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Cognitive impairment in medical inpatients

Gustav Torisson



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DOCTORAL DISSERTATION

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Faculty opponent

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<p>Abstract</p> <p>Background: People aged over 80 years is the most rapidly growing segment of the population in Sweden. This group is susceptible to multimorbidity, disability and cognitive impairment. Managing these issues will be essential in order to obtain a sustainable healthcare system in the near future.</p> <p>Aim: To determine if increased acknowledgement of cognitive impairment could improve healthcare for elderly persons admitted to a general hospital</p> <p>Study population: Two hundred patients at the wards of general internal medicine at Skåne university hospital in Malmö. Results: I. Cognitive impairment was prevalent in 73% of medical inpatients, the majority of which were undetected by healthcare professionals. Cognitive impairment was independently associated with a three-fold risk of one-year mortality.</p> <p>II. A group of 99 patients received an intervention that focused on cognitive impairment. This group had fewer rehospitalisations after 12-months than the control group, receiving standard care. This effect was statistically significant for those patients who survived for 12-months, but not from an intention-to-treat perspective.</p> <p>III. In total, 94 patients had undergone a cranial computed tomography. Of these, 36% had an abnormal medial temporal lobe atrophy (MTA). None of these had been reported originally. Of the patients with abnormal MTA, 93% had cognitive impairment, with a test profile indicating a possible Alzheimer symptomatology.</p> <p>IV. An ADL (activities of daily living) measurement predicted mortality stronger than age, sex, body mass index, albumin, haemoglobin, kidney function and the Charlson comorbidity index. The ADL measurement entailed a substantial added value to these established risk factors.</p> <p>V. Lower quality of life was associated with cognitive impairment, ADL impairment, depression and social factors, but not with physical comorbidity. Conclusion: This thesis emphasises the need to acknowledge cognitive impairment in medical inpatients. The results suggest that increased acknowledgement of cognitive impairment could lead to fewer rehospitalisations, more accurate prognosis estimates and possibly better quality of life.</p>		
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PAPPER



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Abstract

Background: People aged over 80 years is the most rapidly growing segment of the population in Sweden. This group is susceptible to multimorbidity, disability and cognitive impairment. Managing these issues will be essential in order to obtain a sustainable healthcare system in the near future.

Aim: To determine if increased acknowledgement of cognitive impairment could improve healthcare for elderly persons admitted to a general hospital

Study population: Two hundred patients at the wards of general internal medicine at Skåne university hospital in Malmö.

Results:

I. Cognitive impairment was prevalent in 73% of medical inpatients, the majority of which were undetected by healthcare professionals. Cognitive impairment was independently associated with a three-fold risk of one-year mortality.

II. A group of 99 patients received an intervention that focused on cognitive impairment. This group had fewer rehospitalisations after 12-months than the control group, receiving standard care. This effect was statistically significant for those patients who survived for 12-months, but not from an intention-to-treat perspective.

III. In total, 94 patients had undergone a cranial computed tomography. Of these, 36% had an abnormal medial temporal lobe atrophy (MTA). None of these had been reported originally. Of the patients with abnormal MTA, 93% had cognitive impairment, with a test profile indicating a possible Alzheimer symptomatology.

IV. An ADL (activities of daily living) measurement predicted mortality stronger than age, sex, body mass index, albumin, haemoglobin, kidney function and the Charlson comorbidity index. The ADL measurement entailed a substantial added value to these established risk factors.

V. Lower quality of life was associated with cognitive impairment, ADL impairment, depression and social factors, but not with physical comorbidity.

Conclusion: This thesis emphasises the need to acknowledge cognitive impairment in medical inpatients. The results suggest that increased acknowledgement of cognitive impairment could lead to fewer rehospitalisations, more accurate prognosis estimates and possibly better quality of life.

List of publications

- I. Torisson G, Minthon L, Stavenow L, Londos E. Cognitive impairment is undetected in medical inpatients: a study of mortality and recognition amongst healthcare professionals. *BMC Geriatrics* 2012, **12**:47.
- II. Torisson G, Minthon L, Stavenow L, Londos E. Multidisciplinary intervention reducing interventions in medical inpatients: a prospective, non-randomized study. *Clin. Interv. Aging* 2013;**8** 1295-1304
- III. Torisson G, van Westen D, Stavenow L, Minthon L, Londos E. Medial temporal lobe atrophy is underreported and may have important clinical correlates in medical inpatients. *Submitted for publication*
- IV. Torisson G, Stavenow L, Minthon L, Londos E. The importance and added value of functional impairment as a predictor for mortality in an elderly hospital population. *Submitted for publication*
- V. Torisson G, Stavenow L, Minthon L, Londos E. Reliability, validity and clinical correlates of the Quality of Life in Alzheimer's disease (QoL-AD) scale in medical inpatients. *Manuscript*

Abbreviations

MMSE	mini-mental state examination
AD	Alzheimer's disease
DLB	dementia with Lewy bodies
FTD	frontotemporal lobe dementia
ICD	International Statistical Classification of Diseases and Related Health Problems
DSM	Diagnostic and Statistical Manual of Mental Disorders
RCT	randomised controlled trial
GP	general practitioner
CT	computed tomography
MRI	magnetic resonance imaging
WMC	white matter changes
GCA	global cortical atrophy
MTA	medial temporal lobe atrophy
ADL	activities of daily living
ICC	intraclass coefficient
QoL	Quality of Life
SUS	Skånes universitetssjukhus (Skåne University Hospital)
ED	emergency department
CCI	Charlson comorbidity index
CDT	clock drawing test
GBS	Gottfries-Bråne-Steen scale
QoL-AD	Quality of Life in Alzheimer's disease scale
LIMM	Lund integrated medicines management

ANOVA	analysis on variance
IDI	integrated discriminatory improvement
NRI > 0	continuous net reclassification index
SD	standard deviation
IQR	interquartile range
BMI	body mass index
eGFR	estimated glomerular filtration rate
BMJ	British medical journal
OECD	Organisation for Economic Co-operation and Development

Sammanfattning på svenska

Befolkningsutvecklingen i Sverige medför att allt fler människor blir äldre. Detta är ett positivt resultat till följd av att befolkningen är vid bättre hälsa. Dock innebär det att fler människor kommer att uppnå en ålder där multisjuklighet (att ha flera kroniska sjukdomar samtidigt), oförmåga att klara sig själv och kognitiv svikt är vanligt förekommande. Detta kommer att ställa stora krav på flera delar av sjukvårdsapparaten. Denna avhandling fokuserar på hur kognitiv svikt hanteras på sjukhus.

Kognitiv svikt är ett centralt begrepp som i denna avhandling definierats som ett symptom, inte en sjukdom. Detta symptom kan bero på flera underliggande orsaker, t.ex. en demenssjukdom, ett alkoholmissbruk eller en svår kroppslig sjukdom som kan leda till akut förvirring. Kognitiv svikt kan upptäckas och graderas med ett s.k. kognitivt test där olika förmågor testas, t.ex. minne, räkneförmåga eller uppmärksamhet.

Vår studie genomfördes på internmedicinska kliniken vid Skånes universitetssjukhus i Malmö. Det var 200 patienter som deltog och genomsnittsåldern var 83 år.

I vår första studie fann vi att 73% av patienterna hade kognitiv svikt. Trots det var det endast ett fåtal som hade upptäckts av sjukvården tidigare. Personerna med kognitiv svikt löpte en trefaldig risk att avlida inom ett år. Därför tycker vi det är viktigt att undersöka alla äldre sjukhuspatienter avseende kognitiv svikt.

I den andra studien genomförde vi ett program för att förbättra omhändertagandet av patienter med kognitiv svikt. Detta program genomfördes på hälften av patienterna medan den andra hälften fick ordinarie vård. Efter ett år tittade vi hur det hade gått för de olika grupperna. De patienter som var med i vårt program hade mycket färre akutbesök och sjukhusinläggningar. Därför drog vi slutsatsen att man genom att förbättra omhändertagandet av äldre sjukhuspatienter med kognitiv svikt kan förhindra de sjukhusinläggningar som kanske inte är absolut nödvändiga utan beror på att t.ex. den sociala situationen inte fungerar.

I den tredje studien undersökte vi röntgenbilder av hjärnan. Om patienterna hade gjort en s.k. datortomografi av hjärnan av något skäl tidigare så eftergranskade vi bilderna i datorn. Vi letade bl.a. efter ett fynd som är vanligt vid Alzheimer's sjukdom, en skrupning av ett område av hjärnan som kallas hippocampus. Vi såg att 36% av patienterna hade en uttalad skrupning i detta området, av dessa hade ingen beskrivits från början, när det ursprungliga röntgensvaret skrevs. Av de som hade en sjuklig skrupning hade nästan alla

också avvikande resultat på kognitiva tester. Därför tycker vi att det är viktigt att man börjar rapportera denna typ av fynd mer regelbundet.

I den fjärde studien fann vi att ett speciellt test som heter GBS-ADL till viss del kunde förutsäga vilken prognos patienterna hade. GBS-ADL mäter hur en person klarar sig i vardagen, klarar hen att klä sig, tvätta sig etc? Förhoppningsvis kan detta leda till att vården för dessa patienter kan individualiseras. Om man kan förutsäga prognosen säkrare kan man förhoppningsvis undvika onödigt aggressiv vård för de patienter som är framme vid de sista månaderna i livet. Minst lika viktigt är att hitta de patienter som förväntas ha en god prognos, så att dessa inte undanhålls behandling och diskrimineras enbart p.g.a sin ålder.

I den femte studien fann vi tecken till att patienterna ansåg att kognitiv svikt var viktigare för livskvaliteten än vad fysisk sjukdom var. Om dessa fynd skulle upprepas så skulle det vara ytterligare ett skäl att uppmärksamma kognitiv svikt i denna grupp.

Sammanfattningsvis visade våra studier att kognitiv svikt var vanligt på sjukhus men att det är stor risk att den förblir oupptäckt om man inte aktivt letar efter den. Våra studier antyder också att man genom att uppmärksamma kognitiv svikt kan förhindra sjukhusinläggningar, få bättre uppfattning om patienternas prognos och i bästa fall förbättra deras livskvalitet.

I takt med att andelen äldre ökar i vårt samhälle, kommer det bli allt viktigare för sjukvården att förbättra vården av patienter med kognitiv svikt. Denna avhandling ger en viss vägledning i hur en sådan förbättring skulle utformas.

1. The demographic challenge

The population of the western world lives longer than ever before. In the 20th century, 30 years were gained in average life expectancy. This enormous accomplishment was reached by increased healthcare and living standards. However, longer life comes with a challenge; more older people will have to be supported by fewer younger people. The projection for the Swedish population is shown in Figure 1.

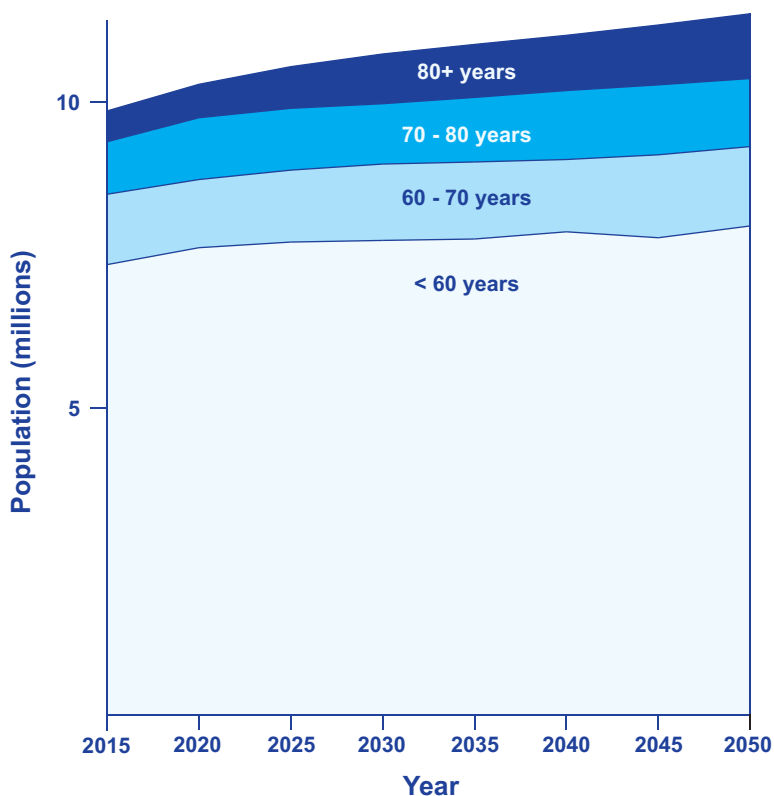


Figure 1. Population in Sweden by 2050.

Projected population in Sweden by age groups until 2050. Data source: Statistiska Centralbyrån (SCB)¹.

This may look undramatic but for healthcare, the largest challenge will be people aged over 80 years; they have a high susceptibility to disease and consume most of the healthcare resources. This group is the most rapidly expanding segment of the population. In Sweden, the proportion of people aged over 80 years will increase from 5% of the population today to 9.2% in 2050, see Figure 2.

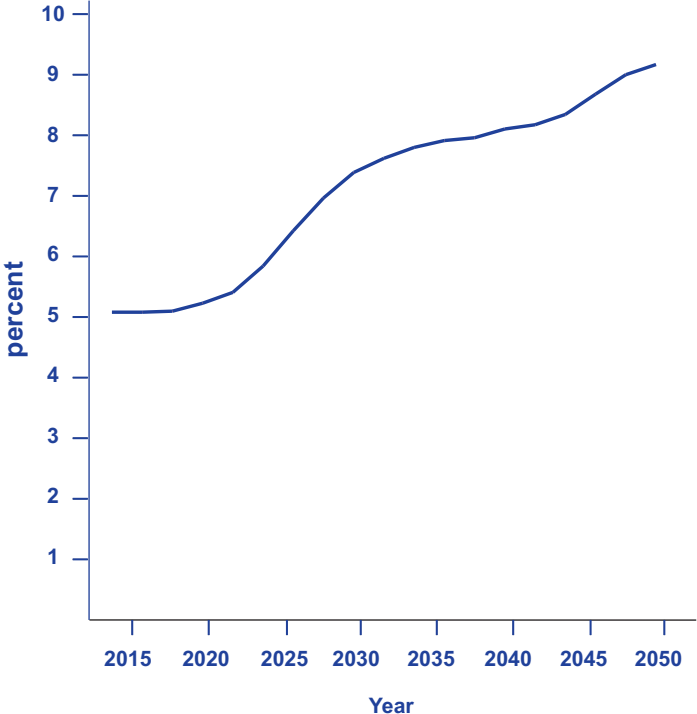


Figure 2. Proportion aged over 80 years.
The projected percentage of the Swedish population aged over 80 years until 2050. Data source: Statistiska Centralbyrån (SCB)¹.

The full impact of this development depends on how illness will develop in the oldest old, see Figure 3.

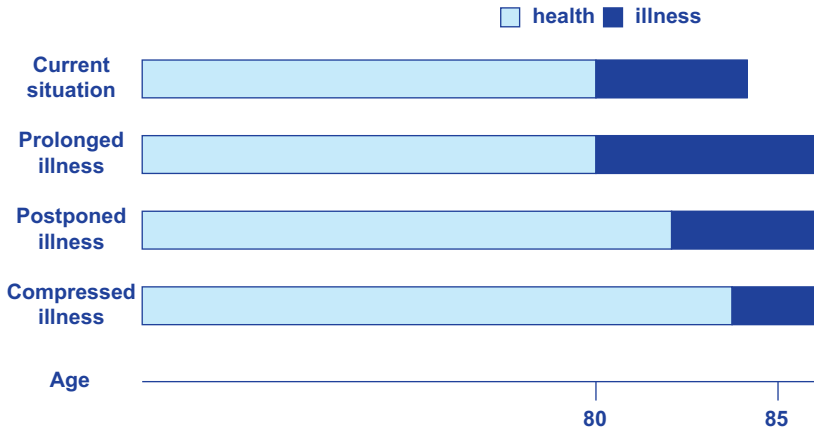


Figure 3. Scenarios for disease development

Three scenarios of how illness could develop when a population grows older: (1) *prolonged* illness, where the healthy part of life is unchanged and illness prolonged, (2) *postponed* illness, where the healthy part of life is prolonged, and illness unchanged and (3) *compressed* illness, where the healthy part is prolonged and the illness part shortened.

However, even in the best-case scenario, with compressed illness, the demographic challenge is so considerable that an increased strain will most likely be put on healthcare systems nevertheless. The impact of aging will be especially large within three areas of interest: (1) multimorbidity (having two or more chronic diseases), (2) disability (not managing everyday life), and (3) cognitive impairment. To obtain a sustainable society, it will be fundamental for all parts of the healthcare system to manage these issues appropriately in the near future.

This thesis focuses on optimising the management of cognitive impairment in a hospital setting.

2. Background

2.1. Introduction to cognitive impairment

2.1.1. Definition of cognitive impairment

Cognitive impairment is not a previously well-defined entity. In this thesis, cognitive impairment will be considered *a symptom with an underlying cause that could be detected using a cognitive test*. The term cognitive impairment will be used as an umbrella term, encompassing more specific symptoms, such as memory symptoms, executive dysfunction, disorientation, language impairment, attention deficits, learning difficulty and visuospatial deficits.

