CAM screenings. During the initial course period, the reliability of the Danish version of CAM was evaluated on 52 patients. The inter-rater agreement as measured by Cohen's kappa was 0.85.

Data collection

From the patient records, the following baseline characteristics were extracted: age, gender, housing conditions (nursing homes, sheltered home or own home), prior diagnosis of dementia, main hospitalization diagnosis, body mass index (BMI), physical functional ability (Barthel 100), body temperature, pulse and respiratory rates, and blood samples: hemoglobin, sodium, creatinine, albumin, white cell count and C-reactive protein.

Dementia was identified using the International Classification of Diseases 10th Revision (ICD-10) codes Dementia in Alzheimer's disease (F00 and G30.1), Vascular dementia (F01), Dementia in other diseases (F02), Unspecified dementia (F03), and Delirium superimposed on dementia (F05.1) [19].

Charlson Comorbidity Index was calculated from all diagnoses recorded in the patient journal for the current admission. The Systemic Inflammatory Response Syndrome (SIRS) was defined as temperature > 38 °C or < 36 °C, pulse > 90 bpm, respiratory rate > 20 breaths per minute and white cell count > 12×10^9/L or < 4×10^9/L with at least two positive criteria for the definition of sepsis [20].

Statistics

Patients' baseline characteristics were compared by Student's *t* test or Wilcoxon's rank sum test for continuous variables, and Pearson's chi-squared test or Fisher's exact test for categorical variables.

The incidence of delirium during hospital stay was compared between the old and the new ward using a Cox regression model adjusted for potential confounders: age, comorbidity, housing conditions, prior diagnosis of dementia, SIRS and main diagnosis (infection, fracture, other). Time at risk began at admission and ended at the first delirium episode or with censoring at the date of discharge or death. Patients with delirium present on admission were excluded from the incidence analysis. Some patients were admitted both once to the old and once to the new ward. To adjust for this clustering, we used robust variance estimates. A test of the proportional hazards assumption was supplemented with inspection of "log–log" plots.

A comparison of time to recovery from a patient's first delirium episode was performed using Cox regression with censoring at discharge and adjusted for Charlson's Comorbidity Index. It included patients with delirium present at admission, but in a secondary analysis these patients were excluded. For these analyses, the duration of a delirium period was defined by consecutive, positive results of the twice-daily CAM assessments after these modifications: a missing assessment was substituted by the result of a non-missing neighbor assessment with positive neighbour assessments taking precedence over negative assessments. If one or two negative assessments were surrounded by positive assessments, they were substituted by positive assessments.

Statistical analyses were performed with Stata software, version 15.1 (StataCorp LLC, College Station, Texas). *p* values less than 0.05 were considered statistically significant.

Ethics

As a quality development project with no intervention, the study was exempted from notification to the Central Denmark Region Ethical Committee (Inquiry number 200/2017). The study protocol was approved by the Danish Data Protection Agency, case no. 1-16-02-254-16. Data were stored according to good research practice in Research Electronic Data Capture (REDCap) hosted at Aarhus University, Denmark [21]. The study was registered at ClinicalTrials.gov (Identifier NCT03199768).

Results

A total of 1,014 consecutive patients were enrolled in the study (Fig. 1). Baseline patient characteristics are shown in Table 1; they were well balanced between the old and the new wards, except for age which was slightly lower for the new wards; mean difference 0.75 years (95% CI 0.04–1.47). A test for interaction showed no effect modification by age. For 105 patients (10%), delirium was present at admission, with no difference between the old and new wards. Among patients with delirium at admission, 21% had a prior diagnosis of dementia; for patients without delirium at admission, this was the case for 7%.

Length of stay (LOS) ranged from 1 to 24 days in the old wards, and 15 (4%) patients had a LOS of 14 days or more. In the new wards, LOS ranged from 1 to 36 days, and 5 (1%) patients had a LOS of 14 days or more.

In total, 14,246 CAM examinations were planned, and 13,923 (98%) of these were completed. At admission, 105 patients had delirium, and among the remaining 909 patients, 140 developed delirium during the hospital stay. During the first 14 days of hospital stay, the cumulative incidence of delirium was 29% in patients admitted to the old wards and 16% in patients admitted to the new wards. The patients in the new wards had a significantly reduced risk of delirium compared with the patients in the old wards; HR = 0.66 (95% CI 0.48–0.93, $p = 0.02$), adjusted for age, comorbidity, housing conditions, prior diagnosis of dementia, SIRS and main diagnosis. Figure 2 shows the cumulative incidence of delirium among patients in the old and the new wards. Development of delirium during hospital stay was associated with a prior diagnosis of dementia (HR: 1.74, 95% CI 1.02–2.98, $p = 0.04$) and with age (HR per 10 years: 1.58, 95% CI 1.18–2.11, $p = 0.002$).

Figure 3 shows the time from diagnosis to recovery of the first period of delirium. There was no difference between the old and the new wards in the duration of first delirium episode; HR: 1.06 (95% CI 0.86–1.32, $p = 0.57$).

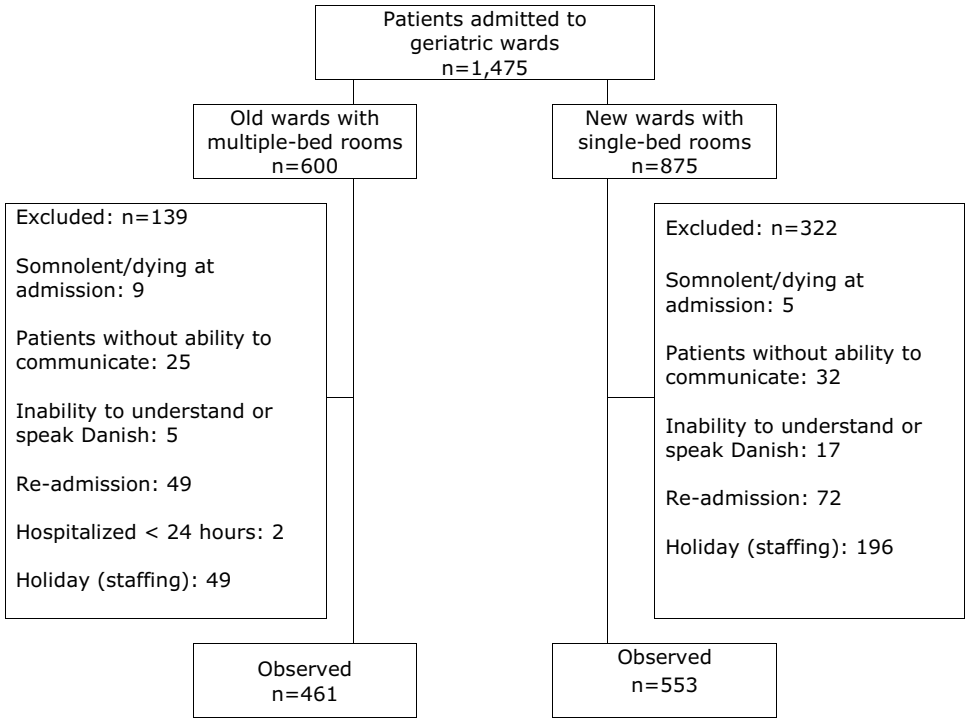

Fig. 1 Flowchart for inclusion

Restricting the analysis to patients without delirium at admission gave a very similar result; HR: 1.04.

In the old ward, 35 (8%) patients stayed in single rooms throughout the hospital stay; of these, 13 patients had delirium at admission, and 4 patients developed delirium during hospital stay.

Discussion

Incidence of delirium

We found a reduced incidence of delirium among geriatric patients staying in single-bed rooms compared with patients staying in multiple-bed rooms, and this finding remained robust after adjustment for baseline risk factors. This supports the hypothesis that a change from multiple-bed rooms to single-bed rooms in geriatric wards can prevent delirium. To our knowledge, there are no similar studies with a geriatric population.

