Delirium in the elderly: biomarkers and outcomes
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Chapter 7

Summary and general discussion
CHAPTER 7

In this concluding chapter the main findings of this thesis are summarized and discussed with reference to current issues in the field of delirium research.

PART 1

Preface
According to the most recent version of the Diagnostic and Statistical Manual of Mental Disorders, the key diagnostic feature of delirium is a disturbance of consciousness with a reduced ability to focus, sustain, or shift attention. Delirium is further characterized by an acute onset and there is evidence that the delirious episode is caused by the direct physiological consequences of a general medical condition, if not the result of substance withdrawal or intoxication. Infections have since long been described as the acute physical illnesses that may cause delirium. As early as 500 BC, Hippocrates described delirious states, labeled ‘phrenitis’, as caused by fever, meningitis, trauma, and pneumonia. In fact, absence of fever has long been considered a diagnostic criterion to separate ‘madness’ from delirium. At present, delirium is strongly associated with ageing. Yet, it is important to note that well into the twentieth century delirium was also common among younger people, for instance in those succumbing to influenza or pneumonia. However, with the advent of modern medicine the severity and the stage that an illness needs to acquire to cause delirium in otherwise healthy younger individuals became a relatively rare thing. At the same time as advancements in medicine significantly improved life expectancy, treatment of chronic and degenerative illnesses associated with ageing were less successful. Hence, people are becoming older and more frail. These developments also transformed ideas concerning the etiology of delirium. Traditional schemes in which a severe state of illness causes delirium and where the characteristics of the patient were of minor importance could not explain why some elderly individuals with relatively benign conditions, such as bacterial cystitis, became severely delirious while others did not. These changes in thinking about the etiology of delirium followed a more general development in the 1960’s in the field of psychiatry, where a gradual shift was noted from exogenous (e.g. infections) to endogenous (vulnerability) factors as the main contributors of disease. Exogenous factors, or stressors, include recent changes that are believed to result in disease only if a patient is vulnerable (as determined by endogenous factors). In the 1990’s Inouye and colleagues translated these ideas to the field of delirium research and showed that occurrence of delirium in elderly patients indeed depends on the interaction between an individual’s susceptibility (endogenous or predisposing factors) and noxious insults (exogenous or precipitating factors). Like most psychiatric
syndromes in the elderly, delirium is rarely caused by a single factor and most often results from multifactorial contributions. Numerical studies have investigated which specific predisposing and precipitating factors increase the likelihood of developing delirium and extensive lists of risk factors have been provided by many authors (e.g. Rolfson). Older age and cognitive impairment have consistently been found as the most important predisposing risk factors for delirium. Infections, trauma, and surgery have been shown to be strong precipitating risk factors. Despite the availability these days of lists with risk factors to identify patients at risk of developing delirium, the nature of the interaction of predisposing and precipitating factors remains unknown and the underlying pathologic mechanisms are largely unexplored. Partly, this is due to the use of heterogeneous patient populations in research. For instance, most studies analyzing correlations between inflammatory markers and delirium have done so in acutely admitted patients at medical wards. The variety of underlying illnesses for which these patients are hospitalized may confound results as each patient may show a unique pattern of interaction between predisposing and precipitating factors, i.e. different pathologic mechanisms may have played a role in the development of delirium. Thus, when studying the pathophysiology of delirium homogenous groups of patients who undergo relatively standardized insults offer great benefits. Identification of these pathologic mechanisms is critical for developing effective preventive and treatment strategies. Therefore, one of the aims of this thesis was to complement the existing multifactorial model of delirium by investigating pathophysiological mechanisms that underlie the increased susceptibility for delirium of elderly and cognitively impaired individuals in a relatively homogenous group of hip fracture patients.

