

Depression in later life –  
The course of depression and depressive  
symptoms among the elderly in Norway

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## Table of Contents

Acknowledgements .....	4
“Study of a profile of an old man” by Leonardo da Vinci .....	6
Sammendrag .....	7
Abstract .....	10
List of papers .....	13
Abbreviations .....	14
Introduction.....	16
Background.....	18
Historical background of depression, later life, old age psychiatry, and nursing homes in Norway	18
Historical background of depression.....	18
What is later life, older/elderly person? .....	19
Old age psychiatry in Norway.....	20
Nursing homes in Norway .....	20
Definitions and classification of depression and depression in later life (DLL).....	22
How is depression classified? .....	22
Classification of depression in later life.....	26
Dementia and cognitive impairment .....	27
Dementia – definition, prevalence, diagnosis, and assessment scales.....	27
Mild cognitive impairment .....	30
Depression in later life (DLL) .....	31
Epidemiology of depression in later life (DLL).....	31
Etiology of depression in later life (DLL).....	32
Clinical picture of depression in later life (DLL).....	36
Depression, cognitive impairment and dementia.....	38
Depression in later life (DLL) and assessment scales. ....	41
Treatment of depression in later life (DLL) .....	45
Prognosis of depression in later life (DLL) .....	49
Tables with previous and relevant studies to the papers in the thesis.....	52
The studies in the thesis.....	61
Objectives.....	61
Design.....	61
Participants.....	62
Study 1, the MADRS validation study.....	62

Study 2, the PRODE study.....	62
Study 3, the PSIN study .....	64
Methods. ....	66
Study 1, Paper I:.....	66
Study 2, Paper II and III:.....	66
Study 3, Paper IV .....	69
Statistics .....	69
Paper I.....	69
Paper II.....	70
Paper III.....	70
Paper IV .....	71
Ethical and legal considerations.....	72
Study 1.....	72
Study 2.....	72
Study 3.....	72
Abstract of the papers with additional results.....	73
Paper I: The validity of the Montgomery–Aasberg depression rating scale as a screening tool for depression in later life.....	73
Paper II: The course of depression in later life as measured by the Montgomery and Asberg Depression Rating Scale in an observational study of hospitalized patients .....	74
Paper III: Clinical prognostic factors and trajectories of depression in late life.....	75
Additional results and relevant figures the from the one-year follow-up examination in PRODE76	
Paper IV: The course of depressive symptoms as measured by the Cornell Scale for Depression in Dementia over 74 months in 1158 nursing home residents.....	79
Discussion.....	80
Discussion of the main results.....	80
Issues related to the methods.....	87
Study 1.....	87
Study 2.....	87
Study 3.....	88
General considerations related to the methods.....	89
Implications .....	90
Future research .....	91
References:.....	93

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Aldring og helse  
Nasjonal kompetansetjeneste

**“Study of a profile of an old man” by Leonardo da Vinci**







## Sammendrag

Depresjon og depressive symptomer er vanlig blant eldre. Studier har vist at depresjon hos eldre (depression in later life [DLL]) er assosiert med økt forekomst av demens, dårlig livskvalitet, redusert funksjon i dagliglivet, institusjonalisering og økt forekomst av selvmord og generell dødelighet. DLL kan således ha alvorlige konsekvenser for den enkelte pasient og for samfunnet og utgjøre en global utfordring. Mange pasienter med DLL har et forløp med kroniske plager eller tilbakefall av depresjon.

### Avhandlingens mål

Hovedmålene i denne avhandlingen var å undersøke forløpet og prognostiske faktorer ved depresjon og depressive symptomer hos eldre. Avhandlingen inneholder fire artikler fra tre kliniske studier av DLL. I den første studien (Artikkel I) ønsket vi å undersøke gyldigheten av Montgomery and Asberg Depression Rating Scale (MADRS) brukt som et diagnostisk hjelpemiddel til å avdekke depresjon i en studiepopulasjon av eldre personer uten demens. Den andre studien, Prognosis of Depression in the Elderly (PRODE) er presentert i to artikler (Artikkel II og Artikkel III). I Artikkel II ønsket vi å undersøke forløpet av DLL hos inneliggende pasienter i spesialisthelsetjenesten i alderspsykiatri målt som respons (forbedring på 50% eller mer på MADRS), remisjon (MADRS < 10 ved utskrivning fra sykehuset) og symptom-spesifikke endringer ved bruk av MADRS. Vi ønsket videre å utforske hvordan kliniske faktorer forholdt seg til respons og remisjon. I Artikkel III brukte vi data fra ett-års oppfølgingen i PRODE-studien. I denne artikkelen undersøkte vi forløpet av DLL ved 1) å estimere ulike forløpsbaner («trajectories») basert på MADRS-skårer og 2) klinisk vurdering av forløpet etter utskrivning fra sykehuset. Vi så på hvordan ulike kliniske variabler målt ved oppholdet på alderspsykiatrisk avdeling var assosiert med forløpsbaner og klinisk forløp etter utskrivning. I den tredje studien, Psychiatric Symptoms in Nursing homes (PSIN), ønsket vi å undersøke langtidsforløpet av depressive symptomer målt ved Cornell Scale for Depression in Dementia (CSDD) og sammenhengen med kliniske variabler hos sykehjemsbeboere. Studien er publisert i Artikkel IV.

### Metode og resultater

Valideringsstudien av MADRS ble utført i henhold til anbefalinger for slike undersøkelser, dvs.: 1) med en kontrollgruppe uten sykdommen (DLL), 2) testen (MADRS) og gullstandard (DSM-IV) skal benyttes på alle deltagerne, 3) i en representativ studiepopulasjon for hvor testen skal bli brukt og 4) de kliniske vurderingene med test og gullstandard er utført «blindet» av hverandre. Studien inkluderte 140 deltagere, som alle ble undersøkt med MADRS og i henhold til DSM-IV kriteriene for depresjon.

Vi fant at arealet under kurven (AUC) var 0.86 (95% konfidensintervall [CI] 0.79-0.93) i en Receiver Operating Characteristic (ROC) analyse med DSM-IV som gullstandard. En terskelverdi på 16/17 på MADRS skilte best personer med depresjon fra personer uten depresjon, med en sensitivitet på 80% og spesifisitet på 82%. Halvparten av de 140 inkluderte pasientene ble undersøkt i henhold til ICD-10 kriteriene for depressiv episode. AUC var 0.92 (95% CI 0.85-1.0), og en terskelverdi på 13/14 på MADRS var best for å skille personer med depresjon fra de uten depresjon med en sensitivitet på

88% og spesifisitet på 88% når ICD-10 ble brukt som gullstandard.

I denne artikkelen konkluderte vi med at MADRS har god evne til å skille deprimerte fra ikke-deprimerte eldre uten demens.

PRODE-studien er en norsk, prospektiv, multisenter observasjonsstudie av pasienter 60 år eller eldre som er henvist til spesialisthelsetjenesten i alderspsykiatri for behandling av depresjon.

Helsearbeidere ved ni alderspsykiatriske avdelinger brukte de samme standardiserte kartleggings skjemaene til å samle inn informasjon om depresjon og psykisk helse, kognisjon, fysisk helse, demografi, bruk av medisiner og annen behandling og funksjonsevne for dagliglivets aktiviteter. PRODE-studien inkluderte 160 inneliggende pasienter.

Hundre og førtifem pasienter med utfylt MADRS både ved inklusjon i studien ( $T_0$ ) og ved utskrivning fra sykehuset ( $T_1$ ) ble inkludert i Artikkel II. Nittini pasienter (68.3%) hadde respons i løpet av oppholdet, og 74 (51.0%) var i remisjon da de ble utskrevet fra sykehuset. Vi beregnet effektstørrelsen (ES) for de enkelte MADRS symptomene for å se hvilket symptom som endret seg mest i løpet av oppholdet. «Tristhet» (ES=0.88) og «initiativløshet» (ES=0.80) bedret seg mest, og «konsentrasjonsvansker» (ES=0.50) bedret seg minst. I regresjonsanalysene fant vi at demensdiagnose var assosiert med mindre bedring av MADRS skår og lavere remisjonsrate. Dårligere fysisk helse var assosiert med lavere responsrate, og tidligere depressive episoder var assosiert med lavere remisjonsrate.

Av de 160 inkluderte pasientene i PRODE-studien, ønsket ikke syv å bli undersøkt ved oppfølgingsundersøkelsen etter ett år ( $T_2$ ) og syv var døde, dvs. 146 fullførte ett-års oppfølgingsstudien, og ble inkludert i analyser som er publisert i Artikkel III. I denne artikkelen brukte vi «growth mixture modeling» til å estimere om pasientene kunne deles inn i ulike forløpsbaner ut fra MADRS skår ved  $T_0$ ,  $T_1$  og  $T_2$ . Forløpet mellom  $T_1$  og  $T_2$  ble vurdert klinisk ved  $T_2$ . Dårlig klinisk forløp ble definert som kontinuerlig depresjon eller tilbakefall som medførte selvmordsforsøk eller reinleggelse på psykiatrisk sykehus.

Vi påviste to distinkte forløpsbaner: en med lavere MADRS skår (klasse A) og en med høyere MADRS skår (klasse B) ved måletidspunktene. Manglende remisjon ved  $T_1$  og lengre opphold i en alderspsykiatrisk sengeavdeling var assosiert med å tilhøre forløpsbanen med høyest MADRS skår (klasse B). En tredjedel av pasientene hadde dårlig klinisk forløp mellom  $T_1$  og  $T_2$ . Tidlig (<60 år) debut av første depresjon i livet (early-onset depression [EOD]) var assosiert med høyere odds for å være i en forløpsgruppe med et klinisk dårligere forløp.

Fra resultatene i PRODE studien konkluderte vi med at tidligere depressive episoder, demensdiagnose og dårlig somatisk helse var negative prognostiske faktorer for depressiv episode blant eldre (Artikkel II) og manglende remisjon ved utskrivelse fra alderspsykiatrisk sengeavdeling og EOD var negative prognostiske faktorer for forløpet av DLL over tid (Artikkel III). Klinikere bør være oppmerksomme på disse faktorene ved oppfølging av pasienter med DLL.

Den tredje studien (Artikkel IV) i denne avhandlingen var del av en større sykehjemstudie (PSIN) som undersøkte atferdsmessige og psykiske symptomer, spesielt depressive, blant sykehjemsbeboere. Vi undersøkte forløpet av depressive symptomer målt ved CSDD over 74 måneder blant 1158 sykehjemsbeboere 50 år eller eldre fra 26 sykehjem i Norge. Seksten studiesykepleiere samlet inn data ved å bruke et standardisert intervju på fem ulike tidspunkt i oppfølgingsperioden. «Irritabilitet»

var det symptomet på CSDD som var mest prevalent (forekommende), insident (ny forekommende) og persistent (vedvarende). Sammenlignet med den første undersøkelsen («baseline»), var det lavere sannsynlighet for at CSDD symptomene «suicidalitet,» «pessimisme» og «depressive vrangforestillinger» var til stede ved de påfølgende undersøkelsene. Denne sammenhengen var til stede også etter å ha justert for grad av demens. Alvorlighetsgraden av depresjon målt ved CSDD over 74 måneder avtok når vi justerte for kliniske variabler (alder, liggetid i sykehjem, kjønn, utdanning, sivilstatus, somatisk helse, alvorlighetsgrad av demens, funksjonsevne i personlige aktiviteter i dagliglivet, bruk av antidepressiva og antall medisiner). Dårligere somatisk helse, bruk av flere medisiner, mer alvorlig grad av demens og bruk av antidepressiva var assosiert med høyere depresjonsskår på CSDD.

Vi konkluderte med at denne studien tilfører viktig kunnskap om langtidsforløpet av depresjon og depressive symptomer blant sykehjemsbeboere og understreker viktigheten av å vurdere symptomer på depresjon i sammenheng med demens i denne populasjonen.



## Abstract

Depression and depressive symptoms are common in the elderly. Studies have shown that depression in later life (DLL) is associated with increased prevalence of dementia, poorer quality of life, considerable functional disability, risk for institutionalization, higher risk of suicide, and overall mortality. Thus, DLL can have vast consequences for the individual patient and society, posing a global challenge. For a substantial proportion of patients with DLL the prognosis can be poor in terms of residual symptoms, chronic course, and relapses.

### Aims of the thesis

The overall aims of this thesis were to study the course and prognostic factors of depression and depressive symptoms in the elderly. The thesis includes four papers from three clinical studies of DLL. In the first study (Paper I), we investigated the validity of the Montgomery and Asberg Depression Rating Scale (MADRS) used as a screening tool to detect a depressive disorder in an elderly study population without dementia. The second study, the Prognosis of Depression in the Elderly (PRODE) study, includes two papers (Paper II and Paper III). In Paper II we investigated the course of DLL in terms of response (50% or more improvement of the MADRS score), remission (MADRS < 10 at discharge from the hospital) and symptom-specific changes as measured by the MADRS in patients during their stay in the hospital at specialist health care services for old age psychiatry. We further explored which clinical variables were associated with remission and response. In Paper III we used data from the one-year follow-up assessment of the PRODE study. In this paper we investigated the course of DLL with outcomes such as trajectory class and relapse and explored which clinical variables were associated with the outcomes. In Paper IV from the third study, the Psychiatric Symptoms in Nursing homes (PSIN) study, we investigated the long-term course of depressive symptoms as measured by the Cornell Scale for Depression in Dementia (CSDD) and associated clinical variables among nursing home residents.

### Methods and results

The validation study of the MADRS was carried out according to the recommendations for such studies including I) a control group without the target disorder (depression), II) the test (the MADRS) and the reference standard (the DSM-IV) were applied to all participants, III) a representative clinical setting where the test will be used, and IV) independent assessments ("blinded"). Paper I included 140 participants and all were examined according to the MADRS and the DSM-IV criteria for major depressive disorder. Using the DSM-IV criteria, the area under the curve (AUC) in a Receiver Operating Characteristic analysis (ROC) was 0.86 (95% confidence interval [CI] 0.79-0.93). The best MADRS cut-off value for a diagnosis of major depressive disorder was 16/17, with a sensitivity of 80% and specificity of 82%. Half of the included 140 patients were also examined according to the ICD-10 criteria for a depressive episode. Using the ICD-10, the AUC was 0.92 (95% CI 0.85-1.0). The best MADRS cut-off value for a depressive episode was 13/14, with a sensitivity of 88% and specificity of 88%.

We concluded that the MADRS has good discriminating power to detect a depressive disorder in elderly persons without dementia.

The PRODE study is an observational, multicenter and prospective study of patients aged 60 years and older who were referred to treatment of depression in the department of old age psychiatry at specialist health care services in Norway. Health professionals working in nine departments of old age psychiatry used the same standardized instruments to collect data on depression and other mental health issues, cognition, physical health, demographic information, use of medications and other treatments, and functions in daily living. The PRODE study included 160 inpatients.

Paper II included 145 inpatients with MADRS both at inclusion to the study ( $T_0$ ) and at discharge from the hospital ( $T_1$ ). Of the 145 patients, 99 (68.3%) responded to treatment during their stay in the hospital. Remission was experienced in 74 (51.0%) of the patients. Effect size (ES) was calculated to determine which individual MADRS symptoms changed most during stay in the hospital. "Reported sadness" (ES = 0.88) and "lassitude" (ES = 0.80) showed the greatest amount of improvement, and "concentration difficulties" (ES = 0.50) showed the least amount of improvement during treatment. Having a diagnosis of dementia was associated with less improvement in the MADRS score and a lower remission rate during the treatment. Poorer physical health was associated with a lower response rate. Having experienced previous episode(s) of depression was associated with a lower remission rate.

Of the 160 inpatients included in the PRODE study, seven had died and seven were unwilling to be assessed at the one-year follow-up ( $T_2$ ), leaving 146 patients completing  $T_2$ . In Paper III, we applied growth mixture modeling to identify trajectories from the PRODE study's junctures:  $T_0$ ,  $T_1$ , and  $T_2$ . At  $T_2$ , the patients' course of depression from  $T_1$  to  $T_2$  was rated clinically by the participating centers using all available information.

We identified two distinct trajectory classes: one with lower MADRS scores (class A) and one with higher MADRS scores (Class B). Not being in remission at  $T_1$  and a longer stay in the hospital were associated with higher odds of being in the trajectory class with a poorer outcome (class B). About one-third of the completers had a clinically poor depression course between  $T_1$  and  $T_2$ , using a strict definition of poor course, i.e., rating of continuous depression or reports of relapse or recurrence that required hospital admission or involved a suicide attempt. Early onset (<60 years) of the first lifetime depression (EOD) was associated with higher odds of being in a group with a clinically poorer course between  $T_1$  and  $T_2$ .

Based on the results of the PRODE study we concluded that recurrent episodes of depression, poor physical health, and a diagnosis of dementia were negative prognostic factors for depressive episodes of DLL (Paper II), and that not being in remission at discharge from the hospital and EOD were negative prognostic factors for the longer term course of DLL (Paper III). Clinicians should be attentive to these factors when planning and assessing treatment of DLL.

Study 3 (Paper IV) was part of a larger longitudinal nursing home study (PSIN) that aimed to describe behavioral and psychological symptoms and particularly depressive symptoms in nursing home residents. Paper IV investigated the course of depressive symptoms as measured by the CSDD over 74 months in 1158 nursing home residents aged 50 years or older from 26 nursing homes in Norway. Data was collected at five time points by sixteen research nurses using a standardized interview. We found that "irritability" was the most prevalent, incident and persistent CSDD symptom. Compared

with the baseline assessment, the likelihood of the CSDD symptoms “suicidal ideation,” “pessimism,” and “delusions” being present was lower at all subsequent assessments. This persisted after adjusting for the severity of dementia. The severity of depression as measured by the CSDD decreased over 74 months when adjusted for resident variables (age, days of stay in the nursing home, gender, education, marital status, physical health, severity of dementia, personal activities of daily living, use of antidepressant, and number of medications). Poorer physical health, higher number of medications, more severe dementia, and use of antidepressants were associated with higher depression scores.