Our observations are in accordance with a study of younger patients conducted by Caruso and colleagues, showing that single-bed rooms could prevent delirium in an intensive care unit (odds ratio: 4.03, 95% CI 2.13–7.62) [11]. Patients were younger, but the methods were similar to those used in the present study, except for the fact that CAM-ICU was used. Like CAM, CAM-ICU is a recognized psychometric instrument validated for intensive-care patients [22]. Caruso et al. excluded patients with prior diagnoses of dementia, while we included patients previously diagnosed with dementia. This may explain the high incidence (16% vs. 29%) in our study compared with the study by Caruso et al. (6.8% vs. 15.1%). It is well known that the risk of delirium increases with age and that delirium is associated with dementia [1, 23]. This was also the case in the present study.

Time to recovery from delirium

When delirium occurred, we found no difference between the old and the new wards in the duration of the first delirium episode. This is in accordance with the study conducted by Caruso et al., who found no difference in the duration of delirium between single-bed rooms and multiple-bed rooms [11]. It seems that single-bed rooms do not reduce the duration of delirium episodes.

Effects of the hospital environment

Problems of noise, sleep disturbance, stress and lack of privacy are frequent in multiple-bed rooms. In a study by Leung and colleagues, preoperative sleep disruption was associated with postoperative delirium [24]. In another study by Weng and colleagues, sleep disturbance was reduced in single-bed rooms compared with multiple-bed rooms in a geriatric department [25].

Table 1 Baseline characteristics of 1014 geriatric patients

Baseline characteristics	Old ward with multiple-bed rooms. Number (%) or median (IQR[a])	New ward with single-bed rooms. Number (%) or median (IQR[a])	*p* value
N	461	553	
Age	87 (82–91)	86 (81–90)	0.05
Sex (male)	169 (36%)	233 (42%)	0.08
Length of stay	7 (5–9)	6 (5–8)	0.35
Living arrangements			
Own home	384 (83%)	437 (79%)	0.14
Sheltered housing facilities	50 (11%)	67 (12%)	
Nursing homes	27 (6%)	49 (9%)	
Medical history			
Prior diagnosis of dementia	40 (9%)	49 (9%)	0.92
Falls	50 (11%)	51 (9%)	0.40
Charlson Comorbidity Index			
0	151 (33%)	183 (33%)	0.83
1–2	216 (47%)	274 (49%)	
3–5	81 (18%)	81 (15%)	
6–12	13 (3%)	15 (3%)	
Diagnosis			
Infection	135 (29%)	183 (33%)	0.19
Cardiac	35 (8%)	32 (6%)	0.25
Stroke	44 (10%)	55 (10%)	0.92
Fracture	97 (21%)	108 (20%)	0.58
Other	150 (33%)	175 (32%)	0.76
SIRS ≥ 2[b]	94 (20%)	114 (21%)	0.94
Delirium at admission	48 (10%)	57 (10%)	0.96
Physical ability (MBI)[c]			0.61
Minor (100–80)	54 (12%)	76 (14%)	
Slight (79–50)	143 (31%)	161 (29%)	
Moderate (49–26)	134 (29%)	162 (30%)	
Severe (25–0)	127 (28%)	150 (27%)	
BMI[d]	23.7 (21-27.1)	23.8 (20.9–26.9)	0.87
Blood samples			
Hemoglobin, mmol/L[e]	7.4 (6.6–8.2)	7.4 (6.5–8.2)	0.82
Sodium, mmol/L[f]	139 (136–142)	139 (136–141)	0.18
Creatinine, µmol/L[f]	83.3 (64-117.5)	80.0 (61.3–116)	0.23
Albumin, g/L[f]	28.0 (25.0-32.3)	28.0 (25–32)	0.42
White blood cells, 10^9/L[g]	9.7 (7.8–12.4)	9.5 (7.5–12.3)	0.19
C-reactive protein, mg/L[g]	56.3 (20.3-103.8)	57.8 (17.5-124.6)	0.37

[a]Interquartile range, i.e., 25% and 75% percentiles

[b]Systemic Inflammatory Response Syndrome (SIRS) (Missing: 5)

[c]Modified Barthel Index-100 (Missing: 7)

[d]Missing: 33

[e]Hemoglobin (Missing: 2) taken in the period: 4 days before or 3 days after admission

[f]Sodium (Missing 2), creatinine (Missing 2), albumin (Missing 3) taken in the period up to 4 days before admission

[g]White blood cells and (Missing: 3) and C-reactive protein (Missing 4) taken in the period: 4 days before to 2 days after admission

Our study shows that multiple-bed rooms are a risk factor for developing delirium during hospital stay. Obviously, this is a modifiable risk factor related to the hospital environment. Decision-makers should incorporate this knowledge when building new wards or renovating old ones. Single-bed room design is associated with higher building cost, but the

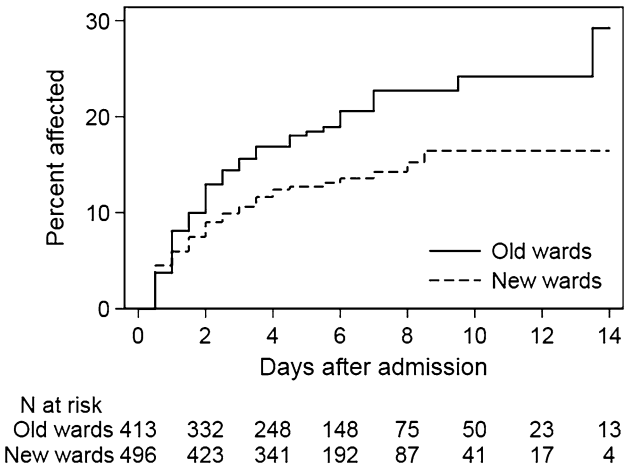

Fig. 2 Cumulative incidence of delirium (105 patients with delirium at admission not included)

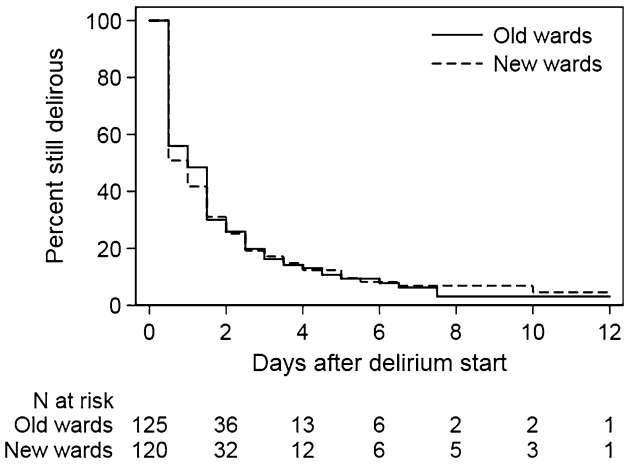

Fig. 3 Time from diagnosis to recovery of the first period of delirium

costs of delirium are a prolonged length of hospital stay, an increased risk of complications during admission and lower functional levels afterwards [26]. Leslie and colleagues estimated the cost of treatment of patients with delirium to be substantially increased compared with costs for other patients [27].

Strengths and limitations of the study

A major strength of the present study is the inclusion of a large population of geriatric patients. A so-called natural experiment allowed us to compare the risk of delirium in two different wards. In the study period, there were no changes in uptake area, staff composition or admission criteria. We, therefore, assume that the patient populations in the old and the new wards were rather similar. Moreover, delirium was identified prospectively by a trained geriatric staff twice a day during hospitalization. The staff completed the same course before using CAM, and the clinical guidelines for delirium did not change. The staff turnover did not change in relation to the relocation of the department. Before the study was performed, a test sample found a satisfactory inter-rater agreement of the diagnostic instrument. Finally, delirium fluctuates, and screening the patients twice a day during the hospital stay reduced the risk of missing episodes of delirium.

Another strength of the present study is the almost complete measurements. Only 2% of all planned CAM examinations were missing. One percent of the patients were out of the department for examinations or were somnolent, and for 0.9%, the CAM score was missing for unknown reasons.

It is well known that transfer of older patients is associated with an increased incidence of delirium [25]. Transfer of patients may have influenced the incidence, but we have no reason to believe that the frequency of transfer was different in the two types of wards.