2.1.2. Cognitive impairment in the context of dementia and delirium

Dementia and delirium are two syndromes, or groups of symptoms, defined by diagnostic criteria. Cognitive impairment is a mandatory symptom in both dementia and delirium. The main difference between dementia and delirium is duration. Dementia criteria call for a six-month duration and therefore dementia could be considered *chronic* cognitive impairment. Delirium, on the other hand, has a rapid onset and could be considered *acute* cognitive impairment.

The relationship between cognitive impairment, dementia and delirium could be illustrated as follows:

At any point, a proportion of a population has cognitive impairment. The proportion varies with setting, it may be small in a grocery store and very large at a nursing home. Some of the persons with cognitive impairment may fulfil the criteria for dementia, others may not. Another group of those with cognitive impairment may have had an acute onset, fulfilling the criteria for delirium, see Figure 4.

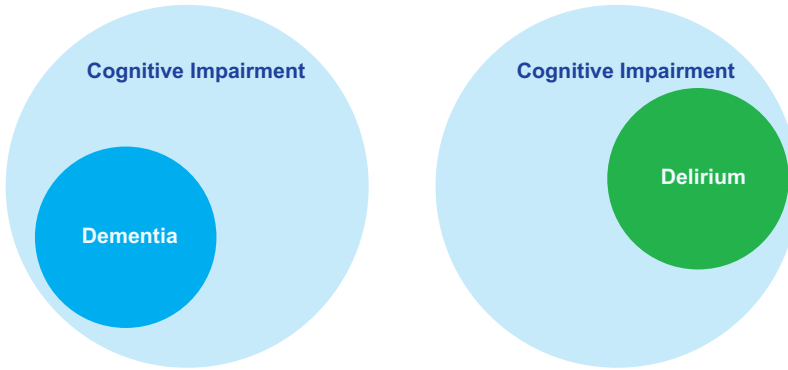


Figure 4. The relationship between cognitive impairment, dementia and delirium

As cognitive impairment is a mandatory symptom, all patients with dementia or delirium will have cognitive impairment but only a part of the patients with cognitive impairment will have dementia or delirium.

The relationship between cognitive impairment, dementia and delirium will vary with setting. For example, at an intensive care unit at a hospital, many persons are exposed to severely stressing factors that may lead to acute delirium (major surgery, mechanical ventilation, general anesthesia etc.). This thesis will focus on medical inpatients, elderly persons hospitalised in order to receive medical treatment. In this setting, some patients will have both delirium and dementia, or what is known as “delirium superimposed on dementia”. This could be considered a chronic cognitive impairment with an acute decompensation, see Figure 5.

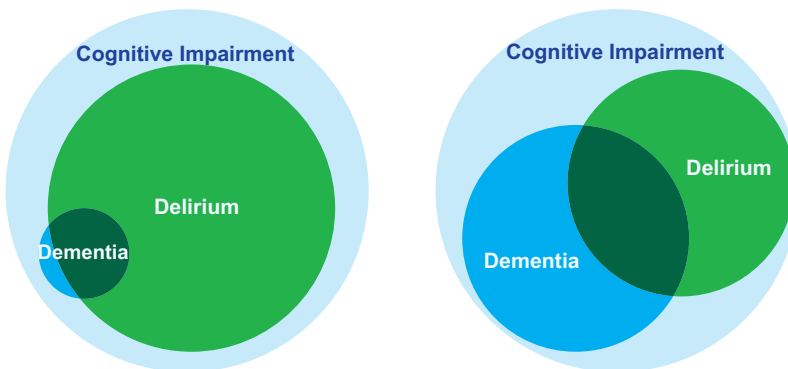


Figure 5. Cognitive impairment, dementia and delirium in different settings

In an intensive care unit (left), dementia patients are rare but almost all of the patients with cognitive impairment will fulfil delirium criteria. In medical inpatients (right), a large proportion of patients will fulfil the criteria for dementia, delirium, or both.

2.1.3. Underlying causes of cognitive impairment

Being a symptom, cognitive impairment has one or several underlying causes. For example, the slow degeneration of the brain known as Alzheimer's disease. However, there are plenty of other diseases that potentially could cause cognitive impairment, see figure 6.

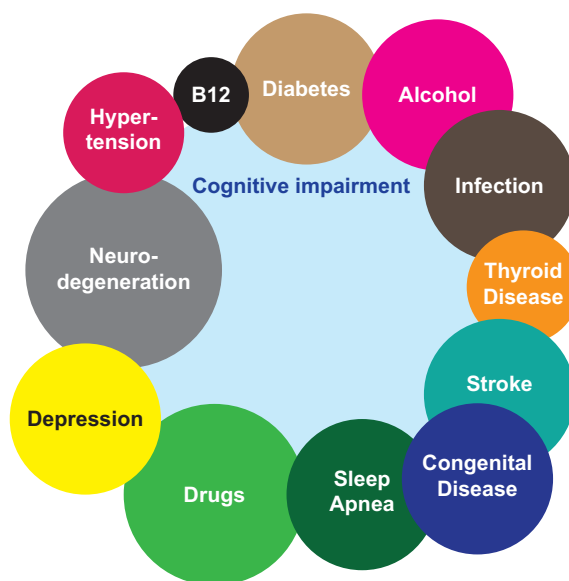


Figure 6. Factors capable of causing cognitive impairment

Examples of underlying diseases and causes that could, but would not necessarily, cause cognitive impairment. A number of these could be prevented or treated, if the symptom cognitive impairment is identified and the underlying cause pursued.

2.1.4. Prevalence of cognitive impairment in medical inpatients

The lack of a common definition of cognitive impairment leads to large variations in prevalence numbers. In this thesis, cognitive impairment is considered a symptom that could be detected and quantified using a cognitive test. One such test is the MMSE (mini-mental state examination). In elderly hospital patients, a score below 24 points on this test is often used to signify cognitive impairment. Using this definition, studies from different countries have reached prevalence numbers ranging from 21 to 59%, with a crude pooled prevalence of 44%, see Table 1.²⁻¹² Despite this high prevalence, cognitive impairment is often missed under normal conditions, where studies show recognition rates among hospital staff ranging from 22 to 79%.^{6,13-18}

Table 1. Prevalence of Cognitive Impairment

Prevalence of cognitive impairment in studies of medical inpatients from different countries.

Study	Setting	n	Age	Female	Prevalence
Dodson (US)	heart failure	282	80	53 %	47 %
Hickey (Ireland)	general	112	75	44 %	22 %
Buurman (Netherlands)	medical	639	78	54 %	40 %
Bilanakis (Greece)	medical	78	61	51 %	21 %
Farid (France)	geriatric	331	87	73 %	42 %
Tirupati (India)	general	130	71	35 %	42 %
Inouye (U.S.)	medical	952	80	59 %	42 %
Goldberg (UK)	mixed	250	84	63 %	50 %
Helvik (Norway)	general	484	81	50 %	55 %
Death (UK)	medical	117	78	59 %	30 %
Swain (UK)	medical	276	81	60 %	59 %
Pooled Analysis		3653	80	57 %	44 %

Note: Cognitive impairment is defined in these studies as a score < 24 points on the mini-mental state examination (MMSE).

2.1.5. Consequences of cognitive impairment in medical inpatients

Already at the emergency department, cognitive impairment is associated with a risk of miscommunication, for example when patients describe their presenting complaint.¹⁹ Further on, cognitive impairment is associated with reduced capacity to consent to treatment (or the withdrawal of treatment) and research.²⁰⁻²² Regarding medication regimes, cognitive impairment is associated with poor compliance and lacking knowledge.²³⁻²⁵ Furthermore, cognitive impairment may be a barrier to drug handling, including managing medication packaging and inhalation technique.²⁶⁻²⁸ Cognitive impairment could obstruct diagnostic procedures, such as spirometry.²⁹ Cognitive impairment is a strong risk factor for pressure sores, incontinence and falls.³⁰ Several studies have shown that cognitive impairment is a predictor of longer hospital stays.³¹⁻⁴⁰ At the day of discharge, patients with cognitive impairment often misunderstand discharge information.¹⁹ After discharge, cognitive impairment is associated with inability to manage everyday life and increased nursing home placement.^{35,41} Cognitively impaired patients also have a higher hospital readmission rate.^{35,42,43} Cognitive impairment is independently associated with increased short- and long-term mortality and lower quality of life.^{2,12,35,44,45}

2.2. Dementia

2.2.1. Prevalence and impact

Dementia is a global public health concern. As of today, 5-7% of people aged over 60 years suffer from dementia; in the group aged over 85, the overall prevalence is estimated to 25%.⁴⁶

Dementia prevalence is thought to increase as a consequence of the aging population of the world. Two population-based reviews predict an increase in sheer numbers of 90 to 100% in Europe and 220 to 230% globally until 2050.^{46,47} However, extrapolating existing prevalence numbers to fit future populations may be inaccurate. Some evidence suggest that incidence rates are declining due to overall increased cardiovascular health, leading to a “compression of disease” scenario for dementia. Studies from Sweden, the UK and the Netherlands have indicated that age-adjusted dementia incidence rates are declining.⁴⁸⁻⁵⁰ Furthermore, two american studies have shown compression of overall cognitive decline.^{51,52}

Even if there is some room for optimism regarding age-adjusted incidences, the demographic load will most likely be accompanied by increased prevalence.⁵³ Today, the global economic impact of dementia is estimated at 604 billion US dollars, equivalent to the economy of Poland, the world’s 20th economy.⁵⁴ In Sweden, the US and the UK, the societal cost of dementia has been shown to match that of cancer and heart disease combined.⁵⁵⁻⁵⁷

2.2.2. Underlying causes

Alzheimer’s disease

Alzheimer’s disease (AD) is the most common cause of dementia, accounting for 50 to 60% of cases.⁵⁸ Typically, symptoms start insidiously and are slowly progressive. Episodic memory is often affected first, followed by general cognitive symptoms. AD is a neurodegenerative disease; with progressive brain atrophy starting in the hippocampus area and subsequently spreading through the brain.⁵⁹

There is no cure for AD, only symptomatic treatment, with acetylcholine esterase inhibitors and memantine. Numerous drug trials show that the effect on cognitive impairment is moderate, at best.⁶⁰ This has lead to a debate of the efficacy.^{61,62} However, in naturalistic populations, other symptoms have also improved, such as ADL impairment. This could possibly postpone nursing home placement, which would have substantial impact economically and on quality of life.^{63,64} Today, medical treatment in AD is promoted by all major clinical guidelines, including the national swedish guidelines.⁶⁵

Lewy-body disease

Dementia with lewy bodies (DLB) is another neurodegenerative disease, believed to account for 15 to 20% of dementia cases.⁶⁶ In DLB, memory is often spared, instead symptoms may start as fluctuating confusion, with attentional deficits. Thus, DLB could mimick delirium.⁶⁷

Fronto-temporal lobe dementia

Fronto-temporal lobe dementia (FTD) is an unusual neurodegenerative disease, accounting for 1% of dementia cases.⁶⁸ The primary symptom is behavioural change and lack of insight; early cognitive deficits include executive dysfunction and inability to plan ahead. Anatomically, FTD is characterised by atrophy of the frontal lobes.

Cerebrovascular disease

Cerebrovascular disease may cause what is known as vascular dementia that accounts for 25 to 30% of dementia cases.⁶⁹ Vascular dementia is divided into large-vessel disease and small-vessel disease. Large-vessel disease is characterised by infarcts of large arteries. In large-vessel disease, symptoms occur when infarcts happen and the character of symptoms depends on the location of the ischemic lesion. Small-vessel disease is characterised by diffuse subcortical white matter lesions and lacunar infarcts. In small-vessel disease, symptoms progress more insidiously and frequently include impaired attention and executive function. Relative to AD, memory function is often quite spared.⁷⁰

2.2.3. Diagnostic criteria and workup

The diagnosis of dementia is based on clinical criteria. There is a number of different sets of criteria in use, for example the ICD (International statistical classification of mental and behavioural disorders) criteria and the DSM criteria (diagnostic and statistic manual of mental disorders).⁷¹⁻⁷³ The co-existence of diverse criteria is a problem as several studies have shown that the choice of diagnostic criteria affects dementia prevalence significantly.⁷⁴⁻⁷⁶ In DSM-5, the latest edition, dementia has been replaced with the term "major neurocognitive disorder", see Text box 1⁷¹. The basic diagnostic workup is shown in Text box 2⁶⁵.

Text box 1. Dementia criteria

Criteria for the syndrome Major Neurocognitive Disorder, replacing dementia in the 5th edition of the Diagnostic and Statistic Manual of Mental Disorders (DSM-5).

DSM - 5 criteria for Major Neurocognitive Disorder

1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains - such as complex attention, executive function, learning, memory, language, perceptual-motor or social cognition.
2. The cognitive deficits interfere with independence in everyday activities (e.g., at a minimum, requiring assistance with complex instrumental activities of daily living, such as paying bills or managing medications).
3. The cognitive deficits don't occur exclusively in context of a delirium, and are not better explained by another mental disorder.

Text box 2. Workup in dementia

The basic workup recommended by the Swedish National Board of Health and Welfare.

Recommended Dementia Workup

- a structured history
- interview with an informant
- evaluation of physical, neurological and mental status
- cognitive tests (the mini-mental state examination and the clock-drawing test)
- a structured evaluation of disability and activities of daily living
- brain imaging using computed tomography or MRI
- blood samples to exclude disturbances in calcium, kobalamins and thyroid hormones

2.2.4. Diagnosis rates

Dementia is underdiagnosed all over the world.⁷⁷⁻⁸² To improve case-finding, community-based screening of elderly has been proposed. However, several reports advise against such screening as there is insufficient evidence of a benefit.⁸³⁻⁸⁵

In the pursuit of increased diagnosis rates, several other policies have been launched recently, for example, the “National Dementia Strategy” and the ”Prime minister’s Challenge on Dementia”, both in the UK.⁸⁶⁻⁹¹ In the latter, emergency hospitals are included in dementia case-finding for the first time. Hospitals will be given financial reimbursement if they offer cognitive assessment to inpatients aged over 75. In Sweden, the National Board of Health and Welfare has also

acknowledged the importance of emergency hospitals in dementia detection, stating:

”the knowledge of dementia among staff should be increased, also in departments not primarily targeting the group, such as emergency departments”⁹²

The notion that hospitals could function as “safety nets” in order to find patients with undiagnosed dementia was one of the underlying conceptions behind this thesis.

2.2.5. Dementia in medical inpatients

In hospitals, one review suggested a dementia prevalence ranging from 13 to 60%.³⁷ In European settings, four prospective studies reached prevalences of 27 to 42%.^{14,18,93,94} In normal conditions, dementia is often undetected, with recognition rates of 27% to 34%.^{14,95} Dementia is associated with inferior outcomes regarding disability and nursing home placement.^{2,35,37,94,96} Dementia is an independent predictor of longer hospital stays and rehospitalisations.⁹⁷⁻¹⁰⁰ These hospitalisations are often caused by factors unrelated to dementia and some studies specifically suggest that patients with dementia have more avoidable hospital admissions.¹⁰¹⁻¹⁰³ Dementia is also associated with increased in-hospital and post-discharge mortality in medical inpatients.^{35,37,104}

2.3. Delirium

2.3.1. Prevalence and impact

The overall community prevalence of delirium is low.^{105,106} Instead, delirium has primarily been considered a problem within hospitals and institutions. At an emergency department, 15 to 35% of elderly will present with delirium.^{107,108} At hospital wards, incident delirium will occur in another 5 to 56%. The most comprehensive recent review suggest an overall occurrence (prevalence + incidence) in medical inpatients of 29 to 64%.¹⁰⁷ In orthopedic, intensive and palliative care, the occurrence is similar or higher.¹⁰⁹⁻¹¹¹ Recognition rates of delirium are low, ranging between 6 to 36% across studies.^{14,15,95,112-114} Delirium is associated with longer hospital stays, functional decline and nursing home placement.^{34,36,115,116} The yearly cost of delirium in the United states has been estimated at \$164 billion, compared to hip fractures (\$7 billion) or diabetes (\$92 billion).¹¹⁷ On an individual level, one-year health costs were 2.5 times higher for patients with delirium, when adjusted for age, comorbidities and mortality.¹¹⁸ Delirium is associated with increased short- and long-term mortality, the one-year mortality of 35 to 40% is comparable with heart attack or sepsis.^{32,33,108,115,116,119-125}

2.3.2. Underlying causes

The development of delirium is often described using the vulnerability-insult model, see figure 7.^{126,127} A number of factors could increase vulnerability or act as noxious insults, or both, see Text box 3. In elderly, delirium development is often multifactorial.

2.3.3. Diagnostic criteria and workup

Delirium is a clinical diagnosis, relying on bedside examination. Clinical criteria are defined within the DSM and ICD systems.^{71,72,128} Key features include an acute onset, fluctuations of symptoms, inattention, impaired consciousness and cognitive disturbances (disorientation, memory impairment, language impairment). Supportive features consist of disturbance in sleep-wake cycle, perceptual disturbance (hallucinations or illusions), delusions, psychomotor disturbance (hyperactivity or hypoactivity), inappropriate behaviour and emotional lability.¹⁰⁷

The workup in delirium includes history, cognitive tests, vital signs, physical examination and targeted laboratory tests.¹⁰⁷ An essential piece of the workup is history obtained from an informant, including duration of symptoms, to help differentiate from chronic cognitive impairment.