Summary
Dementia syndromes are strongly associated with the pathological features of Alzheimer's disease (AD), i.e. senile plaques composed of β-amyloid (Aβ 1–42) and neurofibrillary tangles consisting of hyperphosphorylated tau (Ptau). However, the presence of these pathological features is not limited to patients with dementia only. Up to 40% of individuals aged 80 years and older without dementia harbor the same abnormalities to such a degree that they even meet criteria for the neuropathological diagnosis of AD. The presence of these neuropathological lesions in these older individuals without dementia is associated with impaired performance in multiple cognitive domains. Based upon the strong interrelationship between delirium and dementia we investigated whether cerebrospinal fluid levels (CSF) of β-amyloid and tau, as correlates of the neuropathological lesions that are associated with cognitive impairment in elderly individuals, are risk markers for the incidence of postoperative delirium (chapter 2). Patients were 75 years or older and admitted
for surgical repair of acute hip fracture. CSF samples were collected at the onset of spinal anesthesia and β-amyloid, tau, and hyperphosphorylated tau levels were determined for 76 patients. Postoperative delirium occurred in 30 out of the 76 (39.5%) patients. Although patients who developed delirium after the operation were older and more often cognitively impaired, CSF levels of β-amyloid, tau, and hyperphosphorylated tau did not differ significantly between patients who did or did not develop postoperative delirium.

In chapter 3 we investigated the association between preoperative CSF levels of pro- and anti-inflammatory cytokines and the occurrence of delirium after surgical repair of hip fracture. Based on an exaggerated central nervous system (CNS) immune response to peripheral stimulation in elderly and cognitive impaired individuals, we hypothesized that altered CNS cytokine profiles before the operation, that is, stimulated by the noxious insult of the fracture, are risk markers for delirium after the operation. The same group of patients as described in chapter 2 was used to investigate this hypothesis. CSF cytokine profiles were available for 74 patients of whom 27 became delirious after the operation. The following pro-inflammatory cytokines were determined; tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), and the anti-inflammatory cytokine IL-10. Because the state of inflammation does not depend on the net effect of individual cytokines but rather on the balance between pro- and anti-inflammatory mediators, we also calculated the ratio of IL-6/IL-10 and IL-8/IL-10 to measure the overall inflammatory status in the CSF. We found that higher preoperative ratios of the pro-inflammatory cytokine IL-8 and the anti-inflammatory cytokine IL-10, were positively associated with the incidence and the severity of delirium after the operation. This relationship was most distinct during the first two days post-surgery when immune-to-brain communication is expected to be strongest and peripheral levels of cytokines peak. Analyzed separately none of the cytokines showed any relationship with the incidence or the severity of postoperative delirium.

Chapter 4 focused on the relationship between delirium and elevated levels of cortisol. Ageing, depression, and neurodegenerative disease predispose to delirium and are associated with an increased sensitivity of the brain to stress. Based on these changes in the brain’s reactivity to stress in individuals at risk of delirium, we investigated whether patients who developed delirium after surgical repair of hip fracture already show altered cortisol levels in the CSF before the operation. The same patient sample as described in chapters 2 and 3 was used. CSF cortisol levels were available of 66 patients without corticosteroid therapy at baseline. Twenty-three out of the 66 (35%) patients developed postoperative delirium. We found no significant differences in preoperative CSF cortisol levels between patients who did or did not develop postoperative delirium. Also, no association was found between preoperative CSF cortisol levels and the severity of the delirious episode.
PART 2