It is a limitation of the present study that moving the geriatric department to modern hospital premises involved several changes, and the study does not allow to decide with certainty which changes were responsible for the reduced incidence of delirium. We believe that the change to single-bed rooms had a major impact, but other changes such as more space, quiet rooms, better access to daylight, better working conditions for the staff, or improved indoor climate might also play a role.

Conclusion

Compared with multiple-bed rooms, single-bed rooms seem to prevent delirium during hospitalization of geriatric patients, but other differences between older and newer hospital premises may also be of importance.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Statement of human and animal rights It was a quality development project with no intervention, the study was exempted from notification to the Central Denmark Region Ethical Committee (Inquiry number 200/2017). The study protocol was approved by the Danish Data Protection Agency, case no. 1-16-02-254-16. The study was registered at ClinicalTrials.gov (Identifier NCT03199768).

Informed consent For this type of study, formal consent is not required.

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Appendix 6: Paper II

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-019-01335-y

ORIGINAL ARTICLE

Analgesic and psychoactive medications and the risk of falls in relation to delirium in single-bed rooms compared to multiple-bed rooms in geriatric inpatients

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Abstract

Background Previously, we demonstrated a substantial reduction of delirium incidence among geriatric patients after relocating from old hospital buildings with multiple-bed rooms to a new hospital with single-bed rooms.

Aims To investigate whether (1) the reduced incidence of delirium in single-bed rooms was associated with a simultaneous change in medication use, (2) the relocation had affected the incidence of falls, (3) the use of analgesics and psychoactive medications was associated with the risk of delirium and falls.

Methods We included 461 admissions to the old wards and 553 admissions to the new wards. Delirium was assessed by the Confusion Assessment Method. Data on drug use and falls during hospitalization were extracted from medical records.

Results There was no difference in drug use between the wards. In the new wards, patients who had experienced delirium had a much higher risk of falls than patients without delirium, while in the old wards this contrast was small. The risk of delirium was increased among patients who received antipsychotic drugs and anti-dementia drugs, Patients who received these drugs had an insignificantly increased risk of falls.

Conclusion Medication of analgesics and psychoactive drugs was similar in the old and new wards. In single-bed rooms, but not in multiple-bed rooms there was a much higher risk of falls among inpatients that developed delirium than among other patients. Patients who had used antipsychotics and anti-dementia drugs during hospitalization had increased risk of developing delirium and an insignificantly higher risk of falls.

Keywords Geriatric · Hospital design · Single-bed room · Delirium · Falls · Analgesic · Psychoactive drug

Background

Geriatric patients are characterized by multimorbidity, cognitive impairment, physical disability, malnutrition, falls, polypharmacy and iatrogenic complications, and dependence of personal assistance. All these characteristics increase the risk of delirium. Delirium is a common mental syndrome in hospitalized older patients with serious adverse implications and high health care costs [1]. During hospitalization, the risk of delirium varies from 11 to 42% in general medical inpatients, and for frail older inpatients prevalences up to 60% are described [1, 2]. In our geriatric department, the risk of delirium was reduced from 29% to 16% in connection with relocation from an old hospital with multi-bed rooms to a new hospital with single-bed rooms [3].

Delirium is characterized by acute inception of fluctuations in the mental state. The clinical characteristics of delirium include decreased ability to maintain attention. The patients are incoherent in thinking and speech, and they have reduced memory and a changing level of consciousness, ranging from awake to lethargic, drowsy or inaccessible [1]. Delirium often causes restlessness, gait disturbance, dizziness, blurred vision, muscle weakness, and an increased risk of falls [4–6].

For many years, medications that affect the central nervous system have been suspected of increasing the risk of delirium and falls in older patients. Only few clinical studies have investigated the associations between use of opioids

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and the risk of delirium or falls. Severe pain and especially undertreated pain after surgery has been associated with postoperative delirium [7]. However, Sieber et al. found no association between postoperative delirium and use of opioids neither for cognitively impaired nor cognitively intact patients [8]. On the other hand, a Canadian study found that recent opioid use was associated with an increased risk of falls in older patients [9].

Few drugs for mental illness have been associated with the development of delirium. In a case–control study, Marcantonio et al. found that postoperative delirium was associated with both long-acting and short-acting benzodiazepines [10], and the use of benzodiazepines among older patients has been shown to increase the risk of falls [11]. Evidence for an association between delirium or falls and drugs for mental illness or dementia in older patients is inconsistent or not existing.

Objectives

The aim of this paper is to investigate whether the reduced incidence of delirium in the new hospital with single-bed rooms was associated with a simultaneous change in the use of medications. We also examine whether the relocation of the department to a modern hospital had affected the incidence of falls, both among delirious and non-delirious patients. Finally, we examine whether the use of analgesics and psychoactive medications is associated with the risk of delirium and falls among patients in a geriatric department.

Patients and methods

Study design and patients

The study design is described in detail in a previous paper [3]. Patients 75 years or older admitted for neurological, medical or surgical reasons to the Geriatric Department at Aarhus University Hospital were included. Patients were consecutively admitted to the old hospital with multiple-bed rooms (old wards) between 15 September 2016 and 19 March 2017 and to the new hospital with single-bed rooms (new wards) from 20 March to 19 December 2017. Patients could be included once to the same ward. Exclusion criteria were terminal illness, somnolence and inability to communicate in Danish.

The old wards consisted of two geriatric wards located at different addresses. There were five three-bed rooms, eleven two-bed rooms and two single-bed rooms with 13 shared bathrooms. The new wards are located on two different floors in the same building. In total, there are 32 single-bed rooms with own bathroom. Visiting time is unrestricted, and a relative can stay overnight in the room, which was very inconvenient in the old wards.

Measurements of delirium

At admission to the Geriatric ward, all enrolled patients were tested for delirium by the geriatric staff using a Danish translation of the Confusion Assessment Method (CAM) [12]. Until discharge, the patients were assessed every morning and evening with CAM or, in a few cases, examined by a physician to diagnose delirium. Delirium at admission was defined as a positive CAM score at the first screening. New cases of delirium during hospital stay were defined as occurring after the first screening. For patients who experienced delirium during hospital stay, the observation time was divided in two periods, before and after start of delirium. Other patients were classified as not being exposed to delirium throughout their hospital stay. All measurements of CAM were registered in the electronic patient record and consequently copied to the research database by one of the authors (SB). If CAM was missing in a patient record, the relevant staff member was contacted for completion.

As preparation for the present study, the geriatric staff members, comprising nurses, nurse assistants, occupational therapists and physiotherapists fulfilled a course on delirium and treatment in geriatric patients, including the Danish version of the training manual and coding guide for CAM followed by a test [12]. This preparation took place before inclusion of the first patients, and new staff tended the same course before performing CAM screenings. For more detailed information, see the previous paper [3].

Exposure to analgesics and psychoactive drugs

From the medical records for the current hospitalization, the following ATC-codes were extracted: natural opium alkaloids (opioids) (N02AA), other opioids (N02AX), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), and anti-dementia drugs (N06D) [13]. We recorded the date of first use of a medication and analysed the dosage of risperidone, as risperidone is used for treatment of delirium in our department. We did not include dosage or treatment duration for other medications in the analysis.

Measurements of falls

Falls were defined as fall from chair or bed or from standing or walking, and as episodes where the staff found the patient lying or sitting on the floor. It is mandatory to report falls as accidental events to The Danish Patient Safety Authority Register and in the electronic patient

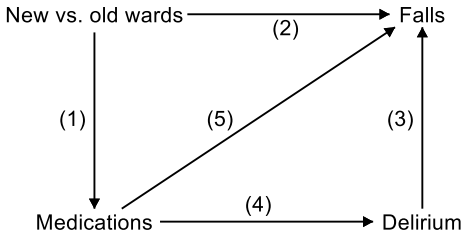

Fig. 1 Associations analysed in this paper

records. Time from admission to the first fall was recorded. The number of falls per patient was not included in the analysis.