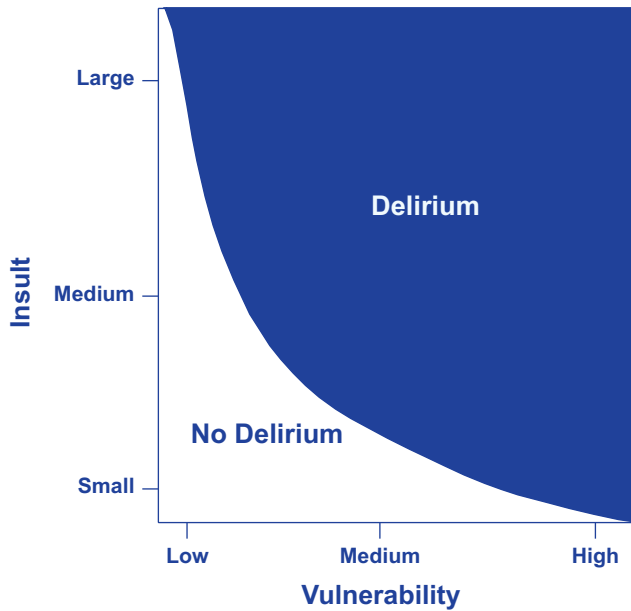


Figure 7. The vulnerability-insult model for delirium

Patients with low vulnerability (healthy elderly) may develop delirium only after repeated major insults (general anesthesia, surgery etc.) while patients with high vulnerability (multimorbid patients with dementia) may develop delirium due to small insults (a single dose of an inappropriate drug).

2.3.4. Preventing delirium

In surgery settings (where the timing of the noxious insult - surgery - is known), prophylactic haloperidol has been used to prevent delirium, with conflicting results.¹²⁹⁻¹³² In medical settings, several high-quality RCTs have successfully reduced delirium incidence by 30-40% by use of non-pharmacological interventions.¹³³⁻¹³⁶ These studies have targeted multiple factors, including sleep deprivation, dehydration, polypharmacy, immobilisation, desorientation and malnutrition. Other studies have lowered delirium incidence merely by the use of staff educational programmes.¹³⁷⁻¹³⁹ Unfortunately, the diversity of these interventions has been an obstacle for meta-analysis of the cumulative evidence.¹⁴⁰

Text box 3. Underlying factors in delirium

The underlying factors are categorised into predisposing factors, that increase vulnerability, and precipitating factors that acts as noxious insults

Predisposing Factors

- age
- cognitive impairment
- functional impairment, immobility
- visual or hearing impairment
- comorbidities
- polypharmacy / drugs
- depression
- alcohol
- dehydration and malnutrition

Precipitating factors

- drugs (anticholinergics, sedatives, narcotics, drug withdrawal)
- environmental factors (physical restraints, bladder catheter, sleep deprivation)
- iatrogenic events (surgery, anesthesia, invasive procedures)
- acute illness (infection, shock, hypoxia, dehydration, anemia, electrolyte imbalance)
- primary neurologic disease (stroke, cerebral infection)

2.3.5. Treatment of delirium

If prevention fails and delirium occurs, three areas should be prioritised:

1. Maintaining patient safety. Preventing aspiration while securing hydration and nutrition, preventing pressure sores and falls.
2. Determine and treat underlying causes. It is important to acknowledge that delirium could be the sign of acute illness; in people aged over 80 years, delirium is a common presentation of myocardial infarction.¹⁰⁷
3. Symptom management. The initial symptom management should be non-pharmacological, including reorientation, environmental measures, encouraging a normal sleep-wake cycle, discontinuation of psychoactive drugs. Pharmacological treatment is recommended only for use in agitated patients with risk for self-harm or in patients with extremely distressing psychotic symptoms.^{107,108}

2.4. Delirium or dementia?

To this point in this thesis, dementia and delirium has been described as two separate entities, divided by length of duration. However, this is a simplification. One review has found that delirium is superimposed on underlying dementia in 22 to 89% of patients.¹⁴² In four prospective cohort studies in older medical inpatients, delirium was superimposed on dementia in 56 to 76%.^{116,122,143,144}

To even further complicate things, delirium, typically thought to be transient, is often persistent in elderly inpatients.¹⁴⁵ A meta-analysis of elderly hospital patients revealed that delirium was present in 45% at discharge, in 33% after 1 month, in 26% after 3 months and in 21% after 6 months.¹⁴⁶

As if this was not enough, there is an entity called “subsyndromal delirium”, for those who have some delirium symptoms but do not fulfil all the diagnostic criteria.¹⁴⁷ In a review with meta-analysis, the combined prevalence of subsyndromal delirium was found to be 23%.¹⁴⁸ Point-prevalence studies have reached prevalences of 13% to 37%.^{149,150}

Furthermore, dementia and delirium are both risk factors for each other. the presence of dementia imparts a five-fold increase in risk of delirium.¹⁵¹ Correspondingly, delirium is a major risk factor for long-term cognitive decline and incident dementia.¹⁵²⁻¹⁵⁴ The “brain reserve” theory could possibly be applied here, a small brain reserve could be a risk factor for both delirium and dementia. At the same time, both delirium and dementia could cause irreversible brain damage, leading to a smaller brain reserve.

The bottom line is that dementia and delirium are thoroughly interrelated. They should probably be seen as part of a continuum of cognitive disorders rather than two separate entities.¹⁰⁸ The common denominator is cognitive impairment which should be the focus of the primary assessment.^{155,156}

2.5. Previous interventions reducing rehospitalisations

Several meta-analyses have found that successful interventions have been nurse-driven and multifaceted.¹⁵⁷⁻¹⁶⁰ Frequently used strategies include:

Medication overview

In the course of hospitalisation, unintentional discrepancies in medication lists, also known as medication errors, often occur. Drugs may be omitted or erroneously added to the patients medication list. The occurrence of such medication errors have ranged between 47 to 67% in studies from the US, Sweden and Canada.¹⁶¹⁻¹⁶³ Apart from medication errors, other drug-related problems, including adverse events, are common in elderly and associated with higher mortality, morbidity and hospital use.^{164,165}

Pharmacist-led interventions have successfully reduced medication errors and drug-related problems.¹⁶⁶⁻¹⁷⁰ A Swedish RCT also managed to show a reduction in all-cause rehospitalisations by medication overview.¹⁷¹ However, these results have been contradicted by another large study and a meta-analysis.^{172 173}

Discharge planning

The transition from hospital to home is a weak link in many healthcare systems. Therefore, several intervention studies have tried to support patients in this transition. A number of high quality RCT:s show that improved discharge arrangements could reduce hospital readmissions.^{160,174-178} This was contradicted by one meta-analysis that found no such effect.¹⁵⁹ Nevertheless, the latest Cochrane report, including meta-analysis of 24 RCTs with 8098 elderly patients, suggested that comprehensive discharge planning decreases both length of stay and rehospitalisation rates.¹⁷⁹

Post-discharge telephone support

To further support the patients in the discharge process, hospital-based post-discharge telephone support has been used. Telephone support has been used as a part of successful multidimensional interventions.¹⁸⁰⁻¹⁸³ However, when telephone support has been used alone, the results have been conflicting.¹⁸⁴⁻¹⁸⁶

Primary care liaison

At discharge, communication gaps between hospital physician and the general practitioner (GP) could lead to adverse events and rehospitalisations.¹⁸⁷ Too often, discharge summaries lack important information or are simply not sent to the GP at all.¹⁸⁸ A Danish study showed that an intervention including a home visit by a GP one week after discharge significantly reduced readmissions and increased treatment adherence.¹⁸⁹

2.6. Neuroradiology and cognitive impairment

Brain imaging, using computed tomography (CT) or magnetic resonance imaging (MRI), is a recommended part of dementia workup in many countries.^{65,190-194} To some extent, brain imaging is used to exclude neurosurgical causes of dementia, such as tumours. This is important as such disorders are potentially curable, albeit they account for less than 1% of dementia.¹⁹⁵

Instead, brain imaging is increasingly used to differentiate between cerebrovascular and neurodegenerative diseases, by assessing white matter changes and atrophy.^{196,197}

2.6.1. Visual rating scales in cognitive impairment

The assessment of white matter changes and atrophy could be carried out using rating scales, where a radiologist visually examines the images. When simple visual rating scales are used, CT and MRI modalities are comparable.¹⁹⁸

White matter changes

White matter changes (WMC) are seen as hyperintensities surrounding the ventricles of the brain. They are presumed to result from inadequate perfusion of the subcortical white matter. WMC are a radiological prerequisite for subcortical vascular dementia (small-vessel disease). White matter changes has been associated with increased disability, cognitive decline, dementia and mortality.¹⁹⁹⁻²⁰⁵ WMC are often rated from 0 (none) to 3 (severe) using the scale of Fazekas et al.²⁰⁶

Global cortical atrophy

Global cortical atrophy (GCA) represents the mean volume loss when the cortex of the brain atrophies. GCA has been shown to be associated with subsequent cognitive decline and dementia.²⁰⁷⁻²⁰⁹ However, GCA is harder to rate consistently than WMC.²¹⁰ GCA is often rated on the scale from 0 (no atrophy) to 3 (severe atrophy) developed by Pasquier et al.²¹¹

Medial temporal lobe atrophy

Medial temporal lobe atrophy (MTA), in the hippocampus area, is strongly associated with Alzheimer's disease (AD), both clinically and neuropathologically.²¹²⁻²¹⁴ Even though MTA is sensitive for AD it is not specific but also associated with Lewy-Body disease as well as unspecific cognitive impairment.^{212,215-217} In prospective studies in non-demented subjects, MTA predicts future dementia, particularly of the Alzheimer's type.^{218,219} Visual rating of MTA is done using the Scheltens scale that is reliable and has shown good

agreement with more sophisticated computerised measures.^{217,220-223} An example of MTA is shown in figure 8.

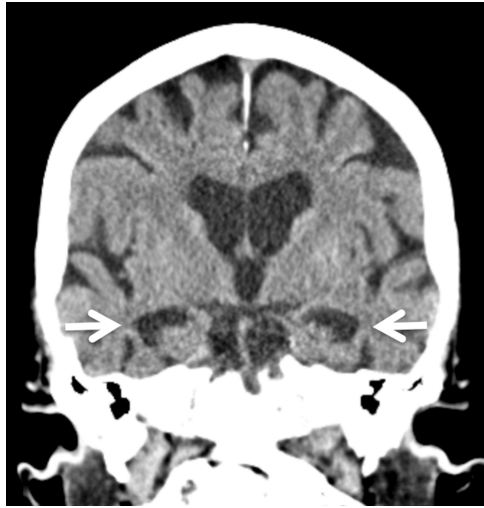


Figure 8. Medial temporal lobe atrophy

An example of medial temporal lobe atrophy seen on axial plane cranial computed tomography. The dark areas at the arrows indicate the loss of brain parenchyma in the hippocampus area.

2.6.2. Neuroradiology in medical inpatients

Many elderly hospital patients undergo cranial CT. In this population, studies have found that very few CT scans actually yield valuable information.^{224,225} Cranial CT is often performed in patients with delirium and a number of studies have concluded that only about 15% have a relevant finding on their CT.²²⁶⁻²²⁹ However, none of these studies have included visual rating scales, the use of these have been exclusive to research in memory clinic settings.

2.7. Activities of daily living

Activities of daily living (ADL) is a term used in healthcare to represent the activities necessary for daily self-care: eating, bathing, dressing, working, home-making, leisure etc. The loss of independence in ADL has been given many labels: ADL impairment, loss of function, impaired ADL status, disability, functional impairment etc. In this thesis, the term *ADL impairment* will be used to signify that a person is not fully independent in self-care.

Elderly hospital patients are at high risk of developing ADL impairment, with an incidence of approximately 30%.²³⁰⁻²³² ADL impairment is closely related to cognitive impairment. This is illustrated by dementia criteria, that require cognitive impairment of such a degree that it affects ADL, see Figure 9.^{233,234}

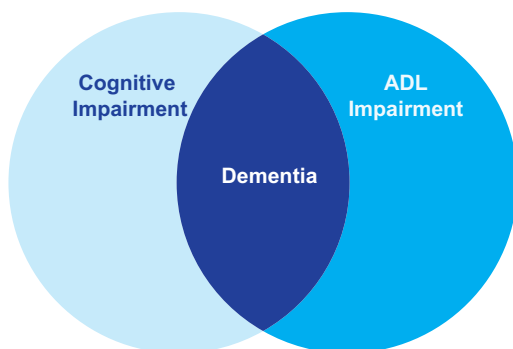


Figure 9. The relationship between cognitive impairment, ADL impairment and dementia. The co-existence of cognitive impairment and ADL impairment is the hallmark of the dementia syndrome, given that these symptoms are not explained by delirium or psychiatric disorders.

If not properly measured, ADL is often underestimated.²³⁵ Scales measuring ADL often include bathing, dressing, feeding, mobility, and using a toilet.^{236,237} Unfortunately, there is a large number of scales used, resulting in variable results and lack of standardisation.²³⁸ Many scales use only a dichotomised rating (independent vs dependent) while others use points to increase discrimination. In addition, ADL can be measured through interviews or direct observation, the latter being the most informative.²³⁹ The results from interviews correlate only moderately with those from direct observation.^{240,241}

In medical inpatients, ADL impairment is associated with longer hospital stays, more hospital readmissions and increased risk of nursing home placement.^{35,242,243} Two studies specifically show that the risk for readmissions is higher when patients leave the hospital with unmet ADL needs.^{244,245} There are many studies showing an association between ADL impairment and mortality, all of which use interview-based measures of ADL.²⁴⁶⁻²⁵²

2.8. Reliability and validity of diagnostic instruments

In this thesis, several scales are utilised to measure cognitive impairment, ADL impairment, quality of life etc. When a scale with multiple items is to be used in research, it should be evaluated for reliability and validity. The classic metaphor is that of a target, see figure 10.



Figure 10. Reliability and validity

Reliability concerns whether the same result is reached if the scale is used repeatedly. Validity regards whether the scale actually measures what it is thought to measure. A scale can be reliable but not valid (middle) but it cannot be valid without being reliable (right).

2.8.1. Reliability

Reproducibility

If a scale is administered repeatedly to a person with stable characteristics, will it provide similar results every time? This desired feature is called test-retest reliability. Another aspect of reproducibility is intra-rater reliability, for example, if a radiology image is rated with a visual rating scale by person A and person B, will they reach the same results? Normally, reproducibility is measured with intra-class coefficients (ICC) for continuous variables, kappa for dichotomous variables and weighted kappa for ordinal variables, with a recommended minimum value of > 0.70 .²⁵³

Internal consistency

Internal consistency is a measure of the correlations between the scale items. If internal consistency is too low, the different items don't measure the same aspect (for example if math and history questions are mixed in a school test). Then, adding them for a total score is probably inappropriate. If the internal consistency is too high, one or several items are most likely redundant and could be removed

(for example a math test containing "3+2", "2+3", "3+4" and "4+3"). The internal consistency is measured by Cronbach's alpha, with an ideal value of 0.70 - 0.95.²⁵³

To analyse each item separately, its correlation with the combined score of all the other items could be used. A low correlation could indicate a floor or ceiling effect for that item. It could also indicate that the specific item measures something different than the others. For example, in a math test with a single sports question, that question will probably have a low item-total correlation. Even though some kids will be interested in both sports and maths, the question probably will stand out on a group level. In general, item-total correlations above 0.3 are recommended.²⁵³

2.8.2 Validity

Content validity

To have content validity, a scale should ideally be applied with the same purpose it was developed for, in a similar population. For example, an ADL scale could be developed in order to (1) identify patients with a high risk of nursing home placement or (2) measure treatment effect of shoulder surgery. These purposes are inherently different, why applying the same scale to both could be inappropriate. The scale developed to identify patients at a high risk of nursing home placement may include items regarding a spouse. These would not be relevant if the scale was used to evaluate a treatment effect. Content validity cannot be quantified but should ideally be reported and discussed.

Criterion validity

Criterion validity is measured by correlating the scale with the best known benchmark test, a "golden standard". However, this requires that there *is* a golden standard and that it is really "golden". Otherwise, concurrent validity cannot be estimated. The correlation with a true gold standard should ideally be > 0.70 .

Construct validity

Construct validity regards whether the scale relates to other measures in a pre-hypothesised way. For example, a new math test should correlate with other math tests but not with the pupils length (given that they are of the same age). At least 75% of prespecified correlations should ideally be true.

2.9. Quality of life

Quality of life (QoL) is a concept that has experienced an exponential increase in research the last decades.²⁵⁴ However, a major problem in QoL research is the multitude of definitions of QoL. As one author ironically describes it:

”the idea of QoL has become a kind of umbrella under which are placed many different indexes dealing with whatever the user wants to focus on”²⁵⁵

Even though a clear definition is lacking, there seems to be a general agreement that QoL is multidimensional, including aspects of physical health, psychological state, independence and social relationships.²⁵⁶

2.9.1. Measuring Quality of life in older persons

The exponential growth in QoL research has been followed by a corresponding increase in QoL instruments.^{254,257} Unfortunately, it is impossible to evaluate criterion validity as there is no, and probably never will be no, golden standard of QoL.²⁵⁸ Many QoL instruments are specific for a certain disease, for example arthritis; others are generic, to be used by everyone.

