LUND UNIVERSITY

Cognitive impairment in medical inpatients

Torisson, Gustav

2015

Link to publication

Total number of authors:
1

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Cognitive impairment in medical inpatients

Gustav Torisson

LUND
UNIVERSITY

Clinical Memory Research Unit	Document name
Dept of Clinical Sciences Malmö	
LUND UNIVERSITY	
	Date of issue 150522
Author(s) Gustav Torisson	Sponsoring organization

Title and subtitle Cognitive impairment in medical inpatients

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.

Key words cognitive impairment, delirium, dementia, Activities of daily living, inpatients

Classification system and/or index terms (if any)

Supplementary bibliographical information	Language english

Recipient's notes	Number of pages	Price
	Security classification	

Signature _[signature]_   Date 2015-04-14

Cognitive impairment in medical inpatients

Gustav Torisson

LUND
UNIVERSITY

Contents

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 disesae (QoL-AD) scale in medical inpatients. *Manuscrip*t

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 disesase 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 om 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 skrumpning av ett område av hjärnan som kallas hippocampus. Vi såg att 36% av patienterna hade en uttalad skrumpning i detta området, av dessa hade ingen beskrivits från början, när det ursprungliga röntgensvaret skrevs. Av de som hade en sjuklig skrumpning hade nästan alla

också avvikande resultat på kognitiva tester. Därför tycker vi att det är viktig 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.
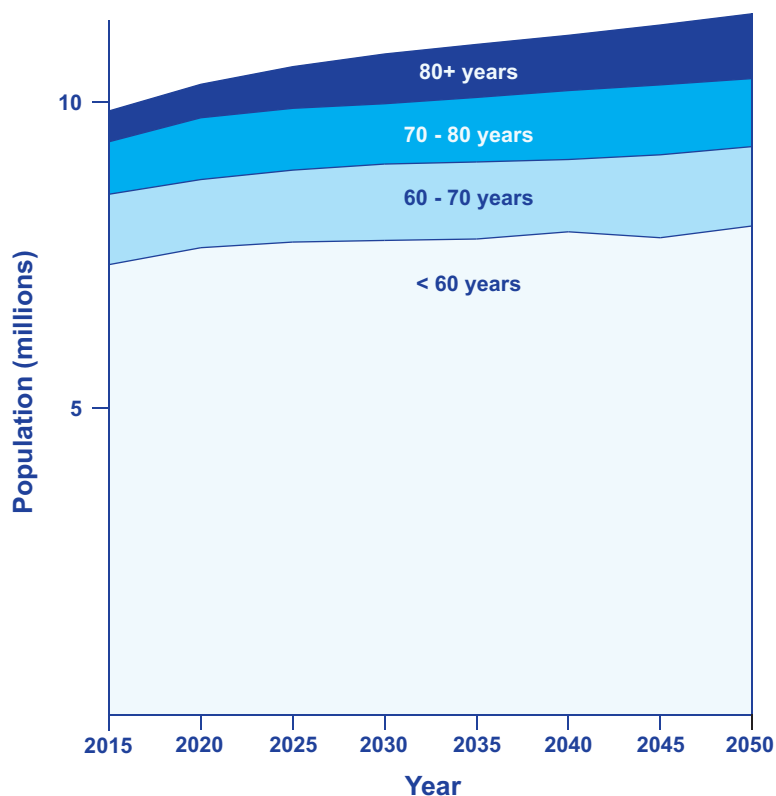
Figure 1. Population in Sweden by 2050.
Projected population in Sweden by age groups until 2050. Data source: Statistiska Centralbyrån (SCB)[1].

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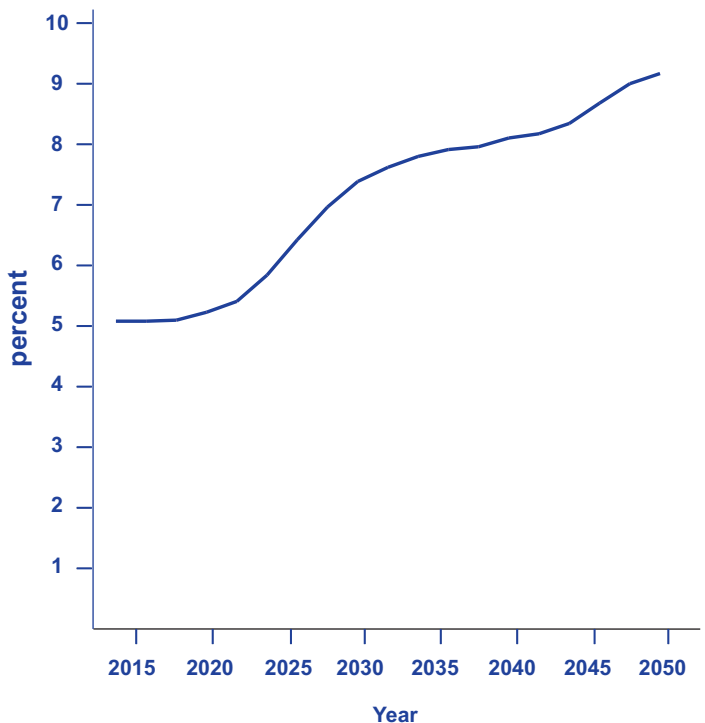
Figure 2. Proportion aged over 80 years.
The projected percentage of the Swedish population aged over 80 years until 2050. Data source: Statistiska Centralbyrån (SCB)[1].

The full impact of this development depends on how illness will develop in the oldest old, see Figure 3.
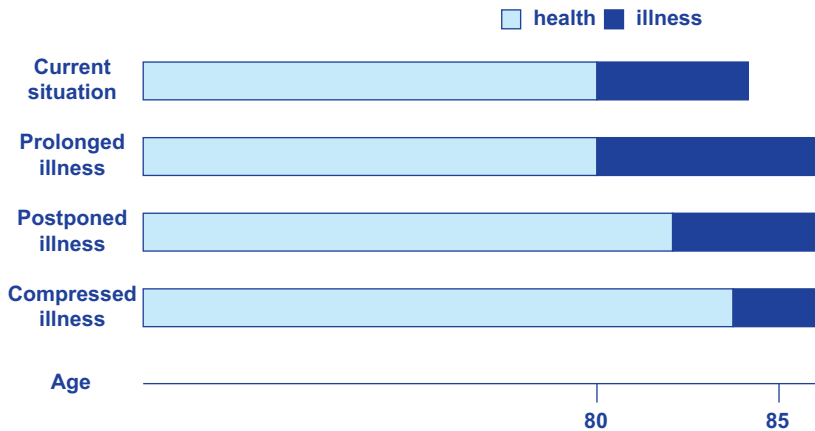
Figure 3. Scenarios for disease development
Three scenarios of how illness could develop when a population grows older: (1) *prolonged* illness, where the healthy part of life is unchanged and illness prolonged, (2) *postponed* illness, where the healthy part of life is prolonged, and illness unchanged 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.
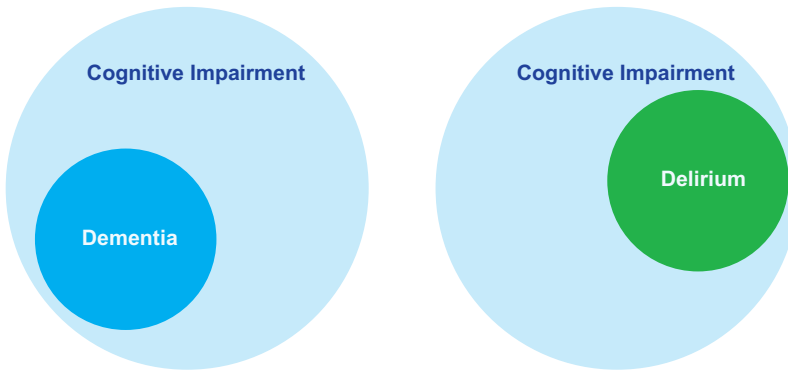
Figure 4. The relationship between cognitive impairment, dementia and delirium
As cognitive impairment is a mandatory symptom, all patients with dementia or delirium will have cognitive impairment but only a part of the patients with cognitive impairment will have dementia or delirium.

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.
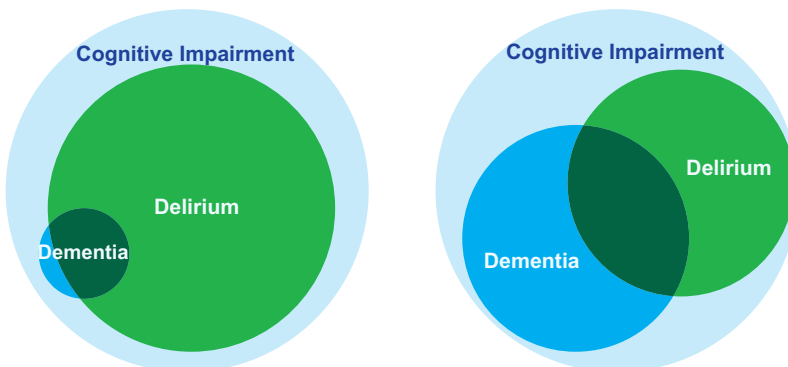
Figure 5. Cognitive impairment, dementia and delirium in different settings
In an intensive care unit (left), dementia patients are rare but almost all of the patients with cognitive impairment will fulfil delirium criteria. In medical inpatients (right), a large proportion of patients will fulfil the criteria for dementia, delirium, or both.

18

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.
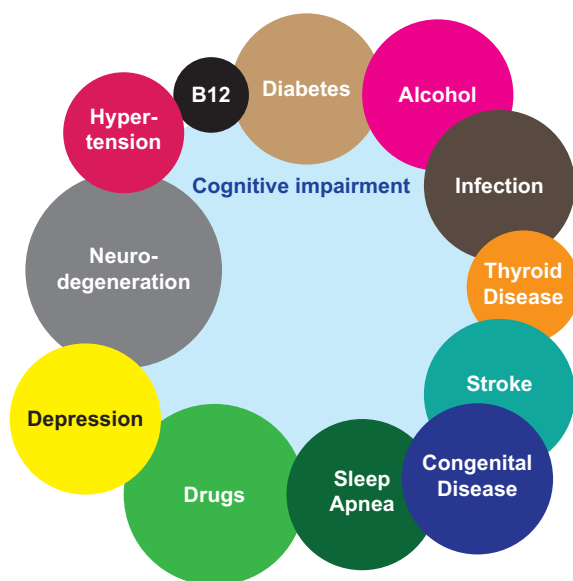
Figure 6. Factors capable of causing cognitive impairment
Examples of underlying diseases and causes that could, but would not necessarily, cause cognitive impairment. A number of these could be prevented or treated, if the symptom cognitive impairment is identified and the underlying cause pursued.

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 delirum.[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 disesase 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 1[71]. The basic diagnostic workup is shown in Text box 2[65].

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 conciousness and cognitive disturbances (disorientation, memory impairment, language impairment). Supportive features consist of disturbance in sleep-wake cycle, perceptional 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.
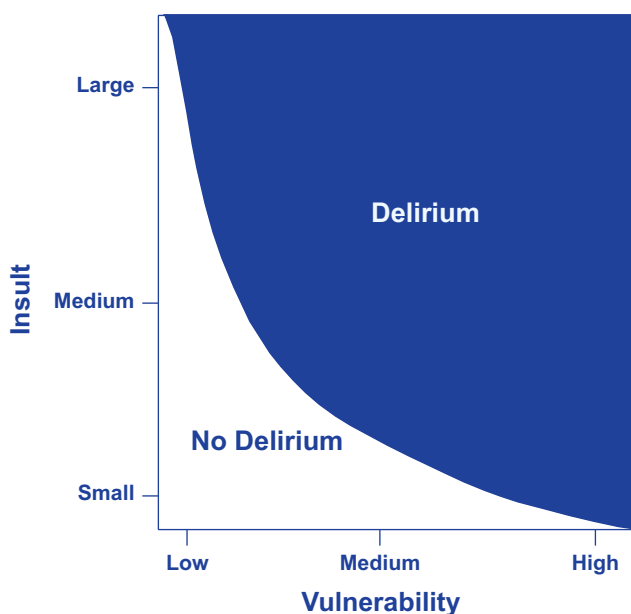
Figure 7. The vulnerability-insult model for delirium
Patients with low vulnerability (healthy elderly) may develop delirium only after repeated major insults (general anesthesia, surgery etc.) while patients with high vulnerability (multimorbid patients with dementia) may develop delirium due to small 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.[140 141]

26

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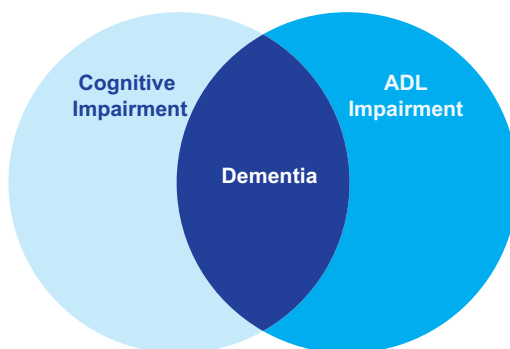
Figure 9. The relationship between cognitive impairment, ADL impairment and dementia.
The co-existence of cognitive impairment and ADL impairment is the hallmark of the dementia syndrome, given that these symptoms are not explained by delirium or psychiatric disorders.