Preface
Over the past millennia delirium has been perceived as a fatal sign and in those who survived poor mental outcomes were often noted.\textsuperscript{2,3} However, in the twentieth century thinking about the prognosis of delirium shifted. Although delirium was still conceived as a lethal syndrome in some, it was considered to lead to full recovery among survivors. This change in thinking was probably fuelled by the desire to clearly differentiate delirium from dementia.\textsuperscript{3} One of the most influential writers of the recent past, Lipowski described delirium as a ‘transient organic mental syndrome of acute onset’.\textsuperscript{20} According to this view, once the acute episode has resolved, the premorbid level of functioning is reached again. Nevertheless, clinical experience and research has shown that the consequences of delirium can be grave, especially in the elderly. Nowadays, most clinicians and investigators agree that delirium is associated with poor outcomes on a range of functional domains in elderly individuals. Despite this consensus among experts several issues concerning the prognosis of delirium need further clarification before effective preventive strategies can be designed aimed at averting delirium’s negative sequelae. The question whether delirium is ‘just’ a marker of physical illness and a fragile constitution or whether delirium contributes to poor outcome by its self is of particular importance. One topic that is engaging many scientists today is the interrelationship between delirium and dementia. Research has shown that those who develop delirium, even those without significant prior cognitive impairment, are at high risk of developing dementia in the near future.\textsuperscript{21,22} However, since most research is conducted in acute hospital populations (where the prevalence of delirium is highest and research is economically and practically most viable) there is no opportunity to conduct a thorough assessment of the cognitive status prior to hospitalization. Instead, most investigators rely on chart review or brief patient examinations such as the Mini Mental Status Examination (MMSE).\textsuperscript{23} Chart review may result in an underestimation of baseline cognitive impairment because most dementia patients lack a formal diagnosis. Since cognition is usually more extensively tested at follow-up an overestimation of the association between delirium and dementia may be the result. On the other hand, cognitive screening instruments (such as the MMSE) may also be unreliable. Many factors, such as stress, use of pain and psychotropic medication, and delirium itself, may lower the baseline measurement of cognition at hospital admission. As a result, newly occurring cognitive decline on follow-up may be masked when cognition is assessed without interference of these disruptive influences.\textsuperscript{24} Therefore, studies should use different and more reliable measures of preexistent cognitive impairment in order to assess whether delirium is indeed
associated with poor cognitive outcomes. A related issue concerns the detailed neuropsychological characterization of the consequences of delirium in the elderly. Neuropsychological test batteries are considered the ‘gold standard’ for investigating the effects of delirium on cognitive functioning at follow-up. Yet, most studies that examined the association of delirium with long-term cognitive impairment merely used screening instruments which are inappropriate for fully characterizing and quantifying defects in specific cognitive domains. Therefore, the precise nature of the cognitive impairments and the extent to which particular cognitive domains are affected after delirium are all but unexplored. Furthermore, it is not clear whether alternative explanations for the association between delirium and cognitive impairment (or dementia) are worth considering. As suggested by Cole et al. symptoms of delirium may persist for months and patients with (apparent) cognitive impairment at follow-up may in fact suffer from persistent delirium. Alternatively, patients with hip fracture have an increased risk of developing depression over time, especially those with high delirium scores during hospitalization. As depression is associated with poor cognitive performance an increase in depressive symptomatology may explain the poor cognitive status at follow-up of patients who earlier experienced delirium. Long-term follow-up studies that assess delirium, cognition, and depression simultaneously are necessary to shed light on the tenability of different explanations for the association between delirium and long-term cognitive impairment.

Summary
In chapter 5 a meta-analytic review of the association between delirium and death, institutionalization and dementia is provided. The main objective of this meta-analysis was to determine if delirium contributes independently to poor clinical outcome or merely represents a marker of an individual’s baseline vulnerability. For this purpose we conducted a systemic search of observational studies published in the past three decades of elderly patients with and without delirium with data on mortality, institutionalization, or dementia after a minimum follow-up of 3 months. Of 2939 references in the original search, 51 relevant articles were identified. To limit heterogeneity we only included studies that diagnosed delirium prospectively with the use of a validated method for delirium ascertainment. Two sets of analyses were performed; primary analyses in which studies were included that provided adequate statistical control for the covariables of age, sex, comorbid illness and/or illness severity, and baseline dementia; and secondary analyses in which unadjusted effect sizes were summarized. The primary analysis with adjusted hazard ratios (HRs) showed that delirium is associated with a significantly increased risk of death, institutionalization, and dementia. Importantly, the association between delirium
and poor outcome persists for years after the occurrence of the delirious episode and, presumably, the resolution of the event(s) that precipitated delirium. Sensitivity, trim-and-fill, and the secondary analyses with unadjusted risk estimates stratified according to the study characteristics confirmed the robustness of these results. Moreover, our stratified secondary analyses even suggest that patients without a given risk factor (e.g. dementia) experience adverse outcomes after delirium at least as often as those with the risk factor.

Chapter 6 describes the association of delirium and long-term cognitive impairment. In a prospective follow-up study the nature of the cognitive deficits and the extent to which the persistence of delirium or depression at follow-up accounts for the association between delirium and long-term cognitive decline were investigated. In total 53 elderly hip fracture patients with and without in-hospital delirium underwent a comprehensive neuropsychological assessment three months after hospital discharge. Because we were specifically interested in the effects of in-hospital delirium on long-term neuropsychological test performance, we excluded five patients with persistent (or recurrent) delirium at follow-up from our analyses. The 22 patients who experienced delirium during hospitalization, in comparison to 26 control patients, showed greater impairments on tests of global cognition and episodic memory, even after adjusting for important covariates such as age, gender and baseline cognitive impairment. In contrast, no clear differences were found on tests that measure attention, the cardinal symptom of (persistent) delirium. Moreover, additional analyses showed that patients with in-hospital delirium, who were free of any delirium symptoms at follow-up, also performed more poorly on a test of episodic memory then patients in the control group. Interestingly, patients with in-hospital delirium showed an increase of depressive symptoms after 3 months. However, in patients with few or no signs of depression delirium remained associated with poor performance on a range of neuropsychological tests, including tests of global cognition and episodic memory.
DISCUSSION