Measurements of comorbidity

Charlson Comorbidity Index was calculated from all diagnoses recorded in the patient journal for the current admission. A diagnosis of dementia was identified at the current or prior admissions or from information from the patient's general practitioner [14]. For more detailed information, see the previous paper [3].

Statistics

An overview of the main analyses in this paper is shown in Fig. 1. We used Cox regression to compare [1] the use of medications and [2] the risk of falls in the old and the new wards, [3] the risk of falls in relation to delirium, and [4] the risk of delirium and [5] the risk of falls in relation to medications. The analyses were validated by a test of the proportional hazards assumption. Some patients were admitted both once to the old and once to the new wards, and to adjust for this clustering, we used robust variance estimates. Any p value less than 0.05 was considered statistically significant. Statistical analyses were performed with Stata software, version 15.1. (StataCorp LLC, College Station, Texas, USA).

Ethics

The study was part of a quality development project with no intervention. It was evaluated by the Central Denmark Region Ethical Committee, which considered it to be non-experimental, and a formal approval was therefore not required. The study protocol was approved by the

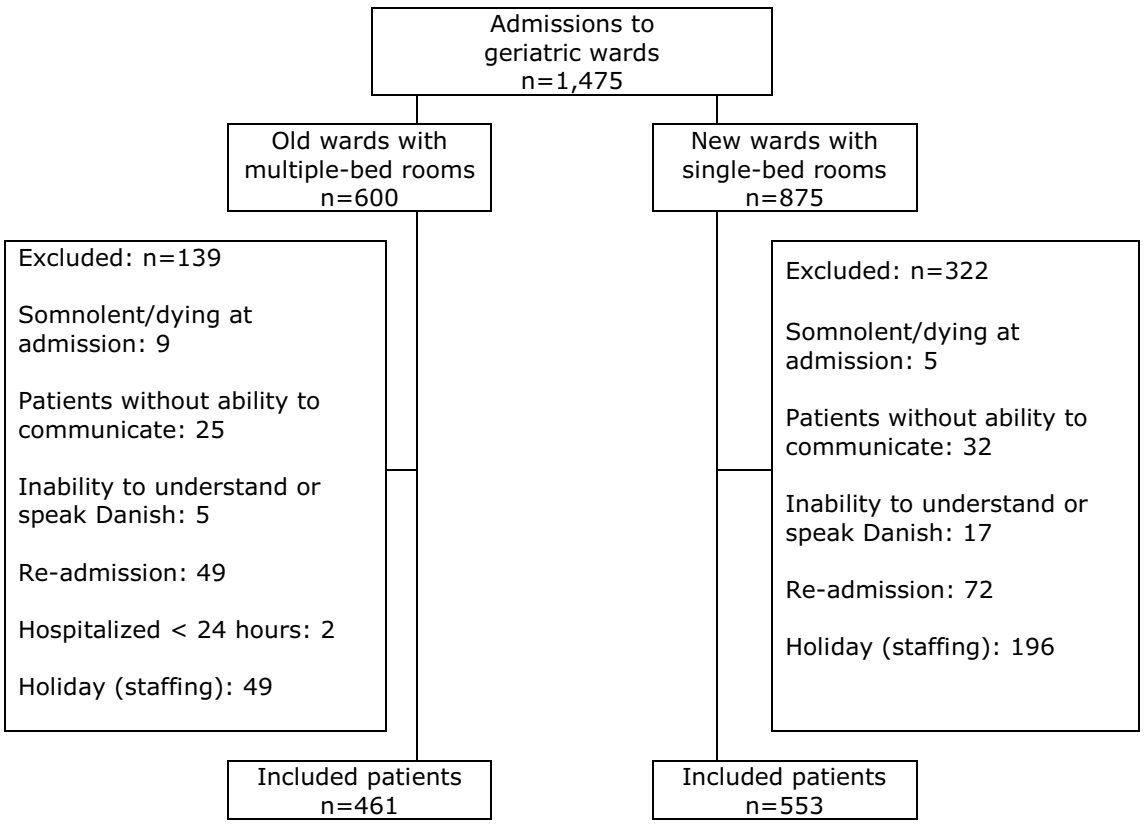

Fig. 2 Flow chart

Danish Data Protection Agency, case no. 1-16-02-254-16. Data were stored according to good research practice. The study was registered at ClinicalTrials.gov (Identifier NCT03199768).

Results

The study includes 1014 admissions among 964 different patients; 50 patients were admitted both to the old and the new ward. See flowchart in Fig. 2.

Baseline patient characteristics were well balanced (Table 1). For 105 admissions (10%), delirium was present at the first screening, with no significant difference between the wards. The most common causes of admission were infection (31%) and fractures (20%) with no statistically significant difference between the wards.

Table 2 shows the use of analgesic and psychoactive drugs. There were no significant differences in use between the two wards. Table 2, fourth column shows hazard ratios (HR) for delirium in relation to prior medications. Patients who received other opioids had a decreased risk to develop delirium, while patients who received antipsychotic or anti-dementia drugs had an increased risk.

In total 36 patients received risperidone; five in the old wards and seven in the new wards received risperidone by admission and for reasons other than delirium. In the old wards the median dose was 1.5 mg (IQR 0.5 mg-5 mg) and in the new wards 2.5 mg (IQR 1 mg-5.5 mg), $p = 0.40$.

In the old wards, 26 (6%) patients and in the new wards 23 (4%) had experienced one or more falls during hospitalization; the difference was insignificant, HR = 0.81 (95% CI 0.46–1.42). Patients with delirium had an increased risk of falls, HR = 4.68 (95% CI 2.58–8.46, $p < 0.001$). There was however, a significant interaction between ward type and delirium on the risk of falls, $p = 0.008$. As illustrated in Fig. 3, the contrast in the incidence of falls between patients with and without delirium was modest in the old wards, while there was a strong contrast in the new wards.

Table 3 shows the risk of falls among patients receiving a particular drug; there was an insignificantly increased risk of falls among users of antipsychotics and anti-dementia drugs.

Table 1 Baseline characteristics of 1014 geriatric admissions

Baseline characteristics	Old wards with multiple-bed rooms. Number (%) or median (IQR[a])	New wards with single-bed rooms. Number (%) or median (IQR[a])	*p* value
N	461	553	
Age	87 (82–91)	86 (81–90)	0.05
Sex (male)	169 (36%)	233 (42%)	0.08
Length of stay, days	7 (5–9)	6 (5–8)	0.35
Living arrangements			
Own home	434 (94%)	504 (91%)	0.14
Nursing homes	27 (6%)	49 (9%)	
Medical history			
Prior diagnosis of dementia	40 (9%)	49 (9%)	0.92
Falls	50 (11%)	51 (9%)	0.40
Delirium at admission	48 (10%)	57 (10%)	0.96
Charlson comorbidity index			
0 (none)	151 (33%)	183 (33%)	0.83
1–2 (low)	216 (47%)	274 (49%)	
3–5 (moderate)	81 (18%)	81 (15%)	
6–12 (severe)	13 (3%)	15 (3%)	
Physical ability (MBI)[b]			
Minor (100–80)	54 (12%)	76 (14%)	0.61
Slight (79–50)	143 (31%)	161 (29%)	
Moderate (49–26)	134 (29%)	162 (30%)	
Severe (25–0)	127 (28%)	150 (27%)	
BMI[c]	23.7 (21–27.1)	23.8 (20.9–26.9)	0.87

[a]Interquartile range, i.e. 25% and 75% percentiles

[b]Modified Barthel Index-100 (Missing: 7)

[c]Missing: 33

Table 2 Use of analgesic, benzodiazepines and antipsychotic drugs during hospitalization

	Old wards with multiple-bed rooms. No. patients (%)	New wards with single-bed rooms. No. patients (%)	Medications new vs. old wards Hazard ratio (95% CI)	Hazard ratio (95% CI) for delirium after medication vs. no prior medication
Natural opium alkaloids (opioids) (N02AA)	228 (49)	268 (48)	1.01 (0.86–1.18)	1.13 (0.88–1.46)
Other opioids (N02AX)	27(6)	39 (7)	1.16 (0.61–2.19)	0.45 (0.21–0.97)[a]
Antipsychotic (N05A)	25 (5)	35 (6)	1.28 (0.68–2.38)	2.54 (1.61–4.01)[a]
Anxiolytics (N05B)	21 (5)	21 (4)	0.81 (0.41–1.62)	0.94 (0.42–2.11)
Hypnotics and sedatives (N05C)	94 (20)	106 (19)	0.97 (0.69–1.35)	1.03 (0.69–1.53)
Antidepressants (N06A)	135 (29)	155 (28)	0.89 (0.72–1.11)	1.13 (0.86–1.48)
Anti-dementia drugs (N06D)	19 (4)	20 (4)	0.69 (0.35–1.37)	2.45 (1.46–4.11)[a]

[a]Statistically significant difference

Discussion

Analgesics

There was no difference in the use of opioids between the old and the new wards. In addition, there was no association between use of natural or other opioids and falls. Also, the use of natural opioids was not associated with delirium.