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.

neither reliable nor valid   **reliable but not valid**   **reliable and valid**

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

Reproducability

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 reproducability 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, reproducability 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 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 reproducability 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 occur 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 illnessess 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 avaliable 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 critiera 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 consituted 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

All available admissions = 651

control phase		intervention phase
382	**(651 admissions)**	269
(91)	**Ineligible (129)**	**(38)**
(35)	Age < 60 years	(11)
(15)	Not living in Malmö	(0)
(29)	Institutional living	(16)
(12)	Prior enrolment	(11)
291	**(522 admissions)**	231
(39)	**Exclusion - hospital (78)**	**(39)**
(9)	Transferred	(13)
(11)	Lost to early discharge	(15)
(13)	Isolation due to norovirus	(6)
(6)	Other	(5)
252	**(444 admissions)**	192
(86)	**Exclusion - patient (136)**	**(50)**
(19)	Terminal disease	(13)
(24)	Language barrier	(2)
(9)	Blindness	(11)
(2)	Deafness	(6)
(3)	Aphasia	(4)
(29)	Severe disease	(14)
166	**(308 admissions)**	142
(37)	**No consent (72)**	**(35)**
129	**(236 admissions)**	107
(28)	**Excluded after consent (36)**	**(8)**
(4)	Transfer	(2)
(11)	Deterioration	(3)
(7)	Lost to early discharge	(2)
(2)	Isolation due to norovirus	(0)
(4)	Other	(1)
101 Included controls		**99 Included in intervention**

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 wegihts 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
	lymphoma
3	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 study [271]. 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, were 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.
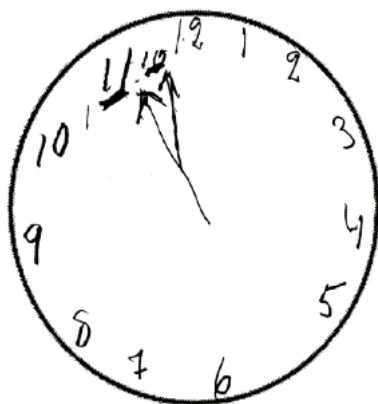
Figure 12. The clock-drawing test
Patients were asked to draw the face of a clock and to make it show "ten past eleven". This clock was drawn by a patient in the study and would be considered abnormal with a Shulman CDT score of 3.

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 at total score ranging from 13 to 52 points. Patient and caregiver reports could be combined for a composite score, weighing the patient rating higher:

composite score = (2* patient rating + 1*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 LIMM 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 = medical 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%)		

Abbrevations: 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 ony one abnormal result, see figure 13
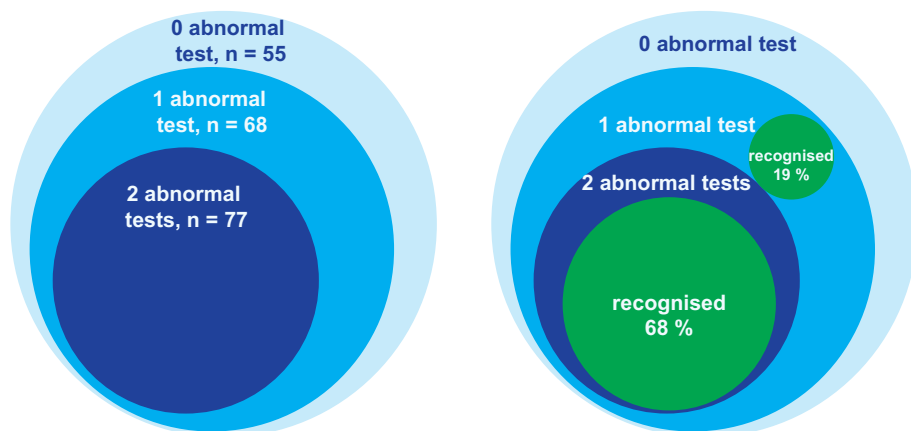
Figure 13. Prevalence and recognition of cognitive impairment.
In total, 68 + 77 = 145 patients (73%) had cognitive impairment, defined as having at least on abnormal test result (left). In the group with only one abnormal test, only 19% had documented recognition (right). In the entire population, 79 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.
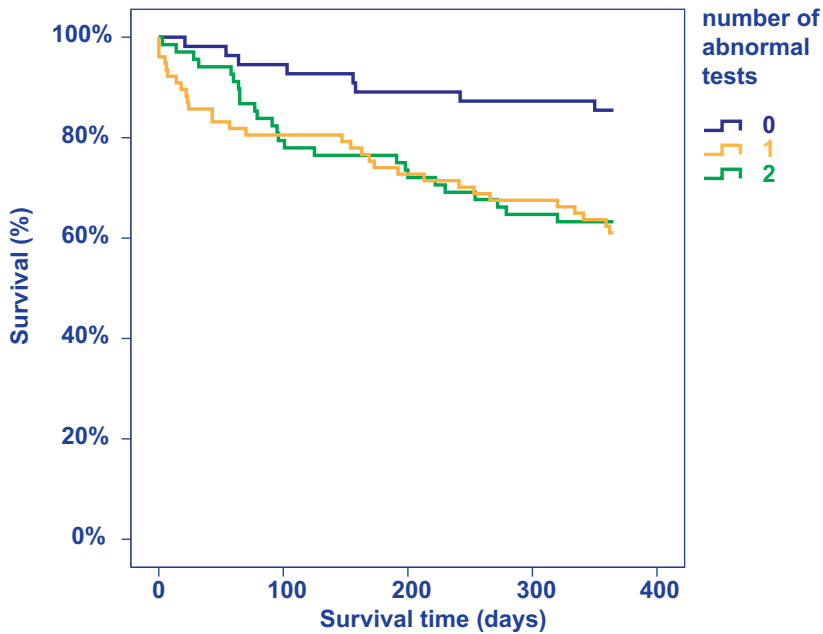
Figure 14. Association with mortality
Bivariate Kaplan-Meier estimates of 12-month survival for the three groups with 0, 1 and 2 abnormal cognitive test results. Log rank $\chi^2 = 9.7$, P = 0.008

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.

51

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 significace, 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.

54
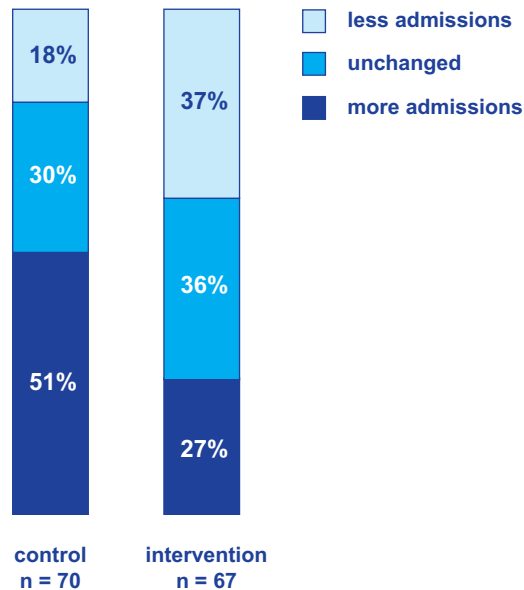
Figure 17. Individual comparisons
In the intervention group 73% had unchanged (36%) or less admissions (37%) after one year when compared to the year before, compared to only 48% in the control group (P for trend = 0.007). Only 12-month survivors were included in the analysis (n = 137).

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.
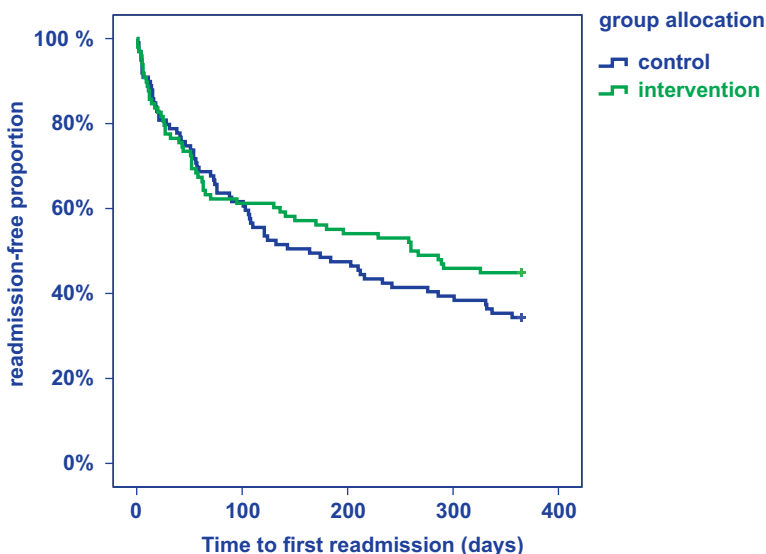
Figure 18. Time to first readmission
Kaplan-Meier estimate of time to first readmission. There was no difference between groups from the intention-to-treat perspective (Logrank χ^2 (*N*=200, 1 df) = 1.4, p = 0.24)
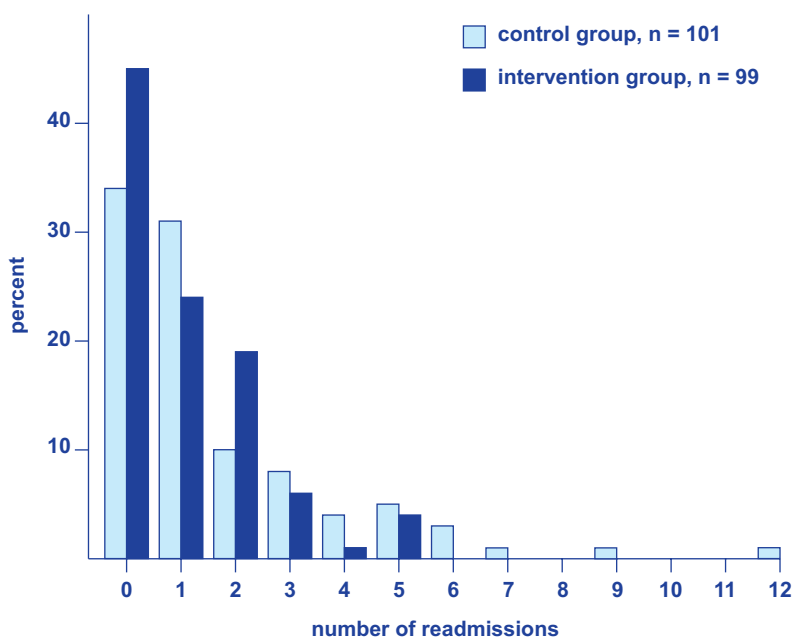
Figure 19. Readmission pattern
Percentage of patients with readmissions in the groups, from the intention-to-treat perspective. More patients in the control group had 3 or more readmissions (26% vs. 12%, χ^2 test, P = 0.01).

56

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 unsuccesful, presumable 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 transtitions 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.
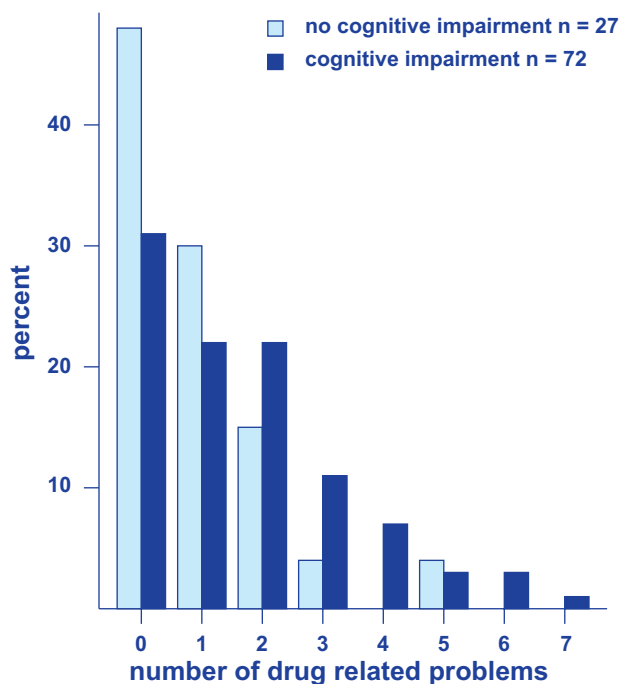
Figure 20. Drug-related problems
Drug-related problems were more frequent in the group with cognitive impairment (Mann-Whitney test, P = 0.02).

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 medical temporal lobe atrophy, see Figure 21.
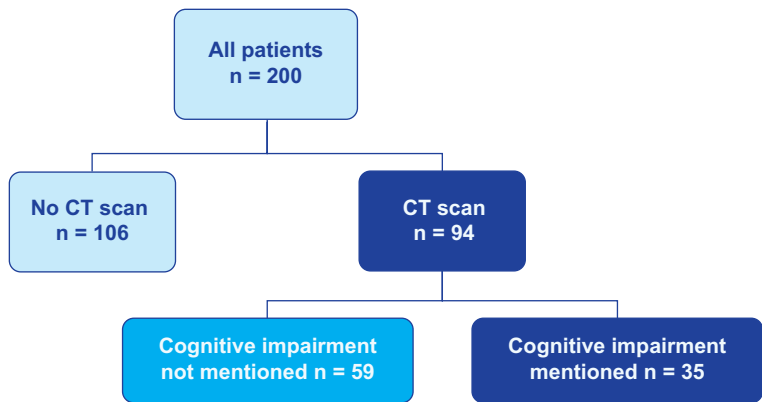
Figure 21. Outline of study III.
Overall, 94 patients had undergone a CT within ±1 year of cognitive tests. In 35 of the referrals, cognitive impairment was mentioned.