Hip fracture
In this thesis we have studied biomarkers and outcomes of delirium in a group of elderly patients who underwent surgical repair of hip fracture. Elderly hip fracture patients present an interesting model for the study of delirium, in particular for studying the pathophysiology of delirium; hip fracture is relatively common in older people; the prevalence of delirium and dementia in this population is high; previous research on delirium has described this patient population in detail; and hip fracture allows for translation of findings in animal experiments to a clinically relevant population. Furthermore, hip fracture patients constitute a relatively homogenous group with less confounding due to diverse underlying illnesses, in contrast to patients who are acutely admitted in medical or intensive care wards. Moreover, hip fracture has a clearly defined onset and all patients who undergo surgery endure the same two stressful events, that is first the fracture, then the surgery. This fixed sequence of events and the relative homogeneity of the population make hip fracture patients particularly suitable for studying the pathophysiology of delirium. These characteristics become especially relevant when studying mechanisms that are highly dynamic and influenced by a multitude of factors, such as the immune system and limbic-hypothalamic-pituitary-adrenal (LHPA) axis. The timing of the hip fracture and the surgery, relative to the sampling of the biomarkers, provide two scenarios for studying the pathophysiology of delirium. For some patients the hip fracture itself is sufficient to elicit an episode of delirium. In these patients, it will not be possible to decide whether a preoperatively (or postoperatively) measured level of a particular biomarker is involved in the pathogenesis of delirium or whether it is a risk marker for delirium (i.e. predisposes to delirium). Risk markers are therefore better studied in those hip fracture patients who develop delirium only after the operation. In such a scenario biomarkers are measured before the operation and their levels are associated with the occurrence of delirium after the operation. However, it must be noted that in modelling postoperative delirium, the difference between a risk marker (for delirium) and a marker that signals the presence of a pathogenetic process (associated with the occurrence of delirium) may seem somewhat artificial as there is no way of knowing for certain that patients who develop postoperative delirium would have remained free from preoperative delirium in the event the operation was cancelled or postponed. Elective hip surgery populations may therefore provide an interesting alternative model for studying delirium. However, the incidence of delirium among elective hip surgery patients is low and the severity of the delirious episodes is generally much more modest making this an impractical and expensive population
for studying delirium. Hence, we studied delirium in hip fracture patients. Based on the exaggerated CNS immune and stress response to peripheral stimulation in patients at high risk of delirium, we hypothesized that hip fracture patients who are prone to develop postoperative delirium already show altered CNS cytokine and cortisol profiles before the operation, that is, stimulated by the fracture. In this sense, the event of hip fracture magnifies any pre-existing vulnerabilities in the immune or stress system, although not to the extent of actually causing preoperative delirium in these patients. As a result, when one fails to find a relationship between postoperative delirium and preoperative cytokine or cortisol levels in hip fracture patients it becomes less likely that these biomarkers (by themselves) signal increased vulnerability for delirium as their preoperative footprint is enlarged by the fracture.