Older people utilise the most healthcare services and health-related QoL could be considered a very important outcome in this population.^{259,260} As older people often have multiple diseases, generic QoL instruments would be preferable to strictly disease-specific ones. However, the majority of generic QoL instruments have low content validity as they were developed for younger populations. As an example, one of the most widely used generic QoL instruments is the EQ-5D, translated to over 160 languages.²⁶¹ In the original publication, age was not at all reported.²⁶² In the Swedish subset of the original study (n=204), the mean age was 46, with 1% of respondents aged over 75 years.²⁶³ A subsequent evaluation of EQ-5D in dementia found poor reproducibility and that overall QoL was not associated with cognitive impairment, independence in ADL or dementia severity.²⁶⁴ Despite this, EQ-5D is quite often used in older people, with and without dementia.²⁵⁴

On the other hand, dementia occurs almost exclusively in old age and dementia-specific QoL instruments have been developed and validated in older populations. Normally, these persons do not only have dementia, they often have multiple other chronic illnesses as well. Therefore, McKee et al. suggest that QoL instruments designed for dementia might be more appropriate for older people in general than generic instruments developed for younger populations.²⁵⁸

3. Aims of the thesis

3.1.1 General aim

The overall aim of this thesis is to determine how an increased acknowledgement of cognitive impairment could improve healthcare for elderly persons admitted to hospital.

3.1.2. Specific aims

To examine the prevalence, recognition rate and consequences of cognitive impairment in order to assess the need for a standardised cognitive assessment.

To evaluate the effect of an intervention targeting cognitive impairment regarding hospital readmissions.

To determine the prevalence and clinical associations of radiological findings indicative of neurodegenerative and cerebrovascular disease.

To determine the added value and importance of a quantitative ADL measure regarding mortality prediction.

To examine the psychometric properties of the Quality of Life in Alzheimer's disease (QoL-AD) scale and its clinical associations.

4. Methods

4.1. Setting - healthcare in Malmö

The patients in the studies of this thesis were recruited at the department of general internal medicine at Skåne University Hospital in Malmö, Sweden.

Malmö has approximately 300.000 residents. In 2010, the city administration was divided into ten boroughs: Centrum, Södra Innerstaden, Västra Innerstaden, Rosengård, Fosie, Oxie, Hyllie, Kirseberg, Limhamn-Bunkeflo and Husie. Each borough has a community services office, managing home care services, rehabilitation services and nursing homes. Primary care is provided by 25 primary care centers within the public healthcare system, as well as a smaller number of private alternatives.

Hospital care is delivered by the Skåne University Hospital (SUS), the only inpatient facility in Malmö, with 700 beds and 85.000 yearly visits at the emergency department (ED). The department of general internal medicine has four wards for a combined 100 beds with 4000 hospitalisations yearly. Patients at the wards of general internal medicine are generally admitted through the ED (90-95%), with the rest admitted directly via their GP.

When a patient arrives at a ward of general internal medicine, a nurse will interview the patient and make an admission note. When the most pressing medical issue has been stabilised, many patients undergo a discharge conference, where community services staff come to the hospital to meet with the patient, family members and hospital staff, to discuss the need for help at home. At discharge, a summary of the conference is sent to the GP, as well as a discharge summary containing medical information. Hospital care, primary care and community care all have separate electronic medical records. These are not available for the other two parts and summaries are sent by fax.

4.1.1. Study sample

The study sample is the same in all five studies of this thesis. The inclusion was based on study II, the non-randomised, controlled intervention study. The number of patients that was needed for study II (100 control + 100 intervention) was estimated using the results of a similar trial.¹⁷⁸

Inclusion

The group allocation (control or intervention) was not randomised, but used a convenience sampling with geographic selection. For the intervention, two boroughs were chosen (Västra Innerstaden and Hyllie), with the eight other acting as controls (Centrum, Södra Innerstaden, Fosie, Oxie, Husie, Limhamn-Bunkeflo, Rosengård or Kirseberg). Numerous exclusion criteria were used, see figure 11 for complete procedure.

4.1.2. Comment on representativity

The reason for the non-randomised design was feasibility, it was impossible to sustain improved cooperation and communication with 10 community services offices and 25 primary care centers. For convenience, two boroughs with a large elderly population were chosen; Hyllie and Västra Innerstaden, with a combined 31% of the citizens aged > 60 years.

Any non-randomised design is prone to selection bias; if the groups are different to begin with, conclusions may be biased. In the baseline measurements, 3 of 23 variables differed between groups: (1) patients in the intervention group were older, (2) patients in the control group had more diabetes, (3) patients in the control group were less well educated. The last two could possibly signify a lower socioeconomic status, known to be associated with hospital admissions.²⁶⁵ This notion is supported by the city welfare rank from 2009, as shown by Table 2.²⁶⁶

Table 2. Socioeconomic structure of the boroughs of Malmö

The number of people aged over 60 years and the official welfare rank of the ten boroughs in Malmö. Patients from V.Innerstaden and Hyllie constituted the intervention group.

Borough	Aged over 60	Welfare Rank
Limhamn-Bunkeflo	9078	1
V. innerstaden	8782	2
Husie	4863	3
Centrum	7200	4
Oxie	2477	5
Hyllie	10098	6
Kirseberg	2724	7
Södra Innerstaden	4207	8
Fosie	9205	9
Rosengård	3046	10

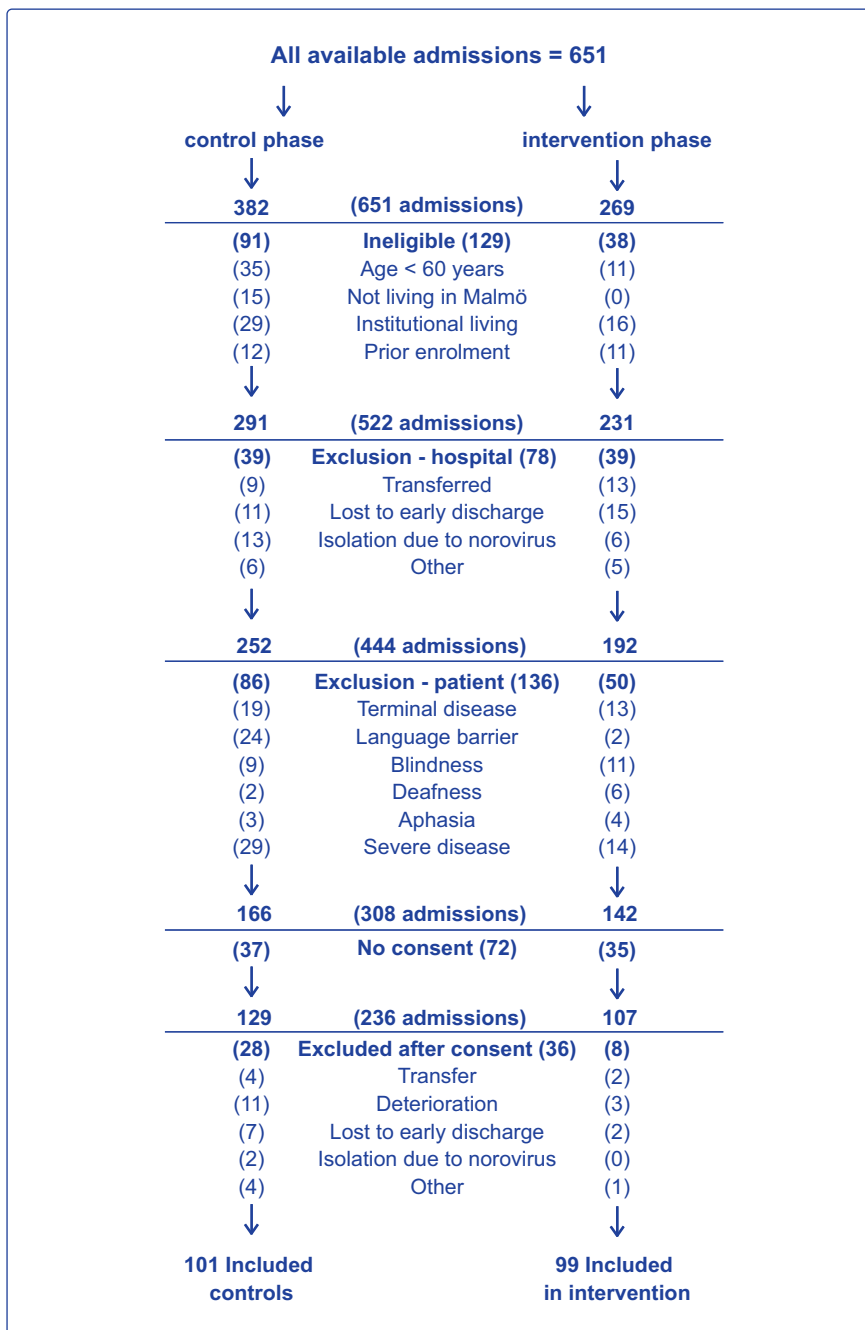


Figure 11. The inclusion procedure.

The control sample was collected first, in a control phase, where patients not living in Västra Innerstaden and Hyllie were considered for eligibility. Then, during the intervention phase, only patients from these two boroughs were considered.

There could also be other differences between the groups that weren't measured. For example, in boroughs with a larger segment of elderly, healthcare professionals could be more attentive to cognitive impairment. There could also be a difference regarding the accessibility to community services and primary care, affecting hospital use. To somewhat compensate for this, the healthcare utilisation in the preceding year was examined.

The full sample

Studies I, III, IV and V use the full sample. Therefore, it is very important to realise the risk of a bias in study II affecting the full sample. Basically, a sample was constructed where 50% lived in two boroughs, instead of the 31% suggested by the population basis. However, at baseline none of the variables regarding combined comorbidity, cognitive impairment, functional impairment, hospital use or perceived Quality of Life differed between groups. In addition, the "control/intervention" variable was included in all analyses in study I, III, IV and V without any indication of group allocation biasing the outcome of interest.

4.2. Baseline measurements

4.2.1 The Charlson comorbidity index

The Charlson comorbidity index was used to obtain a composite comorbidity score, see Table 3. This index was originally developed to predict survival in breast cancer patients in 1987.²⁶⁷ Since then, it has been applied in pneumonia, heart disease, stroke, HIV, cancer and intensive care.²⁶⁸ A recent prospective study found that Charlson index was a valid predictor of short- and long-term mortality in a group of general hospital patients, regardless of cognitive and functional impairment.²⁶⁹

Table 3. Charlson comorbidity index

To rate the Charlson comorbidity index, 19 common diseases are designated a weight each. The weights are combined for a total score

Disease Weight	Condition	
1	myocardial infarct	
	congestive heart failure	
	peripheral vascular disease	
	cerebrovascular disease	
	dementia	
	chronic pulmonary disease	
	connective tissue disease	
	ulcer disease	
	mild liver disease	
	diabetes	
	2	hemiplegia
		moderate or severe renal disease
		diabetes with end organ damage
any tumor		
leukemia		
3	lymphoma	
	moderate or severe liver disease	
6	metastatic solid tumor	
	AIDS	

Comment

The Charlson index clearly reflects the situation in 1987. Ulcer disease is given the same weight as congestive heart failure and dementia, AIDS the same as metastatic tumor. In 1988, the proton pump inhibitors hit the market and the progress in HIV treatment has also been immense. Accordingly, an epidemiologic article from 2011 suggested an updated index, in which ulcer disease is given a score of 0, and the AIDS score is lowered to 4.²⁷⁰ The authors of this article also suggest a doubled weight of 2 for heart failure and dementia, which seems intuitively correct. However, the increase in performance of the updated index was very small.

4.2.2. The mini-mental state examination

The mini-mental state examination, or MMSE, was introduced in 1975 by Folstein and is the most frequently used cognitive test in the world.^{271,272} The MMSE consists of ten items (orientation, registration, attention and calculation, recall, naming of objects, repetition, 3-step command, reading, writing and figure copying). These are combined for a total score ranging from 0 (worst) to 30 (best).

The results on MMSE are influenced by age and education.²⁷³ In a large, community-based canadian study of non-demented elderly, the median MMSE value ranged from 29 (for 65 year olds with 13+ years of education) to 25 (for 85 year olds with less than 4 years of education).²⁷⁴

Regarding the choice of cut-off, a value below 24 of 30 points was proposed in the original study²⁷¹. This cut-off is frequently applied in different settings; in a recent meta-analysis, 18 of 34 studies used this cut-off.²⁷⁵ In a general hospital setting, MMSE has shown high sensitivity but lower specificity regarding both dementia and delirium detection.²⁷⁶⁻²⁷⁸ A meta-analysis has reached a pooled sensitivity of 84% when using the < 24 cut-off.²⁷⁹

4.2.3. The clock-drawing test

The seemingly simple task of drawing a clock could be tested in different ways. There are at least 16 different scoring methods; one review concludes that opting for a simpler, possibly dichotomous approach yields better reliability but not necessarily lower validity.^{280,281} In this thesis, the semi-qualitative scoring method described by Shulman was used, where the scores are rated from 0 (worst) to 5 (best).²⁸² A cut-off of < 4 was used to signify cognitive impairment, see figure 12.

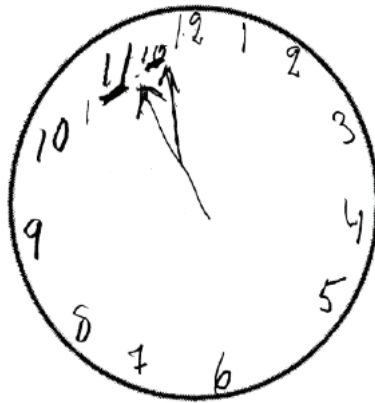


Figure 12. The clock-drawing test

Patients were asked to draw the face of a clock and to make it show “ten past eleven”. This clock was drawn by a patient in the study and would be considered abnormal with a Shulman CDT score of 3.

Combining the CDT with MMSE has been recommended for higher accuracy.²⁸² One study suggests that the CDT is a more sensitive instrument, identifying cognitive impairment earlier than the MMSE, if a cut-off of < 24 points is used.²⁸³

Studies of CDT in medical inpatients are scarce. A few studies have found moderate correlations with MMSE in this setting.^{284,285} One study found that the CDT had an acceptable sensitivity and specificity regarding both delirium and dementia detection and was less affected than MMSE by depression.²⁸⁶ The same author has found good feasibility, reliability and correlation with nurses’ ratings of cognitive impairment.²⁸⁷

4.2.4. The Gottfries-Bråne-Steen scale

The Gottfries-Bråne-Steen (GBS) scale is a semi-structured quantitative scale that was developed in 1982.²⁸⁸ The GBS scale was developed to evaluate global functioning in dementia patients. The rating is done in interview form and through direct observation of the patient.

The GBS scale consists of four subsets: intellectual function (GBS-I), emotional impairment (GBS-E), impairment in ADL (GBS-ADL), and common symptoms in dementia (GBS-S). These items are rated separately on a seven-point scale ranging from 0 (no impairment) to 6 (maximum impairment).

Inter-rater reliability has been shown to be acceptable in previous studies. Regarding concurrent validity, highly significant correlations have been shown with the MMSE, the Geriatric Rating Scale, the Sandoz Clinical Assessment Geriatric scale and the Katz’ index.²⁸⁹ In addition, the GBS scale has been used to assess treatment effects and change over time.²⁹⁰

In this thesis, the GBS-ADL will primarily be used. The GBS-ADL has two distinct advantages when compared to other ADL indices: (1) it is rated by direct observation and (2) each item is rated from 0 to 6, not only as dependent or independent.

4.2.5. The Quality of Life in Alzheimer's Disease scale

The Quality of Life in Alzheimer's Disease (QoL-AD) scale was developed in 1999 by Logsdon et al. with the purpose to assess perceived QoL in patients with Alzheimer's disease.²⁹¹

QoL-AD is rated by patient and caregivers. Thirteen items (physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores, ability to do things for fun, money and life as a whole) are rated on a scale from 1 (poor) to 4 (excellent) for a total score ranging from 13 to 52 points. Patient and caregiver reports could be combined for a composite score, weighing the patient rating higher:

$$\text{composite score} = (2 * \text{patient rating} + 1 * \text{caregiver rating}) / 3$$

The QoL-AD has been used in patients with possible and probably Alzheimer's disease, with Lewy-Body dementia, in healthy elderly and in nursing homes.²⁹²⁻²⁹⁵ Criterion validity has not been thoroughly estimated as there is no golden standard QoL instrument, albeit some studies have shown a correlation with the EQ-5D.^{295,296} In tests of concurrent validity, the QoL-AD has been correlated to depression, cognitive impairment, living alone, female sex, behavioural symptoms, functional impairment and comorbidity.^{291,292,294-301}

4.3. The interventions in study II

The intervention programme was managed by a multidisciplinary team consisting of a nurse, occupational therapists, pharmacists and a doctor. The programme comprised of:

Pharmacist's intervention

A pharmacist performed an intervention according to the L IMM model.¹⁶⁸ First, unintentional medication discrepancies were identified, using interviews and records from primary care, community care and the national pharmacy register. Then, drug-related problems were identified and monitored. Based on this, a recommendation was given to the ward physician, who could choose to follow it or not.³⁰²

Discharge planning

When cognitive and ADL tests were done, the results were communicated to the community services and relatives as soon as possible (if the patient approved of this). Thus, all participators of the discharge conference were aware of the cognitive status well in advance and could prepare accordingly. In addition, study staff attended all discharge conferences, conveying the results on cognitive tests and tests of ADL (activities of daily living) in a standardised way. Thus, they ensured that the needs related to cognitive impairment and ADL impairment were met.