We concluded that this study adds important knowledge about the long-term course of depressive symptoms and depression for residents in nursing homes and underlines the importance of paying close attention to the overlap between depression and dementia symptoms when evaluating depression in this setting.





## List of papers

**Paper I:** Engedal, K., Kvaal, K., Korsnes, M., Barca, M. L., Borza, T., Selbaek, G., & Aakhus, E. (2012). The validity of the Montgomery-Aasberg depression rating scale as a screening tool for depression in later life. *Journal of Affective Disorders*, *141*(2-3), 227-232. doi: 10.1016/j.jad.2012.02.042

**Paper II:** Borza, T., Engedal, K., Bergh, S., Benth, J. S., & Selbaek, G. (2015). The course of depression in late life as measured by the Montgomery and Asberg Depression Rating Scale in an observational study of hospitalized patients. *BMC Psychiatry*, *15*, 191. doi: 10.1186/s12888-015-0577-8

**Paper III:** Borza, T., Engedal, K., Bergh, S., Benth, J. S., & Selbaek, G. (2016). Clinical prognostic factors and trajectories of depression in late life. *Submitted to International Psychogeriatrics*.

**Paper IV:** Borza, T., Engedal, K., Bergh, S., Barca, M. L., Benth, J. S., & Selbaek, G. (2015). The course of depressive symptoms as measured by the Cornell scale for depression in dementia over 74 months in 1158 nursing home residents. *Journal of Affective Disorders*, *175*, 209-216. doi: 10.1016/j.jad.2014.12.053



## Abbreviations

ACC - Anterior cingulate cortex  
AD - Dementia in Alzheimer's disease  
AGECAT - The Automated Geriatric Examination for Computer Assisted Taxonomy  
Apo - Apolipoprotein  
ATC - Anatomical and Therapeutic Chemical  
AUC - Area under the curve  
BDNF - Brain-derived neurotrophic factor  
BEHAVE-AD - Behavioral Pathology in Alzheimer's Disease Rating Scale  
CBT - Cognitive behavioral therapy  
CDR - Clinical Dementia Rating  
CIRS - Cumulative Illness Rating Scale  
CSDD - Cornell Scale for Depression in Dementia  
DDD - Defined daily dose  
DLFPC - Dorsolateral prefrontal cortex  
DLB - Dementia with Lewy Bodies  
DLL - Depression in later life  
ECT - Electroconvulsive therapy  
EOD – Early-onset depression  
ES - Effect size  
FSC - Fronto-subcortical circuits  
FTD - Frontotemporal lobe dementia  
GDS – Geriatric Depression Scale  
GMS - Geriatric Mental State Examination  
HADS - Hospital Anxiety and Depression Scale  
HAM-D - Hamilton Rating Scale for Depression  
HPA - Hypothalamic-pituitary-adrenal  
IADL - Instrumental activities of daily living  
IPT - Interpersonal therapy  
LOD – Late-onset depression  
MADRS - Montgomery and Asberg Depression Rating Scale  
MDD - Major depressive disorder  
MDS - Minimal Data Set  
MRI - Magnetic resonance imaging  
MMSE - Mini Mental State Examination  
NNT - Number needed to treat  
NPI - Neuropsychiatric Inventory  
NPS - Neuropsychiatric symptoms  
OFC - Orbitofrontal cortex  
OR - Odds ratio  
PD - Parkinson's disease with dementia  
PDC-dAD - Provisional Diagnostic Criteria for depression in Alzheimer Disease  
PET - Positron emission tomography  
PRODE- Prognosis of Depression in the Elderly  
PSIN - Psychiatric Symptoms in Nursing homes  
PSMS - The Physical Self-Maintenance Scale  
PST - Problem-solving therapy  
RCTs - Randomized controlled trials  
ROC - Receiver Operating Characteristic  
RT - Reminiscence therapy

RU - Regular units  
SAS - Statistical Analysis System  
SCID - Structured Clinical Interview for DSM-IV  
SCU - Special care units  
SD - Standard deviation  
SPSS - Statistical Program for Social Science package  
SSRI - Selective serotonin reuptake inhibitor  
TCA - Tricyclic antidepressant  
VD - Vascular dementia  
WML- White matter lesions

## Introduction

Why this thesis and what is it about?

Worldwide, 350 million persons suffer from depression (Marcus, Yasamy, van Ommeren, Chisholm, & Saxena, 2012). Depression is projected to be the leading cause of disability by 2030 (World Health Organization (WHO), 2008). In a review, Rosenvinge and Rosenvinge found the prevalence of depression to be 19% in people 60 years or older, and in subgroups at hospitals and nursing homes the prevalence was 31% (Rosenvinge & Rosenvinge, 2003). The aging population is growing, and the median life expectancy worldwide has increased from 68 years in 1990 to 72 years in 2009 (McCall & Kintziger, 2013). Thus, depression in later life (DLL) is a global challenge.

DLL can be difficult to treat and is typically of a chronic or recurrent nature. The characteristics of patients with DLL referred to specialist health psychiatric services have never been examined systematically in Norway. There are no longitudinal studies of DLL in Norway and few from the Nordic countries.

One paper in this thesis deals with the validity of the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), a clinically orientated depression rating scale in DLL. The three other papers in the thesis present clinical results from longitudinal studies of DLL. Two of these studies are of patients with depression referred to specialist health care services and one presents results from a nursing home setting.

When clinicians examine patients suspected to suffer from depression, it is recommended that they use structured depression scales, such as the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), or the MADRS (Montgomery & Asberg, 1979) (Helsedirektoratet, 2009). These scales are generally not developed to diagnose depression, but can aid in the screening and evaluation of the severity of depression. Some structured depression scales like the Geriatric Depression Scale (GDS) (Zigmond & Snaith, 1983) and the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos, Abrams, Young, & Shamoian, 1988) have been developed for use in elderly populations. The MADRS was originally designed to be sensitive to treatment effects, and only a few studies have investigated the validity of the MADRS as a screening scale among elderly persons. In Paper I, we aimed to investigate the validity of the MADRS as a screening scale for depressive disorder among elderly patients without dementia.

Purely observational data on the course of DLL are needed (Thomas, 2013a), and many longitudinal studies on the course of DLL have excluded patients with dementia. To improve knowledge on how to understand and treat DLL in Norway, we have carried out a multicenter longitudinal study of elderly depressed patients with or without dementia admitted to departments of old age psychiatry. This study was entitled "Prognosis of Depression in the Elderly" (PRODE).

In Paper II we aimed to examine the course of DLL during a stay in the hospital in terms of response, remission and effect size for symptom change as measured by the MADRS. We further aimed to investigate which clinical predictors were associated with response and remission.

In Paper III, we used data from the one-year follow-up examination in PRODE, in addition to data collected during a stay in the hospital. Our main aims were to investigate the prognosis of DLL over one year and assess clinical factors related to the prognosis. As part of the analyses, we aimed to

identify possible classes of patients following distinct trajectories (using growth mixture modeling) as well as clinical parameters characterizing these classes.

Sample sizes in longitudinal studies of depression in nursing homes are often small, and there are very few longitudinal studies with follow-up periods of more than one year (Smalbrugge et al., 2006). Nursing home residents are frail, and the results from longitudinal studies of depression in nursing homes with a follow-up period of more than six to twelve months are complicated by drop-outs, mainly due to death. In Paper IV we present results on the course of depressive symptoms as measured by the CSDD from a study of 1158 nursing home residents with five assessments over 74 months. We have used mixed models that are particularly flexible to many drop-outs and repeated measures. In Paper IV we aimed to investigate how the level of dementia influenced depressive symptoms and which demographic and clinical variables correlated with depression as measured by the CSDD.

## Background

### Historical background of depression, later life, old age psychiatry, and nursing homes in Norway

#### Historical background of depression

In ancient Greece, Hippocrates (ca. 460-377 BC) described a melancholic state that included sadness and fear, and he attributed it to an excess of black bile. Aristotle (384-322 BC) was of the opinion that the source of life and human reasoning were in the heart, and that the brain in that sense was less important. Aristotle saw mental disaster as inevitable in old age, and his views on the human body ruled for centuries. Hippocrates' theory that humoral excesses can cause different temperaments was further developed by the Roman physician Galen (129-216 AD). Galen described the melancholic temperament as one of four types: melancholic, optimistic, choleric, and phlegmatic. Galen had a pessimistic view of old age and regarded it as a disease. Before Galen and Aretaeus of Cappadocia (first century AD), melancholy was recognized mostly by its affective dimension. Aretaeus described two dimensions of melancholy, the emotional (affective) and the intellectual (abnormal beliefs).

Psychiatric terms can change their meaning over time, and Richard Burton (1577-1640) tried in his classic work "The Anatomy of Melancholy" first published in 1621, to give an overview of the different meanings of melancholy. Burton described that patients with melancholy could experience multiple symptoms, but most often the signs were fear and sorrow. Interestingly for this thesis, Burton also wrote about melancholy in old age: "Melancholy is a necessary and inseparable accident to all old and decrepit persons."

Pinel (1745-1826) and his student Esquirol (1772-1840) introduced a descriptive and more scientific approach to melancholy, as opposed to the humoral theory. In the nineteenth century the term "mental depression" started to appear, and it indicated a state of sadness. Gradually "depression" replaced "melancholy." In this era Emil Kraepelin (1856-1926) developed his nosology of psychiatric disorders, wherein manic depressive insanity was a major category. Kraepelin studied severely ill patients and emphasized the biological aspects of the diseases. Some years later, psychoanalysts took an interest in patients with milder depression, and psychological theories for causation were also developed. In the 1960s Angst and Perris divided depressive disorders into uni- and bipolar. The diagnostic systems of the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) introduced more specific criteria for depressive disorders beginning in the 1980s (Berchtold & Cotman, 1998; Berrios, 1996; Malt, 1983; Mondimore, 2005; Paykel, 2008; Telles-Correia & Marques, 2015).

### What is later life, older/elderly person?

Historically, when a person is regarded as “old age” has changed. Life expectancy has increased extensively over the last 50-70 years in Western parts of the world (Vaupel, 2010). There is no clear consensus when a person or a patient is referred to as being elderly/of old age/in later life. Currently, the United Nations has agreed to a cut-off age of 60+ years to refer to the older population, but differences exist between continents and countries (["www.who.int/healthinfo/survey/ageingdefnolder/en,"](http://www.who.int/healthinfo/survey/ageingdefnolder/en) 2016).

The aging brain undergoes structural and biochemical changes and these changes are more marked after 75 years (Engedal & Bjørkløf, 2014). The aging process contains several dimensions: chronological, biological, psychological and social, and there is great variety in how an individual ages. The cut-off age when a person is regarded as old, has historically in developed countries been linked to the retirement age, typically 60 or 65 years. It is often said that the cut-off age of 65 years for old age dates back to Bismarck's pension scheme in the late nineteenth century. However, this view has recently been challenged by von Herbay, who in a letter to the editor in *The Gerontologist* argued that it is a common misbelief that Bismarck is the source of the 65 year cut-off (von Herbay, 2014).

Studies of depression in later life have used different cut-off ages to include elderly patients, but age 60 or 65 is frequently used (Kay, Roth, & Hopkins, 1955; Langballe & Evensen, 2011; Roebuck, 1979; Rosenvinge & Rosenvinge, 2003).

*“Synes du dette på alderdom peker?”* (“Do you think this looks as if he were old?”)

From “Peer Gynt,” Henrik Ibsen.



### Old age psychiatry in Norway

Old age psychiatry, also known as geriatric psychiatry or psychogeriatrics, is a discipline of psychiatry that originated in Britain in the 1950s and 1960s. English psychiatrists then started to take interest in psychiatric diseases that started in old age, especially dementia, but also depressive diseases and psychosis. Departments for old people at psychiatric hospitals were created not only to provide care, but also to study and treat psychiatric diseases. Papers and textbooks which dealt specifically with topics for old people were published; i.e., in 1962 Felix Post wrote a monograph entitled "The Significance of Affective Symptoms in Old Age." (Post, 1962). The Ministry of Health recognized old age psychiatry as a field of speciality in 1989.

In Norway the development of old age psychiatry started 20-30 years later than in Britain, but it followed a similar path. The first department of geriatric medicine was established at Ullevål Hospital in Oslo in 1952, and in 1970 the first department for old age psychiatry was established at Dikemark Hospital. During the 1980s several psychiatric hospitals in Norway provided beds for patients of old age, but there were not many departments designed for elderly patients with psychiatric disorders, except for the hospital in Oslo. At this time, patients of old age often stayed in hospitals for months and years. In the last 15-20 years there have been developments to provide more specialized investigations and focused treatment programs and thereby shorter stays in hospitals and to provide more service at outpatient clinics (Engedal, 2008; Engedal, Nordberg, Moksnes, Henriksen, & Bergem, 1997; Moksnes, 2006).

Today, there are 22 departments of old age psychiatry in specialist health care in Norway. Services are provided at outpatient clinics or inpatient wards. In 14 of the 19 Norwegian counties there are inpatient wards, and the remaining five cooperate with a neighboring county with respect to hospital treatment. The departments of old age psychiatry typically offer services to catchment areas with 15,000 to 30,000 people above the age of 65 years. The most common diagnostic categories for patients admitted to treatment at departments of old age psychiatry are depressive disorders, cognitive impairment or dementia related diseases, psychosis, and anxiety. Patients who do not respond to treatment in primary care or patients with severe disease, reduced ability to take care of themselves, high risk of suicide, complicated physical disorders, or polypharmacy can be admitted as inpatients in departments of old age psychiatry (Grønli, 2014; Utvalg for alderspsykiatri, 2010).

### Nursing homes in Norway

Nursing home-care is a public service in Norway. Since 1986, the municipalities have assumed professional, administrative and financial responsibility for nursing homes. Typically, a general practitioner working part time provides medical services, and some municipalities with larger nursing homes have full-time employed physicians. In 2008, i.e., at the time when the nursing home study in this thesis was carried out, there were 435 municipalities in Norway and 37,473 people residing in nursing homes ("[www.ssb.no/a/aarbok/tab/tab-137.html](http://www.ssb.no/a/aarbok/tab/tab-137.html)," 2013). The average age of nursing-home residents was 84 years; 73% were women; and 80% had dementia (Selbaek, 2008). Approximately 20% of the beds at nursing homes were special care units (SCU) for residents with dementia (Eek & Nygård, 2006). These units are often smaller and have a higher staff-resident ratio than regular units (RU).

The last 10-15 years have seen an increasing number of initiatives to improve health care in nursing homes, including various research projects, more SCUs, greater diversity of treatments, and more focus on tailored treatment. In 2011, nursing home medicine was recognized as an independent field of competence by the Norwegian Medical Association, and in 2012 the Centre for Elderly - and Nursing Home Medicine (SEFAS) was established (Husebo et al., 2015). Medical supervisor coverage has increased around 30% in the last few years from an average of 0.37 hours per week per resident around 2010 to 0.49 in 2014 ("www.ssb.no/pleie," 2015).

## Definitions and classification of depression and depression in later life (DLL)

### How is depression classified?

Depression is a clinical diagnosis based on an interview and examination of the patient, supplemental information from relatives or caregivers, and investigations to rule out that the depression is caused by medical conditions or use of psychoactive substances. There is no defined biomarker for depression, and a diagnosis of depression is made according to the official classification systems of the World Health Organization's (WHO) *International Classification of Diseases* (ICD) (World Health Organization (WHO), 1993) and the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Association, 2013). The criteria for a depressive disorder are similar but not identical in the latest editions of the classification systems; the ICD-10 and the DSM-5.

In Norway, the ICD-10 is used in clinical practice. In addition to clinical criteria, the ICD-10 also contains "diagnostic criteria for research of depression", and these criteria are more specific than the clinical criteria. In this thesis we have used the *Diagnostic Criteria for Research* (World Health Organization (WHO), 1993). The major affective (mood) categories (F3x) in the ICD-10 are manic episode (F30), bipolar affective disorder (F31), depressive episode (F32), recurrent depressive disorder (F33), persistent affective disorders (F34), other affective disorders (F38), and unspecified affective disorder (F39). The ICD-10 has a categorical approach to a diagnosis of depression, i.e., a depressive symptom is either present or not and a diagnosis of depression is either present or not. In order to fulfill the criteria for a depressive episode (whether part of bipolar disorder, recurrent disorder or single episode) four depressive symptoms have to be present (yes/no), and two of the symptoms must be core symptoms (see Textbox 1). Depressed mood, loss of interest or pleasure, and decreased energy are the three core symptoms of a depressive episode. The additional symptoms to a diagnosis of a depressive episode are: loss of confidence and self-esteem, worthlessness or guilt, thoughts of suicide or suicidal behavior, concentration difficulties, change in psychomotor activity, sleep disturbances, and change in appetite. The severity of the depressive episode is classified according to the number of depressive symptoms present; mild = at least four symptoms, moderate = at least six symptoms, and severe = all three of the core symptoms and at least eight symptoms.

To be diagnosed with a somatic syndrome (melancholia), four of the following eight symptoms have to be present: marked loss of interest or pleasure in activities that are normally pleasurable, lack of emotional reactions to events or activities that normally produce an emotional response, waking in the morning two hours or more before the usual time, depression worse in the morning, objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people), marked loss of appetite, weight loss (5% or more of body weight in the past month), and marked loss of libido. The presence of a somatic syndrome (melancholia) is marked with an additional specifier. According to the ICD-10, a depressive episode with psychotic symptoms must be severe and include delusions or hallucinations of a non-schizophrenic nature or depressive stupor. The ICD-10 classifies a depressive episode into single episode (F32) or recurrent episodes (F33), but it is debated how useful this distinction is, particularly if a patient has a first depressive episode and is later reclassified as recurrent when a further episode occurs (Paykel, 2008). The ICD-10 criteria for

depression are purely descriptive, and do not reflect that depression can have different etiologies (psychological, biological, social, cultural).