Pathologic mechanisms and risk markers of delirium
The question arises why CSF β-amyloid, tau, and hyperphosphorylated tau were not associated with postoperative delirium in our sample of elderly hip fracture patients. After all, cognitive impairment is an important predisposing risk factor for delirium\(^\text{11}\) and CSF β-amyloid, tau, and hyperphosphorylated tau are associated with mild cognitive impairment and dementia.\(^\text{37}\) Furthermore, the neuropathology of AD is present many years before the clinical onset of the disease\(^\text{38}\) and CSF biomarkers may reflect damage in the brain before any cognitive signs are present.\(^\text{39,40}\) An explanation for our somewhat unexpected findings may relate to the relatively old age of our study population in comparison with the age of individuals in studies that show that CSF biomarkers can differentiate dementia and mild cognitive impairment (MCI) from normal cognition.\(^\text{41,42}\) With increasing age the pathological features of AD become less specific for the clinical expression of dementia, an effect that can be explained by an increasing burden of AD pathology in non-demented individuals.\(^\text{43}\) These findings in post mortem studies are mirrored in the CSF where differences in CSF biomarkers between patients with and without dementia decrease with advancing age.\(^\text{44-46}\) This convergence of AD pathology between individuals with and without dementia suggests that additional factors determine the expression of dementia in the oldest old.\(^\text{43}\) One such an additional factor may be coexisting cerebrovascular pathology. Cerebrovascular damage profoundly impacts the clinical expression of AD\(^\text{47}\) and large proportions of the dementias in the elderly are caused by a combination of AD with vascular pathology.\(^\text{48,49}\) Cerebrovascular damage may exert its detrimental influence on cognition by directly damaging neural pathways and/or by worsening the impact of AD pathology on the brain.\(^\text{50}\) Such an interaction effect may also explain why we did not find an association between delirium and CSF correlates of AD pathology. Thus, other abnormalities, including cerebrovascular pathology, rather than plaque and tangle formation only,
may determine the expression of cognitive impairment in the oldest old and as a result may underlie the susceptibility of these patients for delirium. Of interest here is the observation that the prevalence of delirium is higher in late onset AD and vascular dementia than in early onset AD and frontotemporal dementia\textsuperscript{51,52} and that vascular risk factors and white matter lesions have been associated with delirium.\textsuperscript{53,54} Moreover, cerebrovascular pathology has been suggested to play a common role in the initiation of cholinergic abnormalities in vascular dementia and AD.\textsuperscript{55} Cholinergic neurotransmission is essential for attentional processes\textsuperscript{56} and aberrant cholinergic function has been postulated as the final common pathway in delirium pathophysiology.\textsuperscript{57-59}

The question remains through which mechanisms an extracerebral signal causes a neuropsychiatric syndrome. A profound impairment in the neurovascular unit (i.e. the principal functional component of the blood-brain-barrier (BBB)) resulting in increased blood-brain permeability may underlie the susceptibility for delirium of ‘oldest old’ patients who suffer from cerebrovascular disease and AD.\textsuperscript{50,60,61} The neurovascular unit regulates cerebral blood flow and the exchange of nutrients and signaling molecules (e.g. cytokines) between the body and the brain (BBB). Moreover, this functional structure is crucial for keeping homeostatic balance and exerts important trophic actions that are essential for neuron and glia integrity. Importantly, the neurovascular unit is also an integral part of the neuroimmune axis and of crucial importance for immune surveillance and relaying peripheral immune signals to and from the brain.\textsuperscript{50,61,62} Interestingly, all these processes have been implicated in the pathogenesis of delirium.\textsuperscript{60,63,64} Besides BBB dysfunction associated with ageing and neurodegenerative disease, especially with a vascular pathology,\textsuperscript{65} the integrity of the BBB is further compromised by the surge of cytokines that is associated with important precipitating risk factors of delirium such as infections, trauma, and surgery.\textsuperscript{50,61} When the BBB is compromised the brain becomes more susceptible to the effects of systemic inflammation.\textsuperscript{60,66} Hence, one conceptualization of delirium suggests that it is a state of BBB dysfunction resulting in defective and inappropriately increased immune signaling to the brain.\textsuperscript{60} Yet, the involvement of other brain immune communication pathways (e.g. the vagus nerve) may also be of relevance (and not mutually exclusive) for transferring peripheral immune signals into the cerebrum.\textsuperscript{60,67}

Whatever the precise mechanisms are by which the peripheral immune signals (e.g. cytokines) reach the brain, they can ultimately lead to activation of microglia, the innate immune cells of the central nervous system (CNS).\textsuperscript{16} Once activated, microglia secrete a range of bioactive substances that further modulate immunological actions but can also disrupt homeostasis and compromise neuronal and synaptic function potentially inducing delirium in vulnerable individuals.\textsuperscript{60,67} This is called
the neuroinflammatory hypothesis of delirium. Although speculative, the ongoing neuroinflammation may, among other factors, further compromise the integrity of the neurovascular unit resulting in shifts in glucose levels, oxygen saturation, neurotransmission, and acid based balances leading to a syndrome of ‘cerebral insufficiency’ as originally hypothesized by Engel and Romano. Because the activity of the CNS immune system is increased in ageing and neurodegenerative disease the disruptive actions of cytokines and microglia are more pronounced in elderly and cognitively impaired individuals. In addition, the immune and cholinergic system interact and under normal circumstances microglia are under strict cholinergic control. In ageing and neurodegenerative disease, however, cholinergic inhibition of microglia may fail and the neuroinflammatory process may spin out of control. In turn, cholinergic deficiencies may be further exacerbated as a result of the neuroinflammation itself, BBB dysfunction, and/or changes in the balance between neurotransmitter systems. In this way, cholinergic function is further compromised, thus closing a vicious cycle of ever increasing neuroinflammation and cholinergic deficits as a result of which delirium may develop.