Telephone support

The nurse called all discharged patients within one week of discharge, asking a standardised set of questions. If needed, the nurse could provide support and counseling on medications, complete prescriptions (with the aid of a doctor), make an appointment with primary care or community services on behalf of the patient.

GP liaison

The GP liaison consisted of a recommendation regarding follow-up that was sent along with the discharge summary to GPs. The recommendation was based on the results on cognitive tests.

4.4. Additional retrospective measurements

The prospectively collected baseline measurements above were complemented with retrospective data collection from the medical records for study I, III and IV.

- In study I, documented recognition of cognitive impairment from hospital staff was recorded by scrutinising the medical records.
- In study III, cranial computed tomography was reviewed for white matter changes and atrophy.
- In study IV, additional variables regarding mortality were collected from the charts, these were body mass index, haemoglobin, creatinine, albumin and brain natriuretic peptide.

4.5. Analytic strategy

Table 4. Summary of analytic strategy.

Table summarising the study design, main statistical features and outcomes of the different studies.

Study	Design	Main Statistic	Outcome(s)
I	cross-sectional with longitudinal follow-up	ANOVA, χ^2 -test, Cox regression	prevalence of abnormal cognitive tests, recognition, survival
II	non-randomised controlled trial	Mann-Whitney U-test, Wilcoxon's ranks test	healthcare utilisation after 12 months
III	cross-sectional	Mann-Whitney U-test	prevalence of WMC, GCA and MTA, relation with cognitive tests
IV	prospective cohort with retrospective data	Cox regression, ANOVA, χ^2 , c statistic, IDI, NRI>0	survival, importance and added value of ADL
V	cross-sectional	Cronbach's α , ICC, item-total correlation, PCA	reliability and validity of QoL-AD

Note: ANOVA = analysis of variance, IDI = integrated discriminatory improvement, NRI>0 = continuous net reclassification index, ICC = intraclass correlations, PCA = principal component analysis, WMC = white matter changes, GCA = global cortical atrophy, MTA = medial temporal lobe atrophy, ADL = activities of daily living, QoL-AD = Quality of Life in Alzheimer's Disease scale.

5. Main results

The demographic characteristics of the population are displayed in Table 5.

Table 5. Demographics

Baseline characteristics of the full population

Demographics	mean (SD) or (%)	median (IQR)	min-max
age	83.4 (8.1)	85 (78 - 89)	60 - 100
years of education, n = 188	9.0 (2.8)	8 (7 - 10)	5 - 20
female sex	130 (65%)		
living alone	134 (67%)		
help at home	115 (58%)		

Abbreviations: SD = standard deviation, IQR = interquartile range

5.1. Results study I

5.1.1. Prevalence and recognition of cognitive impairment

Of the 200 patients, 100 (50%) had a score < 24 points on the mini-mental state examination (MMSE) and 122 (61%) had a CDT score < 4 points, see Table 6.

Table 6. Cognitive tests

Results on the MMSE and CDT.

Cognitive Test	mean (SD)	median (IQR)	min-max
MMSE	22.9 (4.2)	23.5 (20.25 - 26)	10 - 30
CDT, n = 198	3.4 (1.2)	3 (3-5)	0 - 5

Abbreviations: MMSE = mini-mental state examination, CDT = clock-drawing test, SD = standard deviation, IQR = interquartile range

The patients were divided into three groups, with 0,1 and 2 abnormal cognitive test results to obtain a crude ranking of cognitive impairment. In total, 145 patients (73%) had at least one abnormal cognitive test result. Recognition of cognitive impairment by hospital staff was low, especially in the group with only one abnormal result, see figure 13

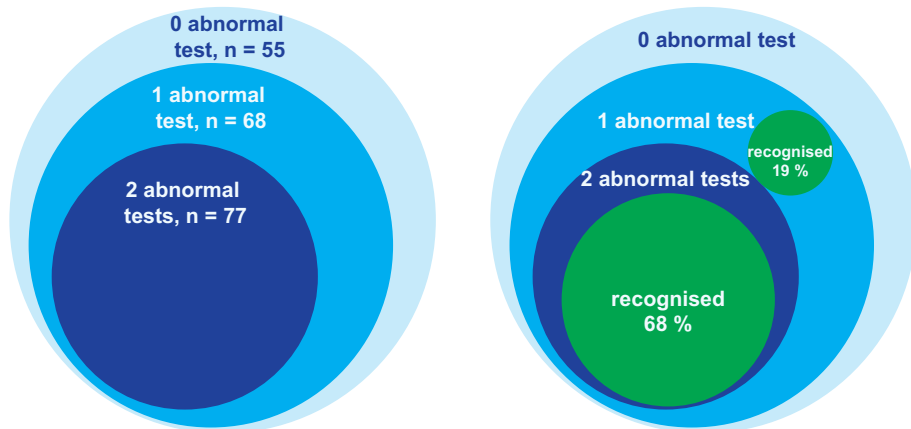


Figure 13. Prevalence and recognition of cognitive impairment.

In total, $68 + 77 = 145$ patients (73%) had cognitive impairment, defined as having at least on abnormal test result (left). In the group with only one abnormal test, only 19% had documented recognition (right). In the entire population, 79 patients (40%) had a cognitive impairment that hadn't been previously documented by a healthcare professional.

5.1.2. Association with mortality

Abnormal results on cognitive tests was an independent risk factor for one-year mortality. The hazard ratios similar for the groups with 1 and 2 abnormal test, see Figure 14.

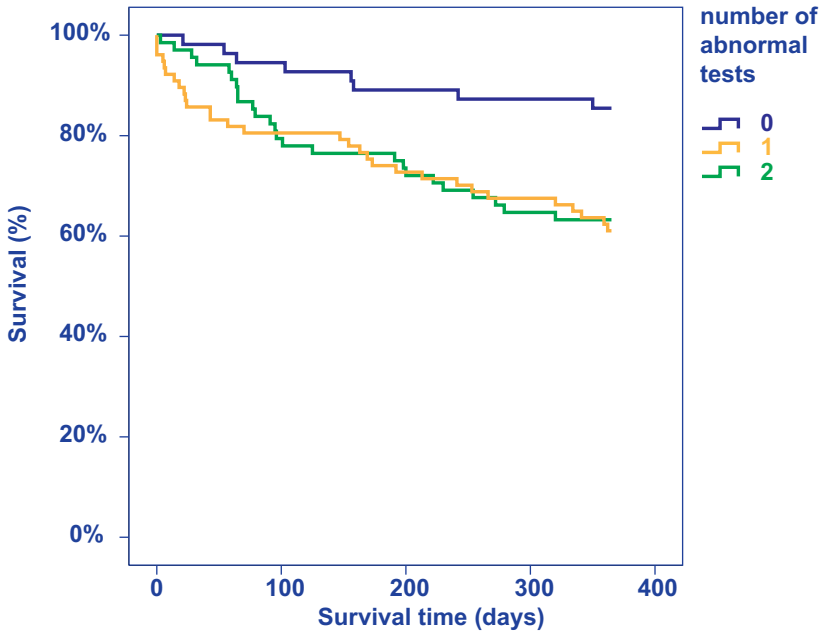


Figure 14. Association with mortality

Bivariate Kaplan-Meier estimates of 12-month survival for the three groups with 0, 1 and 2 abnormal cognitive test results. Log rank $\chi^2 = 9.7$, $P = 0.008$

5.1.3. Comments

Why was the prevalence higher than in previous studies?

The prevalence of cognitive impairment was 73%, much higher than the pooled prevalence of 44% in the previous studies in this setting. If only MMSE < 24 was used, the prevalence would be 50%. However, the CDT detected 45 patients that the MMSE did not, in line with the suggestion that CDT is more sensitive to cognitive impairment than MMSE.²⁸⁰

What is the clinical relevance of having an abnormal CDT?

To study the importance of an isolated abnormal CDT, the patients with only one abnormal test were divided into a MMSE and a CDT category, see Table 7. When the survival model was refitted using the new variable, the association with mortality was also significant for CDT, see Table 8.

Table 7. Recognition of CDT

Recognition rates from hospital staff by abnormal cognitive test results. The patients with abnormal CDT only were not recognised at all.

Recognition	0 abnormal test n = 55	abnormal MMSE n = 23	abnormal CDT n = 45	2 abnormal tests n = 77
physician	9%	22%	7%	44%
nurse	15%	30%	2%	64%

Abbreviations: CDT = clock-drawing test, MMSE = mini-mental state examination.

Table 8. Survival and CDT

Multivariate Cox proportional hazards model with abnormal cognitive tests categorised into MMSE only, CDT only or both.

Cox proportional hazards	hazard ratio (95% CI)	p value
male sex	1.8 (1.1 - 3.0)	0.03
home care	1.8 (1.1 - 3.2)	0.03
Charlson index (points)	1.3(1.1 - 1.5)	0.001
1 abnormal test (MMSE only) vs 0	2.4 (0.9 - 6.8)	0.09
1 abnormal test (CDT only) vs 0	3.1 (1.3 - 7.1)	0.009
2 abnormal tests vs 0	3.4 (1.5 - 7.5)	0.002

Abbreviations: MMSE = mini-mental state examination, CDT = clock-drawing test, CI = confidence interval.

Thus, the CDT seemed to capture some aspect of cognitive impairment and vulnerability that neither the MMSE nor hospital staff detects.

Why do patients with cognitive impairment have a higher mortality, even when the model controlled for age and comorbidities?

1. The most likely reason is that cognitive impairment is a proxy measurement for another factor, not measured by the model. When doing a post hoc analysis of the survival model, the R^2 value was estimated was 0.24, indicating that only 24% of the variation in mortality was explained by the factors in the model. Thus, 76% was due to factors we did not measure. Overall frailty could very well be one such factor.³⁰³
2. Albeit purely speculative, it is also possible that cognitive impairment in itself could contribute to mortality, for example due to communication difficulties. The risk of miscommunication could be illustrated by an example: of the 145 patients with cognitive impairment, 81 had no help with their medications. Of these 81 patients, 54 had no documentation of cognitive impairment by nurses or doctors. Of these 54 patients, 17 could not name a single medication in the interview, despite having an average of 6 medications.

5.1.4. Summary study I

- cognitive impairment, defined as having an abnormal MMSE or CDT result, was prevalent in 73% of medical inpatients.
- cognitive impairment was often undetected by healthcare professionals, especially when only one test result was abnormal.
- cognitive impairment was associated with a three-fold increase in one-year mortality, even if only one test result is abnormal

Novelty value study I

The findings that cognitive impairment is prevalent, often undetected and associated with poor outcome have all been previously described. What is new with this study is really the addition of CDT to the MMSE in this setting. This had a dramatic effect on the prevalence of cognitive impairment. Our results suggest that CDT was clinically relevant and that it should be combined with MMSE in this setting.

5.2. Results Study II

5.2.1. Healthcare utilisation

Study II was the intervention study, in which 99 patients underwent a multicomponent intervention. The intervention group were compared with 101 controls regarding healthcare utilisation after 12 months, from three perspectives:

1. From the intention-to-treat perspective (n= 200), the intervention group had a lower number of ED visits, readmissions, hospital nights and hospital costs. However, the results did not reach statistical significance, see Figure 15.
2. When analysing the 12-month survivors only (n = 137) though, the difference was statistically significant, see Figure 16.
3. Healthcare utilisation in the year after the intervention was compared to the healthcare utilisation in the year preceding the intervention. This was done for the two groups separately. More patients in the control group had increased their resource utilisation compared to the intervention group, see Figure 17.

	Intervention n = 99	Control n = 101	p value Mann-Whitney
ED Visits	133	219	0.23
Admissions	104	171	0.081
Hospital Nights	1008	1827	0.054
Hospital Costs (x 1000 SEK)	5 870	10 576	0.069

Figure 15. Intention-to-treat

From the intention-to-treat perspective (n=200), there were arithmetic differences favouring the intervention group, however these were not statistically significant. ED = Emergency department, SEK = Swedish Kronor

	Intervention n = 67	Control n = 70	p value Mann-Whitney
ED Visits	83	170	0.14
Admissions	58	125	0.021
Hospital Nights	492	1220	0.009
Hospital Costs (x 1000 SEK)	2905	7162	0.012

Figure 16. 12-month survivors

In the 12-month survivors (n=137), the intervention group had significantly fewer readmissions, hospital nights and lower hospital costs. ED = emergency department, SEK = Swedish Kronor.

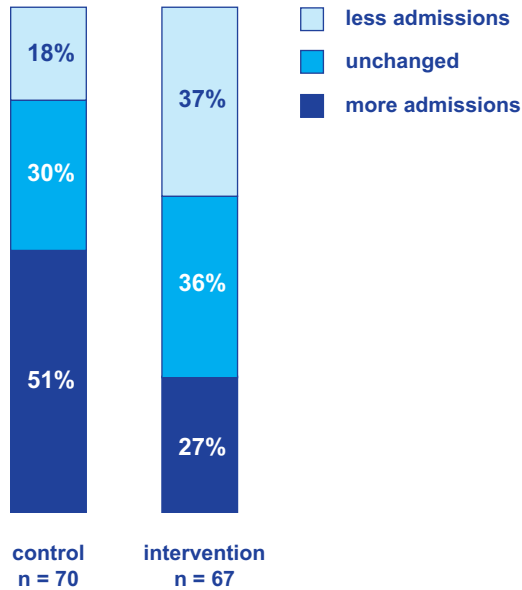


Figure 17. Individual comparisons

In the intervention group 73% had unchanged (36%) or less admissions (37%) after one year when compared to the year before, compared to only 48% in the control group (P for trend = 0.007). Only 12-month survivors were included in the analysis (n = 137).

5.2.2. Comments

In what way did the intervention affect readmissions?

One type of readmissions that are common and have been the target of previous interventions are *early* hospital readmissions, within 30 days of discharge.^{304,305} However, from the intention-to-treat perspective, no effect was seen on these early readmissions, see Figure 18.

Another possibility is that the intervention identified and helped vulnerable individuals, at a high risk of multiple readmissions. This was partly supported by our results, see Figure 19.

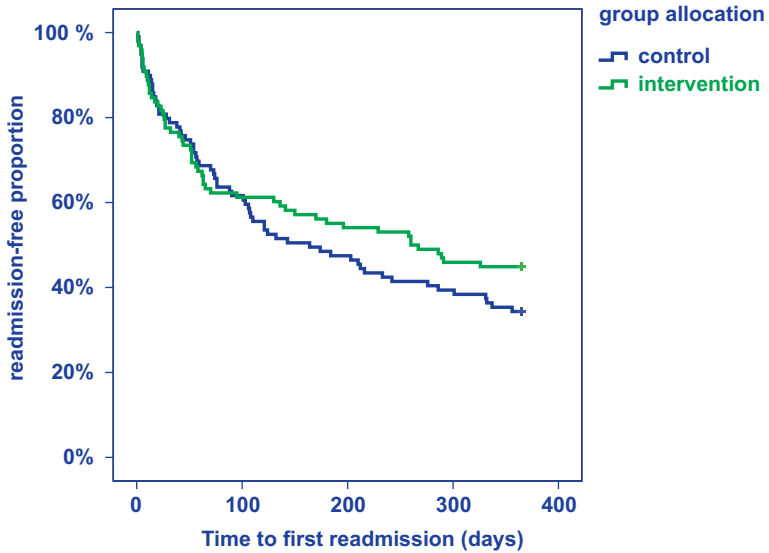


Figure 18. Time to first readmission

Kaplan-Meier estimate of time to first readmission. There was no difference between groups from the intention-to-treat perspective (Logrank χ^2 ($N=200$, 1 df) = 1.4, $p = 0.24$)

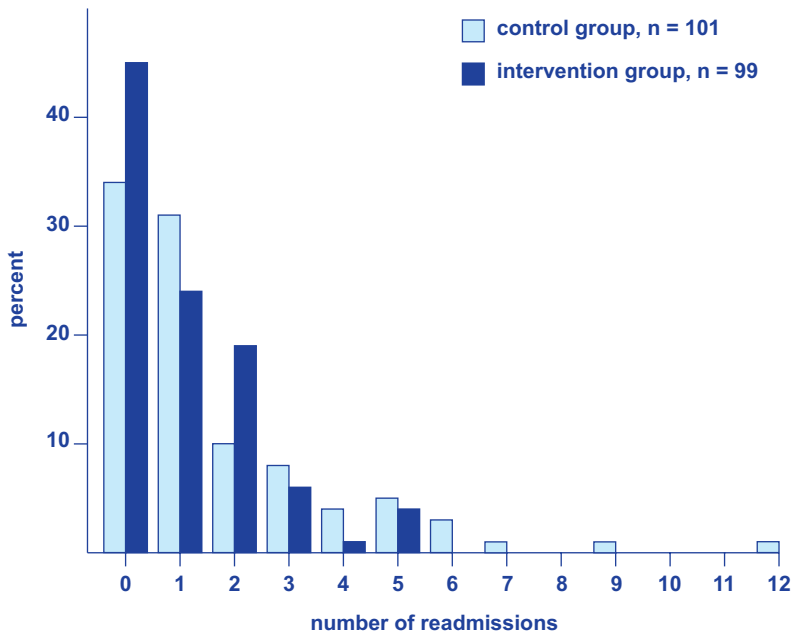


Figure 19. Readmission pattern

Percentage of patients with readmissions in the groups, from the intention-to-treat perspective. More patients in the control group had 3 or more readmissions (26% vs. 12%, χ^2 test, $P = 0.01$).