Textbox 1: Depressive episode (F32.x) according to the ICD-10 research criteria

I. The general criteria for depressive episode (G1-G3) must be met:

- G1. The depressive episode should last for at least two weeks.
- G2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode (F30.-) at any time in the individual's life.
- G3. Most commonly used exclusion clause. The episode is not attributable to psychoactive substance use (F10-F19) or to any organic mental disorder (in the sense of F00-F09).

II. At least two of the following three symptoms must be present:

- (1) Depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least two weeks.
- (2) Loss of interest or pleasure in activities that are normally pleasurable.
- (3) Decreased energy or increased fatiguability.

III. An additional symptom or symptoms from the following list should be present, to give a total of at least four:

- (4) Loss of confidence and self-esteem.
- (5) Unreasonable feelings of self-reproach or excessive and inappropriate guilt.
- (6) Recurrent thoughts of death or suicide, or any suicidal behavior.
- (7) Complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation.
- (8) Change in psychomotor activity, with agitation or retardation (either subjective or objective).
- (9) Sleep disturbance of any type.
- (10) Change in appetite (decrease or increase) with corresponding weight change.

Bipolar depressive disorders (F31) include depressive disorders with episode(s) of hypomania or mania. Mania is defined as “a mood which is predominantly elevated, expansive or irritable and definitely abnormal for the individual concerned. This mood change must be prominent and sustained for at least a week (unless it is severe enough to require hospital admission),” and “at least three of the following must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living: (1) increased activity or physical restlessness; (2) increased talkativeness (pressure of speech); (3) flight of ideas or the subjective experience of thoughts racing; (4) loss of normal social inhibitions resulting in behavior which is inappropriate to the circumstances; (5) decreased need for sleep; (6) inflated self-esteem or grandiosity; (7) distractibility or constant changes in activity or plans; (8) behavior which is foolhardy or reckless and whose risks the subject does not recognize, e.g., spending sprees, foolish enterprises, reckless driving; (9) marked sexual energy or sexual indiscretions.”

Hypomania is defined as “a mood which is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least four consecutive days,” and “at least three of the following must be present, leading to some interference with personal functioning in daily living: (1) increased activity or physical restlessness; (2) increased talkativeness; (3) difficulty in concentration or distractibility; (4) decreased need for sleep; (5) increased sexual energy; (6) mild spending sprees, or other types of reckless or irresponsible behavior; (7) increased sociability or over-familiarity.

The ICD-10 does not contain specific criteria for “minor depression,” “minor depressive disorder” or “subthreshold depression,” Generally, subthreshold depression or corresponding concepts is inconsistently defined.

There are no specific criteria for DLL in the ICD-10, and the described criteria for depression in the ICD-10 apply to elderly patients as well.

The DSM-5 (American Psychiatric Association, 2013) replaced DSM-IV-TR in 2013 (American Psychiatric Association, 2000). In this thesis it is most relevant to describe the DSM-IV-TR criteria for depression as one of the papers in the thesis has used the DSM-IV-TR criteria. The major affective disorders in the DSM-IV-TR are bipolar and related disorders and depressive disorders (major depressive disorder, persistent depressive disorder (dysthymia), substance/medication induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder and unspecified depressive disorder). The DSM-IV-TR like the ICD-10, has a categorical approach to a diagnosis of depression. In order to fulfill the criteria for major depressive disorder, five depressive symptoms have to be present, and one of those has to be the core symptom depressed mood or loss of interest or pleasure (see Textbox 2). Minor depressive disorder is described in the DSM-IV-TR, and in order to fulfill these criteria two depressive symptoms have to be present for two weeks.

The DSM-IV-TR specifies that the symptoms have to be present nearly every day. So, it is somewhat stricter to fulfill the DSM-IV-TR criteria of major depressive disorder, compared to a depressive episode in the ICD-10. The DSM-IV-TR also stresses that the symptoms must cause clinically important impairment in daily functioning, and they cannot be accounted for by bereavement. Studies using the DSM-IV-TR give lower prevalence of depression, compared to the ICD-10 (Barca, Engedal, & Selbaek, 2010; Knapkog, Barca, & Engedal, 2011).

Textbox 2

Major depressive disorder (MDD) according to the DSM-IV-TR

A. Five (or more) of the following symptoms have been present during the previous two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- 1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
- 2) Markedly diminished interest and pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
- 3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
- 4) Insomnia or hypersomnia nearly every day
- 5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- 6) Fatigue or loss of energy nearly every day
- 7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- 8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- 9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan of committing suicide

B. The symptoms do not meet criteria for mixed episode

C. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning

D. The symptoms are not due to direct psychological effects of a substance (e.g., drug abuse, a medication) or a general medical condition (e.g., hypothyroidism)

E. The symptoms cannot be accounted for by bereavement (i.e., the loss of a loved one); the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideas, psychotic symptoms, or psychomotor retardation.

The DSM-5 criteria for affective disorders are very similar to the DSM-IV-TR criteria, but there have been some changes in that the DSM-5 now includes disruptive mood dysregulation disorder and premenstrual dysphoric disorder. In DSM-5, persistent depressive disorder includes both chronic major depressive disorder and the previous dysthymic disorder. Further, the bereavement exclusion criterion is omitted and there are new specifiers to the depressive disorders, i.e., “with mixed symptoms” and “with anxious distress.” Neither the DSM-5 nor the DSM-IV-TR contains specific criteria for depression in elderly patients.

### **Classification of depression in later life**

DLL is most often defined as depression occurring for patients in later life, i.e., after 60 or 65 years (see the different definitions of later life, page 19). Sometimes, DLL is subdivided according to the age of the first lifetime onset of a depressive episode, and different cut-off ages have been applied (e.g. 50, 60 or 65 years). DLL that arises before the specific cut-off age is labeled “early-onset depression” (EOD), and consequently, depression with the first manifestation of the disease after the specific cut-off, “late-onset depression” (LOD).

### **Definitions of transition periods**

In the course of a depressive disorder there are various transition periods. For instance, Frank et al. have defined relevant terms to the change points to be used in research of depression. Other work groups have further operationalized the definitions. Accordingly, the response refers to a significant reduction of depressive symptoms, exemplified by 50% or more reduction of the sum score on a depression rating scale like the MADRS. Remission means absence of or minimal presentation of depressive symptoms, i.e., the person no longer meets the criteria for depression. A cut-off value on a depression rating scale can aid in ascertaining remission. A remission that lasts for four to six months develops into a recovery. Relapse is a return of depression (fulfilling the specified criteria for depression/depressive episode) after remission but before a recovery is established. Recurrence is the appearance of a new depressive episode, and can only happen after the onset of a recovery (Frank et al., 1991; Rush et al., 2006).

## Dementia and cognitive impairment

### Dementia – definition, prevalence, diagnosis, and assessment scales

Dementia is a clinical syndrome characterized by a progressive decline of memory and other cognitive abilities and by a decline in emotional regulation or social behavior (see Textbox 3). Dementia causes functional impairment and nearly all patients experience clinically significant neuropsychiatric symptoms (NPS) in the course of dementia (Selbaek, Engedal, Benth, & Bergh, 2014). NPS of dementia include anxiety, depression, agitation/aggression, irritability, disinhibition, aberrant motor activity, apathy, delusions and hallucinations, for example. During the course of dementia, it is shown that up to two-thirds of patients develop depressive symptoms (Lyketsos, 2010; Selbaek et al., 2014; Steinberg et al., 2008). In a Norwegian investigation of the prevalence among patients referred to memory clinics in specialist health care for dementia assessment, Knapskog et al. reported that 37.5% had depression defined as a CSDD score > 7 (Knapskog, Barca, & Engedal, 2014).

Prince et al. estimated that 35.6 million people worldwide lived with dementia in 2010, and the number is expected to rise to 115.4 million by 2050 (Prince et al., 2013). Alzheimer Europe estimated that 77,000 people lived with dementia in Norway in 2012, and the prevalence is highest in the age group of 85-89 years (*Demensplan 2020. Et mer demensvennlig samfunn.*, 2015; "www.alzheimer-europe.org/Policy-in-Practice2/Country-comparisons/The-prevalence-of-dementia-in-Europe/Norway/," 2014).

A diagnosis of dementia contains two stages. The first part is to diagnose the dementia syndrome according to the standardized criteria of the ICD-10, or correspondingly major neurocognitive disorder in the DSM-5. In Norway we use the ICD-10. The next part is to diagnose the specific disease causing the dementia syndrome. Clinicians often carry out these stages concurrently in daily practice. There are many diseases that can cause dementia, and it is important to assess the patients in a way so that the potentially reversible dementias, such as normal pressure hydrocephalus and subdural hematoma, are discovered. The most frequent dementias are dementia in Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy Bodies (DLB), frontotemporal lobe dementia (FTD), alcoholic dementia, and Parkinson's disease with dementia (PD). The different causes of dementia may require different treatment strategies. The ICD-10 was launched in 1993, and it does not contain explicit criteria for FTD and DLB. Pick's disease with affection of the frontal and temporal lobes is described. Specific criteria for FTD (Neary et al., 1998; Rascovsky et al., 2011) and DLB (McKeith et al., 2005; McKeith et al., 1996) were developed later. In this thesis we used Neary's criteria for FTD and McKeith's criteria from 2005 (third report of the DLB consortium) for DLB and the ICD-10 criteria to the other dementias to classify patients with dementia (presented as additional results related to Paper III).

In the last decades knowledge about biomarkers (amyloid and tau in the cerebrospinal fluid, hippocampal atrophy visible on magnetic resonance [MR] and positron emission tomography-imaging [PET]) has been increased. Subsequently, new diagnostic criteria with biomarkers for Alzheimer's disease have been suggested for use in research, but these have yet to be well validated (Dubois et al., 2010; Dubois et al., 2007; Oksengard et al., 2010).

A clinical assessment of a patient for dementia should include neuropsychological tests of cognitive abilities and reliable information from an informant. The Mini Mental State Examination (MMSE)



(Folstein, Folstein, & McHugh, 1975) is a 30-point questionnaire that examines cognitive abilities such as orientation, attention, calculation, recall, language skills and construction. The MMSE is probably the most used screening test for cognitive dysfunction worldwide, and is frequently used in dementia research. Patients with many years of education tend to perform better on the MMSE than patients with less education, and the MMSE does not always differentiate between patients at the milder stages of dementia. Thus, in these patients it is recommended to consider several other neuropsychological tests like the clock-drawing test, the Trail Making A and B tests, the Controlled Oral Word Association Test (COWA), The Ten Word Recall test from the Consortium to Establish a registry for Alzheimer's disease (CERAD) battery of tests and the Boston naming test (Kaplan, Goodglass, & Weintraub, 1983; Mack, Freed, Williams, & Henderson, 1992; Morris et al., 1989; R. K. Reitan & Wolfson, 1985; R. M. Reitan, 1955).

Information from carer to patients suspected to suffer from dementia should complement the clinical examination of the patient. Jorm et al. have developed a structured questionnaire to provide information from an informant: the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm & Jacomb, 1989). The informant must know the patient's premorbid cognitive level and the IQCODE contains various items to measure change in memory and intelligence during the previous ten years.

The Clinical Dementia Rating (CDR) is a scale where the assessor uses all available information to evaluate the patient in six categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) (Hughes, Berg, Danziger, Coben, & Martin, 1982). The global CDR score is based on an algorithm giving precedence to the memory category, and the score indicates the severity of cognitive impairment/dementia: 0 = no dementia, 0.5 = possible dementia, 1 = mild dementia, 2 = moderate dementia and 3 = severe dementia (Morris, 1993). By summing each of the category scores, it is possible to calculate a CDR sum of boxes score. This method measures a greater variety, which is an advantage in longitudinal studies to track changes over time (O'Bryant et al., 2008). The CDR is used both in clinical and research settings.

Textbox 3. Dementia according to the ICD-10 research criteria

I. Evidence of each of the following:

A): A decline in memory, which is most evident in the learning of new information.

The decline should be objectively verified.

B) A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information.

Deterioration from a previously higher level of performance should be established.

II. Preserved awareness of the environment (i.e., absence of clouding of consciousness).

When there are superimposed episodes of delirium, the diagnosis of dementia should be deferred.

III. A decline in emotional control or motivation, or a change in social behavior, manifested as at least one of the following:

(A) emotional lability

(B) irritability

(C) apathy

(D) coarsening of social behavior.

IV. For a confident clinical diagnosis, Criterion I should have been present for at least six months; if the period since the manifest onset is shorter, the diagnosis can only be tentative.

A character may be used to indicate the severity of the dementia: mild, moderate or severe.

The overall severity of the dementia is best expressed as the level of decline in memory or other cognitive abilities, whichever is the more severe (e.g., mild decline in memory and moderate decline in cognitive abilities indicate a dementia of moderate severity).

## Mild cognitive impairment

Mild cognitive impairment (MCI) often refers to a clinical syndrome in patients with cognitive deficits, who do not fulfill the criteria for dementia, but may be at risk to develop a dementia disorder over time. As there are many possible etiologies to MCI (e.g., vascular, degenerative, metabolic, traumatic, and psychiatric), the patients can be heterogeneous (Portet et al., 2006). The ICD-10 exemplifies difficulties in the following cognitive areas: memory (particularly recall) or new learning, attention or concentration, thinking (e.g., problem solving), language (e.g., word-finding), or visual-spatial functioning. In 1993, the ICD-10 put forward that the criteria for the construct of mild cognitive disorder (F06.7) was tentative and warranted further examinations (World Health Organization (WHO), 1993).

Several definitions of MCI or corresponding constructs have been developed, and they often emphasize memory difficulties. Petersen et al. conceptualized MCI and followed MCI-patients with memory deficits for five years and reported an annual conversion rate of 10-15% for dementia (Petersen et al., 1997). Winblad led a worldwide group of experts that aimed to integrate clinical and research perspectives on MCI and to put forward general criteria for MCI. The group described patients with MCI as “not normal and not demented,” with cognitive decline and no more than minimal impairment in complex instrumental functions (see Textbox 4). Further, the group described the clinical presentations of MCI as amnesic, single non-memory domain or multiple domains (Winblad et al., 2004). With respect to the present thesis, the patients were assessed using Winblad’s criteria for MCI (see Textbox 4) at the one-year follow-up examination in the PRODE study (the results are presented in Table 8, together with Paper III). The DSM-5 also provided criteria for a less severe impairment of cognition: mild neurocognitive disorder.

In a review article Panza et al. found great variation in the prevalence of depression among patients with MCI, and higher prevalence in hospital-based studies (range: 9%-83%, median: 44.3%), than in population-based studies (range: 3%-63%, median: 15.7%) (Panza et al., 2010).

Textbox 4 Mild cognitive impairment according to Winblad’s criteria (Winblad et al., 2004)

I) Not normal, not demented (does not meet criteria (DSM-IV, ICD-10) for a dementia syndrome)

II) Cognitive decline

- Self and/or informant report and impairment on objective cognitive tasks and/or
- Evidence of decline over time on objective cognitive tasks

III) Preserved basic activities of daily living/minimal impairment in complex instrumental functions

## Depression in later life (DLL)

### Epidemiology of depression in later life (DLL)

Studies have shown that DLL can be highly prevalent, but the prevalence estimates of DLL may vary from 0.4-39% (Beekman, Copeland, & Prince, 1999; Blazer & Williams, 1980; Copeland, 1987; Rosenvinge & Rosenvinge, 2003). This variation is related to which definitions of depression have been used, how depression was surveyed, geographical differences, and which population was investigated (Beekman et al., 1999; Copeland et al., 2004; Copeland et al., 1999; Langballe & Evensen, 2011). The prevalence of major depressive disorder (MDD) among elderly persons in the community is frequently estimated to be in the range of 1-4% (Blazer, Hughes, & George, 1987; Blazer, 2003). There is evidence that subthreshold depression among elderly persons is two to three times more prevalent than major depression, and that subthreshold depression is more prevalent in nursing homes than in primary care and community settings (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011).

In a review of the literature on the prevalence of depression in persons aged 60 or older, Rosenvinge and Rosenvinge found the prevalence rate of depression in the general elderly population to be 13%, but estimates varied from 2-39%. Likewise, the prevalence rate of major depression was 2%, and varied from 0-6%. The prevalence rate of depression was higher in nursing homes: 32% with a range of 5-62%, and hospitals: 31%, with a range of 5-58%. Similarly, the prevalence of major depression was 5% with a range of 1-10% in nursing homes and 14% with a range of 4-26% in hospitals. It was also concluded that studies with more specific diagnostic procedures for depression showed lower prevalence (Rosenvinge & Rosenvinge, 2003).

Studies have generally shown that DLL is more prevalent among women than men (Beekman et al., 1999; Thomas, 2013a). However, results on the gender difference in prevalence among those aged 85 years and older are more mixed (Bergdahl, Allard, Alex, Lundman, & Gustafson, 2007; Langballe & Evensen, 2011; Stordal et al., 2001). DLL is common in the context of physical disorders, particularly brain disorders. DLL or significantly depressive symptoms can be present in 20-50% of patients with Parkinson's disease, cerebrovascular disease or dementia (Blazer, 2003; Thomas, 2013a). Authors have reported particularly high prevalence of depression and depressive symptoms in DLB (Borroni, Agosti, & Padovani, 2008; Yamane, Sakai, & Maeda, 2011) and VD (Ballard et al., 2000). There are conflicting results as to whether the prevalence of DLL increases with age. Studies which have used questionnaires to examine depressive symptoms have found an association between increasing age and depression (Stordal, Mykletun, & Dahl, 2003). Major depressive disorder as defined in the DSM classifications does not seem to increase with age (Beekman et al., 1999; Thomas, 2013a). It can be argued that healthy aging itself seems not to be a risk factor for DLL (Roberts, Kaplan, Shema, & Strawbridge, 1997), but the prevalence of DLL has been shown to be considerably higher in elderly subpopulations with high levels of physical comorbidity, particularly brain diseases and disability.