In a similar way as described for the neuroinflammatory hypothesis of delirium, the LHPA-axis may also be involved in the development of this neuropsychiatric syndrome. Sustained high levels of cortisol can have harmful effects on the brain causing inattention and other cognitive deficits and several studies have identified high levels of cortisol in patients with delirium. In addition, older individuals and those with pre-existent cognitive impairment are at increased risk of developing sustained high levels after stressors because feedback regulation of the LHPA-axis is impaired. Furthermore, the immune system and the LHPA-axis are interrelated. Although activation of the LHPA-axis normally down-regulates the inflammatory response it seems that under certain conditions the LHPA-axis may exacerbate the CNS effects of systemic inflammation.

Based on the potential involvement of neuroinflammation and LHPA-axis activity in the pathogenesis of delirium, together with abnormalities in the immune and stress system in elderly and cognitively impaired patients, we investigated whether hip fracture patients who developed postoperative delirium showed altered CNS cytokine or cortisol profiles before the operation. Even though we found the preoperative IL-8/IL-10 ratio to be of relevance for postoperative delirium our results are at best modest as a marked overlap was observed between the IL8/IL-10 ratio of patients with and without delirium and because none of the individual cytokine or cortisol levels were found to be associated with postoperative delirium. Our findings suggest that it is not likely that preoperative CSF cytokine or cortisol levels signal an increased vulnerability for delirium. Thus, it may be that cytokines and cortisol
are only important in relation to the pathogenesis of delirium, a possibility that we did not explore in the present studies. It could be speculated that pathological changes in the immune and stress system are necessary for delirium to develop, however, they only have relevance in the presence of precipitating factors that exceed a certain threshold of compensatory mechanisms aimed to maintain the balance within the brain. Possibly, it is the malfunctioning of these compensatory (or buffering) mechanisms, such as e.g. the cholinergic neurotransmission or BBB, that predispose elderly and cognitively impaired individuals to delirium. Alternatively, abnormalities in the immune system and LHPA-axis may indeed increase the risk for delirium, however, this increased risk is not expressed by pre-morbid levels of cytokines and cortisol. For instance, future studies should more directly examine the activation states of microglia in order to investigate whether these states determines the threshold for delirium. In this respect, it is noteworthy that microglia of mice with chronic neurodegeneration normally express low levels of pro-inflammatory cytokines but are primed to produce high levels of inflammatory cytokines only after a severe stressor such as lipopolysaccharide (LPS) stimulation. On the contrary, this may also mean that in hip fracture patients who develop postoperative delirium, the fracture itself was not sufficient a stressor to elicit a prompt and clear response of the immune and stress system. Future studies should also examine whether it may be the sensitivity of the brain to cytokines or cortisol, rather than the actual levels of these factors, that may confer an increased risk for delirium. Despite our conclusion, that preoperative levels of cytokines do not signal an increased risk of postoperative delirium, we should be cautious as we observed a modest association between IL-8/IL-10 and postoperative delirium. This finding should drive future research because cytokines normally act in concert to propagate their effects. Thus, studies are necessary that examine a range of pro- and anti-inflammatory cytokines simultaneously and in relation with each other to determine the overall state of inflammation in the brain and the extent to which these cytokine profiles put patients at increased risk for delirium.

Outcomes of delirium and the association between delirium and dementia

The main finding of our follow-up and meta-analytic study was that elderly patients who experienced delirium in the hospital showed more cognitive impairment at follow-up when compared with non-delirious controls. In essence, we replicated earlier studies that found that delirium is associated with long-term cognitive impairment and dementia. Excluding the possibility of direct brain insults (e.g. stroke) for the purpose of this discussion, the relationship between delirium and long-term cognitive impairment may reflect one or more of several explanations. First, as described above, both persistent delirium and depression at follow-up
constitute (potential) reversible causes of cognitive impairment. However, our follow-up study shows that it is not likely that the presence of symptoms of delirium or depression at follow-up can fully account for the association between delirium and long-term cognitive impairment. Nevertheless, persistent delirium can affect cognitive outcome at follow-up in some patients since almost 20% of patients with in-hospital delirium were still (or again) delirious 3 months after hospital discharge. Consequently, studies that include patients with reversible causes of cognitive impairment (e.g. persistent delirium) may systematically overestimate the strength of the relationship between delirium and newly acquired long-term cognitive impairment or dementia.