5.3.1. Prevalence and reporting frequency

The prevalence was high for all three measurements. All three measurmeents 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.
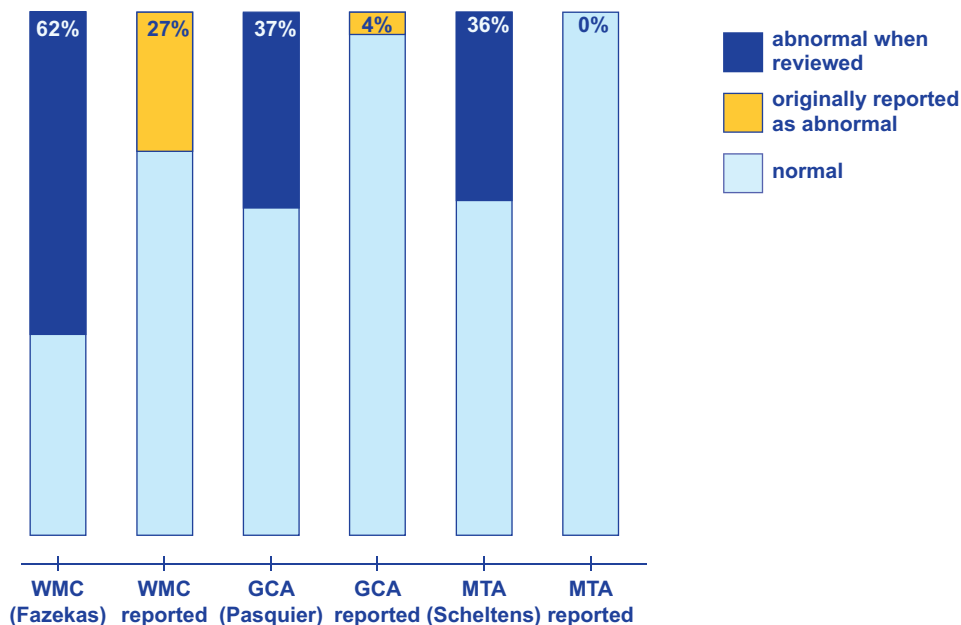
Figure 22. Radiological findings
The proportion of abnormal radiological findings on review, when rated with the scales of Fazekas, Pasquier and Scheltens, are shown in dark blue. The corresponding proportion of the original radiology reports are shown in yellow. **Abbreviations**: WMC = white matter changes, GCA = global cortical atrophy, MTA = medial temporal lobe atrophy.
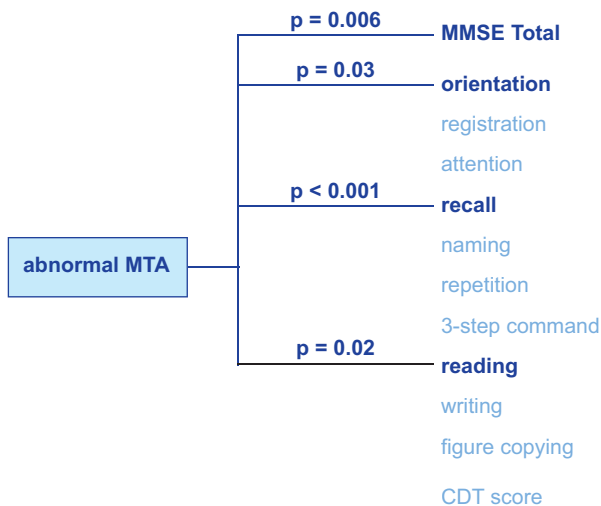
Figure 23. Association between medial temporal lobe atrophy and cognitive tests
MTA was associated with lower total score on MMSE and with lower scores on orientation, recall (memory) and reading. The association between MTA and memory was the strongest of all and the only one that would withstand a conservative Bonferroni correction.

60

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.
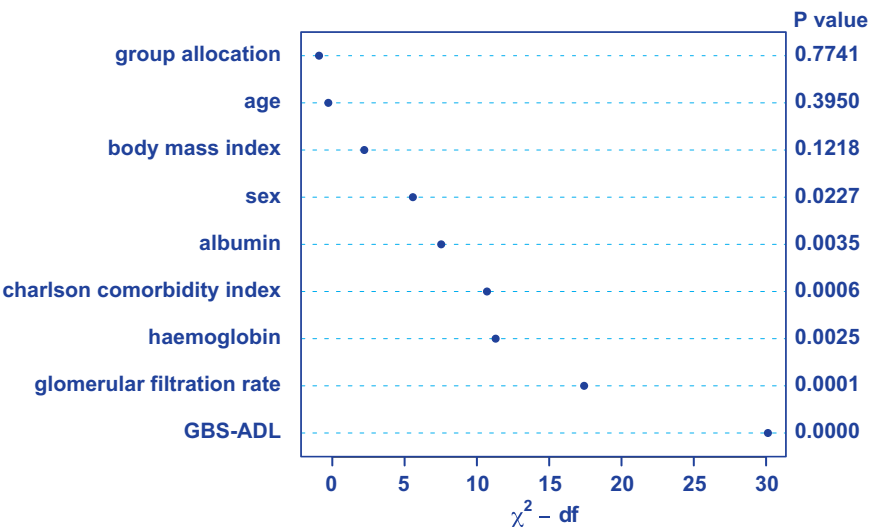
Figure 24. Relative importance of the variables in the full model
Variables with a higher χ^2 - df value are contributing more to the model's overall ability to predict mortality. Interactions and non-linear terms are incorporated into the variables. Group allocation signifies control or intervention 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.
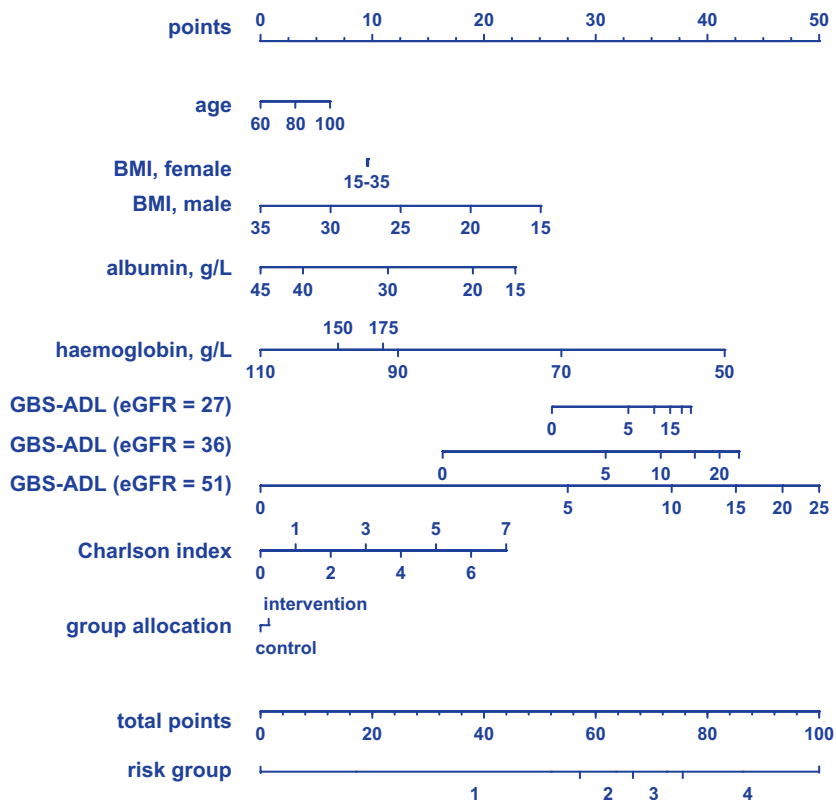
Figure 25. Nomogram
For an individual, the variables are compared with the upper "points" line, one at a time. These scores are then added for a total score that is plotted at the "total points" line at the bottom. This could then be used to designate the person to a "risk group" Notice the effect of 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.
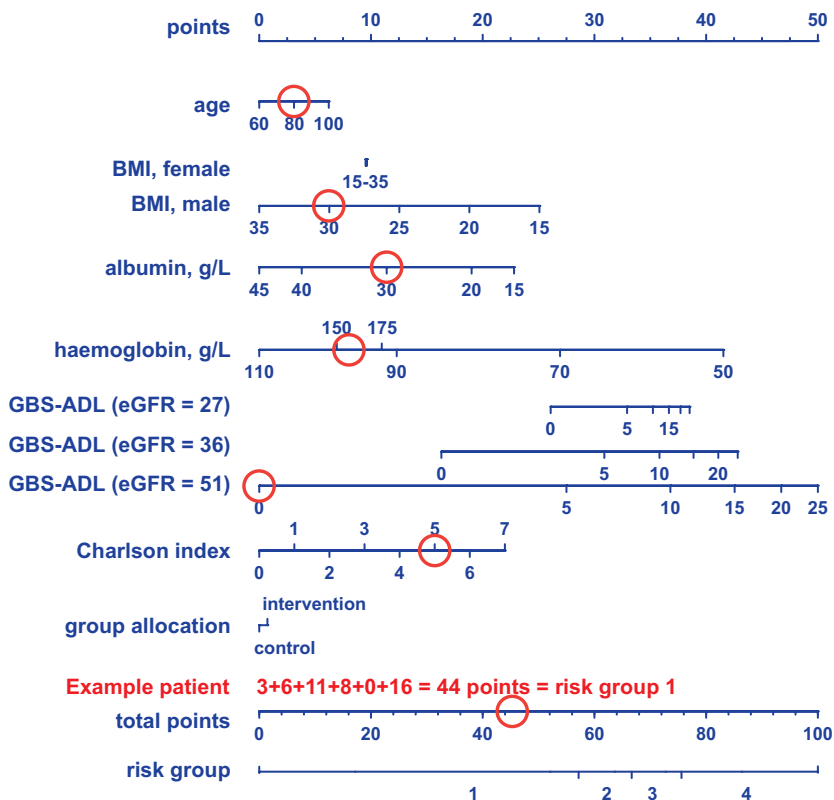
Figure 26. Example of patient score

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?
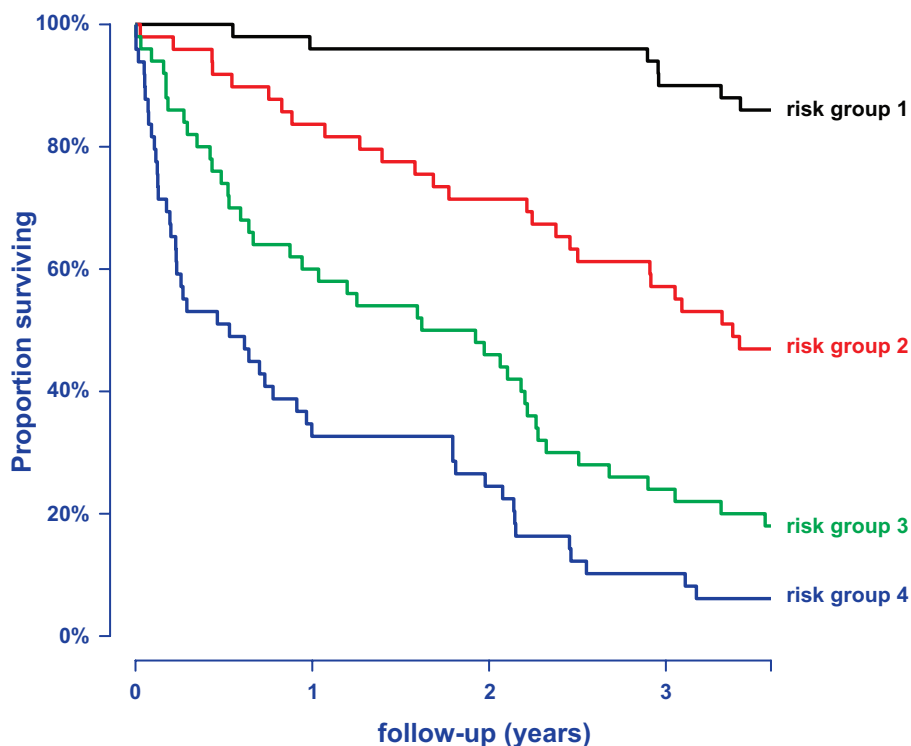
Figure 27. Kaplan-Meier estimates of the four risk groups
Survival curves for the four risk groups from the nomogram. The example patient, in risk group 1, would have a 90% predicted 3-year survival. However, when GBS-ADL increased to seven, he was placed in risk group 3 and the predicted chance of 3-year 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
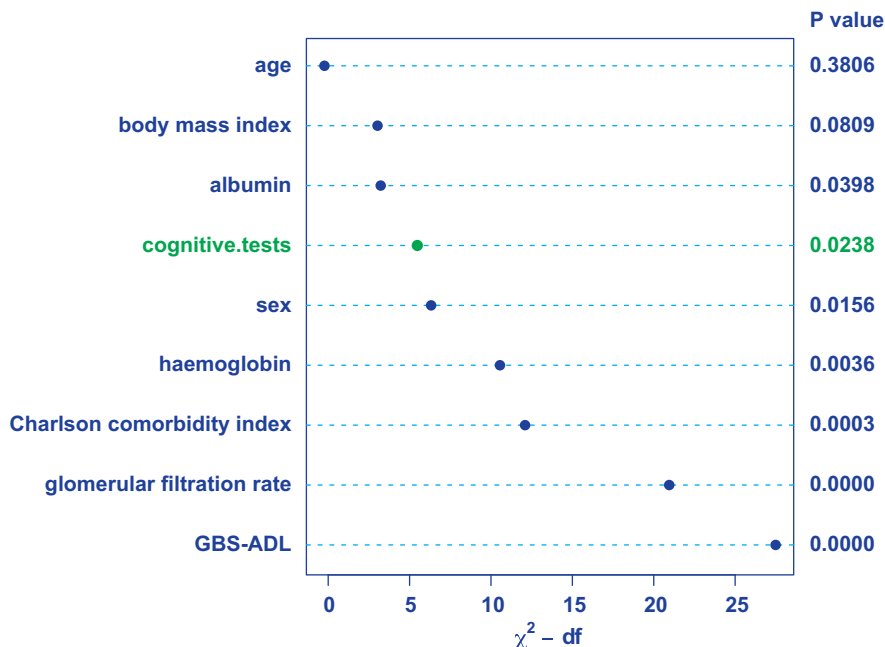
Figure 28. Relative importance of variables including cognitive tests.
Relative importance, displayed by χ^2 - df for the full model, inluding cognitive tests

66

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 neart 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, trombosis 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-resistent 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-dishcarge 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) Multicolinearity 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, adressing 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]

74

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 implemeted into reimbursement systems, this group would be less discrminated.