In recent years there has been an increased focus on bipolar disorders in later life. It can be challenging to diagnose a bipolar disorder in later life correctly due to the complexity of the disorder and heterogeneity in the classification systems. The point prevalence rate of bipolar disorders in later life in the community is estimated to be 0.1 – 0.5% (Lavretsky, Sajatovic, & Reynolds III, 2013; Sajatovic & Chen, 2011). In elderly patients referred to treatment in hospitals the prevalence of

bipolar disorders is substantially higher (Depp et al., 2005; Sajatovic et al., 2015). Depp and Jeste estimated bipolar disorder to be present in 8-10% of psychiatric inpatients over 55 years of age (Depp & Jeste, 2004).

### **Etiology of depression in later life (DLL)**

The causes of DLL are often multifactorial, and authors have described a biopsychosocial approach to the complex etiology of DLL (Blazer, 2003). This approach highlights that several biological, psychological and social factors can interact and contribute to the development of DLL.

### ***Biological and medical factors***

#### **Physical disease, medications and alcohol**

DLL often develops in the context of physical diseases. There are several well established risk factors like ischemic heart disease, chronic obstructive pulmonary disease, diabetes, malignancy, and organic brain diseases, such as dementia, stroke, and Parkinson's disease (Blazer, 2003; Krishnan et al., 2002). Medical diseases have greater impact on DLL if the diseases cause disability, pain and social isolation (Alexopoulos, 2005; Prince, Harwood, Thomas, & Mann, 1998; Thomas, 2013a). Some reports have suggested that the use of certain medications (e.g., non-selective beta blockers and benzodiazepines) is associated with the development of DLL (Alexopoulos, 2005; Dhondt, Beekman, Deeg, & Van Tilburg, 2002). However, these data are difficult to interpret as the indication for which a medication is taken can itself be a risk factor for DLL (Alexopoulos et al., 2002; Thomas, 2013a).

Investigations have shown that DLL and excessive use of alcohol can coexist (Blixen, McDougall, & Suen, 1997), but there are few investigations on the use of alcohol in DLL. Alcohol dependence can have implications for the course of DLL. Depression and depressive symptoms can predict harmful use of alcohol, and heavy use of alcohol can worsen depression and adherence to treatment (Gopalakrishnan, Ross, O'Brien, & Oslin, 2009; Oslin, 2005).

#### **Brain anatomy**

Structural and functional neuroimaging and neuropathological studies have pointed out certain areas and circuits in the brain as important for DLL. The cortical areas include dorsolateral prefrontal cortex (DLFPC), the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). Subcortically, the areas include white matter in the frontal lobes, amygdala, hippocampus, and the basal ganglia (particularly the striatum) (Naismith, Norrie, Mowszowski, & Hickie, 2012; Thomas, 2013a). Several fronto-subcortical circuits (FSC) are relevant to depression, and there is evidence that dysfunction in these circuits has implications for the development, presentation, and outcome of DLL (Alexopoulos, 2005). DLL patients with damage to the fronto-striatal circuit can present more apathy, executive dysfunction, psychomotor retardation, and can show less response to antidepressant therapy (Sneed et al., 2010). Likewise, DLL patients with damages to the hippocampus, or circuits involving the hippocampus, can present memory deficits and could be at greater risk for developing cognitive impairments (Moser & Moser, 1998; Steffens, McQuoid, Payne, & Potter, 2011).

#### **Neurochemistry**

Serotonin, noradrenaline, and dopamine are modulating neurotransmitters in the brain that are

involved in regulation of mood and behavior. More specifically, serotonin is associated with impulse control, sex drive, appetite, anxiety, and obsessions and compulsions; noradrenaline with alertness, energy, and interest in life; and dopamine with attention, motivation, pleasure, reward, and interest in life (Nutt, 2008). Dysfunction in circuits with these neurotransmitters has been shown in DLL (Baldwin, 2014; Thomas, 2013a). This is further evidenced by the fact that antidepressant medications targeted to these neurotransmitters have an effect, although modest and variable, on DLL (Nelson, Delucchi, & Schneider, 2008). There is also research indicating that dysfunction in other neurotransmitters, i.e., gamma-amino butyric acid (GABA) and glutamate, are involved in DLL (Khundakar & Thomas, 2014; Niciu, Ionescu, Richards, & Zarate, 2014; Sanacora & Saricicek, 2007).

### Genetics

A Swedish twin study of middle-aged and older adults (>60) reported that genetic influences accounted for 16% of the total variance of self-reported depressive symptoms (Gatz, Pedersen, Plomin, Nesselroade, & McClearn, 1992). Genetic research in DLL during the last decades has focused on genes that are considered to be important for the plasticity of neurons (brain-derived neurotrophic factor (BDNF) gene), transmission of serotonin (serotonin transporter (5HTTLPR) gene), transport of lipids (apolipoprotein E (apo ε) gene) and vascular risk factors (5-metylenetetrahydrofolate reductase (MTHFR) gene). Genetic susceptibility to DLL seems to be related to small effects of multiple genetic loci, rather than large effects of few loci (Naismith et al., 2012). There is a complex interplay between genes and environment in DLL and it can be challenging to interpret results of relevant studies (Lotrich, 2011).

### The immune and endocrine system

In recent decades there has been growing knowledge about the interplay between the nervous, endocrine, and immune system, and there is evidence of an altered immune response in depressed patients (Hestad, Aukrust, Tønseth, & Reitan, 2009). Aging can change the immune system in the brain to a pro-inflammatory state (Morimoto & Alexopoulos, 2011). Pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF $\alpha$  mediate behavioral effects that can mimic depressive behavior. There is little conclusive information on the role of the immune system in DLL. However, some studies have shown increased levels of IL-1 $\beta$ , IL-6 and TNF $\alpha$ , and that these elevated levels are correlated with the severity of DLL (Morimoto & Alexopoulos, 2011; Thomas, 2013a). Alexopoulos and Morimoto have postulated that elderly patients with inflammation-related comorbidity are vulnerable to at least some types of depressive syndromes (Alexopoulos & Morimoto, 2011).

Dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis is seen in younger and elderly patients with depressive syndromes (Hestad et al., 2009; Stetler & Miller, 2011). Research has indicated that aging increases dysregulation of the HPA axis (Ice, Katz-Stein, Himes, & Kane, 2004). Dysregulation of the HPA axis may lead to increased cortisol levels, and in animal studies high cortisol levels have been linked with neurotoxic effects on the hippocampus. Studies on increased cortisol as a mechanism between DLL and hippocampal atrophy in humans are more conflicting (Naismith et al., 2012; O'Brien, Lloyd, McKeith, Gholkar, & Ferrier, 2004; Sheline, Wang, Gado, Csernansky, & Vannier, 1996).

Subgroups of patients with hyperparathyroidism can present with DLL and treating the hyperparathyroidism may alleviate the depressive symptoms (Gronli & Wynn, 2013).

## Vascular disease

A bidirectional relationship between vascular disease and depression has been advocated (Teper & O'Brien, 2008). In 1997, Alexopoulos et al. put forward the “vascular depression” hypothesis. It stated that cerebrovascular disease may predispose, precipitate, or perpetuate some DLL syndromes. The clinical characteristics of “vascular depression” were described as: evidence of vascular disease (including white matter lesions [WML] on imaging of the brain), onset after 65 years or change in depression course after onset of vascular disease, cognitive impairment with emphasis on executive functions, psychomotor retardation, disability, limited depressive ideation, poor insight, and absence of family history of mood disorders. The two first characteristics were considered as cardinal features, expected to be present in all patients. The authors described the clinical picture as a result of fronto-striatal dysfunction (Alexopoulos et al., 1997). Some later studies have had difficulties in classifying reliable subgroups of patients (Baldwin, 2005), and community studies of DLL have questioned the importance of vascular risk factors in the development of DLL (Naarding et al., 2007). However, vascular disease can play a part in up to 50% of DLL (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008; Thomas, 2013a).

The presence of WML in the brain increases with age and its origin is related to cerebral ischemia, particularly as part of cerebrovascular disease (Colloby & O'Brien, 2013; Teodorczuk et al., 2010; Thomas, 2013a). In a systematic review Herrmann et al. indicated that WML were more common and more severe in DLL patients compared to healthy control persons and this particularly was the case for LOD (Herrmann, Le Masurier, & Ebmeier, 2008). Naismith et al. have reviewed studies that explored whether the total volume of WMLs or strategic WMLs in the orbitofrontal cortex for example was most important in the etiology of DLL and the findings were mixed (Naismith et al., 2012).

## Psychological factors

Personality traits, such as neuroticism, coping strategies, learned hopelessness, and cognitive distortions are psychological factors associated with DLL (Bjorklof, Engedal, Selbaek, Kouwenhoven, & Helvik, 2013; Blazer, 2nd & Hybels, 2005). Studies into the relationship between personality and DLL can be difficult to carry out and to interpret, so there are not many high-quality studies on personality disorders and the development of DLL. In a study that used self-report questionnaires to investigate personality disorders and DLL, Morse and Lynch indicated that patients with a personality disorder were almost four times more likely to experience maintenance or reemergence of depressive symptoms than those without a personality disorder (Morse & Lynch, 2004). Other studies have found neuroticism to be an important personality trait to predict the onset of depressive symptoms in later life (Steunenbergh, Beekman, Deeg, & Kerkhof, 2006), and to be associated with poor outcomes of DLL (Steffens, McQuoid, Smoski, & Potter, 2013).

Studies have identified stressful life events, such as the loss of a loved one, medical illness, disability and functional decline, and giving up one's home to predispose and to sometimes precipitate DLL (Aziz & Steffens, 2013). De Beurs et al. found that death of a partner or relatives was particularly important in predicting the onset of DLL (de Beurs et al., 2001). There is less knowledge about the importance of experiencing traumatic events previously in life to DLL (Arean & Reynolds, 2005). The impact that stressful life events and life stressors have on elderly individuals varies. Elderly people with high levels of mastery and active coping strategies to adverse events in life have been reported to be more resilient to DLL (Bjorklof et al., 2013).

### *Social factors*

Psychological and social etiologies to DLL often coexist, and loneliness can be a key element in the development of DLL. A Finish study of the relationship between loneliness and depressive symptoms in elderly persons has stressed the importance of perceived togetherness in social interactions (Tiikkainen & Heikkinen, 2005). Studies have put forward that the way patients perceive social support is essential for the role of social support in the development of DLL (Aziz & Steffens, 2013).

There are a limited number of studies on the importance of psychosocial factors in the development of DLL in a long-term setting. However, one study of elderly care residents without dementia highlighted psychological factors with respect to environmental mastery, purpose in life, and autonomy, to predict depression (Davison, McCabe, Knight, & Mellor, 2012). A cross-sectional study of DLL in nursing homes found that psychosocial factors, including loneliness, recent negative life events, lack of social support, and perceived inadequacy of care were risk factors for DLL (Jongenelis et al., 2004).

### *Risk factors to depression in later life (DLL)*

In a systematic review and meta-analysis on the risk factors for depression among the elderly in the community, Cole and Nendukuri reported that despite methodological limitations of the 20 included studies, bereavement, sleep disorders, disability, prior depression, and female gender seemed to be important risk factors (Cole & Dendukuri, 2003). Taken from the presentation in this section of the present thesis, we can advocate that the factors described in Table 1 may be risk factors for DLL.

**Table 1. Risk factors for depression in later life (DLL)**

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Female sex
Family history of depression
Medical comorbidity, particularly with brain diseases
Disability
Polypharmacy
Damage to fronto-sub cortical circuits and circuits involving hippocampus
Dysfunction in modulating neurotransmitters
Altered immune system
Presence of WML and vascular disease
Neuroticism, learned hopelessness and passive coping style
Stressful life events
Loneliness and poorly perceived social support

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### **Clinical picture of depression in later life (DLL)**

The aging process may interfere with how an elderly person interprets and communicates depressive symptoms and how clinicians view the symptoms. Elderly persons may also be reluctant to discuss emotions with clinicians. Thus, it can be challenging for clinicians to recognize depressive syndromes in the elderly. Studies on how the clinical picture of DLL differs from depression in younger adults have produced mixed results. A recent meta-analysis on the phenomenology of depression in elderly patients compared with younger patients concluded that DLL differed in part from depression in earlier life. The analysis investigated studies that had used HAM-D and found that elderly patients with major depression showed more agitation, general and gastrointestinal physical symptoms, and hypochondriasis, but less guilt and loss of sexual interest, compared with younger adults with major depression (Hegeman, Kok, van der Mast, & Giltay, 2012). Other studies have highlighted that DLL patients may present more often with atypical symptoms. For instance, Gallo and Rabins described alternative presentations of DLL where sadness is not a core symptom. The authors emphasized that cues like unexplained physical symptoms, hopelessness, and reduced interest in personal care may be characteristics of DLL when sadness is not present, and loss of interest is difficult to assess (Gallo & Rabins, 1999). Brodaty et al. described more psychosis and psychomotor disturbances in depressed patients over 60 years of age compared with depressed patients younger than 60. This study excluded patients with bipolar disorder and depression secondary to organic diseases (Brodaty et al., 1997).

In a cross-sectional study of patients with their first major depressive episode and no dementia Corruble et al. used the MADRS and the DSM-IV to compare the symptom profile of MADRS across three different age categories (18-59, 60-74, 75+). The authors described very modest differences, but noted more retardation/agitation, lassitude, reduced appetite, and apparent sadness, and less sleep disturbances, guilt feelings, pessimism, and inner tension in the oldest group (Corruble, Gorwood, & Falissard, 2008).

### **Early-onset of depression (EOD) and late-onset of depression (LOD)**

Compared to LOD, studies have found EOD to be associated with a more severe course of the depressive disorder, i.e., more residual symptoms, more suicidal ideation and less social support (Comijs et al., 2015; Reynolds et al., 1998; Sachs-Ericsson et al., 2013). LOD-patients can have more cognitive impairments than EOD-patients (Sachs-Ericsson et al., 2013). The differences between EOD and LOD are debated, and there seems to be more evidence for possible etiological differences (including vascular factors and WML), than for phenomenological differences (Brodaty et al., 2001; Grayson & Thomas, 2013; Naismith et al., 2012; Selbaek & Borza, 2015; Thomas, 2013b).

### **Bipolar disorders in later life**

Bipolar disorders in later life include various presentations of mania or hypomania in the course of a depressive disorder. Patients with early and late onset of disorder are included, and a cut-off age of 50 years for bipolar onset is commonly used. Other cut-off ages between 50 and 65 years have also been applied (Sajatovic & Chen, 2011). Studies have shown that approximately half of the patients with bipolar disorder in later life experience depression as their debut symptom. Patients with bipolar disorders in later life often display medical comorbidity, particularly vascular disease. It can be challenging to recognize bipolar disorder correctly in patients with late-onset due to medical

diseases, side effects of medications, and no previous history of mood disorder (Sajatovic & Chen, 2011).

Kessing investigated differences in diagnostic subtypes of bipolar disorder in older (> 50 years) versus younger patients in their first contact with health care services. He reported that for hospitalized patients, severe depression with psychosis, manic episode without psychosis, and hypomania were more common among the older group. No differences were reported for outpatients (Kessing, 2006). In line with these findings, a recent task force report concluded that there seems to be minor phenomenological differences between early and late onset bipolar disorder, and differences were most prominent among hospitalized patients (Sajatovic et al., 2015).

### *Subthreshold depressive syndromes*

Various “subthreshold depressive syndromes” (see page 24) are reported to be two to three times more prevalent than major depression among the elderly (Meeks et al., 2011). These “subthreshold depressive syndromes” can impact quality of life and functions of daily living among the elderly (Bryant, 2010).

*I felt a Funeral, in my brain  
And Mourners to and fro  
Kept treading – treading – till it seemed  
That Sense was breaking through -*

From “I felt a Funeral, in my brain”  
Emily Dickinson

## Depression, cognitive impairment and dementia

### *Depression as a risk factor and/or prodrome for dementia.*

There are many links between depressive syndromes/depression and cognitive impairment/dementia. Depression in early life can be a risk factor for later development of dementia. In a systematic review, Ownby et al. concluded that patients with a history of depression were more likely to be diagnosed with Alzheimer's disease later in life, compared to persons without a history of depression. The authors described that depression was more likely a risk factor than prodrome of Alzheimer's disease (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Others studies have contrasted these findings and found depression in the ten years before onset of dementia to be more important for the risk of dementia than earlier depression (Brommelhoff et al., 2009). Brommelhoff et al. suggest that DLL is a prodrome, rather than a risk factor for dementia. A recent systematic review concluded that depression may be both a risk factor and a prodrome for dementia. This review also put forward that greater frequency and severity of depressive episodes seemed to increase the risk for dementia, and highlighted the risk in patients with bipolar disorders (da Silva, Goncalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013). Additionally, in a systematic review and meta-analysis of community-based cohort studies, Diniz et al. indicated a strong link between the presence of DLL and incident vascular dementia (Diniz, Butters, Albert, Dew, & Reynolds, 2013). In a Danish study, Kessing and Nilsson reported that hospitalized patients with unipolar or bipolar affective disorder had an increased risk of developing dementia over 25-30 years compared to hospitalized patients with diabetes or osteoarthritis (Kessing & Nilsson, 2003).