Why wasn't the intervention significant from the intention-to-treat perspective?

In 12-month survivors, the difference was statistically significant regarding readmissions. However, for the group who died within the 12 months (n = 63) no difference at all was seen. This lowered the overall intention-to-treat effect. Why was there no intervention effect in the group that died within 12 months?

In general, approximately one quarter of healthcare costs are spent in the last 12 months of life.³⁰⁶ Despite this, several interventions aiming to reduce costs in the last year have been unsuccessful, presumably because nursing and caring for this group is very labor-intensive.³⁰⁷

However, even though it is difficult to reduce overall healthcare costs in this group, hospital use could possibly be decreased. This might be desirable as hospital use (including aggressive care) and burdensome healthcare transitions near the end of life is increasing, despite often being inconsistent with patient preferences.³⁰⁸⁻³¹¹ Hospital use could probably be reduced by ensuring appropriate palliative care in other settings, such as hospice, palliative in-home care etc.^{310,312,313} This would require an intervention identifying patients with a short life expectancy, introducing advance care planning and treatment limitation directives.^{308,314-316} The intervention in study II did not address these aspects at all. This could be the reason why no effect was seen on hospitalisations in the group who died within 12 months.

What was the role of cognitive impairment in the interventions?

Two of the four interventions addressed cognitive impairment directly: the GP liaison (recommending follow-up of cognitive tests) and the discharge planning (where cognitive test results were conveyed). However, the other two did not specifically target cognitive impairment (medication overview and telephone support). Therefore, a closer look into the role of cognitive impairment in these is warranted.

In the telephone support, a larger proportion of patients with cognitive impairment needed an action taken by the contact nurse after discharge (57% vs 29%, χ^2 test, P = 0.04). In the medication overview, the same pattern was seen, see Figure 20. Thus, it is likely that patients with cognitive impairment could have had the most benefit from all four interventions.

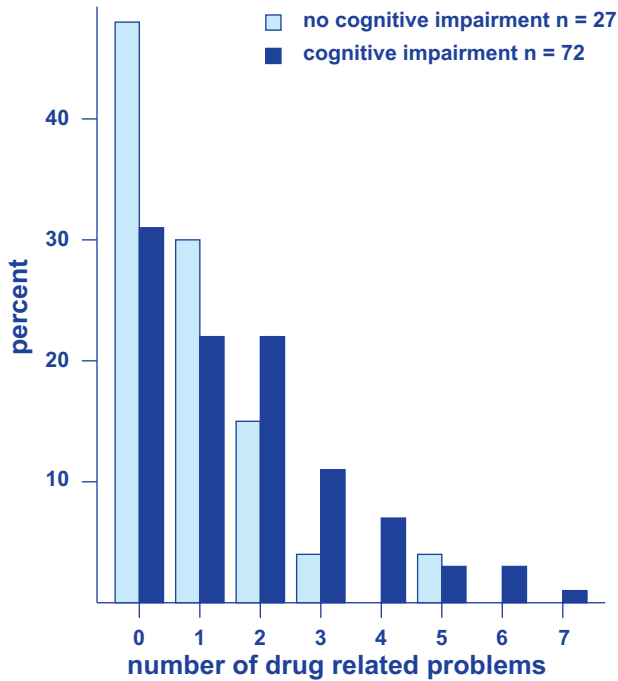


Figure 20. Drug-related problems

Drug-related problems were more frequent in the group with cognitive impairment (Mann-Whitney test, $P = 0.02$).

5.2.3. Summary study II

- a group receiving an intervention targeting cognitive impairment had fewer readmissions after 12 months than a control group, receiving standard care.
- This effect was significant only in 12-month survivors, not from an intention-to-treat perspective.

Novelty value of study II

The intervention programme is new and has not been employed before. The idea of reducing readmissions by acknowledging cognitive impairment specifically is also quite new. If these findings were to be replicated, it would be yet another strong incentive for hospitals to acknowledge cognitive impairment.

5.3. Results study III

In study III, cranial CT was retrospectively reviewed in 94 patients for white matter changes, global cortical atrophy and medial temporal lobe atrophy, see Figure 21.

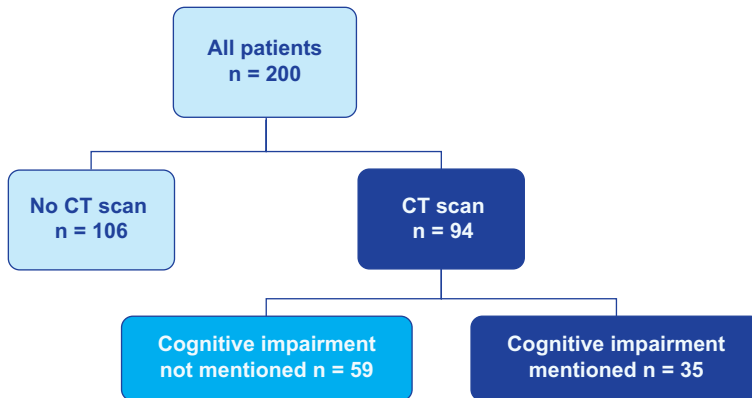


Figure 21. Outline of study III.

Overall, 94 patients had undergone a CT within ± 1 year of cognitive tests. In 35 of the referrals, cognitive impairment was mentioned.

5.3.1. Prevalence and reporting frequency

The prevalence was high for all three measurements. All three measurements were also underreported, especially MTA, see Figure 22.

5.3.2. Relationship with cognitive tests

Medial temporal lobe atrophy was the test with the strongest association with lower scores on the MMSE, see figure 23.

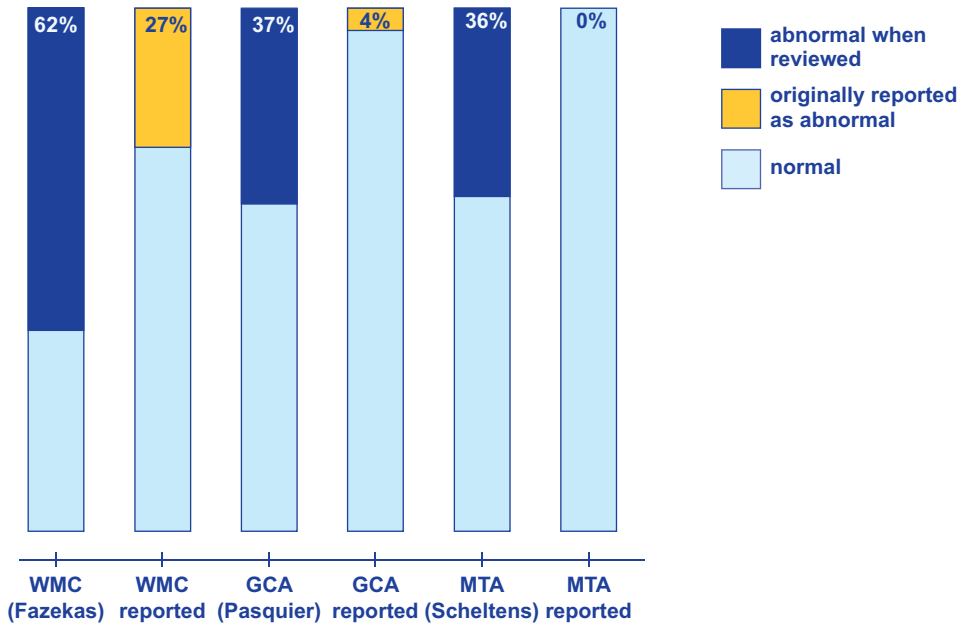


Figure 22. Radiological findings

The proportion of abnormal radiological findings on review, when rated with the scales of Fazekas, Pasquier and Scheltens, are shown in dark blue. The corresponding proportion of the original radiology reports are shown in yellow. **Abbreviations:** WMC = white matter changes, GCA = global cortical atrophy, MTA = medial temporal lobe atrophy.

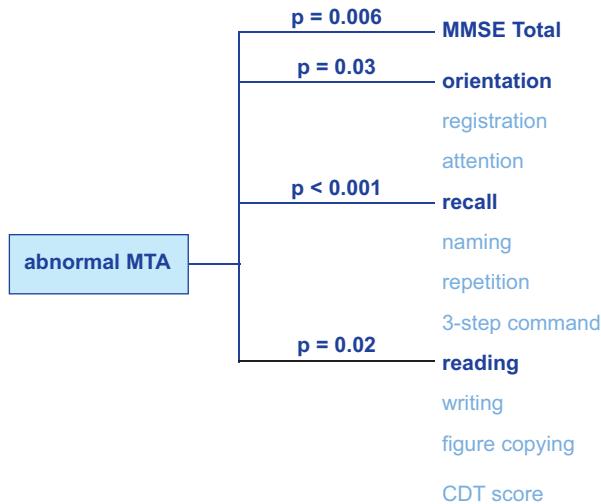


Figure 23. Association between medial temporal lobe atrophy and cognitive tests

MTA was associated with lower total score on MMSE and with lower scores on orientation, recall (memory) and reading. The association between MTA and memory was the strongest of all and the only one that would withstand a conservative Bonferroni correction.

5.3.3. Comments

What is the clinical importance of reporting these findings in medical inpatients?

The sensitivity, specificity, positive and negative predictive values of the visual rating scales in relation to cognitive impairment are shown in Table 9.

Table 9. Classification

Sensitivity, specificity and predictive values for the three visual rating scales when compared to cognitive impairment.

Characteristic	WMC	GCA	MTA
sensitivity	68 %	40 %	39 %
specificity	79 %	71 %	79 %
positive predictive value	92 %	91 %	91 %
negative predictive value	28 %	18 %	18 %

Abbreviations: WMC = white matter changes, GCA = global cortical atrophy, MTA = medial temporal lobe atrophy

Sensitivity and specificity is of little interest as no-one would recommend performing a CT scan in order to detect cognitive impairment. More interesting though, are the positive predictive values, albeit they are dependent on the high prevalence of cognitive impairment. If a CT has been done and an abnormal finding is present, there is a 90% risk that the patient will actually have cognitive impairment.

5.3.4. Summary study III

- abnormal WMC, GCA and MTA were all frequent in medical inpatients
- all three measurements were underreported, especially MTA
- MTA had the strongest associations with cognitive tests

Novelty value of study III

The novelty value of study III is applying these visual rating scales into a multimorbid elderly hospital population. They have been almost exclusively used in memory clinic research populations before. Our results suggest that implementing these scales in the routine reporting could possibly increase the yield of cranial CT in elderly medical inpatients.

5.4. Results study IV

5.4.1. Relative importance and added value of ADL

In study IV, GBS-ADL was shown to be the strongest predictor of mortality when compared to a set of established clinical predictors, see Figure 24. In addition, the model with GBS-ADL showed significant added value compared to a model using only the traditional predictors of mortality.

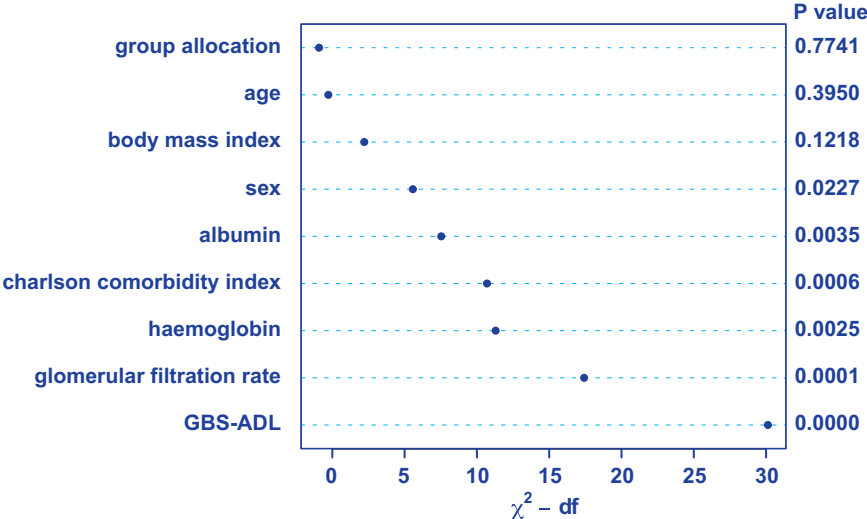


Figure 24. Relative importance of the variables in the full model
 Variables with a higher $\chi^2 - df$ value are contributing more to the model’s overall ability to predict mortality. Interactions and non-linear terms are incorporated into the variables. Group allocation signifies control or intervention group in study II, this variable is included to detect bias.

5.4.2. The prediction model

To facilitate interpretation of the rather complex model and to illustrate the effect of the variables, a nomogram was constructed, see Figure 25. The nomogram of an example patient is shown in Figure 26. To illustrate the discriminatory effect of the model, a Kaplan-Meier chart is presented in Figure 27.

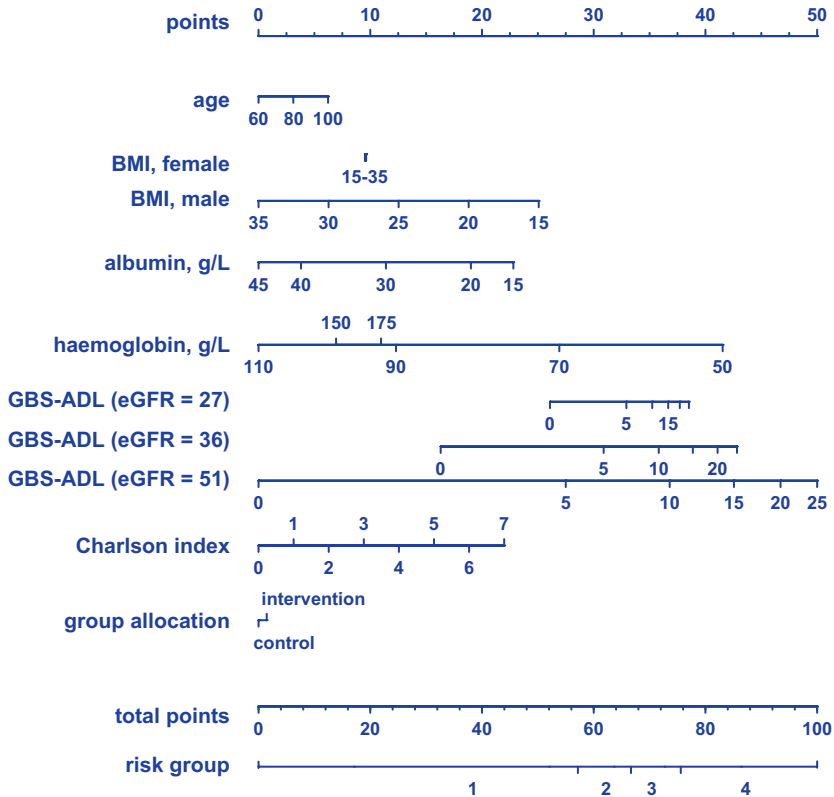


Figure 25. Nomogram

For an individual, the variables are compared with the upper "points" line, one at a time. These scores are then added for a total score that is plotted at the "total points" line at the bottom. This could then be used to designate the person to a "risk group". Notice the effect of interactions, low BMI is only a risk factor in men and the risk of GBS-ADL is moderated by GFR, which is presented by median and quartiles. The cutoffs in the nomogram for the risk groups are completely arbitrary here, created to obtain 4 equally sized groups. In another scenario, cutoffs could be established to obtain for example 90 % 3-year survival.