7.2.3. Brain failure?

> "a stigmatised person is in essence viewed by others as less than human" [367]

This qoute 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
septichemia/severe disease	septichemia/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.
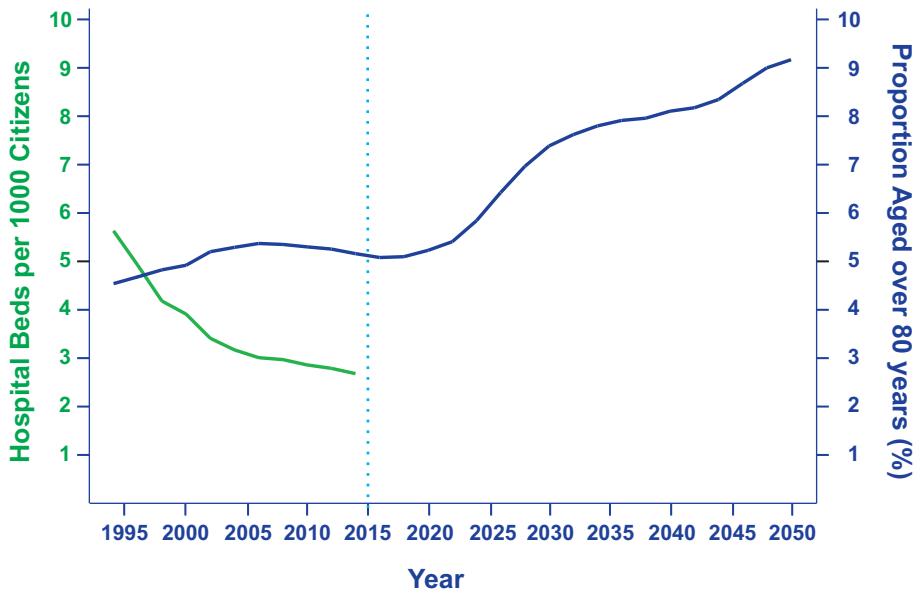

Figure 29. Facing the demographic challenge
Proportion of peopled aged over 80 years and number of hospital beds/1000 citizens.

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 reoccuring. 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 inititate 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 entrepenör 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.

Jenny Cappelin, Sofia Raccuia och Anna Johansson, som träffade alla patienter. Eran envishet och erat engagemang i detta projekt har varit enastående. Jag kunde inte hoppas på att få arbeta med en bättre grupp. Jag hoppas att denna avhandling får fler att inse den speciella kompetens arbetsterapeuter utgör och hur viktigt ert dagliga arbete är.

Annika Dobszai och Cecilia Lenander, extremt kompetenta kliniska apotekare. Era läkemedelsgenomgångar i artikel 2 har gett nya perspektiv och ni har lyckats bringa ordning i det kaos som moderna läkemedelslistor utgör.

Danielle van Westen, medförfattare på artikel 3. Jag uppskattar verkligen vårt samarbete och ser fram emot att arbeta med dig igen i framtiden.

Kajsa Stubendorff, min vän och kollega. Det har varit ett privilegium att dela Elisabet med dig. Tack för allt stöd och alla roliga stunder under denna tiden.

Victoria Larsson, tack för hjälp med språkgranskning med betydligt mer input på innehållet än vanlig språkgranskning.

Erik, Sebastian, Anna-Märta, Iris, Axel, Erik, Oskar, Katarina, Håkan, Åsa, Agneta, Carina vid enheten för klinisk minnesforskning. Ni är en prestigelös grupp

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

Alla andra på Minneskliniken i Malmö som alltid har gjort att jag har känt mig välkommen till Simrisbanvägen. Alla roliga icke jobbrelaterade diskussioner på lunchen är ett sundhetstecken.

Peter Lanbeck och Peter Wiksell, mina chefer på infektionskliniken i Malmö. Den flexibilitet och uppmuntran som ni visat mig angående min forskning från dag ett uppskattar jag enormt mycket.

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

Min familj, med mamma, pappa, Fredrik och Justina. Tack för ert ovillkorliga, kärleksfulla och kloka stöd. Det är få förunnat att ha de förutsättningar jag har fått.

Rebecca, min sambo, som har varit med de sista två åren av detta projekt. Du har varit en fast punkt och hjälpt mig att komma ihåg vad som är viktigt egentligen. Tack för allt tålamod och för att du får mig att må bra.

10. References

1.   Statistiska Centralbyrån (SCB). *Folkmängd efter ålder och kön 2014 - 2110.* www.statistikdatabasen.scb.se [accessed 2015-04-13]
2.   Buurman BM, Hoogerduijn JG, de Haan RJ, et al. Geriatric conditions in acutely hospitalized older patients: prevalence and one-year survival and functional decline. *PloS one.* 2011;6(11):e26951.
3.   Hickey A, Clinch D, Groarke EP. Prevalence of cognitive impairment in the hospitalized elderly. *International journal of geriatric psychiatry.* Jan 1997;12(1):27-33.
4.   Dodson JA, Truong TT, Towle VR, Kerins G, Chaudhry SI. Cognitive impairment in older adults with heart failure: prevalence, documentation, and impact on outcomes. *The American journal of medicine.* Feb 2013;126(2):120-126.
5.   Douzenis A, Michopoulos I, Gournellis R, et al. Cognitive decline and dementia in elderly medical inpatients remain underestimated and underdiagnosed in a recently established university general hospital in Greece. *Archives of gerontology and geriatrics.* Mar-Apr 2010;50(2):147-150.
6.   Joray S, Wietlisbach V, Bula CJ. Cognitive impairment in elderly medical inpatients: detection and associated six-month outcomes. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Nov-Dec 2004;12(6):639-647.
7.   Bilanakis N, Vratsista A, Athanasiou E, Niakas D, Peritogiannis V. Medical patients' treatment decision making capacity: a report from a general hospital in Greece. *Clinical practice and epidemiology in mental health : CP & EMH.* 2014;10:133-139.
8.   Farid K, Zhang Y, Bachelier D, et al. Cognitive impairment and malnutrition, predictors of all-cause mortality in hospitalized elderly subjects with cardiovascular disease. *Archives of cardiovascular diseases.* Apr 2013;106(4):188-195.
9.   Tirupati SN, Punitha RN. Cognitive decline in elderly medical and surgical inpatients. *Indian journal of psychiatry.* Apr 2005;47(2):99-101.
10.   Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER. Risk factors for delirium at discharge: development and validation of a predictive model. *Archives of internal medicine.* Jul 9 2007;167(13):1406-1413.
11.   Goldberg SE, Whittamore KH, Harwood RH, Bradshaw LE, Gladman JR, Jones RG. The prevalence of mental health problems among older adults admitted as an emergency to a general hospital. *Age and ageing.* Jan 2012;41(1):80-86.

12. Helvik AS, Engedal K, Selbaek G. The quality of life and factors associated with it in the medically hospitalised elderly. *Aging & mental health.* Sep 2010;14(7):861-869.

13. Boustani M, Baker MS, Campbell N, et al. Impact and recognition of cognitive impairment among hospitalized elders. *Journal of hospital medicine.* Feb 2010;5(2):69-75.

14. Bowler C, Boyle A, Branford M, Cooper SA, Harper R, Lindesay J. Detection of psychiatric disorders in elderly medical inpatients. *Age and ageing.* Jul 1994;23(4):307-311.

15. Campbell NL, Cantor BB, Hui SL, et al. Race and documentation of cognitive impairment in hospitalized older adults. *Journal of the American Geriatrics Society.* Mar 2014;62(3):506-511.

16. Harwood DM, Hope T, Jacoby R. Cognitive impairment in medical inpatients. II: Do physicians miss cognitive impairment? *Age and ageing.* Jan 1997;26(1):37-39.

17. Hustey FM, Meldon SW. The prevalence and documentation of impaired mental status in elderly emergency department patients. *Annals of emergency medicine.* Mar 2002;39(3):248-253.

18. Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. Detection and documentation of dementia and delirium in acute geriatric wards. *General hospital psychiatry.* Jan-Feb 2004;26(1):31-35.

19. Han JH, Bryce SN, Ely EW, et al. The effect of cognitive impairment on the accuracy of the presenting complaint and discharge instruction comprehension in older emergency department patients. *Annals of emergency medicine.* Jun 2011;57(6):662-671 e662.

20. Raymont V, Bingley W, Buchanan A, et al. Prevalence of mental incapacity in medical inpatients and associated risk factors: cross-sectional study. *Lancet.* Oct 16-22 2004;364(9443):1421-1427.

21. Sessums LL, Zembrzuska H, Jackson JL. Does this patient have medical decision-making capacity? *JAMA : the journal of the American Medical Association.* Jul 27 2011;306(4):420-427.

22. Whelan PJ, Oleszek J, Macdonald A, Gaughran F. The utility of the Mini-Mental State Examination in guiding assessment of capacity to consent to research. *International psychogeriatrics / IPA.* Apr 2009;21(2):338-344.

23. Gray SL, Mahoney JE, Blough DK. Medication adherence in elderly patients receiving home health services following hospital discharge. *The Annals of pharmacotherapy.* May 2001;35(5):539-545.

24. Okuno J, Yanagi H, Tomura S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community? *European journal of clinical pharmacology.* Oct 2001;57(8):589-594.

25. Sela-Katz P, Rabinowitz I, Shugaev I, Shigorina G. Basic knowledge of the medication regimen correlates with performance on cognitive function tests and diagnosis of dementia in elderly patients referred to a geriatric assessment unit. *Gerontology.* 2010;56(5):491-495.

26. Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age and ageing.* May 2003;32(3):299-302.

27. Atkin PA, Finnegan TP, Ogle SJ, Shenfield GM. Functional ability of patients to manage medication packaging: a survey of geriatric inpatients. *Age and ageing.* Mar 1994;23(2):113-116.

28. Nikolaus T, Kruse W, Bach M, Specht-Leible N, Oster P, Schlierf G. Elderly patients' problems with medication. An in-hospital and follow-up study. *European journal of clinical pharmacology.* 1996;49(4):255-259.

29. Allen SC, Baxter M. A comparison of four tests of cognition as predictors of inability to perform spirometry in old age. *Age and ageing.* Sep 2009;38(5):537-541.

30. Mecocci P, von Strauss E, Cherubini A, et al. Cognitive impairment is the major risk factor for development of geriatric syndromes during hospitalization: results from the GIFA study. *Dementia and geriatric cognitive disorders.* 2005;20(4):262-269.

31. Cole M, McCusker J, Dendukuri N, Han L. The prognostic significance of subsyndromal delirium in elderly medical inpatients. *Journal of the American Geriatrics Society.* Jun 2003;51(6):754-760.

32. Cole MG, Primeau FJ. Prognosis of delirium in elderly hospital patients. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Jul 1 1993;149(1):41-46.

33. Edlund A, Lundstrom M, Karlsson S, Brannstrom B, Bucht G, Gustafson Y. Delirium in older patients admitted to general internal medicine. *Journal of geriatric psychiatry and neurology.* Jun 2006;19(2):83-90.

34. Han JH, Eden S, Shintani A, et al. Delirium in older emergency department patients is an independent predictor of hospital length of stay. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* May 2011;18(5):451-457.

35. Campbell SE, Seymour DG, Primrose WR. A systematic literature review of factors affecting outcome in older medical patients admitted to hospital. *Age and ageing.* Mar 2004;33(2):110-115.

36. McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? *Journal of the American Geriatrics Society.* Nov 2003;51(11):1539-1546.

37. Mukadam N, Sampson EL. A systematic review of the prevalence, associations and outcomes of dementia in older general hospital inpatients. *International psychogeriatrics / IPA.* Apr 2011;23(3):344-355.

38. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age and ageing.* Jul 2006;35(4):350-364.

39. Fulop G, Strain JJ, Fahs MC, Schmeidler J, Snyder S. A prospective study of the impact of psychiatric comorbidity on length of hospital stays of elderly medical-surgical inpatients. *Psychosomatics.* May-Jun 1998;39(3):273-280.

40. Furlanetto LM, da Silva RV, Bueno JR. The impact of psychiatric comorbidity on length of stay of medical inpatients. *General hospital psychiatry.* Jan-Feb 2003;25(1):14-19.

41. Helvik AS, Skancke RH, Selbaek G, Engedal K. Nursing home admission during the first year after hospitalization - the contribution of cognitive impairment. *PloS one.* 2014;9(1):e86116.

42.   Daiello LA, Gardner R, Epstein-Lubow G, Butterfield K, Gravenstein S. Association of dementia with early rehospitalization among Medicare beneficiaries. *Archives of gerontology and geriatrics.* Jul-Aug 2014;59(1):162-168.