For patients who used other opioids such as tramadol, the incidence of delirium was decreased. This is in contrast to previous studies. In a frail geriatric population, Laurila et al. found tramadol and codeine as precipitating factors for delirium [15]. This was confirmed by Brouquet et al. who found tramadol administration to be a strong risk factor for delirium in older postoperative patients [16]. We believe that the contrast between these studies and our more recent study is due to an increased awareness of tramadol being a risk factor for delirium, leading to restrictive use in high-risk patients. Only 66 (7%) inpatients used tramadol, and we do not know whether they used it prior to the admission.

Psychoactive drugs

There was no difference in the use of psychoactive drugs in the old wards and the new wards. Holdensen et al. investigated the use of haloperidol, expressed as defined daily dosages, during a change from multiple-bed rooms to single-bed rooms. They found that the use decreased by 50%. We used risperidone rather than haloperidol in the treatment of delirium, and we found neither difference in the number treated nor the dosage between the old and the new wards. Holdensen et al. did not record the occurrence of delirium [17].

The incidence of delirium was increased among patients who had used antipsychotics prior the first episode of delirium. It probably reflects that the underlying psychiatric disorder both increases the risk of delirium and affects the use of antipsychotics, but a direct effect of the medication on the risk of delirium cannot be excluded in the present observational study.

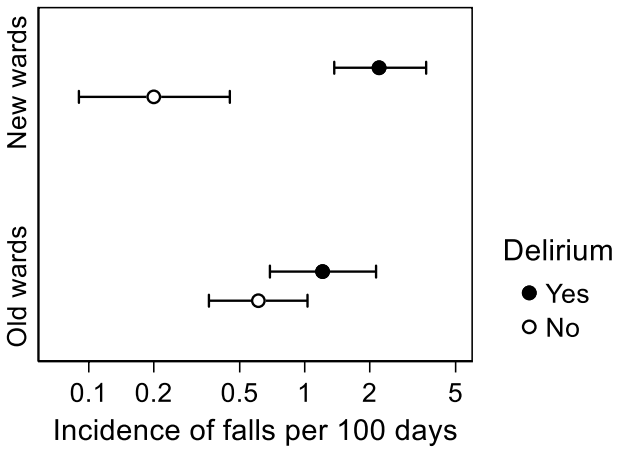

Fig. 3 Incidence of falls in relation to ward type and delirium

For patients who used anti-dementia drugs, the risk of delirium was increased. It is well-known that the risk of delirium is associated with dementia [1, 18, 19], and it might explain the observed association between anti-dementia drugs and delirium. However, the present observational study cannot determine whether there is a direct positive or negative effect of anti-dementia drugs on the risk of delirium.

Use of psychoactive drugs was not associated to the risk of falls among older hospitalized patients.

Falls

We found an apparently strong and significant effect of delirium on the incidence of falls in the new wards, while

Table 3 Use of analgesic and psychoactive medications and the risk of falls

Medication exposure	Number exposed	Patients with falls (%)	Risk ratio (95% CI)[a]
Regardless of exposure	1014	49 (5)	–
Natural opium alkaloids (opioids) (N02AA)	496	23 (5)	0.92 (0.53–1.60)
Other opioids (N02AX)	66	2 (3)	0.61 (0.15–2.46)
Antipsychotics (N05A)	60	6 (10)	2.22 (0.98–5.00)
Anxiolytics (N05B)	42	1 (2)	0.48 (0.07–3.41)
Hypnotics and sedatives (N05C)	200	10 (5)	1.04 (0.53–2.05)
Antidepressants (N06A)	290	19 (7)	1.58 (0.90–2.76)
Anti-dementia drugs (N06D)	39	4 (10)	2.22 (0.84–5.87)

[a]The risk ratio compares users and non-users of the medication

the effect of delirium in the old wards seemed modest. We hesitate to attempt explaining this finding. As previously demonstrated, the risk of delirium was reduced among patients in the new wards [3]. This could point to a high degree of frailty among patients who developed delirium despite the favourable environment in the new wards, while the remaining patients could benefit from the environment in new wards. We can not exclude that absence of supervision in single-bed rooms could be a risk factor for fall in delirious patients.

The higher risk of falls among delirious inpatients is in agreement with results by Mazur et al. and by Stenvall et al. [5, 6].

Strengths and limitations of the study

It is a strength of the study that we were able to calculate a precise assessment of whether the medication was given before or after delirium started.

The main limitation of the study is the lack of knowledge about the patients' use of medications prior to admission. Therefore, it is unknown whether there was a different use of opioids and psychoactive drugs prior to admission in the two wards and for patients with and without delirium. Furthermore, it was only possible to compare the dosages of risperidone in the analysis, and there might have been differences in the dosage of other medications between the two wards.

We believe that there were very few, if any, missed falls. In the geriatric wards, the staff is focusing on fall registration, and typically, geriatric patients can hardly get up from the floor without assistance after a fall.

Moving the geriatric department to modern hospital involved several changes, and the study does not allow deciding with certainty which changes were responsible for the reduced incidence of delirium. The staff completed the same course before using CAM, and the clinical guidelines for delirium did not change. The staff turnover did not change in relation to the relocation of the department and there was no change in uptake area. We believe that the change to single-bed rooms had a major impact, but other changes like more space, quiet rooms, better access to daylight, better working conditions for the staff, or improved indoor climate might also play a role.

Conclusion

New wards with single bedrooms were not associated with change in medication use for analgesic and psychoactive drugs compared to old wards with multiple-bed rooms. Patients who had used antipsychotics and anti-dementia drugs during hospitalization had increased risk of developing delirium, but this was most likely due to the condition both leading to medication and the risk of delirium. The present study cannot determine whether there is a direct positive or negative effect of the use of these drugs and the risk of delirium.

Finally, in the new wards with single-bed rooms there was a higher risk of falls among inpatients that developed delirium compared to inpatients without delirium. We did not find the same contrast in the old wards with multiple-bed rooms. Antipsychotics and anti-dementia drug may increase the risk of falls.

Compliance with ethical standards

The cost of data collection, analysis, and preparation of the manuscript was covered by the Department of Geriatrics, Aarhus University Hospital.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Research involving Human Participants It was a quality development project with no intervention, the study was exempted from notification to the Central Denmark Region Ethical Committee (Inquiry number 200/2017). The study protocol was approved by the Danish Data Protection Agency, case no. 1-16-02-254-16. The study was registered at ClinicalTrials.gov (Identifier NCT03199768).

Informed consent Not needed according to Ethical Committee.

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Appendix 7: Paper III

Aging Clinical and Experimental Research
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ORIGINAL ARTICLE

The short IQCODE as a predictor for delirium in hospitalized geriatric patients

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Abstract

Background Delirium is a serious complication, which occurs frequently in older patients with pre-existing cognitive impairment. There is a need for a simple tool to assess chronic cognitive impairment and the associated risk of delirium during hospitalization.

Aims To assess the usefulness of the short IQCODE questionnaire in predicting delirium during hospitalization in older patients in a geriatric ward.