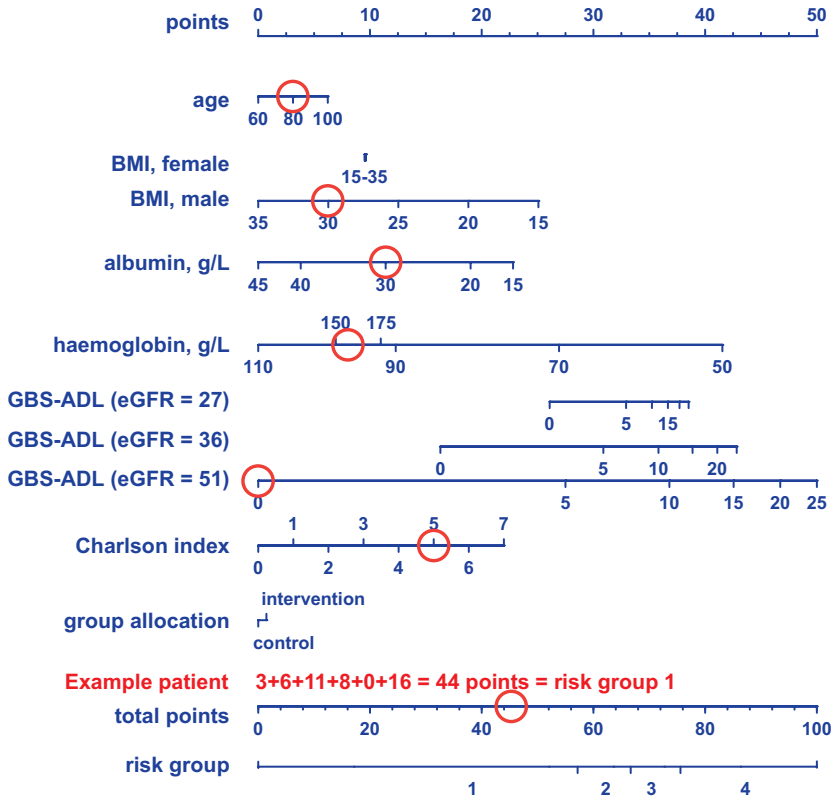
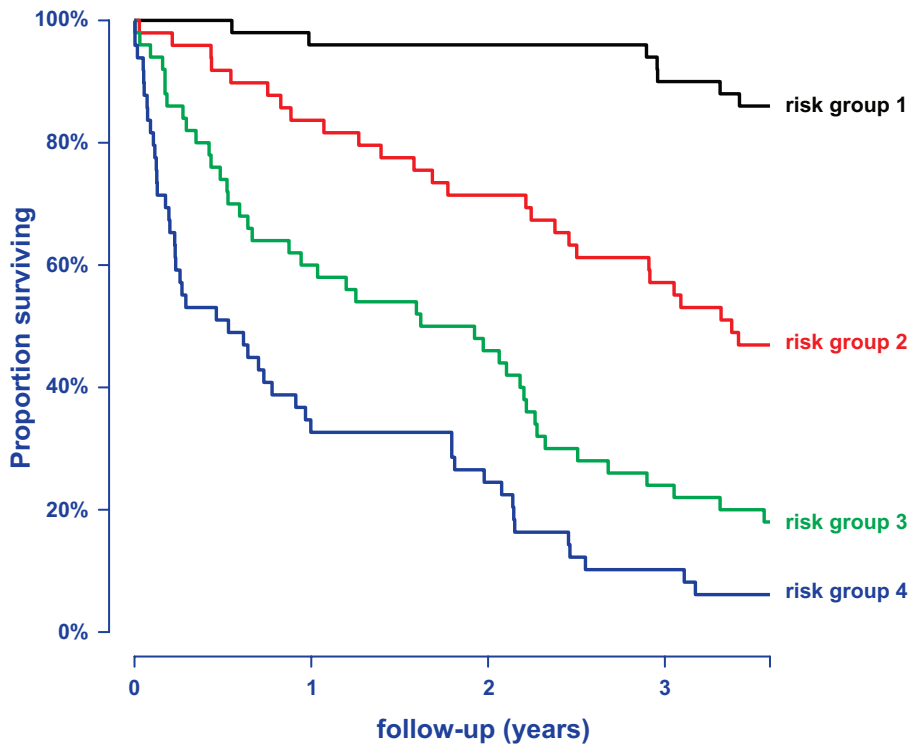


Figure 26. Example of patient score

This patient is 80 years old (3 points), male with BMI 30 (6 points), has an albumin of 30 (11 points) and a haemoglobin of 98 (8 points), normal kidney function and ADL (0 points) and a Charlson index score of 5 (16 points). The total score would be $3+6+11+8+0+16 = 44$ points, placing this patient well within risk group 1. If this patient had all other variables constant but a functional decline, with a GBS-ADL score of 7, this would result in a total score of $44+30 = 74$, placing the patient in risk group 3. The risk attributed to the functional decline would be equivalent to a haemoglobin drop from 98 to 55 g/L. Would it infer the same sense of urgency to the clinician?



Number at risk

risk group 1	50	48	48	45
risk group 2	49	41	35	28
risk group 3	50	30	23	12
risk group 4	49	16	12	5

Figure 27. Kaplan-Meier estimates of the four risk groups

Survival curves for the four risk groups from the nomogram. The example patient, in risk group 1, would have a 90% predicted 3-year survival. However, when GBS-ADL increased to seven, he was placed in risk group 3 and the predicted chance of 3-year survival plummeted to 24%.

5.4.3. Comments

Among the other variables, cognitive tests had the strongest association with GBS-ADL, see Table 10. Thus, cognitive impairment and ADL impairment are correlated. In study I, cognitive impairment was found to be a mortality predictor. In study IV, the same was found for GBS-ADL. Which one is best? see Figure 28.

Table 10. Correlations with GBS-ADL
Spearman correlations with the other baseline variables.

Variable	correlation with GBS-ADL	p value
age	.29	<0.001
sex	-.05	0.47
body mass index	-.23	0.001
albumin	-.17	0.02
haemoglobin	-.17	0.02
estimated glomerular filtration rate	-.22	0.002
charlson index	.08	0.28
number of abnormal cognitive tests	.50	<0.001

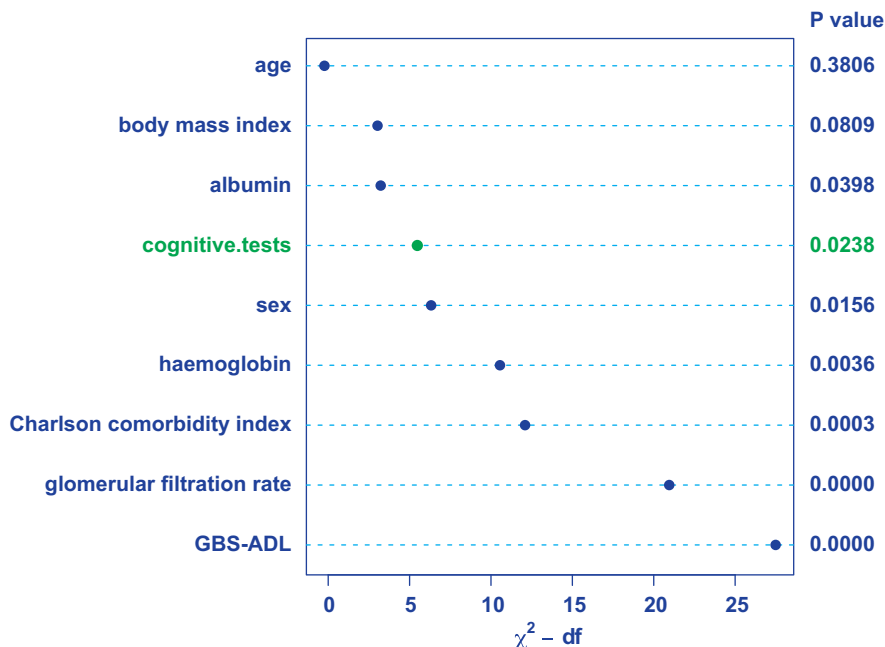


Figure 28. Relative importance of variables including cognitive tests.
Relative importance, displayed by $\chi^2 - df$ for the full model, including cognitive tests

Why is ADL predicting mortality?

1. The same applies here as for cognitive impairment in study I, ADL could be a proxy for a confounder not measured by the model. Again, a possible confounder is frailty, the vulnerability seen in many elderly near the end-of-life. If so, ADL is a better proxy for frailty than cognitive tests, which seems intuitive as ADL is a more global measurement.
2. Another possibility is that ADL impairment directly contributes to mortality in some aspect. There are several obvious and dangerous complications to functional decline and immobility, such as pressure sores, muscle atrophy, falls, thrombosis etc. But there could also be other, less intuitive factors. For example, studies have shown that patients with ADL impairment have larger risk of attaining multi-resistant bacteria and Clostridium Difficile.^{317,318}

5.4.4. Summary study IV

- ADL impairment was by far the strongest mortality predictor when compared to age, sex, body mass index, albumin, haemoglobin, glomerular filtration rate and the Charlson comorbidity index.
- adding ADL to these established risk factors gives a substantial added value in mortality prediction

Novelty value of study IV

The finding that ADL is associated with mortality in this population has been described before. However, the rigorous statistical approach has not been applied to this research question before. In addition, the use of an observation-based quantitative ADL scale is also new. Taken together, these additions to previous research should emphasise the importance of acknowledging ADL impairment in a standardised way.

5.5. Results study V

5.5.1. Properties of the QoL-AD scale

Reliability

Overall, the reliability of patient ratings was slightly lower than in previous studies. The internal consistency was just above the stipulated cut-off (> 0.7) with a Cronbach's alpha at 0.74. Both proxy and composite scores were more robust with 0.86 and 0.80, respectively.

Validity

Regarding concurrent validity, all correlations with other measurements had the expected direction. Again, the composite score seemed more valid, with stronger correlations than for patients' scores, see Table 11.

Table 11. Correlations of QoL-AD with other measures

Spearman correlations with other measures for the total QoL-AD score as rated by patients, proxies and the composite score.

variable	expected	patient	proxy	composite
age	-	-.08	-.21	-.16
female sex	-	-.14	-.14	-.22
charlson index	-	-.05	-.11	-.11
number of drugs	-	-.11	-.10	-.16
GBS - mood	-	-.26	-.24	-.28
antidepressant use	-	-.10	-.26	-.23
MMSE	+	.17	.41	.35
CDT	+	.06	.36	.31
GBS-ADL	-	-.22	-.42	-.38
home care	-	-.26	-.39	-.40
living alone	-	-.24	-.35	-.32
group in original study	none	.03	.01	.01

Note: The correlations in color were significant after Bonferroni correction. MMSE = mini-mental state examination, CDT = clock-drawing test, GBS = Gottfries-Bråne-Steen scale, ADL = Activities of Daily Living.

Factor analysis

The factor analysis was carried out on the composite score. This revealed that there were three underlying constructs measured by the QoL-AD, these were labelled "social", "physical" and "psychological". The items in these three factors

were intuitively plausible and exactly the same as reached by a comprehensive study of QoL-AD in healthy elderly.³¹⁹

5.5.2. Comment

The reliability analysis suggest that the patients' rating may be less reliable than in other studies. The composite score seems more robust. Further research is needed and if this finding should be replicated, probably only composite scores should be used. This would however exclude all the patients that don't have a proxy.

In the concurrent validity analysis, Bonferroni corrections were done. Possibly, it shouldn't have been done, as correlations were hypothesised à priori rather than randomly explored. If Bonferroni correction was removed, only the two comorbidity variables, Charlson index and number of drugs, were left without a significant association with QoL-AD. This is unexpected in a somatic hospital setting.

A closer look on the comorbidity variables reveal that the Charlson index correlated with number of drugs at $r = 0.46$, $p < 0.001$, which is clinically plausible. As seen in study I and IV, the Charlson index predicts mortality independently and strongly, as a comorbidity variable should. To further examine the association of QoL-AD with physiological parameters, it was correlated to the other variables from study IV (eGFR, haemoglobin, BMI and albumin). Again, no significant correlations were found. Thus, the total score on the QoL-AD scale was not at all correlated with physical comorbidities.

There are two alternative explanations why this is the case:

1. The QoL-AD simply doesn't have content validity for this population. It was developed with another purpose, in another setting.
2. Patients in this setting consider other factors, such as cognitive impairment, depression, social situation and disability to have a larger impact on quality of life than physical comorbidity.

The latter was supported by one of the questions in the study interview. This was an open question "What is your largest concern today?" Of the 200 answers, surprisingly few were about physical disease. Instead, the majority of answers concerned loneliness, worry or grief over a relative, frustration over not being able to remember, fear of becoming dependent or not being able to live at home etc. This supports the notion that patients hospitalised for a severe acute somatic disease may consider aspects other than physical health to be important for their QoL.

5.5.3. Summary study V

- the QoL-AD had lower reliability when patients rated their own QoL in this setting than in previous studies. The composite score was more robust.
- Lower QoL-AD was associated with cognitive impairment, ADL impairment, depression and social factors, but not with physical comorbidity

Novelty value of study V

The QoL-AD has never been applied in this setting before. Another new scale, the WHOQOL-AGE, has been developed and validated as a generic QoL scale for use in the elderly.³²⁰ This scale is very similar to QoL-AD, with 13 items, of which 9 have direct counterparts in the QoL-AD. Unfortunately, the WHOQOL-AGE has no memory item, which seems important in a population with a 73% prevalence of cognitive impairment. The factor analysis also suggest generic properties of QoL-AD as exactly the same factors were found in a healthy elderly population. Thus, further validation of QoL-AD in this population could be valuable.

6. Conclusions

6.1. Study I

Cognitive impairment should be formally assessed in all medical inpatients aged over 60 years.

Elaboration

The need for standardised cognitive assessment was obvious given the results in study I. Which cognitive test that should be used for this assessment remains to be seen. Cognitive tests should be seen as part of the normal examination, in which detecting cognitive impairment, seeking its underlying cause, and ensuring the appropriate follow-up are essential to deliver a high-quality care.³²¹

6.2. Study II

Managing cognitive impairment in a comprehensive way could reduce resource utilisation in non-terminal medical inpatients.

Elaboration

The intervention appeared to be efficient, at least in 12-month survivors. One might argue that before the interventions are to be implemented into standard care, the results should be confirmed by another, preferably randomised, trial. On the other hand, the descriptive results alone should cause some alarm. The fact that (1) 65% had drug-related problems, (2) 40% had unacknowledged cognitive impairment (3) 30% needed an action within one week after discharge and (4) only 2 patients were previously diagnosed by their GPs, should signal that improvements are needed.

6.3. Study III

If a cranial CT is done in this setting, MTA should be reported.

Elaboration

MTA was most the most underreported finding. It is reliable and easy to learn to rate. It had the most important clinical correlations, with an Alzheimer-like profile on cognitive tests. This is important as there is specific treatment for this disease. The positive predictive value of 91% was similar to the other measurements. When abnormal MTA is reported, the clinician on the receiving end should initiate a cognitive workup, including a post-discharge follow-up.

6.4. Study IV

The implementation of a quantitative ADL measurement in elderly inpatients could help clinicians deliver a more appropriate care.

Elaboration

ADL is very often assessed in medical inpatients, to assess the individuals' needs, at hospital and at discharge. Changing to a quantitative measurement is quite simple and could have many benefits apart from the prognostic value, such as increased standardisation and the possibility to follow a patient over time. An important point regarding mortality prediction is that appropriate care is not all about avoiding overtreatment due to a poor prognosis. The model identified 50 elderly multimorbid medical inpatients with a 90% chance of 3-year survival. This group should not be undertreated simply due to age discrimination.^{322,323}

6.5. Study V

The association of QoL with cognitive and ADL impairment could be another reason to acknowledge these issues in this population.

Elaboration

More studies on the use of QoL-AD in this population are necessary to make further conclusions. If QoL is indeed associated with cognitive impairment but not with somatic disease, it would mean that (1) interventions targeting cognitive impairment could possibly also increase QoL, (2) if these aspects are not acknowledged, these patients may feel that healthcare professionals do not help them with their largest concern.

7. Reflections

7.1. Reflections on methods

7.1.1. Scale validity

In this thesis, the MMSE, CDT, GBS, QoL-AD, WMC, GCA and MTA scales were used. All of these have been developed in other settings, making their content validity in medical inpatients questionable.

Take MMSE as an example, it was developed with the purpose to identify patients with dementia, in a psychiatric population. Only one study, from 1982, with 41 patients, seems to have validated the MMSE properly in a general hospital setting.^{278,324} In our material, the MMSE had a Cronbachs alpha of 0.67, with three items showing pronounced ceiling effects. Thus, the extensively used MMSE did not reach the minimum requirements for reliability and validity. Despite this, many studies have used the MMSE not only as a test in itself but as a "golden" standard for other cognitive tests.²⁷⁸

This represents a major problem. There is a large need for development and standardisation of scales to be used in medical inpatients. The current habit of presuming that they have the same properties as in outpatients at a memory clinic is not recommendable.

7.1.2. Multivariate statistics

In study I and IV, the Cox proportional hazards regression was used. However, study I has several shortcomings: (1) too many variables were included and a stepwise variable selection was done, this has been condemned due to biased and over-optimistic estimates^{325,326} (2) Continuous variables were not tested for non-linearity and some were dichotomised.³²⁷ (3) Missing data was not adressed, complete case analysis was done, albeit recommendations state otherwise.^{328,329} (4) Multicollinearity was improperly adressed. (5) No analysis of outliers or influential observations was done. (6) No internal validation was performed.^{330,331} (7) No overall performance statistic was presented.

So, why was study I published without these remarks? The reason is probably that it is in good company, shortcomings like these have been shown to be very

common, even in top-tier journals.³³²⁻³³⁵ This is also a major problem. One solution to this could be specific reporting guidelines. For example, if Cox regression is used, a checklist must be supplemented, including management of missing data etc, otherwise the paper will be rejected. One promising such example is the "Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis" or TRIPOD statement from 2015.³³⁶

At the moment, there are too many potentially biased high impact papers, and a real risk that policies will be changed on an incorrect basis.

7.2. Reflections in general

7.2.1. Thoughts on multimorbidity

Two thirds of people aged > 65 years are multimorbid, defined as having two or more chronic conditions.³³⁷ Multimorbidity is associated with poor outcome, high healthcare costs, functional disability and lower quality of life.³³⁷⁻³⁴²

However, healthcare systems, medical research and medical education are all based on individual diseases. Treatment guidelines are often developed by specialists on a basis of sponsored drug trials where patients have only one disease. Reimbursement systems encourage doctors to comply with these guidelines. However, for the multimorbid patient, adhering to several guidelines at a time is potentially dangerous due to polypharmacy, adverse events etc.^{343,344} This "industrialisation of medicine" means that the healthcare system is not designed for the ones who use it.³⁴⁵ Given the demographic development to come, addressing multimorbidity will be a key issue for policy-makers.