43.   Saravay SM, Pollack S, Steinberg MD, Weinschel B, Habert M. Four-year follow-up of the influence of psychological comorbidity on medical rehospitalization. *The American journal of psychiatry.* Mar 1996;153(3):397-403.

44.   Freedberg DE, Dave J, Kurth T, Gaziano JM, Bludau JH. Cognitive impairment over the age of 85: hospitalization and mortality. *Archives of gerontology and geriatrics.* Mar-Apr 2008;46(2):137-145.

45.   Zuccala G, Pedone C, Cesari M, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *The American journal of medicine.* Aug 1 2003;115(2):97-103.

46.   Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet.* Dec 17 2005;366(9503):2112-2117.

47.   Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Jan 2013;9(1):63-75 e62.

48.   Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet.* Oct 26 2013;382(9902):1405-1412.

49.   Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology.* May 8 2012;78(19):1456-1463.

50.   Qiu C, von Strauss E, Backman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology.* May 14 2013;80(20):1888-1894.

51.   Langa KM, Larson EB, Karlawish JH, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Mar 2008;4(2):134-144.

52.   Rocca WA, Petersen RC, Knopman DS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Jan 2011;7(1):80-93.

53.   Brayne C, Gao L, Dewey M, Matthews FE. Dementia before death in ageing societies--the promise of prevention and the reality. *PLoS medicine.* Oct 2006;3(10):e397.

54.   Wimo A, Jonsson L, Bond J, Prince M, Winblad B, Alzheimer Disease I. The worldwide economic impact of dementia 2010. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Jan 2013;9(1):1-11 e13.

55.   Luengo-Fernandez R, Leal J, Gray A. *Dementia 2010. The economic burden of dementia and associated research funding in the United Kingdom.* 2010.

56.   Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *The New England journal of medicine.* Apr 4 2013;368(14):1326-1334.

57. Socialstyrelsen. *Demenssjukdomarnas samhällskostnader i Sverige 2012.* Socialstyrelsen 2014-6-3. Stockholm 2014.

58. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet.* Jul 29 2006;368(9533):387-403.

59. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet.* Mar 19 2011;377(9770):1019-1031.

60. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev.* 2006(1):Cd005593.

61. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *Bmj.* Aug 6 2005;331(7512):321-327.

62. Ames D, Kaduszkiewicz H, van den Bussche H, Zimmermann T, Birks J, Ashby D. For debate: is the evidence for the efficacy of cholinesterase inhibitors in the symptomatic treatment of Alzheimer's disease convincing or not? *International psychogeriatrics / IPA.* Apr 2008;20(2):259-292.

63. Wattmo C, Wallin AK, Londos E, Minthon L. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. *The Gerontologist.* Feb 2011;51(1):17-27.

64. Wattmo C, Paulsson E, Minthon L, Londos E. A longitudinal study of risk factors for community-based home help services in Alzheimer's disease: the influence of cholinesterase inhibitor therapy. *Clinical interventions in aging.* 2013;8:329-339.

65. Socialstyrelsen. *Nationella riktlinjer för vård och omsorg vid demenssjukdom* Socialstyrelsen 2010-5-1. Stockholm 2010

66. McKeith I, Mintzer J, Aarsland D, et al. Dementia with Lewy bodies. *Lancet neurology.* Jan 2004;3(1):19-28.

67. Gore RL, Vardy ER, O'Brien JT. Delirium and dementia with Lewy bodies: distinct diagnoses or part of the same spectrum? *Journal of neurology, neurosurgery, and psychiatry.* Jan 2015;86(1):50-59.

68. Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet neurology.* Nov 2005;4(11):771-780.

69. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. *Lancet neurology.* Nov 2002;1(7):426-436.

70. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet neurology.* Feb 2003;2(2):89-98.

71. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (5th ed.): DSM-5. Washington DC. 2013

72. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (4th ed.): DSM-IV-TR. Washington, DC. 2000.

73. World Health Organisation. *The ICD-10 International Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostice Guidelines.* Geneva, Switzerland. 1992.

74. Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. *The New England journal of medicine.* Dec 4 1997;337(23):1667-1674.

75. Naik M, Nygaard HA. Diagnosing dementia -- ICD-10 not so bad after all: a comparison between dementia criteria according to DSM-IV and ICD-10. *International journal of geriatric psychiatry.* Mar 2008;23(3):279-282.

76. Wancata J, Borjesson-Hanson A, Ostling S, Sjogren K, Skoog I. Diagnostic criteria influence dementia prevalence. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Dec 2007;15(12):1034-1045.

77. Connolly A, Gaehl E, Martin H, Morris J, Purandare N. Underdiagnosis of dementia in primary care: variations in the observed prevalence and comparisons to the expected prevalence. *Aging & mental health.* Nov 2011;15(8):978-984.

78. Lopponen M, Raiha I, Isoaho R, Vahlberg T, Kivela SL. Diagnosing cognitive impairment and dementia in primary health care -- a more active approach is needed. *Age and ageing.* Nov 2003;32(6):606-612.

79. Olafsdottir M, Skoog I, Marcusson J. Detection of dementia in primary care: the Linkoping study. *Dementia and geriatric cognitive disorders.* Jul-Aug 2000;11(4):223-229.

80. Sternberg SA, Wolfson C, Baumgarten M. Undetected dementia in community-dwelling older people: the Canadian Study of Health and Aging. *Journal of the American Geriatrics Society.* Nov 2000;48(11):1430-1434.

81. Thies W, Bleiler L. 2013 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Mar 2013;9(2):208-245.

82. Chodosh J, Petitti DB, Elliott M, et al. Physician recognition of cognitive impairment: evaluating the need for improvement. *Journal of the American Geriatrics Society.* Jul 2004;52(7):1051-1059.

83. Brayne C, Fox C, Boustani M. Dementia screening in primary care: is it time? *JAMA : the journal of the American Medical Association.* Nov 28 2007;298(20):2409-2411.

84. Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. *Annals of internal medicine.* Nov 5 2013;159(9):601-612.

85. Brunet MD, McCartney M, Heath I, et al. There is no evidence base for proposed dementia screening. *Bmj.* 2012;345:e8588.

86. Department of Health (UK). *Prime Minister's Challenge on Dementia - Delivering major improvements in dementia care and research by 2015.* London 2012.

87. Department of Health (UK). *Living well with dementia - a national dementia strategy.* London 2009.

88. Banerjee S. Living well with dementia--development of the national dementia strategy for England. *International journal of geriatric psychiatry.* Sep 2010;25(9):917-922.

89. Burns A, Robert P. The National Dementia strategy in England. *Bmj.* 2009;338:b931.

90. Benbow SM, Greaves I, Jolley D. All people with dementia need accurate assessment and ongoing support. *Bmj.* 2013;347:f6108.

91. Kmietowicz Z. Cameron launches challenge to end "national crisis" of poor dementia care. *Bmj.* 2012;344:e2347.

92

92.   Socialstyrelsen. *Nationell utvärdering – Vård och omsorg vid demenssjukdom 2014 – Indikatorer och underlag för bedömningar* Socialstyrelsen *2014-2-1*. Stockholm. 2014.

93.   Sampson EL, Blanchard MR, Jones L, Tookman A, King M. Dementia in the acute hospital: prospective cohort study of prevalence and mortality. *The British journal of psychiatry : the journal of mental science.* Jul 2009;195(1):61-66.

94.   Zekry D, Herrmann FR, Grandjean R, et al. Does dementia predict adverse hospitalization outcomes? A prospective study in aged inpatients. *International journal of geriatric psychiatry.* Mar 2009;24(3):283-291.

95.   Wand AP, Thoo W, Ting V, Baker J, Sciuriaga H, Hunt GE. Identification and rates of delirium in elderly medical inpatients from diverse language groups. *Geriatric nursing (New York, N.Y.).* Sep-Oct 2013;34(5):355-360.

96.   Zekry D, Herrmann FR, Grandjean R, et al. Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status. *Age and ageing.* Jan 2008;37(1):83-89.

97.   Albert SM, Costa R, Merchant C, Small S, Jenders RA, Stern Y. Hospitalization and Alzheimer's disease: results from a community-based study. *The journals of gerontology. Series A, Biological sciences and medical sciences.* May 1999;54(5):M267-271.

98.   Malone DC, McLaughlin TP, Wahl PM, et al. Burden of Alzheimer's disease and association with negative health outcomes. *The American journal of managed care.* Aug 2009;15(8):481-488.

99.   Natalwala A, Potluri R, Uppal H, Heun R. Reasons for hospital admissions in dementia patients in Birmingham, UK, during 2002-2007. *Dementia and geriatric cognitive disorders.* 2008;26(6):499-505.

100.   Zhao Y, Kuo TC, Weir S, Kramer MS, Ash AS. Healthcare costs and utilization for Medicare beneficiaries with Alzheimer's. *BMC health services research.* 2008;8:108.

101.   Bynum JP, Rabins PV, Weller W, Niefeld M, Anderson GF, Wu AW. The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. *Journal of the American Geriatrics Society.* Feb 2004;52(2):187-194.

102.   Phelan EA, Borson S, Grothaus L, Balch S, Larson EB. Association of incident dementia with hospitalizations. *JAMA : the journal of the American Medical Association.* Jan 11 2012;307(2):165-172.

103.   Rudolph JL, Zanin NM, Jones RN, et al. Hospitalization in community-dwelling persons with Alzheimer's disease: frequency and causes. *Journal of the American Geriatrics Society.* Aug 2010;58(8):1542-1548.

104.   Guijarro R, San Roman CM, Gomez-Huelgas R, et al. Impact of dementia on hospitalization. *Neuroepidemiology.* Aug 2010;35(2):101-108.

105.   Folstein MF, Bassett SS, Romanoski AJ, Nestadt G. The epidemiology of delirium in the community: the Eastern Baltimore Mental Health Survey. *International psychogeriatrics / IPA.* Winter 1991;3(2):169-176.

106.   Rahkonen T, Eloniemi-Sulkava U, Paanila S, Halonen P, Sivenius J, Sulkava R. Systematic intervention for supporting community care of elderly people after a delirium episode. *International psychogeriatrics / IPA.* Mar 2001;13(1):37-49.

107. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* Mar 8 2014;383(9920):911-922.
108. Inouye SK. Delirium in older persons. *The New England journal of medicine.* Mar 16 2006;354(11):1157-1165.
109. Fang CK, Chen HW, Liu SI, Lin CJ, Tsai LY, Lai YL. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. *Japanese journal of clinical oncology.* Jan 2008;38(1):56-63.
110. Krogseth M, Wyller TB, Engedal K, Juliebo V. Delirium is an important predictor of incident dementia among elderly hip fracture patients. *Dementia and geriatric cognitive disorders.* 2011;31(1):63-70.
111. Pisani MA, Murphy TE, Van Ness PH, Araujo KL, Inouye SK. Characteristics associated with delirium in older patients in a medical intensive care unit. *Archives of internal medicine.* Aug 13-27 2007;167(15):1629-1634.
112. Han JH, Zimmerman EE, Cutler N, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* Mar 2009;16(3):193-200.
113. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM, Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Archives of internal medicine.* Nov 12 2001;161(20):2467-2473.
114. Elie M, Rousseau F, Cole M, Primeau F, McCusker J, Bellavance F. Prevalence and detection of delirium in elderly emergency department patients. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Oct 17 2000;163(8):977-981.
115. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *Journal of general internal medicine.* Apr 1998;13(4):234-242.
116. McCusker J, Cole M, Dendukuri N, Belzile E, Primeau F. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Sep 4 2001;165(5):575-583.
117. Leslie DL, Inouye SK. The importance of delirium: economic and societal costs. *Journal of the American Geriatrics Society.* Nov 2011;59 Suppl 2:S241-243.
118. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Archives of internal medicine.* Jan 14 2008;168(1):27-32.
119. George J, Bleasdale S, Singleton SJ. Causes and prognosis of delirium in elderly patients admitted to a district general hospital. *Age and ageing.* Nov 1997;26(6):423-427.
120. Han JH, Shintani A, Eden S, et al. Delirium in the emergency department: an independent predictor of death within 6 months. *Annals of emergency medicine.* Sep 2010;56(3):244-252.e241.
121. McAvay GJ, Van Ness PH, Bogardus ST, Jr., et al. Older adults discharged from the hospital with delirium: 1-year outcomes. *Journal of the American Geriatrics Society.* Aug 2006;54(8):1245-1250.
122. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Archives of internal medicine.* Feb 25 2002;162(4):457-463.

94

123.   Kakuma R, du Fort GG, Arsenault L, et al. Delirium in older emergency department patients discharged home: effect on survival. *Journal of the American Geriatrics Society.* Apr 2003;51(4):443-450.

124.   O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *Journal of the American Geriatrics Society.* Feb 1997;45(2):174-178.

125.   Eeles EM, Hubbard RE, White SV, O'Mahony MS, Savva GM, Bayer AJ. Hospital use, institutionalisation and mortality associated with delirium. *Age and ageing.* Jul 2010;39(4):470-475.

126.   Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA : the journal of the American Medical Association.* Mar 20 1996;275(11):852-857.

127.   Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dementia and geriatric cognitive disorders.* Sep-Oct 1999;10(5):393-400.

128.   World Health Organisation. *International statistical classification of diseases and related health problems.* Geneva: World Health Organization; 1992.

129.   Tabet N, Howard R. Pharmacological treatment for the prevention of delirium: review of current evidence. *International journal of geriatric psychiatry.* Oct 2009;24(10):1037-1044.

130.   Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *Journal of the American Geriatrics Society.* Oct 2005;53(10):1658-1666.