### *Common biological pathways for depression and dementia.*

Depression and dementia can have several common biological pathways, i.e., vascular disease, inflammation, alterations in nerve growth factors like BDNF, abnormalities in hippocampus and fronto-striatal circuits, and increased deposition of  $\beta$ -amyloid plaques (Butters et al., 2008; Byers & Yaffe, 2011). These biological pathways can interact and thus contribute to various presentations of DLL and cognitive impairments. Symptoms of DLL and dementia can also overlap, i.e., psychomotor changes, lack of interest or pleasure, concentration difficulties and sleeping disturbances (Bennett & Thomas, 2014; Starkstein, Ingram, Garau, & Mizrahi, 2005).

### *DLL and cognitive impairment*

DLL patients with cognitive impairment most often present amnesic-, learning- and executive difficulties. All these problems can be secondary to slowed information processing (Butters et al., 2004; Naismith et al., 2012; Sheline et al., 2006). In a much cited article, Alexopoulos et al. investigated DLL patients with "reversible dementia," i.e., the dementia syndrome subsided after depression had improved. "Reversible dementia" is often also described as pseudodementia. The patients were followed for 34 months on an average, and patients with "reversible dementia" had an almost five times higher risk for having dementia at follow-up, compared to the group without the dementia syndrome (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993). Later investigations found cognitive impairments in DLL to be more persistent, with visuospatial ability, information processing, delayed memory, and executive functioning being frequently cited (Bhalla et al., 2006; Kohler, Thomas, Barnett, & O'Brien, 2010).

### *DLL in pre-existing dementia*

As described in this section and elsewhere in the thesis (page 30), depression or depressive symptoms can be displayed in the course of dementia disease as a prodromal feature even before cognitive impairments or later in the MCI-stages (Knapskog et al., 2014; Lyketsos, 2010; Panza et al., 2010). Patients with an established diagnosis of dementia also frequently encounter depression or depressive symptoms (Barca, Engedal, Laks, & Selbaek, 2010; Knapskog et al., 2014). Patients with vascular dementia (Ballard et al., 2000) and DLB (Auning et al., 2011; Ballard et al., 1999) seem to be particularly at risk for depression and depressive symptoms. Janzing et al. described that patients with dementia can present more depressive symptoms of “motivational character” and less depressive symptoms of “mood character” compared to patients without dementia (Janzing, Hooijer, van 't Hof, & Zitman, 2002). Later studies contrasted these findings and reported that the core symptoms of depression are similar in patients with or without dementia (Engedal, Barca, Laks, & Selbaek, 2011; Starkstein, Mizrahi, & Garau, 2005).

Other authors have suggested that depression in patients with Alzheimer’s disease may differ greatly from depression according to the standardized criteria and have developed specific criteria for depression in Alzheimer’s disease (PDC-dAD) (see Textbox 5) (Olin, Katz, Meyers, Schneider, & Lebowitz, 2002). These criteria include social withdrawal or isolation and irritability as depressive symptoms and emphasize that depressive symptoms can have a fluctuating course in dementia (Olin, Schneider, et al., 2002; Selbaek & Borza, 2015). These criteria have not been validated sufficiently for use in clinical practice (Engedal et al., 2011).

Textbox 5: Provisional diagnostic criteria for depression of Alzheimer's disease (PDC-dAD)

A. Three (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) decreased positive affect or pleasure.

- (1) Clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful)
- (2) Decreased positive affect or pleasure in response to social contacts and usual activities
- (3) Social isolation or withdrawal
- (4) Disruption in appetite
- (5) Disruption in sleep
- (6) Psychomotor changes (e.g., agitation or retardation)
- (7) Irritability
- (8) Fatigue or loss of energy
- (9) Feelings of worthlessness, hopelessness, or excessive, or inappropriate guilt
- (10) Recurrent thoughts of death, suicidal ideation, plan, or attempt

B. All criteria are met for dementia of the Alzheimer type (DSM-IV).

C. The symptoms cause clinically significant distress or disruption in functioning.

D. The symptoms do not occur exclusively during the course of a delirium.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication).

F. The symptoms are not better accounted for by other conditions, such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorder.

### **Depression in later life (DLL) and assessment scales.**

Standardized assessment scales are generally recommended when evaluating DLL. Some scales are designed to aid the screening of the patient, and others are developed more to monitor depressive symptoms and effect of treatment. In this thesis we have used the MADRS and the CSDD in Paper I, the MADRS and the HADS in Paper II, the MADRS in Paper III, and the CSDD in Paper IV. These scales will therefore be described more comprehensively in the following part of this section. Other assessment scales used in DLL are, e.g., the HAM-D, the GDS, the BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease Rating Scale), and the NPI (Neuropsychiatric Inventory).

#### ***The Montgomery Asberg Depression Rating Scale -MADRS***

The MADRS is a ten-item clinician rated depression scale designed as a sensitive measure to change in treatment effects (Montgomery & Asberg, 1979). The items are apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is rated from 0 points (no symptoms) to 6 points (severe symptoms), and a higher score on the MADRS denotes more severe depression. The items are rated based on the week prior to the interview, but other time periods can be applied (Montgomery & Asberg, 1979; Snaith, Harrop, Newby, & Teale, 1986). In the original MADRS article, the study sample consisted of depressed patients aged 18-69 from Sweden and England.

Montgomery and Asberg described high test-retest reliability at various stages in the treatment course (correlation coefficient [ $r$ ]= 0.89-0.95) and high inter-reliability among clinicians in different countries and among different health professionals ( $r$ =0.93-0.97). The authors measured validity by how well the MADRS differentiated responders to treatment compared to clinicians' global judgment ( $r$ = 0.70). (Montgomery & Asberg, 1979). Snaith et al. suggested grade scores for severity of depression based on the MADRS scores: 0-6 recovered/depression is absent; 7-19, mild depression, (low scores in this category were worthy of consideration for treatment in a clinical assessment); 20-34, moderate depression, with a probable need for treatment; and 35-60, severe depression and with an undoubted need for treatment of depression (Snaith et al., 1986). Later studies investigated the psychometric properties of the MADRS (Davidson, Turnbull, Strickland, Miller, & Graves, 1986) and outlined how to enhance the usefulness of the scale (Williams & Kobak, 2008).

An advantage of using the MADRS in elderly people is the relatively few items tapping physical health. Many clinical trials, particularly with antidepressants, have used the MADRS to evaluate treatment effects in DLL (Baudic, Tzortzis, Barba, & Traykov, 2004; Cipriani, Barbui, Butler, Hatcher, & Geddes, 2011; Heo, Murphy, & Meyers, 2007; Kok, Nolen, & Heeren, 2012; O'Brien et al., 2004). In an exploratory factor analysis of MADRS, Parker et al. found three interpretable factors in patients aged 59 years and older diagnosed with major depression and no neurological disorder. The first factor, "dysphoric apathy/retardation," included the items apparent sadness, reported sadness, lassitude, concentration difficulties, and inability to feel. The second factor, "psychic anxiety," included inner tension, pessimistic thoughts, and suicidal thoughts. The third factor, "vegetative symptoms," included reduced sleep and reduced appetite (Parker, Flint, Bosworth, Pieper, & Steffens, 2003). Some other studies have investigated the psychometric properties of the MADRS in elderly samples. For instance, Mottram et al. investigated the validity of MADRS in elderly depressed community residents. The MADRS was compared to cases defined by the Automated Geriatric

Examination for Computer Assisted Taxonomy (AGECAT) of the Geriatric Mental State Examination (GMS). The authors concluded that the MADRS had good diagnostic accuracy (Mottram, Wilson, & Copeland, 2000). Sagen et al. investigated the properties of the MADRS in screening for depression in stroke patients and found acceptable results compared to a clinical diagnosis of depression according to a structured interview for DSM-IV (Sagen et al., 2009). Other studies have investigated the properties of the MADRS in samples with Parkinson's disease (Leentjens, Verhey, Lousberg, Spitsbergen, & Wilmsink, 2000; Silberman et al., 2006) and with various degrees of cognitive impairment (Knapskog et al., 2011; Leontjevas, Gerritsen, Vernooij-Dassen, Smalbrugge, & Koopmans, 2012).

In summary, the MADRS is useful in evaluating treatment effects in DLL. Although less investigated, it seems to have acceptable psychometric properties in elderly patients and in those with MCI and mild dementia.

### *The Hospital Anxiety and Depression Scale - HADS*

The Hospital Anxiety and Depression scale (HADS) is a 14-item self-administered scale with seven items assessing anxiety symptoms and seven assessing depressive symptoms. The scale was developed to detect common aspects of neurosis for patients aged 18-65 in medical clinics, but the subscales (HADS-A and HADS-D) also proved to be valid as measures of the severity of the two psychiatric diseases. Each item is rated from 0 to 3, based on the previous week, and a higher score denotes more severe symptoms (total maximum score is 42, and on each subscale maximum score is 21) (Zigmond & Snaith, 1983). A score of 8 or more on the subscales is often recommended as a cut-off value (Bjelland, Dahl, Haug, & Neckelmann, 2002; Olsson, Mykletun, & Dahl, 2005). The HADS has shown good internal consistency and is well validated in the adult populations.

There are some studies on the psychometric properties of the HADS in elderly samples. A factor analysis of the HADS in healthy elderly persons has confirmed its two-dimensional structure (Gale et al., 2010). Helvik et al. found the HADS to have satisfactory internal consistency in medically hospitalized elderly patients (Helvik, Engedal, Skancke, & Selbaek, 2011). In addition, several studies on elderly patients in different settings have used the HADS to evaluate anxiety and depression (Drageset, Eide, & Ranhoff, 2013; Helvik, Engedal, & Selbaek, 2013; Stordal et al., 2001).

### *The Cornell Scale for Depression in Dementia - CSDD*

The CSDD is a 19-item scale developed to assess depressive symptoms in patients with dementia (Alexopoulos, Abrams, et al., 1988). The 19 items are anxiety, sadness, lack of joy, irritability, agitation, retardation, multiple physical complaints, loss of interest, appetite loss, weight loss, lack of energy, diurnal variation, difficulty falling asleep, multiple awakening, early morning awakening, suicidal ideation, poor self-esteem, pessimism, and delusion. Even though the authors of the original study of the CSDD did not carry out a factor analysis, they grouped the depressive symptoms into five clusters: mood-related signs, behavioral disturbances, physical signs, cyclic functions, and ideational disturbances. The CSDD includes information provided by caregivers and a rating by the clinician after an interview with the patient. The CSDD should be based on information from the week prior to the interview. The depressive symptoms are rated 0=absent, 1=mild or intermittent and 2=severe

and the CSDD also allows a rating of “item unable to evaluate.” The maximum score is 38, and a higher score denotes more severe depressive symptoms. In the original publication of the CSDD, Alexopoulos et al. included patients from a psychiatric hospital in the inter-rater reliability study and patients from a psychiatric hospital and nursing homes in the internal consistency, concurrent validity, and sensitivity studies. The authors reported high inter-rater reliability across dementia groups with different severity, good internal consistency (Cronbach  $\alpha=0.84$ ), and good ability to detect depression compared to clinical diagnosis (Alexopoulos, Abrams, et al., 1988). The CSDD was also validated in elderly patients without dementia in the same year as the original publication (Alexopoulos, Abrams, Young, & Shamoian, 1988).

A variety of studies later investigated the psychometric properties of the CSDD. For example, a Danish study of 145 individuals aged 65 years and older with and without dementia reported high inter-reliability on the CSDD. In that study the CSDD was found to be better than the GDS to screen the study sample for ICD-10 depression (Korner et al., 2006). A Norwegian reliability and validity study of the CSDD among elderly patients in hospitals and nursing homes found satisfactory reliability, in line with the works of others (Barca, Engedal, & Selbaek, 2010). The study investigated different cut-off values on the CSDD using Receiver Operating Characteristic (ROC) analysis, and reported the highest accuracy for ICD-10 depression at a cut-off value of 8/9. In nursing home patients only, 9/10 was reported as the best cut-off value (Barca, Engedal, & Selbaek, 2010). Kurlowicz et al. carried out a psychometric evaluation of the CSDD through factor analysis and assessment of criteria validity in a nursing home population. The factor analysis resulted in a four-factor solution: depression, somatic/vegetative, disturbed sleep and anxiety. The authors reported adequate internal consistency and reliability (Kurlowicz, Evans, Strumpf, & Maislin, 2002).

Barca et al. also carried out a factor analysis of the CSDD in a study sample of 902 nursing home residents in Norway. This factor analysis resulted in five factors the authors described as “mood-,” “physical,” “cyclic,” “retardation” and “behavioral.” These factors accounted for 54.4% of the explained variance. The authors further classified the factors in mood (“mood”) and non-mood factors (“physical,” “cyclic,” “retardation” and “behavioral”) (Barca, Engedal, Laks, et al., 2010).

Knapskog et al. reported cultural variations between how caregivers in Norway and Brazil rate the CSDD items (Knapskog, Portugal Mda, et al., 2013). Additionally, various longitudinal studies on the effect on medications in patients with dementia have used the CSDD to assess depression (Banerjee et al., 2011; Bergh, Selbaek, & Engedal, 2012; Weintraub et al., 2010).

### ***The Hamilton Rating Scale for Depression - HAM-D***

The HAM-D is a depression scale where the clinician rates 21 individual symptoms, 11 symptoms with a rating of 0-2 and 10 symptoms with a rating of 0-4 (Hamilton, 1960). The HAM-D has been widely used in several depressed populations, particularly in clinical trials (Nelson, Clary, Leon, & Schneider, 2005).

Authors have investigated the properties of the scale for use in elderly samples (Heo et al., 2007; Mottram et al., 2000; Onega & Abraham, 1997). One challenge is that the scale contains a number of items that measure physical symptoms, and, therefore, can yield too high of a symptom-score in elderly samples with high medical comorbidity (Baldwin, 2014).



### *The Geriatric Depression Scale - GDS*

The GDS was specifically developed to aid screening of depression in elderly samples (Yesavage et al., 1982). The original version contains 30 yes/no questions regarding how the individual felt over the past week, but versions with fewer questions have been developed and validated (Herrmann et al., 1996). The GDS can be self-administered or administered by a clinician, and studies have shown that the scale can be useful in many settings with good overall validity (Glover & Srinivasan, 2013).

### *Scales assessing depressive symptoms as part of neuropsychiatric symptoms*

#### *The Behavioral Pathology in Alzheimer's Disease Rating Scale - BEHAVE-AD and the Neuropsychiatric Inventory- NPI*

The BEHAVE-AD (Reisberg et al., 1987) and the NPI (Cummings et al., 1994) were developed to assess neuropsychiatric symptoms, including depressive symptoms, commonly seen in patients with Alzheimer's dementia and other dementias from information provided by caregivers. The BEHAVE-AD contains seven main categories with 25 behavioral symptoms, which are rated according to severity (0-3, where higher score denotes more severe symptoms) based on the previous two weeks. One of the categories is labeled "affective disturbance," and here the assessors must rate the symptoms tearfulness and depressed mood. The total severity score on the BEHAVE-AD is 0-75 points (a higher score denotes more severe symptoms) and affective disturbance is considered with 0-6 points. The BEHAVE-AD has been further developed to include frequency measures, too (Monteiro et al., 2001; Reisberg et al., 2014).

The NPI rates the occurrence, frequency and severity of 12 neuropsychiatric symptoms, where dysphoria/depression is one of the 12 items. The rating of the NPI is often based on the previous month. The score of the 12 different neuropsychiatric symptoms are calculated by multiplying frequency (1-4) and severity (1-3), where a higher score denotes more symptom load from the specific item. Thus, the maximum score of the total scale is 144, and the maximum score on the dysphoria/depression item is 12. A score of four or higher on an individual item is often used to indicate a clinically significant symptom (Cummings et al., 1994; Margallo-Lana et al., 2001). Studies have investigated the prevalence, incidence and persistence of clinically significant depressive symptoms by this method among residents in care facilities with high rates of dementia (Ballard et al., 2001; Bergh, Engedal, Roen, & Selbaek, 2011; Selbaek et al., 2014). Other authors have defined presence of a symptom on the NPI as an item-score of more than 0 for patients with dementia. Using this definition of "depression" up to two-thirds of dementia sufferers will present depression over a five-year period (Lyketsos, 2010; Steinberg et al., 2008). Kaufer et al. have developed a shorter form of the NPI, namely the Neuropsychiatric Inventory Questionnaire (NPI-Q). The NPI-Q contains the same 12 neuropsychiatric categories as the NPI, and the informants are first asked if the items are present (yes/no). If present, the neuropsychiatric symptoms are rated according to severity (1=mild, 2=moderate, 3=severe). The total severity score of the NPI-Q ranges from 0-36, and a higher score denotes more severe symptoms. The individual NPI-Q item score and total score have been found to correlate adequately with the equivalents on the NPI (Kaufer et al., 2000).

## Treatment of depression in later life (DLL)

Cure her of that.