Methods A prognostic study in the Geriatric Department at Aarhus University Hospital, Aarhus Denmark. Consecutive patients were enrolled during March to December, 2017. After consent of the patient, the staff interviewed the relatives by phone using the short IQCODE questionnaire. Delirium was assessed morning and evening until discharge by the Confusion Assessment Method. The ability of short IQCODE to predict delirium was examined.

Results Three hundred and fifty-three patients were eligible, and 306 completed the IQCODE. Delirium occurred among 19% of the patients during hospitalization. The IQCODE score was associated with the risk of delirium with a receiver operating characteristic (ROC) area of 0.72. A cut-point of 3.3 could separate the patients in a larger group with a risk of approximately 26% to develop delirium and a smaller group having a risk of approximately 6%.

Conclusion The IQCODE is a useful tool to predict delirium among older inpatients, but it may not stand alone. It can be a useful supplement to other clinical information and observations in detecting patients needing dementia-friendly treatment and care.

Keywords IQCODE · Delirium predictor · Older patient · Geriatrics

Background

Delirium is an acute state of confusion characterized by inattention and cognitive dysfunction. It is estimated that delirium is present in up to 56% of older inpatients [1]. Delirium affects health adversely in terms of increased morbidity and mortality, poor rehabilitation outcomes, prolonged hospitalization, and increased institutionalization [2–9].

Delirium is most prevalent in older patients with pre-existing cognitive impairment [2, 10, 11]. The cause of delirium is thought to be multifactorial, dependent on a complex interplay of predisposing and precipitating factors [12]. Predisposing factors are in particular high age and dementia [11, 13, 14]. In a meta-analysis of older medical patients, Ahmed et al. found that higher age is associated with delirium and that dementia increases the probability of delirium nearly seven times [14].

In Denmark, 6% of persons aged 75 years or older have a dementia-related diagnosis [15]. Based on international population surveys, the Danish Health and Medicines Authority considers that dementia is under-diagnosed and has estimated a three times higher prevalence in Denmark [15–17]. Accordingly, it is needed to find an easy tool by which clinicians can assess chronic cognitive impairment and the risk of delirium during hospitalization.

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a sensitive tool for detecting clinical dementia. The original IQCODE questionnaire includes 26 items. It was developed in the 1980s as a tool for assessing

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a change from previous to current levels of cognitive function [18]. In 1994, a validated short form IQCODE questionnaire with 16 items gave similar results [18–20]. The score ranges from 1 to 5, low scores being favorable. Harrison et al. examined the diagnostic accuracy in a systematic review from 2015. They found that a cut-point of 3.3 had a sensitivity of 0.91 and a specificity of 0.66 to detect undifferentiated dementia in adult patients in the secondary sector [21]. The test involves family or friends, but not the patients, and it may be used on delirious and cognitively impaired patients [20].

Priner et al. [22] demonstrated that the short IQCODE could predict postoperative delirium in older patients undergoing elective surgery. We located no studies of the usefulness of the short IQCODE in predicting delirium in patients hospitalized with medical problems.

Objectives

We aimed to assess the usefulness of the short IQCODE questionnaire in predicting delirium in older patients during hospitalization in a geriatric ward.

Patients and methods

Study design and patients

The project was conducted as a prognostic study as part of a quality development project in the Geriatric Department of Aarhus University Hospital, Denmark. Consecutive patients were enrolled in the emergency department between 20 March and 19 December in 2017. Delirium was assessed using the Confusion Assessment Method (CAM), and patients who had no CAM assessments during hospital stay were excluded from the analysis. The reasons for exclusion were that the patient (1) had been included before; (2) was somnolent or dying at the time of admission; (3) was unable to communicate for various reasons, e.g., aphasia, dementia or were deaf-mute; (4) was unable to communicate in Danish; (5) was hospitalized during Easter 2017 (1 week) and summer holiday 2017 (4 weeks) when staff was reduced.

IQCODE measurements

When a patient was included, the geriatric staff in the emergency department asked the patient for consent to contact a family member or a close friend to complete the short IQCODE questionnaire. The interviews with relatives were most often done while the patient was in the emergency department, in some cases, the interview was done after the patient had left the emergency department or arrived in the geriatric ward. Most interviews were performed by phone, but in a few cases face to face. The interview was conducted in the same way in both situations, with a typical duration of 10 min.

IQCODE asks about changes in the older patient's cognitive performance over the previous 10 years. The informant must assess the patient's ability for each question on a five-point scale; (1) much improved, (2) a bit improved, (3) not much changed, (4) a bit worse, (5) much worse. The IQCODE score is calculated as the mean of item responses, with a possible range of 1–5, low scores being favorable and three corresponding to no overall change in cognitive performance. The questions concern various everyday situations where the patient needs memory and intellect, e.g., remembering recent things, learning new things, handling money, etc. [19]. The geriatric staff was educated in using the short form IQCODE (Danish-version) [23] by a research assistant and peer-to-peer training.

Measurements of delirium

The method to measure delirium is presented in more detail in a previous paper [11]. At admission, all enrolled patients were assessed for delirium by the geriatric staff using a Danish translation of the Confusion Assessment Method (CAM), originally developed by Inouye [24]. Every morning and evening until discharge, the patients were assessed by CAM.

CAM is the most widespread psychometric test for diagnosing delirium [13]. The method is an easy-to-use screening tool that includes four criteria: (1) an acute beginning and a fluctuating course, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness. A delirium diagnosis requires the presence of criteria 1 and 2, and at least one of criteria 3 and 4 [25, 26].

Data collection

From the patient records, the following information was extracted: age, gender, length of hospital stay (LOS), housing conditions, prior diagnosis of dementia, main hospitalization diagnosis, body mass index (BMI), physical functional ability (Modified Barthel-100 index, MBI) [27], and the usual clinical and biochemical measurements.

Charlson Comorbidity Index [28] was calculated from all diagnoses recorded in the patient records of the current admission. The systemic inflammatory response syndrome (SIRS) was defined as temperature > 38 °C or < 36 °C, pulse > 90 bpm, respiratory rate > 20 breaths per minute and white cell count > 12×10^9/L or < 4×10^9/L with at least two positive criteria for the definition of sepsis [29].

Statistics

To compare delirious and non-delirious patients, we used Student's *t* test or Wilcoxon's rank-sum test for continuous variables and Pearson's Chi-squared test or Fisher's exact test for categorical variables.

A receiver operating characteristic (ROC) curve was prepared, and the area under the curve was calculated. Sensitivity, specificity, and positive (PV +) and negative predictive (PV −) values were calculated at selected IQCODE cut-points. The association between IQCODE score and the occurrence of delirium was examined by logistic regression with a nested analysis to estimate the independent predictive contribution of IQCODE beyond other available information.

Statistical analyses were performed with Stata software, version 15.1 (StataCorp LLC, College Station, Texas). We used 95% confidence intervals, and *p* values less than 0.05 were considered statistically significant.

Ethics

As a quality development project with no intervention, the study was exempted from notification to the Central Denmark Region Ethical Committee (Inquiry number 200/2017). The IQCODE is a recognized method for assessing cognitive status [16]. It is not perceived as a burden on the older patient. Patients and relatives had the right to renounce participation. The study protocol was approved by the Danish Data Protection Agency, case no. 1-16-02-254-16. Data were stored according to good research practice in Research Electronic Data Capture (REDCap) hosted at Aarhus University, Denmark [30]. The study was registered at ClinicalTrials.gov (Identifier NCT03175276).