131.   Schrader SL, Wellik KE, Demaerschalk BM, Caselli RJ, Woodruff BK, Wingerchuk DM. Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. *The neurologist.* Mar 2008;14(2):134-137.

132.   Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. *Psychosomatics.* Mar-Apr 2013;54(2):124-131.

133.   Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *The New England journal of medicine.* Mar 4 1999;340(9):669-676.

134.   Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *Journal of the American Geriatrics Society.* May 2001;49(5):516-522.

135.   Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *Journal of the American Geriatrics Society.* Nov 2009;57(11):2029-2036.

136.   Inouye SK, Bogardus ST, Jr., Baker DI, Leo-Summers L, Cooney LM, Jr. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program. *Journal of the American Geriatrics Society.* Dec 2000;48(12):1697-1706.

137.   Lundstrom M, Edlund A, Karlsson S, Brannstrom B, Bucht G, Gustafson Y. A multifactorial intervention program reduces the duration of delirium, length of

hospitalization, and mortality in delirious patients. *Journal of the American Geriatrics Society.* Apr 2005;53(4):622-628.

138.   Naughton BJ, Saltzman S, Ramadan F, Chadha N, Priore R, Mylotte JM. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. *Journal of the American Geriatrics Society.* Jan 2005;53(1):18-23.

139.   Tabet N, Hudson S, Sweeney V, et al. An educational intervention can prevent delirium on acute medical wards. *Age and ageing.* Mar 2005;34(2):152-156.

140.   Tabet N, Howard R. Non-pharmacological interventions in the prevention of delirium. *Age and ageing.* Jul 2009;38(4):374-379.

141.   Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev.* 2007(2):Cd005563.

142.   Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *Journal of the American Geriatrics Society.* Oct 2002;50(10):1723-1732.

143.   Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. *Age and ageing.* Oct 1999;28(6):551-556.

144.   Cole MG, McCusker J, Dendukuri N, Han L. Symptoms of delirium among elderly medical inpatients with or without dementia. *The Journal of neuropsychiatry and clinical neurosciences.* Spring 2002;14(2):167-175.

145.   Dasgupta M, Hillier LM. Factors associated with prolonged delirium: a systematic review. *International psychogeriatrics / IPA.* May 2010;22(3):373-394.

146.   Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age and ageing.* Jan 2009;38(1):19-26.

147.   Levkoff SE, Liptzin B, Cleary PD, et al. Subsyndromal Delirium. *The American Journal of Geriatric Psychiatry.* 1996;4(4):320-320.

148.   Cole MG, Ciampi A, Belzile E, Dubuc-Sarrasin M. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *International journal of geriatric psychiatry.* Aug 2013;28(8):771-780.

149.   Meagher D, O'Regan N, Ryan D, et al. Frequency of delirium and subsyndromal delirium in an adult acute hospital population. *The British journal of psychiatry : the journal of mental science.* Dec 2014;205(6):478-485.

150.   Zuliani G, Bonetti F, Magon S, et al. Subsyndromal delirium and its determinants in elderly patients hospitalized for acute medical illness. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Oct 2013;68(10):1296-1302.

151.   Cole MG. Delirium in elderly patients. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Jan-Feb 2004;12(1):7-21.

152.   Davis DH, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain : a journal of neurology.* Sep 2012;135(Pt 9):2809-2816.

153.   Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *The New England journal of medicine.* Jul 5 2012;367(1):30-39.

154.   Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool
        WA. Delirium in elderly patients and the risk of postdischarge mortality,
        institutionalization, and dementia: a meta-analysis. *JAMA : the journal of the
        American Medical Association.* Jul 28 2010;304(4):443-451.
155.   Young J, Meagher D, Maclullich A. Cognitive assessment of older people. *Bmj.*
        2011;343:d5042.
156.   Russ TC, Shenkin SD, Reynish E, Ryan T, Anderson D, Maclullich AM.
        Dementia in acute hospital inpatients: the role of the geriatrician. *Age and ageing.*
        May 2012;41(3):282-284.
157.   Holland R, Battersby J, Harvey I, Lenaghan E, Smith J, Hay L. Systematic review
        of multidisciplinary interventions in heart failure. *Heart.* Jul 2005;91(7):899-906.
158.   Lambrinou E, Kalogirou F, Lamnisos D, Sourtzi P. Effectiveness of heart failure
        management programmes with nurse-led discharge planning in reducing re-
        admissions: a systematic review and meta-analysis. *International journal of
        nursing studies.* May 2012;49(5):610-624.
159.   Mistiaen P, Francke AL, Poot E. Interventions aimed at reducing problems in
        adult patients discharged from hospital to home: a systematic meta-review. *BMC
        health services research.* 2007;7:47.
160.   Phillips CO, Wright SM, Kern DE, Singa RM, Shepperd S, Rubin HR.
        Comprehensive discharge planning with postdischarge support for older patients
        with congestive heart failure: a meta-analysis. *JAMA : the journal of the
        American Medical Association.* Mar 17 2004;291(11):1358-1367.
161.   Cornish PL, Knowles SR, Marchesano R, et al. Unintended medication
        discrepancies at the time of hospital admission. *Archives of internal medicine.* Feb
        28 2005;165(4):424-429.
162.   Hellstrom LM, Bondesson A, Hoglund P, Eriksson T. Errors in medication
        history at hospital admission: prevalence and predicting factors. *BMC clinical
        pharmacology.* 2012;12:9.
163.   Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE.
        Frequency, type and clinical importance of medication history errors at admission
        to hospital: a systematic review. *CMAJ : Canadian Medical Association journal
        = journal de l'Association medicale canadienne.* Aug 30 2005;173(5):510-515.
164.   Ruiz B, Garcia M, Aguirre U, Aguirre C. Factors predicting hospital readmissions
        related to adverse drug reactions. *European journal of clinical pharmacology.* Jul
        2008;64(7):715-722.
165.   Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of
        admission to hospital: prospective analysis of 18 820 patients. *BMJ.* Jul 3
        2004;329(7456):15-19.
166.   Schnipper JL, Hamann C, Ndumele CD, et al. Effect of an electronic medication
        reconciliation application and process redesign on potential adverse drug events: a
        cluster-randomized trial. *Archives of internal medicine.* Apr 27 2009;169(8):771-
        780.
167.   Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication
        reconciliation practices: a systematic review. *Archives of internal medicine.* Jul 23
        2012;172(14):1057-1069.
168.   Bergkvist A, Midlov P, Hoglund P, Larsson L, Eriksson T. A multi-intervention
        approach on drug therapy can lead to a more appropriate drug use in the elderly.

LIMM-Landskrona Integrated Medicines Management. *Journal of evaluation in clinical practice.* Aug 2009;15(4):660-667.

169. Bondesson A, Eriksson T, Kragh A, Holmdahl L, Midlov P, Hoglund P. In-hospital medication reviews reduce unidentified drug-related problems. *European journal of clinical pharmacology.* Sep 7 2012.

170. Hellstrom LM, Bondesson A, Hoglund P, et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. *European journal of clinical pharmacology.* Jul 2011;67(7):741-752.

171. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Archives of internal medicine.* May 11 2009;169(9):894-900.

172. Thomas R, Huntley AL, Mann M, et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. *Age and ageing.* Mar 2014;43(2):174-187.

173. Hellstrom LM, Hoglund P, Bondesson A, Petersson G, Eriksson T. Clinical implementation of systematic medication reconciliation and review as part of the Lund Integrated Medicines Management model--impact on all-cause emergency department revisits. *Journal of clinical pharmacy and therapeutics.* Dec 2012;37(6):686-692.

174. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *Journal of the American Geriatrics Society.* May 2004;52(5):675-684.

175. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *The New England journal of medicine.* Nov 2 1995;333(18):1190-1195.

176. Jack BW, Chetty VK, Anthony D, et al. A reengineered hospital discharge program to decrease rehospitalization: a randomized trial. *Annals of internal medicine.* Feb 3 2009;150(3):178-187.

177. Legrain S, Tubach F, Bonnet-Zamponi D, et al. A new multimodal geriatric discharge-planning intervention to prevent emergency visits and rehospitalizations of older adults: the optimization of medication in AGEd multicenter randomized controlled trial. *Journal of the American Geriatrics Society.* Nov 2011;59(11):2017-2028.

178. Naylor MD, Brooten D, Campbell R, et al. Comprehensive discharge planning and home follow-up of hospitalized elders: a randomized clinical trial. *JAMA : the journal of the American Medical Association.* Feb 17 1999;281(7):613-620.

179. Shepperd S, Lannin NA, Clemson LM, McCluskey A, Cameron ID, Barras SL. Discharge planning from hospital to home. *Cochrane Database Syst Rev.* 2013;1:Cd000313.

180. Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. *Archives of internal medicine.* Sep 25 2006;166(17):1822-1828.

181. Courtney M, Edwards H, Chang A, Parker A, Finlayson K, Hamilton K. Fewer emergency readmissions and better quality of life for older adults at risk of

hospital readmission: a randomized controlled trial to determine the effectiveness of a 24-week exercise and telephone follow-up program. *Journal of the American Geriatrics Society.* Mar 2009;57(3):395-402.

182.   Graves N, Courtney M, Edwards H, Chang A, Parker A, Finlayson K. Cost-effectiveness of an intervention to reduce emergency re-admissions to hospital among older patients. *PloS one.* 2009;4(10):e7455.

183.   Paquin AM, Salow M, Rudolph JL. Pharmacist Calls to Older Adults with Cognitive Difficulties After Discharge in a Tertiary Veterans Administration Medical Center: A Quality Improvement Program. *Journal of the American Geriatrics Society.* Mar 2 2015.

184.   Harrison JD, Auerbach AD, Quinn K, Kynoch E, Mourad M. Assessing the impact of nurse post-discharge telephone calls on 30-day hospital readmission rates. *Journal of general internal medicine.* Nov 2014;29(11):1519-1525.

185.   Harrison PL, Hara PA, Pope JE, Young MC, Rula EY. The impact of postdischarge telephonic follow-up on hospital readmissions. *Population health management.* Feb 2011;14(1):27-32.

186.   Mistiaen P, Poot E. Telephone follow-up, initiated by a hospital-based health professional, for postdischarge problems in patients discharged from hospital to home. *Cochrane Database Syst Rev.* 2006(4):Cd004510.

187.   Witherington EM, Pirzada OM, Avery AJ. Communication gaps and readmissions to hospital for patients aged 75 years and older: observational study. *Quality & safety in health care.* Feb 2008;17(1):71-75.

188.   Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. *JAMA : the journal of the American Medical Association.* Feb 28 2007;297(8):831-841.

189.   Rytter L, Jakobsen HN, Ronholt F, et al. Comprehensive discharge follow-up in patients' homes by GPs and district nurses of elderly patients. A randomized controlled trial. *Scandinavian journal of primary health care.* Sep 2010;28(3):146-153.

190.   Feldman HH, Jacova C, Robillard A, et al. Diagnosis and treatment of dementia: 2. Diagnosis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Mar 25 2008;178(7):825-836.

191.   Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* Sep 2012;19(9):1159-1179.

192.   Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* Jan 2007;14(1):e1-26.

193.   Holzer S, Warner JP, Iliffe S. Diagnosis and management of the patient with suspected dementia in primary care. *Drugs & aging.* Sep 2013;30(9):667-676.

194.   Statens beredning för medicinsk utvärdering (SBU). *Demenssjukdomar - en systematisk litteraturöversikt.* SBU rapport 172. Stockholm 2006.

195. Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. *Journal of neurology, neurosurgery, and psychiatry.* Oct 2002;73(4):390-394.

196. Scheltens P, Fox N, Barkhof F, De Carli C. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet neurology.* May 2002;1(1):13-21.

197. Bhogal P, Mahoney C, Graeme-Baker S, et al. The common dementias: a pictorial review. *European radiology.* Dec 2013;23(12):3405-3417.

198. Wattjes MP, Henneman WJ, van der Flier WM, et al. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64-detector row CT. *Radiology.* Oct 2009;253(1):174-183.

199. Poggesi A, Pantoni L, Inzitari D, et al. 2001-2011: A Decade of the LADIS (Leukoaraiosis And DISability) Study: What Have We Learned about White Matter Changes and Small-Vessel Disease? *Cerebrovascular diseases (Basel, Switzerland).* 2011;32(6):577-588.

200. Inzitari D, Pracucci G, Poggesi A, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *Bmj.* 2009;339:b2477.

201. Inzitari D, Simoni M, Pracucci G, et al. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: the LADIS study. *Archives of internal medicine.* Jan 8 2007;167(1):81-88.

202. Jokinen H, Kalska H, Ylikoski R, et al. Longitudinal cognitive decline in subcortical ischemic vascular disease--the LADIS Study. *Cerebrovascular diseases (Basel, Switzerland).* 2009;27(4):384-391.

203. Verdelho A, Madureira S, Moleiro C, et al. White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology.* Jul 13 2010;75(2):160-167.

204. van der Flier WM, van Straaten EC, Barkhof F, et al. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke; a journal of cerebral circulation.* Oct 2005;36(10):2116-2120.

205. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ.* 2010;341:c3666.

206. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR. American journal of roentgenology.* Aug 1987;149(2):351-356.

207. Jokinen H, Lipsanen J, Schmidt R, et al. Brain atrophy accelerates cognitive decline in cerebral small vessel disease: the LADIS study. *Neurology.* May 29 2012;78(22):1785-1792.

208. Mungas D, Reed BR, Jagust WJ, et al. Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. *Neurology.* Sep 24 2002;59(6):867-873.

209. Smith EE, Egorova S, Blacker D, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Archives of neurology.* Jan 2008;65(1):94-100.