*Canst thou not minister to a mind  
diseased.*

*Pluck from the memory a rooted  
sorrow.*

*Raze out the written troubles of the brain*

*And with some sweet oblivious  
antidote*

*Cleanse the stuffed bosom of that  
perilous stuff*

*Which weighs upon the heart.*

From "Macbeth" by  
William Shakespeare

The management of DLL can be divided into three phases: acute, continuation, and maintenance (Frank et al., 1991). In the acute phase, the goals are remission and to restore previous everyday functioning. The continuation phase typically lasts six to twelve months and the focus is recovery. In the maintenance phase the emphasis lies on prevention of recurrence. There are various guidelines on how to deal with depression in adults that also apply to DLL (Helsedirektoratet, 2009; National Institute of Clinical Excellence (NICE), 2010). These guidelines also describe relevant treatment approaches, such as stepped care and collaborative care. Stepped care means that patients firstly are provided with the least intensive and least costly intervention to the presenting problems. If the initial treatment is not appropriate, more intensive levels of care to match the patient's individual needs are offered. Collaborative care places emphasis on treatment in primary care. Mental health specialists and primary care practitioners cooperate and approach the problems broadly involving the patient, carers and a personalized treatment plan. Studies have investigated collaborative care in DLL specifically, and it has been found to improve outcomes (Unutzer et al., 2002). Specific guidelines for DLL also exist, e.g., in 2006 the Canadian Coalition for Seniors' Mental Health published "National Guidelines for Senior's Mental Health, the Assessment and Treatment of Depression" ("[www.ccsmh.ca/en/natlGuidelines/initiative.cfm](http://www.ccsmh.ca/en/natlGuidelines/initiative.cfm)," 2006).

### ***Pharmacological treatment***

A systematic review of 51 double-blind randomized controlled trials (RCTs) concluded that antidepressant treatment is efficacious in DLL (55 + years) (Kok et al., 2012). The review included acute phase treatment of patients with unipolar depression and without dementia, and described a response rate of 48.0% and a remission rate of 33.7%. These numbers support the view that antidepressants are equally efficacious in the elderly as in younger adults (Kok, 2013). There is also evidence of no difference in antidepressant response between age-subgroups (59-69 years, 70-75 years and 76-99 years) of DLL (Gildengers et al., 2002). Kok et al. confirmed findings from a Cochrane review that different classes of antidepressants (tricyclic antidepressant (TCA), selective Serotonin reuptake inhibitors (SSRI) and other antidepressants) seem to have the same efficacy in DLL (Kok et

al., 2012; Mottram, Wilson, & Strobl, 2006). The review from Kok et al. found no differences in efficacy between the antidepressants in severely depressed patients either, but reported that few RCTs have focused on this group of patients. The authors further reported that with regard to RCTs, treatment-resistant depression, psychotic depression, minor depression, and depression in nursing homes were understudied (Kok et al., 2012).

The Cochrane review described higher withdrawal rates related to side effects from TCAs compared to SSRIs. Patients who received TCAs experienced more side effects, like dry-mouth and neuropsychiatric side effects (e.g., drowsiness, dizziness, lethargy). SSRI-recipients experienced more nausea and vomiting (Mottram et al., 2006).

Approximately 50% of patients with DLL do not respond to the initial antidepressant. Factors associated with more treatment-resistant DLL include high medical burden, comorbid anxiety, poor sleep, low self-esteem, coexisting cognitive impairment (Andreescu & Reynolds, 2011; Driscoll, Karp, Dew, & Reynolds, 2007), and the total volume of WML on magnetic resonance imaging (MRI) (Sneed et al., 2011). A systematic review on treatments for refractory depression in elderly patients (>55 years) included mostly open-label studies and no RCTs, and concluded that about half of the patients responded to additional pharmacological treatment. There was best evidence for augmentation with lithium (Cooper et al., 2011). A recent randomized, double-blind and placebo-controlled trial of treatment-resistant major depression in later life found that augmentation with Aripiprazole (a second generation antipsychotic) to Venlafaxine (an antidepressant) was effective in achieving and maintaining remission (Lenze et al., 2015).

Studies on pharmacological treatment of patients with depression and dementia do not show a clear effect of antidepressants. This may be related to the fact that it can be difficult to define homogenous groups of patients with depression and dementia. Nelson and Devanand carried out a meta-analysis of acute-phase, placebo-controlled antidepressant studies of patients with depression and dementia and found great variety in methods and design of relevant studies. Seven studies met the selection criteria and the authors concluded that evidence does not support efficacy of antidepressants (Nelson & Devanand, 2011). Subsequently, placebo-controlled studies supported these findings (Banerjee et al., 2011). Kok et al. have investigated the efficacy of continuation or maintenance treatment with antidepressants on patients over 55 years with depression. The meta-analysis and systematic review included eight RCTs. The authors found antidepressants to be efficacious compared with placebos in preventing relapses and recurrences, and reported no differences between the different antidepressants (Kok, Heeren, & Nolen, 2011). The number of patients needed to treat (NNT) has been calculated to be around four for maintenance treatments and seven to eight for acute treatment (Andreescu & Reynolds, 2011; Kok et al., 2011; Reynolds et al., 2006).

### *Psychological treatment*

Various psychotherapeutic interventions including cognitive behavioral therapy (CBT), problem-solving therapy (PST), interpersonal therapy (IPT), psychodynamic orientated therapy, and reminiscence therapy (RT) may be effective in the acute phase of DLL (Francis & Kumar, 2013; Pinquart, Duberstein, & Lyness, 2006). However, a lack of high-quality studies exists to confirm the evidence of efficacy, which can partly be related to difficulties in evaluating studies methodologically according to good scientific practice (Thomas, 2013a; Wilson, Mottram, & Vassilas, 2008). Currently,

the most evidence supports cognitive behavioral therapy (CBT), but there is little indication that supports that one intervention is more efficacious than the other (Francis & Kumar, 2013). For patients with major depression and executive dysfunction some studies have indicated that PST may be effective in terms of symptom reduction, response, and remission (Arean et al., 2010).

Guidelines generally recommend psychotherapeutic interventions for depression of mild to moderate degree as the first-line treatment, either alone or sometimes in combination with antidepressants (Helsedirektoratet, 2009; "www.ccsmh.ca/en/natlGuidelines/initiative.cfm," 2006). There are few studies about the effects of psychotherapy for patients with more severe DLL, comorbid physical diseases, and cognitive impairment (Francis & Kumar, 2013).

In a randomized, double-blind and placebo controlled study of maintenance treatment for DLL conducted with patients 70 years or older over two years, Reynolds et al. compared the efficacy of a SSRI and monthly IPT. The study showed that patients with an initial effect of SSRI and IPT were less likely to have recurrent depression if they received SSRI as maintenance therapy over two years, whereas monthly maintenance IPT did not prevent recurrent depression (Reynolds et al., 2006).

### *Electroconvulsive therapy (ECT)*

Studies have supported the use of ECT in DLL. ECT is particularly recommended as a treatment option in patients with severe DLL, treatment-resistant DLL, good previous experience from ECT, and intolerance to medications (Riva-Posse, Hermida, & McDonald, 2013). Some studies have indicated better outcomes of ECT in the elderly in terms of more rapid remission (Rhebergen et al., 2014) and higher remission rates (O'Connor et al., 2001). However, there have been safety concerns about ECT in DLL, particularly with regard to cognitive side-effects (Dybedal, Tanum, Sundet, Gaarden, & Bjølseth, 2014; Van der Wurff, Stek, Hoogendijk, & Beekman, 2003). Studies on electrode placements and electrical charge in ECT have focused on ways to maximize clinical effect and minimize cognitive side-effects. Bjølseth et al. found bifrontal and right unilateral electrode placement to be equally efficacious and with no differences of the mean MMSE score between the two groups across the treatment course in a study of ECT in DLL (Bjølseth et al., 2015).

The high relapse rate after use of ECT in DLL is a therapeutic challenge (Moksnes, 2011; Sackeim et al., 2001). There are insufficient studies on the role of ECT as continuation treatment, but some studies have shown a good effect in DLL patients with successful response to the initial ECT series (van Schaik et al., 2012).

### *Physical exercise*

Findings from studies on the efficacy of various physical exercises in DLL are inconclusive (Steffens, 2013). A key factor to this is the heterogeneity in exercises, methods, and patient-groups. A systematic review from Finland on the effects of physical exercise in DLL concluded that physical exercise may be efficient to reduce depression and depressive symptoms, but more controlled studies were warranted (Sjosten & Kivela, 2006). Later studies have emphasized tailoring the physical exercise to each individual's ability (Bridle, Spanjers, Patel, Atherton, & Lamb, 2012). A large-scale study of a moderate intensity exercise program for elderly residents of care homes found no effect of depressive symptoms as measured by the GDS (Underwood et al., 2013). Furthermore, there is limited evidence to support the effect of physical exercise on depression in patients with dementia (Potter, Ellard, Rees, & Thorogood, 2011).

### *Multifaceted interventions*

Studies have supported the efficacy of treatment delivered in combinations of interventions tailored to DLL patients. Many such studies have been carried out among outpatients (Alexopoulos et al., 2009; Klug et al., 2010; Unutzer et al., 2002). Treatment of DLL in hospitals is often multidisciplinary and typically includes psychotherapies, physical exercise, ECT, medications, and supportive care (Zubenko et al., 1994).

### *Prevention of depression in later life (DLL)*

In recent years, there has been increasing interest in efforts to prevent the development of DLL (Okereke, 2015). Primary prevention focuses on stopping the onset of DLL and secondary prevention refers to deterring future recurrences after a depressive episode. With respect to primary prevention, different strategies such as universal, selective, and indicated prevention, have been applied (Baldwin, 2010; Beekman, Smit, Stek, Reynolds, & Cuijpers, 2010; Cole, 2008; Lyness, Yu, Tang, Tu, & Conwell, 2009). There is no evidence to support that interventions targeted at the entire elderly population (universal prevention) will be effective (Beekman et al., 2010). Selective prevention for individuals at risk for depression (e.g., those with functional impairments, several chronic diseases, living alone, or with a low level of mastery of their environment) (Smits et al., 2008) has been shown to reduce the development of depressive symptoms (Baldwin, 2010). For instance, Rasmussen et al. found Sertraline to be effective in non-depressed, acute stroke patients in order to prevent post-stroke depression over a 12-month period. They showed a “sparing effect” of Sertraline over placebos of between 15-18% (Rasmussen et al., 2003). Indicated prevention refers to strategies targeted at individuals who have some symptoms of DLL (i.e., “subthreshold depression”) but do not meet a diagnosis of MDD according to the DSM-5 or depressive episode according to the ICD-10. Veer-Tazelaar et al. investigated a stepped care approach targeted toward individuals 75 years or older with “subthreshold depression” or “subthreshold anxiety.” They found that the intervention halved the development of new episodes at both one year (van't Veer-Tazelaar et al., 2009) and two years (van't Veer-Tazelaar et al., 2011) compared to usual care. At two years the NNT was calculated to be five.

### *Treatment in nursing homes*

Studies of interventions for depression among nursing home residents are scarce (Ruset, 2005; Stewart, 2013). Psychotherapeutic interventions targeted to DLL residents in nursing home may be effective, but firm conclusions have generally been hampered by methodological limitations. A review of psychotherapy in long-term care described reminiscence therapy as the most investigated. (Bharucha, Dew, Miller, Borson, & Reynolds, 2006). The effectiveness and safety of antidepressants among nursing home residents with DLL is debatable (Boyce et al., 2012). However, Bergh et al. found that discontinuation of antidepressants in nursing home residents with dementia and neuropsychiatric symptoms resulted in more depressive symptoms as measured by the CSDD after 25 weeks. Secondary analyses revealed that 83% of the residents discontinuing antidepressants remained unchanged in the CSDD category 0-13, three per cent of the residents remained unchanged in the CSDD category 14+, and the remaining 14% switched from scoring 0-13 on the CSDD to 14+. Participants in the study had dementia, were prescribed antidepressants due to NPS, and had no history of a depressive disorder (Bergh et al., 2011). Some recent studies on DLL in nursing homes

have shown positive results from behavioral treatment (Meeks, Van Haitsma, Schoenbachler, & Looney, 2015) and multidisciplinary interventions (Leontjevas et al., 2013).

## Prognosis of depression in later life (DLL)

### *Course of depression in later life (DLL)*

There are various studies on the course of DLL from different settings including community, primary health care, medical units, and out- and inpatients units in specialist health care services of psychiatry. Observational studies with a follow-up period of 12-24 months and studies reporting trajectories are described in more detail in Table 4, as they are particularly relevant for Paper III in the present thesis. Thus, in the following part of this section, we will focus on meta-analyses and studies with a follow-up period of more than two years.

Cole and Bellavance reviewed the prognosis of depression in the elderly based on 16 studies from psychiatric hospitals. In patients followed for at least 12 months; 60% were either well or had relapses with good recovery; 14-22% were continuously ill; and the remainder had poor outcomes, such as death, dementia, or residual symptoms. Many of the included studies had methodological limitations, but the authors reported that physical illness, cognitive impairment, and severe depressive symptoms might be correlated with a poorer prognosis. In the review the authors also compared the results from hospitals with five community-based studies and reported better prognoses in the hospital studies. This finding might be related to under-treatment in the included community-based studies (Cole & Bellavance, 1997b).

The same authors carried out a meta-analysis of outcomes of depression in medically ill patients aged 60 years or older. The analysis included 8 studies and reported that by 12 months, 29% were still depressed, 19% were well, and 53% had died. The authors concluded that the recovery rate of depression in this patient group was low, and factors associated with worse outcomes included more severe depression, more severe physical illness, and symptoms of depression before admission to the hospital (Cole & Bellavance, 1997a).

In a prospective study over a six-year period with 277 DLL patients in the community, Beekman et al. reported persistent remission in 23% of the patients, remissions with recurrence in 12%, chronic-intermittent course in 33%, and chronic depression in 33%. The authors found that outcome correlated with the baseline diagnosis in that subthreshold depression had the best outcome; major depressive disorder and dysthymia had intermediate outcomes; and double depression (both dysthymia and major depressive disorder) had the poorest outcome (Beekman et al., 2002).

Another prospective study over a three-year period with 234 patients aged 55 years or older with major depressive disorder in primary care investigated the duration of depression and recovery over time. The patients were evaluated with the MADRS and a diagnostic interview for primary care every sixth months and recovery was defined when the MADRS score was less than 10 and the criteria for major depressive disorder no longer were present. The mean time for recovery was 19 months, and within one year, 35% had recovered; within two years, 60%; and within three years, 68%. More severe depression at baseline, a family history of depression, and poorer physical functioning was associated with poor outcome (no recovery during follow-up) (Licht-Strunk et al., 2009).

In a systematic review Mitchell and Subramaniam compared the prognosis of depression in old age to middle age. The authors reported similar response and remission rates to treatment in the acute phase of depression for the two groups. Medical comorbidity was put forward as a risk factor for worse treatment response. A main finding was that elderly patients were associated with a higher risk of relapses compared to the younger patients (Mitchell & Subramaniam, 2005).

### *Dementia as an outcome of depression in later life (DLL)*

As discussed in section “Depression, cognitive impairment and dementia” (page 38), there is evidence that depression can be both a risk factor and a prodrome to dementia, and for a dose-response association between depression and dementia (Bennett & Thomas, 2014; da Silva et al., 2013). The presence of DLL is associated with an increased risk for all-cause dementia (Diniz et al., 2013).

### *Depression in later life (DLL) and disability*

There are reports of a bidirectional relationship between disability and DLL (Lenze et al., 2001). In a review of longitudinal studies on DLL and disability, Schillerstrøm et al. concluded that baseline and incident DLL consistently predicted functional decline. The mediational pathways were not completely mapped, but included behavior changes, such as apathy, cognitive impairment like executive dysfunction, and medical comorbidities. Particularly, cerebrovascular disease has been proposed as important to consider (Schillerstrom, Royall, & Palmer, 2008).

### *Mortality of depression in later life (DLL)*

Studies have shown that DLL is associated with increased mortality (Blazer, 2003; Pulska, Pahkala, Laippala, & Kivela, 1999; Schoevers et al., 2009), and that the severity and duration of depression are related to mortality (H. R. Bogner, K. H. Morales, C. F. Reynolds, 3rd, M. S. Cary, & M. L. Bruce, 2012a; Geerlings, Beekman, Deeg, Twisk, & Van Tilburg, 2002). Several mechanisms can underlie why depression may increase mortality in DLL patients, including effects of comorbid illness (e.g., vascular disease), behavioral factors (less physical exercise, smoking, alcohol habits), poor adherence to treatment, increased vulnerability to disease, side-effects of medications, and suicide (Baldwin, 2014).

A suicide most often includes a complex interplay of personality factors, comorbidities and stressful life events. Depression is a strong risk factor for suicide. Conwell et al. indicated that the odds of suicide were between 12 and 36 times higher for an elderly person having major depressive episode compared to matched controls (Conwell, Van Orden, & Caine, 2011). Another study of suicide among the elderly found that 75% of those who had committed suicide were clinically depressed at the time of death (Snowdon & Baume, 2002). Males were more prone to suicide, while other risk factors included physical or psychiatric illness with suffering, disability, losses including bereavement, and untenable situations. Thirty percent of those who had committed suicide had attempted suicide previously. The authors concluded that recognizing and managing distress- and depressive symptoms appropriately could reduce suicides in the elderly (Snowdon & Baume, 2002). High suicide rates in later life, particularly in men (Manthorpe & Iliffe, 2010), are a public health concern (Kjolseth, Ekeberg, & Steihaug, 2009, 2010).

### *Course of depression in nursing homes*

A six-month study of nursing home residents in the Netherlands described a persistency rate of 63% for depressive symptoms assessed with the GDS-30 (Smalbrugge et al., 2006). Residents with a GDS-score of > 10 at baseline were categorized as having clinically relevant depressive symptoms, and remitters had a decrease of at least 4 points on the GDS and GDS score <11 at follow-up. Thus, non-remitters had persistence of depressive symptoms. A score above 18 on the GDS at baseline was associated with more persistent depressive symptoms (Smalbrugge et al., 2006). A Norwegian study on depression in nursing home residents over 12 months reported a persistency rate of 45%. Clinically significant depression was defined as a score of >7 on the CSDD. A higher CSDD score at baseline, use of anxiolytics at baseline and not being married were predictors for persistent depression. Additionally, depression was a predictor for mortality (Barca, Engedal, Laks, et al., 2010).