Results

A total of 353 patients were eligible, and 306 patients (87%) participated in the study, see Fig. 1. About a third of non-participants were relatives that could not answer all or some

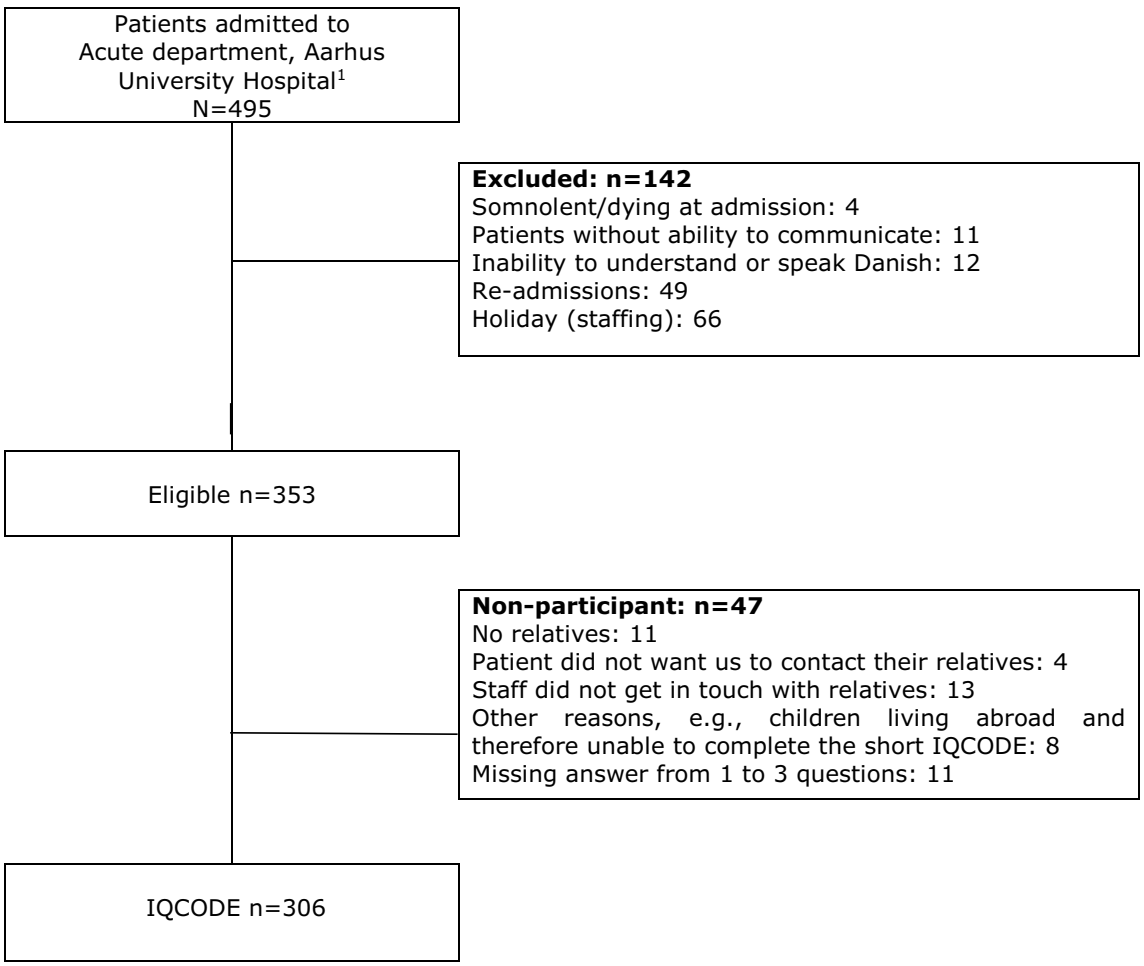

Fig. 1 Included and excluded patients, flowchart

of the IQCODE items. There was no substantial difference between participants and non-participants in age, gender, living arrangements, prior diagnosis of dementia, comorbidity, physical ability, length of stay (LOS), and risk of delirium.

In Table 1, baseline patient characteristics are shown in patients with and without delirium during hospitalization. Patients with delirium were significantly older than patients without delirium; mean difference 2.1 years (95% CI 0.5–3.8, $p=0.01$). There was a significant difference between the two groups in IQCODE score, physical ability, prior diagnosis of dementia and body mass index (BMI).

At the first CAM screening after admission, 28 patients had delirium, and later, during hospital stay, 30 patients developed delirium, in total 58 patients (19%). In Table 2, a crude analysis shows associations between the risk of delirium and high IQCODE score, high age, a prior diagnosis of dementia, and impaired physical ability, while overweight appeared to protect against delirium. In an analysis with mutual adjustment for the other risk factors, the IQCODE score retained its predictive value, while a prior diagnosis of dementia did not contribute further to prediction once the IQCODE score was known.

Table 3 shows the association between the IQCODE score level and the risk of delirium. Figure 2 and Table 4 show the sensitivity and specificity of IQCODE at various cut-points as a predictor of development of delirium.

The ROC area was 0.72, and choosing an IQCODE cut-point of 3.3, a third of the patients would be in a low-risk group with a risk of 6% of developing delirium, and two-thirds would be in a high-risk group with a risk of 26%. It would predict 51 (88%) of the 58 patients with delirium with a cost of 144 false-positive predictions. Increasing the cut-point would reduce the number of false-positive predictions, but also reduce the number of true-positive predictions.

The above analyses included patients who had delirium at the first CAM test after admission, and some of these may have had delirium before admission. In a supplementary analysis, we excluded these patients without any substantial changes in the main results.

Discussion

The geriatric patients in this study were a high-risk group with an overall risk to develop delirium during hospitalization of 19%. The IQCODE score at admission was associated with the risk to develop delirium, and with an ROC area of 0.72, IQCODE has a predictive potential. Selecting an IQCODE cut-point of 3.3 could identify two-thirds of the patients with a risk of approximately 26% to develop delirium and one-third of the patients with a lower risk of approximately 6%. IQCODE retained its predictive value after adjustment for a number of known risk factors for delirium.

In principle, a triage of patients according to the risk to develop delirium could help allocating attention and resources to the high-risk patients to prevent delirium episodes. The relevant interventions could be frequent screening, e.g., CAM, multi-component non-pharmacological risk reduction as single-bed room, promoting sleep hygiene, early mobilization, ensuring that patients have their glasses and hearing aids, optimizing hydration, nutrition, and bladder and bowel function, and, if needed, providing supplementary oxygen [11, 31, 32].

The cost of applying the IQCODE questionnaire is modest, and the information obtained may also be useful in the general clinical care. It is not a burden to the patient, and we have not experienced complaints from the informants. On the contrary, many informants expressed satisfaction with the perceived relevance of the questions.

Although it is possible to categorize patients in a larger high-risk group and a smaller lower risk group, patients in the lower risk group still had a risk of approximately 6% to develop delirium during hospitalization. This reflects the fact that patients hospitalized at a geriatric department in general are quite vulnerable, typically with multiple diseases and physical and mental impairments.

For these patients, we do not suggest the use of IQCODE as a strict screening tool with a fixed cut-point to decide which patients require special attention and care. First, even patients in the low-risk group have a considerable risk to develop delirium. Second, IQCODE does not make other information about risk factors unimportant. The IQCODE score and the individual responses can be a useful supplement to other clinical information.

Two-thirds of the older inpatients had an IQCODE score of 3.3 or higher. Only 7% of inpatients had a prior diagnosis of dementia. It seems that there is a marked underdiagnosing of dementia in these older inpatients. This is in agreement with the estimates of the Danish Health Authority [15–17].

We found that delirium is a common incident in the older inpatients with high age, dementia, and low physical ability. Our observations are in accordance with other studies [14, 33, 34]. Carrasco et al. found that low physical ability measured by the Barthel Index and a proxy score for dehydration measured by blood urea nitrogen creatinine ratio predict delirium. The Barthel Index was compared with a test for cognitive impairment; the Pfeffer Functional Activities Questionnaire. The two tests were highly correlated [35].