210. Henneman WJ, Sluimer JD, Cordonnier C, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. *Stroke; a journal of cerebral circulation.* Feb 2009;40(2):492-498.

211. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. *European neurology.* 1996;36(5):268-272.

212. Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. *Neurology.* Apr 12 1999;52(6):1153-1158.

213. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* May 2011;7(3):263-269.

214. Burton EJ, Barber R, Mukaetova-Ladinska EB, et al. Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. *Brain : a journal of neurology.* Jan 2009;132(Pt 1):195-203.

215. Jokinen H, Kalska H, Ylikoski R, et al. Medial temporal lobe atrophy and memory deficits in elderly stroke patients. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* Dec 2004;11(12):825-832.

216. Kim YS, Lee KM, Choi BH, Sohn EH, Lee AY. Relation between the clock drawing test (CDT) and structural changes of brain in dementia. *Archives of gerontology and geriatrics.* Mar-Apr 2009;48(2):218-221.

217. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *Journal of neurology, neurosurgery, and psychiatry.* Oct 1992;55(10):967-972.

218. Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology.* Jul 13 2004;63(1):94-100.

219. Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J. Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *Journal of neurology, neurosurgery, and psychiatry.* Apr 2002;72(4):491-497.

220. Cavallin L, Bronge L, Zhang Y, et al. Comparison between visual assessment of MTA and hippocampal volumes in an elderly, non-demented population. *Acta radiologica.* Jun 1 2012;53(5):573-579.

221. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *Journal of neurology.* Sep 1995;242(9):557-560.

222. Scheltens P, Pasquier F, Weerts JG, Barkhof F, Leys D. Qualitative assessment of cerebral atrophy on MRI: inter- and intra-observer reproducibility in dementia and normal aging. *European neurology.* 1997;37(2):95-99.

223. Scheltens P, van de Pol L. Impact commentaries. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic

value and neuropsychological correlates. *Journal of neurology, neurosurgery, and psychiatry.* Nov 2012;83(11):1038-1040.

224. Hirano LA, Bogardus ST, Jr., Saluja S, Leo-Summers L, Inouye SK. Clinical yield of computed tomography brain scans in older general medical patients. *Journal of the American Geriatrics Society.* Apr 2006;54(4):587-592.

225. Tung C, Lindgren A, Siemund R, van Westen D. Emergency room decision-making for urgent cranial computed tomography: selection criteria for subsets of non-trauma patients. *Acta radiologica.* Sep 23 2013.

226. Hardy JE, Brennan N. Computerized tomography of the brain for elderly patients presenting to the emergency department with acute confusion. *Emergency medicine Australasia : EMA.* Oct 2008;20(5):420-424.

227. Lai MM, Wong Tin Niam DM. Intracranial cause of delirium: computed tomography yield and predictive factors. *Internal medicine journal.* Apr 2012;42(4):422-427.

228. Hufschmidt A, Shabarin V. Diagnostic yield of cerebral imaging in patients with acute confusion. *Acta neurologica Scandinavica.* Oct 2008;118(4):245-250.

229. Soiza RL, Sharma V, Ferguson K, Shenkin SD, Seymour DG, Maclullich AM. Neuroimaging studies of delirium: a systematic review. *Journal of psychosomatic research.* Sep 2008;65(3):239-248.

230. Covinsky KE, Palmer RM, Fortinsky RH, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. *Journal of the American Geriatrics Society.* Apr 2003;51(4):451-458.

231. McVey LJ, Becker PM, Saltz CC, Feussner JR, Cohen HJ. Effect of a geriatric consultation team on functional status of elderly hospitalized patients. A randomized, controlled clinical trial. *Annals of internal medicine.* Jan 1 1989;110(1):79-84.

232. Sager MA, Franke T, Inouye SK, et al. Functional outcomes of acute medical illness and hospitalization in older persons. *Archives of internal medicine.* Mar 25 1996;156(6):645-652.

233. Sands LP, Yaffe K, Covinsky K, et al. Cognitive screening predicts magnitude of functional recovery from admission to 3 months after discharge in hospitalized elders. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Jan 2003;58(1):37-45.

234. Sands LP, Yaffe K, Lui LY, Stewart A, Eng C, Covinsky K. The effects of acute illness on ADL decline over 1 year in frail older adults with and without cognitive impairment. *The journals of gerontology. Series A, Biological sciences and medical sciences.* Jul 2002;57(7):M449-454.

235. Calkins DR, Rubenstein LV, Cleary PD, et al. Failure of physicians to recognize functional disability in ambulatory patients. *Annals of internal medicine.* Mar 15 1991;114(6):451-454.

236. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. STUDIES OF ILLNESS IN THE AGED. THE INDEX OF ADL: A STANDARDIZED MEASURE OF BIOLOGICAL AND PSYCHOSOCIAL FUNCTION. *JAMA : the journal of the American Medical Association.* Sep 21 1963;185:914-919.

237. Mahoney FI, Barthel DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Maryland state medical journal.* Feb 1965;14:61-65.

238. Buurman BM, van Munster BC, Korevaar JC, de Haan RJ, de Rooij SE. Variability in measuring (instrumental) activities of daily living functioning and functional decline in hospitalized older medical patients: a systematic review. *Journal of clinical epidemiology.* Jun 2011;64(6):619-627.

239. Quinn TJ, McArthur K, Ellis G, Stott DJ. Functional assessment in older people. *BMJ.* 2011;343:d4681.

240. Sherman SE, Reuben D. Measures of functional status in community-dwelling elders. *Journal of general internal medicine.* Dec 1998;13(12):817-823.

241. Magaziner J, Zimmerman SI, Gruber-Baldini AL, Hebel JR, Fox KM. Proxy reporting in five areas of functional status. Comparison with self-reports and observations of performance. *American journal of epidemiology.* Sep 1 1997;146(5):418-428.

242. Greysen SR, Stijacic Cenzer I, Auerbach AD, Covinsky KE. Functional Impairment and Hospital Readmission in Medicare Seniors. *JAMA internal medicine.* Feb 2 2015.

243. Laniece I, Couturier P, Drame M, et al. Incidence and main factors associated with early unplanned hospital readmission among French medical inpatients aged 75 and over admitted through emergency units. *Age and ageing.* Jul 2008;37(4):416-422.

244. Depalma G, Xu H, Covinsky KE, et al. Hospital readmission among older adults who return home with unmet need for ADL disability. *The Gerontologist.* Jun 2013;53(3):454-461.

245. Sands LP, Wang Y, McCabe GP, Jennings K, Eng C, Covinsky KE. Rates of acute care admissions for frail older people living with met versus unmet activity of daily living needs. *Journal of the American Geriatrics Society.* Feb 2006;54(2):339-344.

246. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA : the journal of the American Medical Association.* Jun 20 2001;285(23):2987-2994.

247. Smith AK, Walter LC, Miao Y, Boscardin WJ, Covinsky KE. Disability during the last two years of life. *JAMA internal medicine.* Sep 9 2013;173(16):1506-1513.

248. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional Trajectories Among Older Persons Before and After Critical Illness. *JAMA internal medicine.* Feb 9 2015.

249. Covinsky KE, Justice AC, Rosenthal GE, Palmer RM, Landefeld CS. Measuring prognosis and case mix in hospitalized elders. The importance of functional status. *Journal of general internal medicine.* Apr 1997;12(4):203-208.

250. Han PK, Lee M, Reeve BB, et al. Development of a prognostic model for six-month mortality in older adults with declining health. *Journal of pain and symptom management.* Mar 2012;43(3):527-539.

251. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA : the journal of the American Medical Association.* Apr 15 1998;279(15):1187-1193.

252. Teno JM, Harrell FE, Jr., Knaus W, et al. Prediction of survival for older hospitalized patients: the HELP survival model. Hospitalized Elderly Longitudinal Project. *Journal of the American Geriatrics Society.* May 2000;48(5 Suppl):S16-24.

253. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of clinical epidemiology.* Jan 2007;60(1):34-42.

254. Hickey A, Barker M, McGee H, O'Boyle C. Measuring health-related quality of life in older patient populations: a review of current approaches. *PharmacoEconomics.* 2005;23(10):971-993.

255. Feinstein AR. Clinimetric perspectives. *Journal of chronic diseases.* 1987;40(6):635-640.

256. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Social science & medicine (1982).* Nov 1995;41(10):1403-1409.

257. Taillefer MC, Dupuis G, Roberge M, Lemay S. Health-related Quality of Life Models: Systematic review of the literature. *Social Indicators Research.* 2003;64:293-323.

258. McKee KJ, Houston DM, Barnes S. Methods for Assessing Quality of Life and Well-Being in Frail Older People. *Psychology&Health.* 2002;17(6):737-751.

259. Farquhar M. Elderly people's definitions of quality of life. *Social science & medicine (1982).* Nov 1995;41(10):1439-1446.

260. Statens beredning för medicinsk utvärdering (SBU). Svårt men viktigt att mäta livskvalitet. *Medicinsk vetenskap och Praxis* 2012:1-3.

261. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Annals of medicine.* Jul 2001;33(5):337-343.

262. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* Dec 1990;16(3):199-208.

263. Brooks RG, Jendteg S, Lindgren B, Persson U, Bjork S. EuroQol: health-related quality of life measurement. Results of the Swedish questionnaire exercise. *Health Policy.* Jun 1991;18(1):37-48.

264. Ankri J, Beaufils B, Novella JL, et al. Use of the EQ-5D among patients suffering from dementia. *Journal of clinical epidemiology.* Nov 2003;56(11):1055-1063.

265. Philbin EF, Dec GW, Jenkins PL, DiSalvo TG. Socioeconomic status as an independent risk factor for hospital readmission for heart failure. *The American journal of cardiology.* Jun 15 2001;87(12):1367-1371.

266. Malmö stad. *Välfärdsredovisning 2010.* http://redovisningar.malmo.se/arkiv/ Malmö 2010.

267. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases.* 1987;40(5):373-383.

268. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. *Journal of clinical epidemiology.* Mar 2003;56(3):221-229.

269. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, van Munster BC, de Rooij SE. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly

adults: a prospective cohort study. *Journal of the American Geriatrics Society.* Feb 2014;62(2):342-346.

270. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American journal of epidemiology.* Mar 15 2011;173(6):676-682.

271. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research.* Nov 1975;12(3):189-198.

272. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. *International journal of geriatric psychiatry.* Feb 2010;25(2):111-120.

273. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society.* Sep 1992;40(9):922-935.

274. Bravo G, Hebert R. Age- and education-specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population. *International journal of geriatric psychiatry.* Oct 1997;12(10):1008-1018.

275. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of psychiatric research.* Jan 2009;43(4):411-431.

276. Ringdal GI, Ringdal K, Juliebo V, Wyller TB, Hjermstad MJ, Loge JH. Using the Mini-Mental State Examination to screen for delirium in elderly patients with hip fracture. *Dementia and geriatric cognitive disorders.* 2011;32(6):394-400.

277. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. *JAMA : the journal of the American Medical Association.* Aug 18 2010;304(7):779-786.

278. Jackson TA, Naqvi SH, Sheehan B. Screening for dementia in general hospital inpatients: a systematic review and meta-analysis of available instruments. *Age and ageing.* Nov 2013;42(6):689-695.

279. Mitchell AJ, Shukla D, Ajumal HA, Stubbs B, Tahir TA. The Mini-Mental State Examination as a diagnostic and screening test for delirium: systematic review and meta-analysis. *General hospital psychiatry.* Nov-Dec 2014;36(6):627-633.

280. Pinto E, Peters R. Literature review of the Clock Drawing Test as a tool for cognitive screening. *Dementia and geriatric cognitive disorders.* 2009;27(3):201-213.

281. Mainland BJ, Amodeo S, Shulman KI. Multiple clock drawing scoring systems: simpler is better. *International journal of geriatric psychiatry.* Feb 2014;29(2):127-136.

282. Shulman KI. Clock-drawing: is it the ideal cognitive screening test? *International journal of geriatric psychiatry.* Jun 2000;15(6):548-561.

283. Peters R, Pinto EM. Predictive value of the Clock Drawing Test. A review of the literature. *Dementia and geriatric cognitive disorders.* 2008;26(4):351-355.

284. Adamis D, Morrison C, Treloar A, Macdonald AJ, Martin FC. The performance of the Clock Drawing Test in elderly medical inpatients: does it have utility in the identification of delirium? *Journal of geriatric psychiatry and neurology.* Sep 2005;18(3):129-133.

285. Death J, Douglas A, Kenny RA. Comparison of clock drawing with Mini Mental State Examination as a screening test in elderly acute hospital admissions. *Postgraduate medical journal.* Sep 1993;69(815):696-700.

286. Manos PJ. The utility of the ten-point clock test as a screen for cognitive impairment in general hospital patients. *General hospital psychiatry.* Nov 1997;19(6):439-444.

287. Manos PJ, Wu R. The ten point clock test: a quick screen and grading method for cognitive impairment in medical and surgical patients. *International journal of psychiatry in medicine.* 1994;24(3):229-244.

288. Gottfries CG, Brane G, Gullberg B, Steen G. A new rating scale for dementia syndromes. *Archives of gerontology and geriatrics.* Dec 1982;1(4):311-330.

289. Dencker K, Gottfries CG. Activities of daily living ratings of elderly people using Katz' ADL Index and the GBS-M scale. *Scandinavian journal of caring sciences.* 1995;9(1):35-40.

290. Brane G, Gottfries CG, Winblad B. The Gottfries-Brane-Steen scale: validity, reliability and application in anti-dementia drug trials. *Dementia and geriatric cognitive disorders.* Jan-Feb 2001;12(1):1-14.