In a longitudinal study of depression and mortality in nursing homes over one year, Rovner et al. found that major depressive disorder increased the likelihood of death by 59% (Rovner et al., 1991). In that study, major depressive disorder was a significant predictor for death, even after controlling for physical health. More recent studies have confirmed these findings (Kane, Yochim, & Lichtenberg, 2010). Conversely, other studies have not found depression to be independently associated with mortality in institutionalized elderly residents (Parmelee, Katz, & Lawton, 1992a). Sutcliffe et al. reported that depressed mood was not related to mortality over 21 months in an English study of survival in care homes. However, further analyses showed higher GDS-scores at baseline in the residents who died earliest, i.e., within five months (Sutcliffe et al., 2007).

Taken together, we argue that the prognosis of DLL is generally poor in terms of relapse and recurrence of depression, chronicity or residual symptoms, disability, and development of dementia. Furthermore, DLL is a risk factor for suicides and is associated with increased mortality.

*“Do not go gently into that good night,  
Old age should burn and rage at close of day;  
Rage, rage against the dying of the light”*

From “Do not go gently into that good night”  
by Dylan Thomas



## Tables with previous and relevant studies to the papers in the thesis

### Paper I:

As described in this thesis, the MADRS is a useful scale to assess DLL. However, there are not many studies on the validity of the MADRS as a screening scale in elderly persons without dementia. The validity studies have often used different reference standards for a diagnosis of depression, and the optimal cut-off values are inconsistent (Table 2). Several of the validity studies have been carried out in people with Parkinson's disease. Thus, we wanted to carry out a validity study of the MADRS in elderly persons without dementia.

### Paper II:

Table 3 presents results from observational studies of early treatment responses in elderly depressed inpatients. As can be seen, the outcome measures are heterogeneously defined. With respect to the methods and findings of the studies presented in Table 3, it is most relevant to compare Paper II to the studies of Hereen et al. (the Netherlands) and Zubenko et al. (the USA).

Additionally, in an analysis of symptom-specific changes of the HAM-D during treatment with SSRI in 728 patients aged 60 years or older with MDD and without dementia, Nelson et al. reported the HAM-D items "depressed mood" and "decreased interest and activity" to show greatest improvement (Nelson et al., 2005). The study used effect size (ES) statistics to determine symptom-specific changes, a technique that has been previously described (Leon, Shear, Portera, & Klerman, 1993), and which we used to estimate the symptom-specific changes of the MADRS in Paper II. We found no other studies that estimated the symptom-specific changes of the MADRS in DLL patients.

### Paper III:

Table 4 shows observational studies of depression in later life (DLL) with a follow-up period of 12-24 months and studies of DLL reporting results from various trajectory analyses. Observational studies with longer follow-up period are described in the section "Prognosis in depression in later life (DLL)."

The observational studies in Table 4 show that DLL can have a chronic or relapsing nature in 50% or more of the patients over the course of 12-24 months. The predictors for worse outcome are somewhat mixed, but include worsened physical health, previous depressive episodes, psychiatric comorbidity, less social support, and cognitive impairment.

Studies of trajectories in DLL seek to capture the course of depression using repeated measurements. Different statistical techniques can identify how individuals may follow a similar pattern, and variables or outcomes that are associated with the different trajectories. The studies in Table 4 have identified various numbers of trajectories of DLL, probably due to differences in methods and study samples. More severe depression scores at baseline, higher medical burden, and EOD are variables found to be associated with worse trajectories. Membership to trajectory classes with high and persistent depressive symptoms was associated with poorer future outcomes in terms of presence of MDD-diagnosis and death. Many of the studies in Table 4 have excluded patients with dementia, and a very few with trajectory analyses have included hospitalized patients from specialist health care

services. Hence, observational, longitudinal studies, including analyses of trajectories, on outcome in DLL in different clinical settings are warranted.

Paper IV:

Table 5 shows longitudinal studies on the course of depressive symptoms and depression in nursing home residents. Depression and depressive symptom have been measured with different scales and criteria. The studies have followed nursing home residents clinically for 6-14 months and up to 33 months for mortality data. Incidence rates of depression vary between 1.8%-14.9% and persistence rates of clinically significant depressive symptoms vary between 11.0% and 63.3%, but time periods, definitions of relevant terms and study samples differ.

Hence, there is a need for large-scale longitudinal studies of depression and depressive symptoms in nursing homes with a follow-up period longer than a year. Such studies can be complicated by drop-outs due to deaths.

**Table 2. Validity studies of the Montgomery and Asberg Depression Rating Scale (MADRS) in elderly study samples.**

Author	Study sample	n	Reference standard	Results
Mottram et al. 2000	Depressed community residents aged 65+	414	GMS/AGECAT	Optimal cut-off value = 20/21 with sensitivity = 72% and specificity = 99%. AUC = 0.95.
Leentjens et al. 2000	Non-demented Parkinson patients; mean age 68 years	63	DSM-IV	Optimal cut-off value of 14/15 with sensitivity = 88% and specificity = 89% AUC = 0.90.
Silbermann et al. 2006	Non-demented Parkinson patients; mean age 68 years	46	DSM-IV	Optimal cut-off value = 9/10 with sensitivity = 56% and specificity = 96%. AUC = 0.84.
Reijnders et al. 2009	Non-demented Parkinson patients; mean age 66 years	154	DSM-IV (SCID-D)	Optimal cut-off value = 13/14 with sensitivity = 79% and specificity = 80%. AUC = 0.88.
Leontjevas et al. 2009	Early onset dementia patients in nursing home; mean age 59 years	63	PDC-dAD	Proxy-based MADRS. Optimal cut-off value = 19/20 with sensitivity = 75% and specificity = 84%. AUC = 0.87.
Sagen et al. 2009	Stroke patients; mean age 65 years	104	DSM-IV (SCID)	Optimal cut-off value = 8/9 with sensitivity = 85% and specificity = 71%. AUC = 0.91
Knapkog et al. 2011	Memory clinic patients; mean age 67 years	98	DSM-IV and ICD-10	DSM-IV: Optimal cut-off value = 7/8 with sensitivity = 89% and specificity = 67%. AUC =: 0.84 ICD-10: Optimal cut-off value = 6/7 with sensitivity = 90% and specificity = 76%. AUC = 0.88.
Leontjevas et al. 2012	Nursing home residents with dementia; mean age 84 years	101	PDC-dAD	Proxy-based MADRS. Optimal cut-off value = 13/14 with sensitivity = 78% and specificity = 66%. AUC = 0.73.
Portugal Mda et al. 2012	Outpatients with and without dementia; aged 65+	95	DSM-IV, ICD-10 and PDC-dAD	DSM-IV: Optimal cut-off value = 9/10 with sensitivity = 83% and specificity = 60%. AUC = 0.75. ICD-10: Optimal cut-off value = 9/10 with sensitivity = 77% and specificity = 60%. AUC = 0.75. PDC-dAC: Optimal cut-off value = 8/9 with sensitivity = 75% and specificity = 75%. AUC = 0.80.

GMS = The Geriatric Mental State Examination;

AGECAT = The Automated Geriatric Examination for Computer Assisted Taxonomy;

AUC = Area under curve; SCID = Structured Clinical Interview for the DSM-IV

PDC-dAC = Provisional Diagnostic Criteria for depression of Alzheimer's Disease

(Knapkog et al., 2011; Leentjens et al., 2000; Leontjevas et al., 2012; Leontjevas, van Hooren, & Mulders, 2009; Mottram et al., 2000; Portugal Mda et al., 2012; Reijnders, Lousberg, & Leentjens, 2010; Sagen et al., 2009; Silberman et al., 2006)

**Table 3. Observational studies of early treatment response in elderly depressed inpatients**

Author	n	Study sample	Mean stay	Results
Cole 1983	38	Mean age 70, 74% females, 27% with first lifetime depressive episode.	10 weeks	At discharge: 50% much improved, 34% moderately improved, 11 % failed to respond, and 5% died.
Baldwin & Jolley 1986	100	Patients with Feighner's criteria for depression. Patients with "organic psychosyndrome" and previous history of mania were excluded. Mean age 74 years, 79% females, 54% with first lifetime depressive episode. Mean HAM-D = 27.5	76 % less than 3 months	69% were well (free from depressive symptoms) at discharge, 21% improved (incomplete symptomatic recovery), 8% little or no change, 2% died.
Rubin et al. 1991	101	Chart review of patients with DSM-III diagnosis of depression, without possible/probable dementia and bipolar affective disorder. Mean age 76 and 81% females. Mean GDS-30: 18.	33 days	Physician-rated global improvement showed that 58% had major improvement, 38% some improvement and 4% no improvement. Advanced age was not associated with poorer outcome.
Zubenko et al. 1994	205	Patients with DSM-III-R diagnosis of mood disorder, without dementia. Mean age 70 years, 74% females, 27% with first lifetime depressive episode. Mean HAM-D = 22. 10% with MMSE score < 22.	32 days	46% with complete response (HAM-D ≤ 10 at discharge), 5% partial responders (HAM-D > 10 and ≥ 50% reduction of HAM-D score) and 49% non-responders. Black race, better cognition, lower medical burden, treatment with ECT and shorter stay in the hospital favored a better response to inpatient treatment.
Heeren et al. 1997	215	Patients with DSM-III-R mood disorder, without dementia. Mean age 74 years, 72% females, 38% with first lifetime depressive episode. Median MADRS: 34.	19 weeks	40% with full recovery) (= MADRS < 10 at discharge), 53% with partial recovery (> 50% reduction in MADRS score), and 7% not recovered.
Brodaty et al. 2000	81; n=53 ≥ 65+ years	Patients with DSM-III-R diagnosis of major depressive disorder and no dementia, divided into 3 age groups: < 65, 65-74 and 75+ years. All patients were treated with ECT. The group of 65+ years had a mean of 3 previous depressive episodes and 67% were females. Mean HAM-D = 29.	Not reported	64% of patients 65+ years were defined as "responders," as evaluated by a 5-point clinical rating scale. Improvement on HAM-D and clinical outcome ratings were comparable in the three age groups.
Zanardi et al. 2003	327; n=174 ≥ 61 years	An observational pharmacotherapy (Fluvoxamine) study over 6 weeks of inpatients with HAM-D score ≥ 21 and MMSE score ≥ 23. The 61+-group had a mean of 7 previous depressive episodes and 66% were females. Mean HAM-D-21 = 31.	6 weeks	55% of patients 61+ years were defined as responders (HAM-D ≤ 8 and no delusions). The group of 61+ had poorer response compared to those <61 years.
Muller 2004 et al.	332; n=32 age 65-79	This observational study of 4 age groups (17-30, 31-50, 51-64 and 65-79) of inpatients with MDD (RDC/DSM-IV) reported results from the index episode of MDD. (The patients were followed for up to 15 years in terms of recurrence of depression)	Not reported	Median time to recovery, as evaluated by the Psychiatric Status Rating, was similar for the four groups.

HAM-D = The Hamilton Rating Scale for Depression; GDS = The Geriatric Depression Scale; MADRS=The Montgomery and Asberg Depression Rating Scale; MMSE = The Mini Mental State Examination; ECT = Electroconvulsive therapy; MDD = Major depressive disorder; RDC = The Research Diagnostic Criteria (Baldwin & Jolley, 1986; Brodady, Hickie, Mason, & Prenter, 2000; Cole, 1983; Heeren, Derksen, van Heycop Ten Ham, & van Gent, 1997; Mueller et al., 2004; Rubin, Kinscherf, & Wehrman, 1991; Zanardi, Cusin, Rossini, De Ronchi, & Serretti, 2003; Zubenko et al., 1994)

**Table 4. Observational studies of with a follow-up period of 12-24 months and studies of depression in later life (DLL) reporting trajectories.**

Author	n	Study sample	Method/ measure	Follow- up	Results
Cole & Bellavance 1997	1487 + 249	Meta-analysis of 16 hospital-based (1487 patients) and 5 community-based (249 patients) studies of depressed patients 60+ years.	Meta-analysis	12-24 months	Many studies had methodological limitations. Combined results (may not sum up to 100%) in the hospital-based studies with follow-up of 12-24 months: 44% of the patients were well, 16% relapse with recovery, 22% continuously ill, 22% other (e.g., dead, dementia, invalidism, residual symptoms). Combined results (may not sum up to 100%) in the community-based studies with follow-up period of 12-24 months: 34% of the patients were well, 27% continuously ill, 30% other (e.g., dead, dementia, invalidism, residual symptoms). Physical health, cognitive impairment and severe depressive symptoms were associated with poor prognosis.
Bosworth et al. 2002	166	Patients 60+ with MDD. Patients with other psychiatric (e.g., bipolar disorder) and neurologic disorder (e.g., dementia and Parkinson's disease) were excluded.	DSM-IV and MADRS	12 months	45% of the study sample were in remission (MADRS < 7) after one year. More depressive episodes, using anxiolytics/sedatives, more IADL problems, and decreased social support at baseline predicted poor depressive outcome after one year.
Lyness et al. 2009	484	Patients aged ≥ 65 years from primary care medicine and family medicine practices.	SCID (DSM-IV) and HAM-D	12 months	Patients with minor and subsyndromal depression at baseline had a higher risk of developing MDD and were more depressed on the HAM-D at one-year follow-up, compared to non-depressed controls. White race, baseline depression diagnosis, GAF score, social interaction, and perceived social support were significant predictors of depression diagnosis at one year.
Magnil et al. 2013	54	Patients aged 60+ years with mild and moderate depression from a primary care center. Patients with dementia were excluded.	PRIME-MD CEG, MADRS-S, and DSM-IV	24 months	The study reported a declining median MADRS-S score and three course patterns during follow-up: remitting, stable, and fluctuating. History of depression, significant life events, lacking leisure activities, and use of sedatives were risk factors for depression at the 24-month follow-up.
Comijs et al. 2014	285	Clinically depressed patients according to DSM (MDD, minor depression, dysthymia) aged 60 years or older. Patients with dementia or suspected dementia were excluded.	DSM-IV (CIDI) and IDS	24 months	48.4% of the patients fulfilled the criteria for depression after 24 months. Patients with more severe depressive symptoms, comorbid dysthymia, younger age of onset and more chronic diseases were more likely to be depressed at 24-month follow-up. 61% of the patients that were depressed at baseline had a chronic course of depressive symptoms during follow-up.

**Table 4 Continued**

Studies of DLL reporting trajectories:					
Author	n	Study sample	Method/ measure	Follow-up	Results
McCusker et al. 2007	232	Patients aged 65+ admitted to medical services without dementia (at most MCI).	HAM-D	12 months	The patients were grouped in minimal, mild, and moderate/severe course of depressive symptoms, according to clustering analysis. A higher initial HAM-D score, depressive core symptoms lasting 6 months or more and female sex predicted more severe course.
Andreescu et al. 2008	1260	Community based patients aged 65+ years, without dementia.	mCES-D	12 years	The study identified 6 trajectories. Two trajectories had few or no depressive symptoms during baseline and follow-ups. Two trajectories had few symptoms at baseline and then diverged. Two trajectories began with significant depressive symptoms at baseline and then had different slopes. The trajectory with highest depression scores was associated with higher medical burden, higher baseline scores and a symptom profile at baseline of low self-esteem, interpersonal difficulties, neurovegetative symptoms, and anhedonia.
Cui et al. 2008	392	Primary care patients	DSM-IV, HAM-D, and PSR	2 years	The study identified 6 trajectory clusters. Non-depressed and subsyndromal depression at baseline had a wide range of outcomes over 2 years. Baseline symptom severity, medical burden and psychiatric functional status were predictors for depression trajectory.
Bogner et al. 2012	599	Patients 60+ years from primary care with MDD or clinically significant minor depression with MMSE > 17 recruited from an intervention study.	HAM-D	12/24 months	Over the course of 12 months, 3 trajectories of depressive symptoms were identified: high persistent course (19.1%), high declining course (14.4%), and low declining course (66.5%). Patients with high and persistent course were more likely to have a diagnosis of MDD at 24 months compared with patients with a course of low and declining depressive symptoms.
Bogner et al. 2012	599	Patients 60+ years from primary care with MDD or clinically significant minor depression with MMSE > 17 recruited from an intervention study.	HAM-D	1/5 years	The study identified 3 trajectories in the first years of the study: high persistent course, high declining course, and low declining course. Patients with course of high persistent depressive symptoms the first year were more likely to have died after 5 years, compared with patients with a course of high but declining depressive symptoms.
Hybels et al. 2015	368	Patients of 60+ years with MDD from primary care and psychiatry clinics; free of dementia and suspected cognitive impairment, other psychiatric conditions, and primary neurological illness.	MADRS	3 years	A model with 4 trajectories of recovery was identified; quick recovery class (43%), persistent moderate class (27%), persistent high symptom class (15%) and slow recovery class (15%). Patients in the slow recovery class had a younger age of onset compared with those in the quick recovery group. Levels of perceived stress and social support at baseline differed significantly across the classes of recovery.
McCusker et al. 2016	130	Residents in long-term care with MMSE of 15+ at baseline and GDS-scores at least at one-thirds of the follow-ups.	GDS	6 months	The study identified 3 symptom clusters of trajectory over time; "lower", "intermediate" and "higher" levels of depressive symptoms. Baseline GDS >7, female sex, stay in long term care < 12 months and corrected visual impairment were predictors for a more severe trajectory.
Kaup et al. 2016	2488	Community living elderly person aged 70-79 years	CES-D-10	11 years	Three trajectories in the period from baseline to year 5 were identified: consistently minimal depressive symptom (62%), moderate and increasing symptoms (32%), and high and increasing symptoms (6%). The trajectory of high and increasing symptoms had higher risk of incident dementia at year 11, compared with the consistently minimal symptoms trajectory.