Different tests for cognitive impairment have been part of the predictive models for incident delirium [35, 36]. In many studies, the Mini Mental State Examination (MMSE) has been used. This test may have some problems in patients just

Table 1 Baseline characteristics of delirious and non-delirious patients

Baseline characteristics	Patient without delirium Number (%) or median (IQR[1])	Patient with delirium Number (%) or median (IQR[1])	*p* value
N	248 (100%)	58 (100%)	
Age	86 (82–89)	88 (83–93)	0.01
Sex			
Male	94 (38%)	27 (47%)	0.22
Female	154(62%)	31 (53%)	
Length of stay	7 (5–8)	7 (5–9)	0.88
Living arrangements			
Own home	221 (89%)	53 (91%)	0.61
Nursing home	27 (11%)	5 (8%)	
Medical history			
Prior diagnosis of dementia	14 (6%)	8 (14%)	0.03
Falls	29 (12%)	5 (9%)	0.50
Charlson comorbidity index			
0	92 (37%)	22 (38%)	0.45
1–2	117 (47%)	31 (53%)	
3–5	33 (13%)	5 (9%)	
6–12	6 (2%)	0	
Diagnosis at admission			
Infection	88 (35%)	23 (40%)	0.56
Fracture	54 (22%)	13 (22%)	0.92
SIRS ≥ 2[2]	56 (23%)	13 (22%)	0.98
Physical ability (MBI)[3]			
Minor (100–80)	35 (14%)	2 (4%)	<0.001
Slight (79–50)	88 (36%)	11 (19%)	
Moderate (49–25)	78 (32%)	14 (25%)	
Severe (24–0)	46 (19%)	30 (53%)	
BMI[4]			
Underweight (<18.5)	21 (9%)	8 (15%)	<0.001
Normal weight (18.5–24.9)	121 (50%)	38 (70%)	
Overweight (≥ 25)	102 (42%)	8 (15%)	
IQCODE	3.5 (3.1–4.1)	4.3 (3.6–4.8)	<0.001
Blood samples			
Hemoglobin, mmol/L[5]	7.4 (6.4–8.2)	7.3 (6.5–8.1)	0.53
Sodium, mmol/L[6]	139 (136–142)	138 (137–142)	0.78
Creatinine, µmol/L[6]	80 (61–116)	81 (62–119)	0.91
Albumin, g/L[6]	28 (25–31)	28 (24–31)	0.72
White blood cells, 10/L[7]	9.9 (7.7–12.8)	9.2 (7.7–11.9)	0.47
C-reactive protein, mg/L[7]	72 (26–140)	69 (26–117)	0.99

[1]Interquartile range, i.e. 25% and 75% percentiles

[2]Systemic inflammatoric response syndrome (SIRS)

[3]Modified Barthel Index-100 (Missing: 2)

[4]Missing: 9

[5]Hemoglobin taken in the period: 4 days before or 3 days after admission

[6]Sodium, creatinine, and albumin (missing 1) taken in the period up to 4 days before admission

[7]White blood cells and C-reactive protein taken in the period: 4 days before to 2 days after admission

Table 2 Risk factors for development of delirium

	Crude odds ratio (95% CI)	*p* value	Mutually adjusted Odds ratio (95% CI)	*p* value
IQCODE per unit	3.53 (2.22–5.60)	< 0.001	2.64 (1.54–4.53)	< 0.001
Age per 10 years	1.92 (1.15–3.20)	0.01	1.89 (1.05–3.39)	0.03
Prior diagnosis of dementia	2.67 (1.06–6.72)	0.04	1.14 (0.36–3.58)	0.82
Severe to moderate physical disability	3.36 (1.72–6.54)	< 0.001	1.97 (0.94–4.12)	0.07
BMI < 18.5	1.21 (0.50–2.97)	0.67	0.91 (0.33–2.52)	0.86
18.5 ≤ BMI ≤ 25	1 (reference)			
BMI > 25	0.25 (0.11–0.58)	< 0.001	0.29 (0.12–0.67)	< 0.01

Table 3 IQCODE score and risk of delirium

IQCODE score	All patients	Patients with delirium
< 3.0	1	1 (100%)
3.0 to < 3.3	110	6 (5%)
3.3 to < 3.5	23	5 (22%)
3.5 to < 4.0	62	8 (13%)
4.0 to < 4.5	48	12 (25%)
4.5–5.0	62	26 (42%)
Total	306	58 (19%)

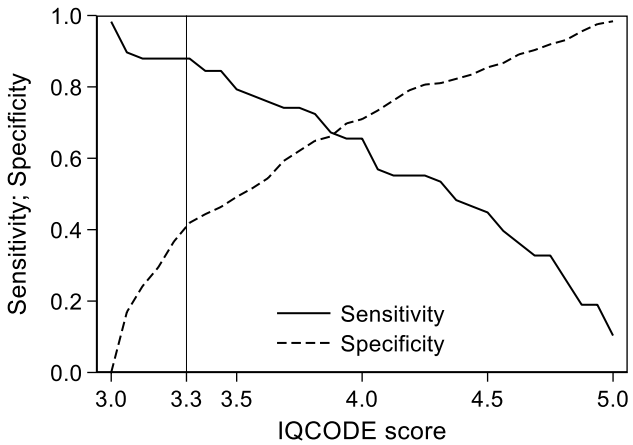

Fig. 2 Sensitivity and specificity in relation to IQCODE's ability to predict delirium during hospitalization

Table 4 Sensitivity, specificity, and predictive values at selected IQCODE cut-points

IQCODE cut-point	Sensitivity	Specificity	PV +	PV −	OR
≥ 3.0	0.98	0	0.19	0	0
≥ 3.3	0.88	0.42	0.26	0.94	5.3 (2.3–12.1)
≥ 3.5	0.79	0.49	0.27	0.91	3.7 (1.9–8.0)
≥ 4.0	0.66	0.71	0.35	0.90	4.6 (2.5–8.5)

admitted to hospital with acute illness [36]. The IQCODE has the advantage that no patient involvement is required [20, 37] and can, therefore, be a part of a predictive model including risk factors.

Strengths and limitations of the study

In this study, only 13% of the questionnaires were not completed. A normal procedure in our department is to invite one of the patients' family or closest friend to set goals for the admission and to plan the discharge, unless the patients refuse involvement of their relatives. This regular contact with relatives made it easy to collect the IQCODE data. In some cases, the relatives who responded to the IQCODE questionnaire told that the questions were spot on the difficulties in the patient's everyday life.

Moreover, the interviews were made by a trained geriatric staff. Also, a trained staff completed the CAM assessments twice a day during the hospitalization. The staff completed the same course before using IQCODE and CAM, and the clinical guidelines for delirium did not change during the study. Finally, as delirium fluctuates, the CAM screening twice a day during the hospital stay reduced the risk of missing episodes of delirium.

We excluded 11 patients who were unable to communicate for various reasons. A part of this group was very sick of dementia and had no language. However, the high risk of delirium among such patients is evident, also without using an instrument like IQCODE.

The patients that are hospitalized at our geriatric department are a selected group of quite vulnerable older patients and it might be different in other hospitals with geriatric department or beds.

Conclusion

The IQCODE is a useful tool to predict the risk of delirium among hospitalized geriatric patients. A previous study of IQCODE as a predictor of dementia recommended a cut-point of 3.3. The overall risk to develop delirium during

hospitalization was 19%, but using IQCODE with a cut-point of 3.3 allowed to identify a low-risk group with a risk of 6% and a high-risk group with a risk of 26% to develop delirium during hospitalization. The IQCODE does not stand alone, but it is a useful supplement to other observations in detecting patients needing dementia-friendly treatment and care.

The cost of data collection, analysis, and preparation of the manuscript was covered by the Department of Geriatrics, Aarhus University Hospital.

Compliance with ethical standards

Conflict of interest The cost of data collection, analysis, and preparation of the manuscript was covered by the Department of Geriatrics, Aarhus University Hospital. The authors declare no conflicts of interest.

Research involving human participants It was a quality development project with no intervention, the study was exempted from notification to the Central Denmark Region Ethical Committee (Inquiry number 200/2017). The study protocol was approved by the Danish Data Protection Agency, case no. 1-16-02-254-16. The study was registered at ClinicalTrials.gov (Identifier NCT03175276).

Informed consent Not needed according to Ethical Committee.

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Full name of the PhD student: Sif Sund Blandfort

This declaration concerns the following article/manuscript:

Title:	Single-bed rooms in a geriatric ward prevent delirium in older patients.
Authors:	Blandfort S, Gregersen M, Rahbek K, Juul S, Damsgaard EM.

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

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The acquisition, analysis, or interpretation of data:	A
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Drafting the manuscript:	A
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Submission process including revisions:	A

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Drafting the manuscript:	B
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Drafting the manuscript:	A
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Submission process including revisions:	B

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