291. Logsdon R, L.E. G, McCurry SM, Teri L. Quality of Life in Alzheimer's Disease: Patient and Caregiver Reports. *Journal of Mental Health and Aging.* 1999;5(1):21-32.

292. Bosboom PR, Alfonso H, Eaton J, Almeida OP. Quality of life in Alzheimer's disease: different factors associated with complementary ratings by patients and family carers. *International psychogeriatrics / IPA.* May 2012;24(5):708-721.

293. Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, Londos E. Quality of life and the effect of memantine in dementia with lewy bodies and Parkinson's disease dementia. *Dementia and geriatric cognitive disorders.* 2011;32(4):227-234.

294. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. *Psychosomatic medicine.* May-Jun 2002;64(3):510-519.

295. Thorgrimsen L, Selwood A, Spector A, et al. Whose quality of life is it anyway? The validity and reliability of the Quality of Life-Alzheimer's Disease (QoL-AD) scale. *Alzheimer disease and associated disorders.* Oct-Dec 2003;17(4):201-208.

296. Leon-Salas B, Logsdon RG, Olazaran J, Martinez-Martin P, The M-A. Psychometric properties of the Spanish QoL-AD with institutionalized dementia patients and their family caregivers in Spain. *Aging & mental health.* Aug 2011;15(6):775-783.

297. Barrios H, Verdelho A, Narciso S, Goncalves-Pereira M, Logsdon R, de Mendonca A. Quality of life in patients with cognitive impairment: validation of the Quality of Life-Alzheimer's Disease scale in Portugal. *International psychogeriatrics / IPA.* Jul 2013;25(7):1085-1096.

298. Conde-Sala JL, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S, Vilalta-Franch J. Factors related to perceived quality of life in patients with Alzheimer's disease: the patient's perception compared with that of caregivers. *International journal of geriatric psychiatry.* Jun 2009;24(6):585-594.

299. Matsui T, Nakaaki S, Murata Y, et al. Determinants of the quality of life in Alzheimer's disease patients as assessed by the Japanese version of the Quality of

Life-Alzheimer's disease scale. *Dementia and geriatric cognitive disorders.* 2006;21(3):182-191.

300.   Novelli MM, Nitrini R, Caramelli P. Validation of the Brazilian version of the quality of life scale for patients with Alzheimer's disease and their caregivers (QOL-AD). *Aging & mental health.* Jul 2010;14(5):624-631.

301.   Wolak A, Novella JL, Drame M, et al. Transcultural adaptation and psychometric validation of a French-language version of the QoL-AD. *Aging & mental health.* Jul 2009;13(4):593-600.

302.   Bondesson A, Holmdahl L, Midlov P, Hoglund P, Andersson E, Eriksson T. Acceptance and importance of clinical pharmacists' LIMM-based recommendations. *International journal of clinical pharmacy.* Apr 2012;34(2):272-276.

303.   Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* Mar 2 2013;381(9868):752-762.

304.   Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *The New England journal of medicine.* Apr 2 2009;360(14):1418-1428.

305.   Dharmarajan K, Hsieh AF, Lin Z, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA : the journal of the American Medical Association.* Jan 23 2013;309(4):355-363.

306.   Riley GF, Lubitz JD. Long-term trends in Medicare payments in the last year of life. *Health services research.* Apr 2010;45(2):565-576.

307.   Emanuel EJ, Emanuel LL. The economics of dying. The illusion of cost savings at the end of life. *The New England journal of medicine.* Feb 24 1994;330(8):540-544.

308.   Teno JM, Gozalo PL, Bynum JP, et al. Change in end-of-life care for Medicare beneficiaries: site of death, place of care, and health care transitions in 2000, 2005, and 2009. *JAMA : the journal of the American Medical Association.* Feb 6 2013;309(5):470-477.

309.   Gozalo P, Teno JM, Mitchell SL, et al. End-of-life transitions among nursing home residents with cognitive issues. *The New England journal of medicine.* Sep 29 2011;365(13):1212-1221.

310.   Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *The New England journal of medicine.* Oct 15 2009;361(16):1529-1538.

311.   Somogyi-Zalud E, Zhong Z, Hamel MB, Lynn J. The use of life-sustaining treatments in hospitalized persons aged 80 and older. *Journal of the American Geriatrics Society.* May 2002;50(5):930-934.

312.   Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA : the journal of the American Medical Association.* Oct 8 2008;300(14):1665-1673.

313.   Heyland DK, Barwich D, Pichora D, et al. Failure to engage hospitalized elderly patients and their families in advance care planning. *JAMA internal medicine.* May 13 2013;173(9):778-787.

314.   Emanuel EJ. Cost savings at the end of life. What do the data show? *JAMA : the journal of the American Medical Association.* Jun 26 1996;275(24):1907-1914.

315. Nicholas LH, Langa KM, Iwashyna TJ, Weir DR. Regional variation in the association between advance directives and end-of-life Medicare expenditures. *JAMA : the journal of the American Medical Association.* Oct 5 2011;306(13):1447-1453.

316. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ.* 2010;340:c1345.

317. Chen TY, Anderson DJ, Chopra T, Choi Y, Schmader KE, Kaye KS. Poor functional status is an independent predictor of surgical site infections due to methicillin-resistant Staphylococcus aureus in older adults. *Journal of the American Geriatrics Society.* Mar 2010;58(3):527-532.

318. Rao K, Micic D, Chenoweth E, et al. Poor functional status as a risk factor for severe Clostridium difficile infection in hospitalized older adults. *Journal of the American Geriatrics Society.* Oct 2013;61(10):1738-1742.

319. Revell AJ, Caskie GI, Willis SL, Schaie KW. Factor structure and invariance of the Quality of Life in Alzheimer's Disease (QoL-AD) Scale. *Experimental aging research.* Apr-Jun 2009;35(2):250-267.

320. Caballero FF, Miret M, Power M, et al. Validation of an instrument to evaluate quality of life in the aging population: WHOQOL-AGE. *Health and quality of life outcomes.* 2013;11:177.

321. Shenkin SD, Russ TC, Ryan TM, MacLullich AM. Screening for dementia and other causes of cognitive impairment in general hospital in-patients. *Age and ageing.* Mar 2014;43(2):166-168.

322. Hakim RB, Teno JM, Harrell Jr FE, et al. Factors Associated with Do-Not-Resuscitate Orders: Patients' Preferences, Prognoses, and Physicians' Judgments. *Annals of internal medicine.* 1996;125(4):284-293.

323. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *The Lancet. Oncology.* Apr 2012;13(4):e148-160.

324. Anthony JC, LeResche L, Niaz U, von Korff MR, Folstein MF. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. *Psychological medicine.* May 1982;12(2):397-408.

325. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in medicine.* Feb 28 1996;15(4):361-387.

326. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *Journal of clinical epidemiology.* Dec 1995;48(12):1503-1510.

327. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Statistics in medicine.* Jan 15 2006;25(1):127-141.

328. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *Journal of clinical epidemiology.* Oct 2006;59(10):1087-1091.

329. Janssen KJ, Donders AR, Harrell FE, Jr., et al. Missing covariate data in medical research: to impute is better than to ignore. *Journal of clinical epidemiology.* Jul 2010;63(7):721-727.

330. Harrell Jr FE. *Regression Modeling Strategies - With Applications to Linear Models, Logistic Regression, and Survival Analysis.* New York: Springer-Verlag; 2001.

331. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *Journal of clinical epidemiology.* Aug 2001;54(8):774-781.

332. Bouwmeester W, Zuithoff NP, Mallett S, et al. Reporting and methods in clinical prediction research: a systematic review. *PLoS medicine.* 2012;9(5):1-12.

333. Concato J, Feinstein AR, Holford TR. The Risk of Determining Risk with Multivariable Models. *Annals of internal medicine.* 1993;118(3):201-210.

334. Moss M, Wellman DA, Cotsonis GA. An appraisal of multivariable logistic models in the pulmonary and critical care literature. *Chest.* Mar 2003;123(3):923-928.

335. Ottenbacher KJ, Ottenbacher HR, Tooth L, Ostir GV. A review of two journals found that articles using multivariable logistic regression frequently did not report commonly recommended assumptions. *Journal of clinical epidemiology.* Nov 2004;57(11):1147-1152.

336. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Bmj.* 2015;350:g7594.

337. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* Jul 7 2012;380(9836):37-43.

338. Brettschneider C, Leicht H, Bickel H, et al. Relative impact of multimorbid chronic conditions on health-related quality of life--results from the MultiCare Cohort Study. *PloS one.* 2013;8(6):e66742.

339. Garin N, Olaya B, Moneta MV, et al. Impact of multimorbidity on disability and quality of life in the spanish older population. *PloS one.* 2014;9(11):e111498.

340. Heyworth IT, Hazell ML, Linehan MF, Frank TL. How do common chronic conditions affect health-related quality of life? *The British journal of general practice : the journal of the Royal College of General Practitioners.* Nov 2009;59(568):e353-358.

341. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing research reviews.* Sep 2011;10(4):430-439.

342. Mujica-Mota RE, Roberts M, Abel G, et al. Common patterns of morbidity and multi-morbidity and their impact on health-related quality of life: evidence from a national survey. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* Oct 26 2014.

343. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA : the journal of the American Medical Association.* Aug 10 2005;294(6):716-724.

344. Dumbreck S, Flynn A, Nairn M, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *Bmj.* 2015;350:h949.

345. Salisbury C. Multimorbidity: redesigning health care for people who use it. *Lancet.* Jul 7 2012;380(9836):7-9.

346. Batsch NL, Mittelman MS. *World Alzheimer report 2012: Overcoming the stigma of dementia.* London: Alzheimer's Disease International;2012.

347. Gove D, Downs M, Vernooij-Dassen M, Small N. Stigma and GPs' perceptions of dementia. *Aging & mental health.* Mar 13 2015:1-10.

348. Vernooij-Dassen MJ, Moniz-Cook ED, Woods RT, et al. Factors affecting timely recognition and diagnosis of dementia across Europe: from awareness to stigma. *International journal of geriatric psychiatry.* Apr 2005;20(4):377-386.

349. Corrigan P. How stigma interferes with mental health care. *The American psychologist.* Oct 2004;59(7):614-625.

350. Tullo ES, Gordon AL. Teaching and learning about dementia in UK medical schools: a national survey. *BMC geriatrics.* 2013;13:29.

351. Turner S, Iliffe S, Downs M, et al. General practitioners' knowledge, confidence and attitudes in the diagnosis and management of dementia. *Age and ageing.* Sep 2004;33(5):461-467.

352. Olafsdottir M, Foldevi M, Marcusson J. Dementia in primary care: why the low detection rate? *Scandinavian journal of primary health care.* Sep 2001;19(3):194-198.

353. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer disease and associated disorders.* Oct-Dec 2009;23(4):306-314.

354. Burns A. The benefits of early diagnosis of dementia. *Bmj.* 2012;344:e3556.

355. Burns A. Alistair Burns and 51 colleagues reply to David Le Couteur and colleagues. *Bmj.* 2013;347:f6125.

356. prince M, Bryce R, Ferri CP. *World Alzheimer report 2011 - The benefits of early diagnosis and intervention.* Alzheimer's Disease International;2011.

357. Jha A, Tabet N, Orrell M. To tell or not to tell-comparison of older patients' reaction to their diagnosis of dementia and depression. *International journal of geriatric psychiatry.* Sep 2001;16(9):879-885.

358. Brunet MD. Dementia statistic is misleading. *Bmj.* 2013;347:f6704.

359. Le Couteur DG, Doust J, Creasey H, Brayne C. Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis. *Bmj.* 2013;347:f5125.

360. Sharvill NJ. What are the benefits of an early diagnosis? *Bmj.* 2012;344:e2747.

361. Svensk förening för allmänmedicin (SFAM). *Onödiga eller skadliga åtgärder i svensk allmänmedicin - ett diskussionunderlag.* Stockholm 2014.

362. Rudebeck CE, Gustafsson T, Hovelius B, Sjonell G. [In Process Citation]. *Lakartidningen.* 2015;112.

363. Pentzek M, Wollny A, Wiese B, et al. Apart from nihilism and stigma: what influences general practitioners' accuracy in identifying incident dementia? *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Nov 2009;17(11):965-975.

364. Hansen EC, Hughes C, Routley G, Robinson AL. General practitioners' experiences and understandings of diagnosing dementia: factors impacting on early diagnosis. *Social science & medicine (1982).* Dec 2008;67(11):1776-1783.
365. Holland JC. History of psycho-oncology: overcoming attitudinal and conceptual barriers. *Psychosomatic medicine.* Mar-Apr 2002;64(2):206-221.
366. Chuang KH, Covinsky KE, Sands LP, Fortinsky RH, Palmer RM, Landefeld CS. Diagnosis-related group-adjusted hospital costs are higher in older medical patients with lower functional status. *Journal of the American Geriatrics Society.* Dec 2003;51(12):1729-1734.
367. Goffman E. *Stigma: Notes on the Management of Spoiled Identity.* Englewood cliffs, New Jersey: Prentice-Hall; 1963.
368. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *European heart journal.* Oct 2008;29(19):2388-2442.
369. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. *JAMA : the journal of the American Medical Association.* Jun 2 2010;303(21):2141-2147.
370. Regeringskansliet. *Den ljusnande framtid är vård - delresultat från LEV-projektet.* Stockholm 2010.
371. The Organisation for Economic Co-operation and Development (OECD). OECD Health Data. http://www.oecd.org/els/health-systems/health-data.htm.