Second, delirium may unmask early or subclinical (undetected) dementia or may actually initiate or accelerate a process of cognitive decline. The results of our follow-up study together with the outcomes of our meta-analytic review suggest that delirium may be more than a marker of pre-existent cognitive decline. Delirium remained associated with long-term cognitive impairment in multivariate analyses that controlled for relevant confounders, most notably pre-existent cognitive impairment, and in subgroup analyses among patients without any signs of prior cognitive impairment or dementia. Nevertheless, caution should be taken because the validity of such a conclusion depends on a reliable estimate of the cognitive status prior to delirium. As mentioned earlier, this is especially challenging in (acute) hospital situations. In this respect it is relevant, that we replicated previous findings that showed that the MMSE is sensitive to stressors that accompany hospital admission. This may result in an overestimation of cognitive impairment at baseline making it difficult to accurately measure cognitive deterioration over time. On the basis of our follow-up study the Informant Questionnaire on Cognitive Decline in the Elderly - short version (IQCODE-N) may provide a welcome addition to the MMSE as this instrument seems less prone to stress at admission (probably because the rating is based on an informant, and not on the patient itself). While a decline in cognition between baseline and follow-up could be observed in patients with in-hospital delirium with the IQCODE-N, such an effect was masked by the MMSE. Although the MMSE is considered to be the ‘golden standard’ for measuring cognition in hospital settings, the IQCODE-N may provide a more reliable measurement of baseline cognition which is especially important for following changes over time.

The mechanisms through which delirium may contribute to cognitive deterioration remain unclear. Delirium itself may have an effect on long-term cognitive impairment through alterations in behaviour during the delirious episode itself (e.g. apathy and inactivity may lead to pressure ulcers and possibly infections) or as a consequence of possible neurotoxic effects of drugs used to treat delirium. On the other hand,
factors that precipitate delirium may incite a detrimental sequence of events in the brain. While overactivated microglia and LHPA axis dysregulation may lead to delirium in the short term, after time, the resulting neuroinflammation and sustained high levels of cortisol may cause or accelerate (existing) neurodegeneration.\textsuperscript{19,33,60,67} In this context it is noteworthy, that microglia activation and neuroinflammation is an early event in the pathogenesis of AD,\textsuperscript{84} and as such, delirium from extracerebral origin may influence the rate of cognitive decline in AD.\textsuperscript{60} This may explain why permanent cognitive deficits are seen especially in patients with some pre-existent cognitive impairment\textsuperscript{60} and why delirium can accelerate the trajectory of cognitive decline in patients with AD.\textsuperscript{85} The increased risk of long-term cognitive impairment (or even dementia) is just one of the poor outcomes that have been associated with delirium in elderly populations. Numerous other studies have addressed the long-term prognosis of older individuals who experienced delirium during hospitalization and a meta-analysis summarizing these findings for mortality, institutionalization, and dementia was needed to draw conclusions based on a body of research instead of individual investigations. The most important conclusion of our meta-analytic review is that delirium by itself seems to contribute to long-term mortality, institutionalization, and dementia. This is a very significant finding as delirium is commonly viewed as merely a transient reflection of underlying (brain) pathology, rather than as an indication of a serious acute condition that warrants consideration in its own right. This perspective of delirium puts extra emphasis on strategies that prevent delirium. As prevention is better than cure, optimizing the ‘primary prevention’ of delirium is also the best way to ward off delirium’s poor outcomes. Indeed, once delirium is present, management of delirium has not been found to improve the long-term prognosis.\textsuperscript{86} Unfortunately, delirium prevention is ineffective in a majority of cases.\textsuperscript{67} This known fact, together with delirium’s poor prognosis, justify the development of preventive strategies that are specifically aimed at averting the negative consequences of delirium. At present, however, no such intervention trials are known although the proposed mechanisms through which delirium may contribute to cognitive deterioration offer scope for intervention.\textsuperscript{67} Nonetheless, regardless of the lack of scientific underpinning at this moment, patients who have experienced delirium should be considered an especially vulnerable population.
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