7.2.2. The view on cognitively impaired persons

The very low diagnosis and recognition rates in our study suggest that persons with memory disorders are not treated in the same way as persons with other disorders. Possibly, this is due to the stigma associated with cognitive symptoms.³⁴⁶⁻³⁴⁸ On a personal level, stigma is associated with reluctance to seek help for memory-related symptoms.³⁴⁹ On a society level, stigma could be divided into problems of knowledge (ignorance), problems of attitude (prejudice) and problems of behaviour (discrimination).³⁴⁶

Problems of knowledge (ignorance)

The lack of knowledge probably starts in education; in many nursing and medical schools, memory disorders make up for a minimal and inconsistent part of the curriculum.³⁵⁰ Several studies show that lacking knowledge of dementia is common among doctors and perceived as an obstacle towards diagnosing the patient.³⁵¹⁻³⁵³ Another example of ignorance is the pervasive myth that dementia is a part of normal aging.³⁴⁶ Regarding delirium, the need for increased knowledge in a broader sense was expressed by dr Naji Tabet expressed in a 2009 review:

*”What is really needed is a change of culture through increasing awareness and knowledge of staff caring for older people on acute wards.”*¹⁴⁰

One contributing factor to the lack of knowledge is the lack of research funding, where dementia research receives 4% of the funding of cancer research, when adjusted for societal costs.⁵⁵

Problems of attitude (prejudice)

Receiving an appropriate and formalised dementia diagnosis enables patients to plan ahead, to make decisions regarding their care, to get advice and support, to obtain drug and non-drug treatment and participate in research.^{354,355} More importantly, being informed of the diagnosis is what patients with dementia and their relatives want.^{354,356,357}

Despite this, the need for diagnosis is frequently questioned; some critics claim that diagnosis is harmful or primarily in the interest of the medical industry.^{358,359} Others claim that the vascular risk factors are already addressed anyhow.³⁶⁰ When the Swedish association of primary care physicians listed seven unnecessary or harmful measures in the whole field of primary care in 2014, brain imaging in dementia was one of them.^{220,361,362}

The main reason for all this skepticism is most likely the perceived lack of efficient medical treatment.^{351,360,363,364} Apart from the obvious answer, that the AD treatment is in most major guidelines, there are two other answers to this:

1. When a more efficient treatment is developed, we cannot afford to be far behind. As a warning example, cancer, in general, could be used. In the 1800s, cancer was a death sentence, followed by immense stigma. In the very early 1900s, surgical treatment and radiotherapy emerged. In the 1940s, chemotherapy was introduced. Yet, in 1961, 90% of doctors in the US did not inform their patients of a cancer diagnosis, as they thought it may harm the patient.³⁶⁵ Only in the late 70s, 60 years after treatments had emerged, patients were told of their cancer diagnosis. How many people died in vain due to the cancer stigma? Possibly, dementia is now where cancer was a hundred years ago, let's not do it again.

2. Is the unwillingness to address memory disorders due to lacking treatments or is it really the other way round; *that treatments are lacking due to the unwillingness to address memory disorders?*

Problems of behaviour (discrimination)

Ignorance and prejudice could culminate in discrimination, that patients with memory disorders are treated differently than patients with other diseases. Or, as professor Alistair Burns put it in the BMJ:

*"In any other branch of medicine, a diagnosis rate of 42% would be scandalous"*³⁵⁴

Regarding dementia, the 2014 survey from the Swedish national board of health and welfare, evaluating the national dementia guidelines found that:

1. 27% of the expected prevalence had a registered diagnosis.
2. Less than 50% of patients with a diagnosis have undergone the full workup.
3. Dementia "not otherwise specified" is by far the most common diagnosis. This is not seen in diabetes, "we don't need to know if it is type 1 or type 2".
4. Less than a third of the expected number of patients with Alzheimer's disease receive the medical treatment emphasised by guidelines.⁹²

Regarding delirium, this syndrome has absolutely devastating consequences. At the same time, several high-quality studies show that it could be prevented in 30-40% of cases. Thus, one would expect delirium to be at the top of the healthcare agenda for policy change but this has not been the case. Imagine if someone said: "We have an intervention that is proven cost-effective, has no side effects and could prevent 30-40% of heart attacks".

Regarding ADL impairment, one study has showed that patients with ADL impairment were much more costly for hospitals, even when adjusted for diagnosis groups (DRG groups). This meant that all reimbursement systems based on diagnosis codes (1) give hospital wards an incentive to avoid these patients and (2) disadvantage those wards that care for this group.³⁶⁶ Hopefully, this could also be a more general application of quantitative ADL measurements. If they are implemented into reimbursement systems, this group would be less discriminated.

7.2.3. Brain failure?

*"a stigmatised person is in essence viewed by others as less than human"*³⁶⁷

This quote from stigma researcher Ervin Goffman could indeed be applied to dementia. In Latin, the term "dementia" translates to "without soul", if anyone is

less than human it is a person without soul. Despite this, the term dementia has not been questioned until recently; in the 2014 version of DSM-5, it is replaced by “major neurocognitive disorder”.

However, “Major neurocognitive disorder” will probably never replace “dementia” among the masses. An alternative name could be to call cognitive impairment “brain failure” - a multifactorial syndrome similar to heart failure.¹⁰⁷ There are many similarities, both heart failure and brain failure diagnoses are based on criteria.³⁶⁸ There is no cure, only symptomatic treatment. Both could be acute, chronic or acutely decompensated. Untreated, the prognosis is poor. They have almost exactly the same underlying causes, see Text box 4

Text box 4. Underlying causes of heart and brain failure

Causes are divided into those causing chronic, acute and decompensated heart and brain failure.

Chronic heart failure	Chronic brain failure
congenital disease	congenital disease
hypertension	hypertension
atherosclerosis	atherosclerosis
parenchymal disease (cardiomyopathy)	parenchymal disease (neurodegeneration)
toxicity (alcohol, drugs, chemotherapy)	toxicity (alcohol, drugs, chemotherapy)
diabetes	diabetes
amyloidosis	cerebral amyloid angiopathy
thyroid disease	thyroid disease
anemia	anemia
HIV	HIV
sleep apnea	sleep apnea
structural disease (valvular disease)	structural disease (tumor, hydrocephalus)
Acute heart failure	Acute brain failure
parenchymal inflammation (myocarditis)	parenchymal inflammation (encephalitis)
surrounding structure (pericarditis)	surrounding structure (meningitis)
acute ischemic event	acute ischemic event
septicemia/severe disease	septicemia/severe disease
intoxication	intoxication
Decompensation of chronic heart failure	Decompensation of chronic brain failure
infection elsewhere (pneumonia)	infection elsewhere (pneumonia)
poor compliance with medication	poor compliance with medication
new ischemic event	new ischemic event
anemia	anemia
new medications	new medications

Albeit similar, an important difference is that there is no stigma in heart failure. This might have affected the outcomes which have improved substantially the last decades.³⁶⁹ To illustrate the non-stigmatised view upon heart failure, a statement of the American Association of Heart Failure Nurses could be used:

”Heart failure nursing is the provision of holistic care to the specific individual with heart failure due to any etiology. Heart failure nursing care can take place in any inpatient or outpatient setting and address the acute or chronic needs of patients and their support systems. Prevention can be viewed in relation to individuals, high risk families, the community and population.”

What would it take to exchange ”heart failure” to ”brain failure” in such a statement?

7.3. Facing the demographic challenge

The demographic challenge means that the proportion of elderly people will increase in the coming decades, with a subsequent increase in healthcare utilisation.³⁷⁰ How do hospitals prepare for this anticipated demographic boom? Well, Sweden is the OECD country with the most rapid decline in hospital beds per 1000 inhabitants.³⁷¹ It is evident that in the near future we will have to make the most of every hospitalisation in this age group, see figure 29.

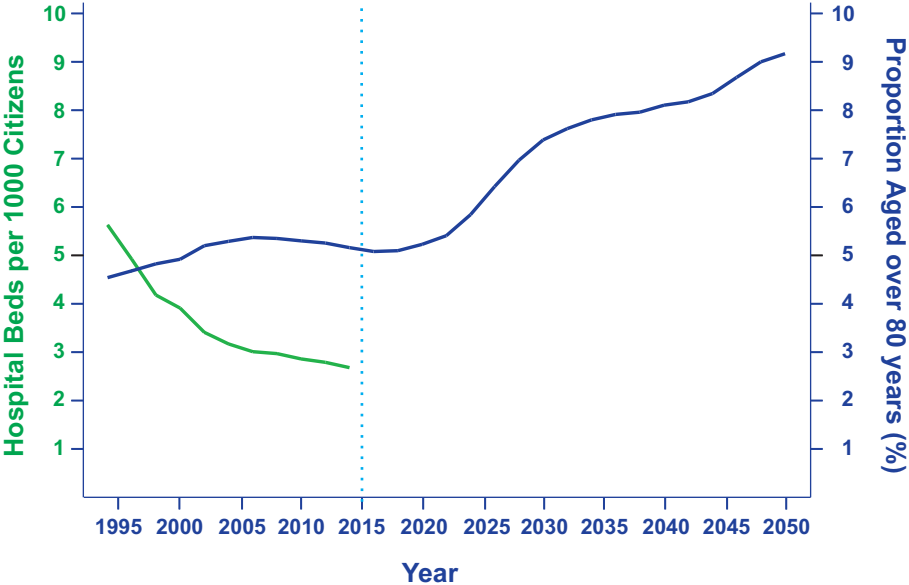


Figure 29. Facing the demographic challenge
 Proportion of people aged over 80 years and number of hospital beds/1000 citizens.

7.3.1. How to make the most of a hospitalisation with brain failure

At the emergency department

- All patients, aged over 65, arriving at the emergency department should undergo a very brief initial cognitive assessment. The results should be documented in a standardised way in the physician's admission note.
- Electronic medical records from primary care and community care should be instantly accessible. Thus, the admitting physician could easily determine the duration and whether the brain failure has been previously acknowledged. The latest list of medications should also be instantly available, to minimise the risk for medication errors.

At the hospital ward

- if the ED assessment signals brain failure, a mini-workup should be offered at the ward, consisting of one or two slightly longer cognitive tests and a quantitative ADL assessment. A standardised interview with an informant regarding the development of symptoms could determine whether the brain failure is acute, chronic or chronic with acute decompensation. Any cranial CT in the preceding year could be reviewed for white matter changes and atrophy. All results from the mini-workup should be documented in a standardised way that is easy to find, if the patient is readmitted in the future.
- if the mini-workup signals brain failure, the underlying cause should be examined closely. This could be done using a checklist with a number of conditions to be negated, starting with the most likely suspects (drugs, infection, alcohol, stroke, electrolyte imbalance etc.). Medications should be scrutinised with the help of a clinical pharmacist. If an underlying cause is found, it should always be documented and treated accordingly.
- In addition, all patients should receive non-pharmacological treatment (normalising sleep-wake cycle, ensuring calm environment, provide vision and hearing aids, minimise catheterisation, encourage visits from relatives etc.) and prevention of adverse events (including falls, pressure sores, malnutrition, immobilisation).
- in all patients with brain failure, information should be given as soon as possible to: (1) the patient and relatives, to acknowledge the symptom, to answer their questions, to minimise stigma and to reassure them that there is a plan for the follow-up. (2) community services, including standardised reports on cognitive and functional impairment, in order to facilitate preparation of post-discharge services. (3) primary care since they, in most cases, are responsible for the follow-up.

Discharge

- At discharge, patients with brain failure should be given adapted information regarding their hospitalisation and the follow-up. In addition, they could be subjected to post-discharge telephone support. The discharge summary to GP should clearly state that brain failure is present, its duration, underlying cause and planned follow-up.
- Possibly, there should be one coordinating person at each primary care center, this could be a "brain failure nurse", the equivalent of diabetes nurses. This person will ensure follow-up, including the work-up in dementia, according to the national guidelines. Contacting this coordinator should be very simple for patients with brain failure. To start with, this coordinator should probably also be proactive, contacting patients and performing home visits. In addition, physician continuity should be prioritised in this group.
- If a patient has been hospitalised several times in a short period, a discussion on how to support this patient should be initiated. If the patient is considered to be nearing the end of life, advance care planning should be discussed, what are the expectations and goals of care? What is to be done in the case of deteriorating health. Is the patient a candidate for in-home palliative care. What are the most important quality of life aspects?

8. Frequently Asked Questions

When talking about this project, certain questions are reoccurring. Suggested answers are presented in this section.

Q: Is dementia workup really something for acute hospital? Shouldn't this be done in primary care?

- Yes, dementia workup could be done in primary care. However, cognitive impairment could be secondary to a large number of acute conditions. Ignoring this will put the patient at risk.
- In our study, 145 patients had cognitive impairment. Two of these were previously diagnosed with dementia by their GPs. This signals that hospitals, are needed as a "safety net" for dementia patients.
- These patients do not contact their primary care center asking for an extra long appointment to sort out their memory issues. Rather, they tend to seek care when everything is failing, preferably to an emergency department. Therefore, a hospitalisation is a good opportunity to detect the symptoms and initiate the appropriate follow-up.
- Comparing a 15-minute minute visit at a primary care center with a 6-day overnight stay at the hospital, who has the best chances of identifying a fluctuating cognitive impairment?

Q: Will a cognitive test done at the hospital be representative?

- No, the results will not be representative for ever and ever. For some reason, cognitive test results are often required to be valid also out of the present context. This does not apply to many other diagnostic procedures we do. For example, if a patient has a paroxysmal atrial fibrillation during an infectious episode, no-one will question the representativity of the ECG if the pulse is regular a month later. More importantly, no-one would refrain from doing the ECG cause the pulse might be regular later on.

Q: If a patient scores 15/30 on the MMSE and this is written in the chart, maybe this will be a liability to this patient in the future, possibly disqualifying from intensive care or invasive procedures.

- This is true and we need to think how this ignorance among colleagues should be addressed. Is the correct strategy to avoid a diagnostic procedure due the assumption that someone else, in the future, might not be able to interpret the results in the same way as we do? I don't think so, the correct strategy is to perform the procedure and document the results, including an interpretation of the context. And ensure follow-up.

Q: Is it really appropriate to perform cognitive tests if the patient is having a raging delirium?

- No, not necessarily. In this setting, cognitive tests should be primarily performed as a standardised way of detecting cognitive impairment. If the patient obviously has delirium, there is no need for further detection. We would not make an orthopedic patient with both legs in cast do a walking test. However, many patients have hypoactive delirium, these will not be obvious. If delirium is obvious, the energy should be spent in seeking and treating the underlying causes and protecting the patient from harm rather than in performing cognitive tests. In addition, the impairment should be documented, properly diagnosed and follow-up ensured.

Q: Should we screen everyone for cognitive impairment at the hospital?

- Yes and No.
- Yes, I think we should formally assess the cognition in all medical inpatients aged over 65 years. I think this is appropriate when a dangerous condition is prevalent in 73%, of which the vast majority is unknown. If it was diabetes, there would be a blood glucose machine next to the door.
- But no, I don't think we should label this "screening". To me, screening suggests briefly studying a large population, where few have the disease. If there was a setting where 73% had breast cancer, mammography would not be considered screening, it would be "part of standard procedure". No-one regards heart auscultation in elderly inpatients as an "atrial fibrillation screening". It is just done, with the results interpreted and documented accordingly and appropriate follow-up ensured.

Q: This project will bring an impossible workload to primary care, diagnosing all these patients

- In my opinion, the diagnosis is not the problem, it is a part of the solution. The symptoms are there regardless, as are the patients. Undiagnosed symptoms cause insecurity and support structures are often insufficient. In

my experience, these patients seek care all over the healthcare system for diffuse problems, problems due to poor compliance etc. rather than stating that they have memory concerns. In our study, one patient with undiagnosed cognitive impairment had had 59 visits to primary care physicians in one year. Most likely, some support structure was lacking in that case.

- Usually it is illustrative to compare with other diseases. If we found that 73% had undiagnosed tumours, wouldn't the reaction be "we need more resources, these patients need help"?

9. Tack

Det finns många personer att tacka för den här tiden.

Först och främst Elisabet Londos, min handledare. Du kan konsten att vara professionell och personlig på samma gång. Du är en fantastisk lärare, forskare och framför allt doktor. Jag uppskattar den tillit som du visat mig från början och den frihet jag har fått i detta arbete. Du har ett väldigt speciellt sätt att få en forskare att känna att "allting är möjligt". Ditt engagemang för Lewy-Body-patienter och oss yngre kollegor kan inte prisas tillräckligt. Tack!

Lennart Minthon, min bihandledare. Du är något så ovanligt som en entreprenör med hjärtat på rätta stället, som dessutom jobbar inom vården. Ditt livsverk minneskliniken har utgjort en fantastisk bas under detta avhandlingsarbete. Och hur många gånger har vi inte löst sjukvårdens problem på din whiteboard?

Lars Stavenow, medförfattare till samtliga artiklar. Det var du och Lennart som lade grunden till denna avhandling. Du tillför alltid kloka och genomtänkta saker till diskussioner och artiklar.

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och det har alltid varit öppna dörrar hos er och man har kunnat komma med vilken fråga som helst.

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Alla kollegor på infektionskliniken i Malmö. Den speciella stämningen och det intresse för människor som ni alltid visar ger energi och hopp.

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