MADRS = The Montgomery Asberg Depression Rating Scale; SCID = Structured Clinical Interview for DSM-IV; HAM-D = The Hamilton Rating Scale for Depression; MDD = Major depressive disorder, GDS = The Geriatric Depression Scale; IADL = Instrumental activities of daily living; ECT = Electroconvulsive therapy; mCESD = modified Center for Epidemiological Studies-Depression Scale; PRIME-MD CEG = PRIME-MD Clinical Evaluation Guide; MADRS-S = Self-rated version of the MADRS; CIDI = Composite International Diagnostic Interview; IDS = The Inventory of Depressive Symptoms; PSR = Psychiatric State Rating; GDS = The Geriatric Depression Scale; CES-D-10 = Center for Epidemiologic Studies Depression Scale Short Form (Andreescu, Chang, Mulsant, & Ganguli, 2008; Bogner et al., 2012a; H. R. Bogner, K. H. Morales, C. F. Reynolds, M. S. Cary, & M. L. Bruce, 2012b; Bosworth, Hays, George, & Steffens, 2002; Cole & Bellavance, 1997b; Cornijs et al., 2015; Cui, Lyness, Tang, Tu, & Conwell, 2008; Hybels, Pieper, Blazer, & Steffens, 2015; Kaup et al., 2016; Lyness, Chapman, McGriff, Drayer, & Duberstein, 2009; Magnil, Janmarker, Gunnarsson, & Bjorkelund, 2013; McCusker et al., 2007; McCusker et al., 2016)

**Table 5. Longitudinal studies on the course of depressive symptoms and depression in nursing home residents**

Author	Study sample	n*	Method	Follow-up period	Results
Payne et al. 2002	Newly admitted nursing home residents with dementia, mean age 80 years	201(201*)	CSDD, depression=CSDD > 12	12 months after admission to nursing home	20% with depression at admission. Recurrence/persistence rate of depression at 6 months: 11.0% and incidence rate: 1.8%. At 12 months recurrence/persistence rate: 13.8% and incidence rate: 6.4%.
Sutcliffe et al. 2007	Newly admitted nursing home (n=158) and residential home residents (n=150), mean age 83 years, mean MMSE 14.0	308(188*)	GDS-15(GDS-12R), cut-off=4/5	9-12 months (clinically at 5 and 9 months, telephone at 12)	38% depressed at baseline, 43% of these were still depressed at 5 and 9 months. Depressed mood at baseline was not related to mortality at 12 months; however, residents who died before 5 months had higher depression score at baseline than those who survived longer.
Barca et al. 2010	Nursing home residents, mean age 85 years, mean CDR sum of boxes score 10.6	872(639*)	CSDD, depression = CSDD ≥ 8	12 months	Persistence rate: 44.8%, incidence rate: 14.9%. A higher score on the CSDD and shorter stay in nursing home at baseline were predictors for incidence and persistence of clinically significant depressive symptoms.
Rozzini et al. 1996	Nursing home residents >11 on the MMSE, mean age 81 years	56(43*)	GDS-30, depression= GDS ≥ 18	12 months	At baseline 48.2% had GDS score >15, 33% had a persistent status of depression (GDS score ≥ 18). Increasing GDS score was associated with decreasing activities of daily living, increasing number of clinical problems and younger age.
Smallbrugge et al. 2006	Nursing home residents from 14 nursing homes with MMSE ≥ 15, 51.7% > 80 years	350(218*)	GDS-30, GDS score > 10 = clinically relevant depressive symptoms	6 months	The prevalence of depressive symptoms decreased from 41.3% to 28.9% during follow-up. Persistence rate: 63.3%, incidence rate: 4.7%. Persistence of depressive symptoms was more frequent in residents with higher GDS score (18-30). Preadmission factors and transition may largely be responsible for depressive symptoms among nursing home residents.
Boorsma et al. 2012	Nursing home residents from 6 nursing homes, 32.7% > 85 yrs. and 31.3% with dementia	1324(621**)	RAI-LTCF (DSM-IV), depr. = diagn. or use of antidepressants	Average follow-up period of 13.7 months	The incidence rate of depression was 13.6 pr. 100 person years. Dementia and a score of 3 or more the Depression Rating Scale were risk factors for onset of depression.
Katz et al. 1989	Nursing home residents without moderate and severe dementia, mean age 83 years	51(45*)	GDS-30 (≥11 = "significant depression") and DSM-III.	6 months + mortality data at 33 months	Prevalence rate of MDD ranged between 18-20%. Incidence rate: 13.5%. Dysphoria, loss of energy, loss of interest, and psychomotor retardation were more present in those with depression compared to those without depression. Higher mortality after 33 months for those with clinical depression at baseline than for the non-depressed.
McSweeney & O'Connor 2008	Newly admitted nursing home residents, mean age 84 years, 75% with MMSE <23	51(40*)	CSDD and DSM-IV	6 months	Only residents with MMSE < 23 were diagnosed with MDD. Prevalence of MDD at 1, 3 and 6 months post-admission were 20%, 14% and 15%, respectively. 20% had chronic depression.
Parmalee et al. 1992 b	Predominately Jewish nursing home (n=337) and congregate apartment residents (n=531) not "cognitive disorientated," mean age 84 years	868(448*)	GDS-20 and DSM-III-R.	12 months	Incidence rate of MDD: 5.6% and minor depression: 6.3%. More than 40% of residents with MDD showed no remission after 12 months. Persistence of depression was associated with cognitive decline and decline in functional ability. Patients with remitted depression displayed greater decline in physical health than residents with persistent depression, incident depression, or no depression.



**Table 5 continued.**

<b>Author</b>	<b>Study sample</b>	<b>n*</b>	<b>Method</b>	<b>Follow-up period</b>	<b>Results</b>
Wancata et al. 2003	Newly admitted nursing home residents 60 years or older (69.9% >80 years), 63.9% with dementia	249(179*)	Epidemiological survey with CIS and DSM-III-R.	6 months	Among residents with dementia (n=86) "depressed mood" showed highest remission and "retardation in speech/movement" highest chronicity of the depressive symptoms on the CIS-interview.
Foster et al. 1991	Newly admitted residents in a medical long-term care facility with MMSE $\geq$ 18 and GDS greater than stage 3, mean age 49 years	104(25*)	HAM-D and GDS-30 and RDC-diagnosis of depression	12 months	The incidence rate of depression was calculated in two ways (the cumulative incidence rate and incidence density rate) and was approximately 14%.
Hoover et al. 2010	Newly admitted long-term nursing home residents aged $\geq$ 65 years, 29.5% "cognitive intact"	634060	MDS on nursing home residents from 1999-2005 in the USA. Depression = Physician diagnosed depression	12 months	Recorded depression at admission and during first year (cumulative depression) increased from 1999 (42.2%) to 2005 (54.4%). Pain and physical comorbidity were positively associated with depression identified throughout the first year.
Parmelee et al. 1992	Predominately Jewish nursing home and congregate apartment residents not "cognitive disorientated," mean age 84 years	898(711*)	GDS-30, GDS-15 and DSM-III-R	30 months	Residents with MDD had higher mortality rates compared to residents with minor depression and no depression. However, these associations seemed to disappear when controlled for effects of physical health, cognitive status and functional disability.

\*Completed the follow period \*\* Study sample for the analysis of incidence

MMSE = Mini Mental State Examination; CDR = The Clinical Dementia Rating; CSDD = The Cornell Scale for Depression in Dementia; MDD=Major depressive disorder; GDS = The Geriatric Depression Scale; RAI-LTCF = Resident Assessment Instrument- Long-Term Care Facility Database; CIS= Clinical Interview Schedule; HAM-D = Hamilton Rating Scale for Depression; RDS = Research Diagnostic Criteria; MDS = Minimal Data Set

(Barca, Engedal, Laks, et al., 2010; Boorsma et al., 2012; Foster, Cataldo, & Boksay, 1991; Hoover et al., 2010; Katz, Leshner, Kleban, Jethanandani, & Parmelee, 1989; McSweeney & O'Connor, 2008; Parmelee et al., 1992a; Parmelee, Katz, & Lawton, 1992b; Payne et al., 2002; Rozzini, Boffelli, & Franzoni, 1996; Smalbrugge et al., 2006; Sutcliffe et al., 2007; Wancata, Benda, Meise, & Windhaber, 2003)

## The studies in the thesis

### Objectives

The overall objective of this thesis was to study the course and prognostic factors of depression and depressive symptoms in the elderly. The thesis includes results from different study samples with DLL and with various follow-up periods. More specifically, the main objectives of the different papers included in this thesis were:

- To investigate the validity of the MADRS as a screening aid to detect depressive disorder in an elderly study population without dementia.
- To investigate the course of DLL in terms of response, remission and symptom-specific changes as measured by the MADRS during a stay in the hospital and to explore which clinical variables were associated with remission and response.
- To investigate the course of DLL over one year in terms of outcomes such as trajectory classes and relapse/recurrence and to explore which clinical variables were associated with the outcomes.
- To investigate the long-term course of depressive symptoms as measured by the CSDD in nursing home residents and associated clinical variables.

### Design

We have carried out three different studies in this thesis:

Study 1 (Paper I) is a validation study of the MADRS among in- and outpatients older than 65 years without dementia.

Study 2 (Papers II and III), the Prognosis of depression in the elderly (PRODE) study, is a multicenter, observational, and longitudinal study of elderly inpatients (60 years or older) with depression admitted to departments of old age psychiatry. The PRODE study has four assessments: at inclusion to the study ( $T_0$ ), at discharge from the hospital ( $T_1$ ), one year after inclusion ( $T_2$ ), and three-years after inclusion to the study. Results from the latest assessment are not included in the present thesis. The PRODE study will be more comprehensively described in the methods section of this chapter.

Study 3 (Paper IV), the Psychiatric Symptoms in Nursing homes (PSIN) study, is a longitudinal study of nursing home residents with five assessments over 74 months.

## Participants

### Study 1, the MADRS validation study

The MADRS validation study included patients older than 65 years who suffered from a disease other than dementia that caused a need for health care services. Patients were excluded if they had a diagnosis of dementia, scored below 20 on the MMSE, had aphasia, or a physical disorder with a life expectancy of less than three months.

The validation study included 140 participants recruited from two study centers. Center 1 recruited 70 inpatients from a department of geriatric medicine (Oslo University Hospital, Ullevål). Center 2 (Department of Old Age Psychiatry, Innlandet Hospital Trust) recruited 70 participants, 44 of whom were inpatients from two departments of old age psychiatry (Reinsvoll and Sanderud) or outpatients attending a day-hospital within old age psychiatry. The remaining 26 were nursing home residents (Haugtun Nursing Home) in the catchment area of the Department of Old Age Psychiatry at Reinsvoll.

### Study 2, the PRODE study



The PRODE study included patients 60 years or older with or without dementia referred to treatment for depression in the departments of old age psychiatry at specialist psychiatric health services. Patients with acute life-threatening diseases as well as patients with dementia who had severe aphasia were excluded from the study.

The nine participating study centers (Oslo University Hospital, Vardåsen (Ullevål) and Aker, Diakonhjemmet Hospital, Innlandet Hospital Trust, Sanderud and Reinsvoll, Vestre Viken Hospital Trust, Lier, Stavanger University Hospital, St. Olav Hospital, University Hospital of Trondheim, and Haukeland University Hospital, Bergen) recruited 169 patients; 160 inpatients and 9 outpatients. Six of the nine study centers were able to collect data on age and gender of patients who declined participation, as seen in Table 6. In these six study centers, 174 patients were approached and 38 refused to participate in the study. There were no significant differences in age ( $p=0.88$ ) or gender ( $p=0.13$ ) between those who participated in the study and those who refused to participate. Papers II and III both deal with the inpatients of the PRODE study. Of the 160 inpatients, 14 (8.8%) had a diagnosis of dementia according to the ICD-10 established during their stay in the hospital.

In Paper II, 15 of the 160 included inpatients were excluded due to incomplete MADRS records, leaving 145 remaining inpatients for this paper. In Paper III, all 160 included inpatients were analyzed

in the trajectory analysis. Seven had died and seven were unwilling to participate at the one-year follow-up examination, leaving 146 patients for the analysis of the clinical course of depression reported in this paper.

**Table 6. Participating study centers and included patients in the Prognosis of Depression in the Elderly (PRODE) study**

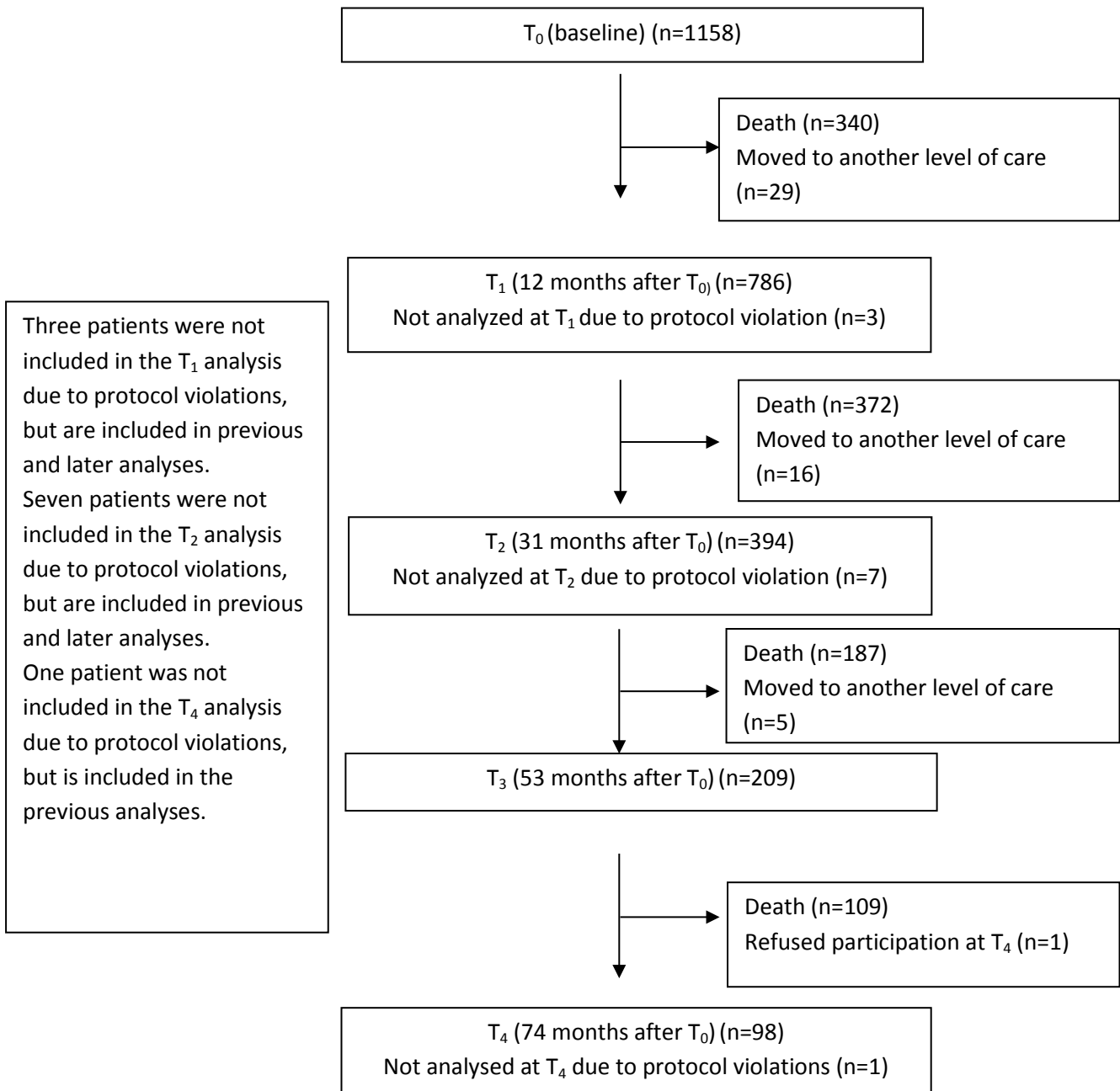
<b>Department of Old Age Psychiatry:</b>	<b>Number of eligible patients:</b>	<b>Total number of included patients:</b>	<b>Total number of inpatients:</b>
Oslo University Hospital, Vardåsen	*)	22	22
Diakonhjemmet Hospital	15	11	11
Oslo University Hospital, Aker	*)	4	4
Innlandet Hospital Trust, Sanderud	51	38	38
Innlandet Hospital Trust, Reinsvoll	9	5	5
Vestre Viken Hospital Trust, Lier	55	50	46
Stavanger University Hospital, Stavanger	8	4	4
St. Olav Hospital, University Hospital of Trondheim	36	28	23
Haukeland University Hospital, Bergen	*)	7	7
<b>Total</b>		<b>169</b>	<b>160</b>

\*) = information not available

### **Study 3, the PSIN study**

The PSIN study included nursing home residents 50 years or older with a minimum stay of 14 days. All eligible residents in 26 nursing homes in 18 municipalities in four Norwegian counties (Aust-Agder, Vest-Agder, Hedmark and Oppland) were asked to participate. Nursing homes were selected in order to reflect the distribution of the entire nursing home population in terms of size of municipalities and urban versus rural areas in the four counties. A total of 1165 residents were eligible, of which two refused to participate and five were excluded due to age < 50 years, leaving 1158 residents for Paper IV. At baseline, 80.5% of the residents had dementia, as evaluated by the Clinical Dementia Rating (CDR), and 33.7% had severe dementia (CDR=3). The attrition from baseline to the last assessment is shown in Figure 1. At the last follow-up, 98 residents were assessed.

**Figure 1. Flow chart describing attrition from baseline (T<sub>0</sub>) to the last assessment (T<sub>4</sub>) in the Psychiatric Symptoms in Nursing homes (PSIN) study**



## Methods.

### Study 1, Paper I:

The validation study of the MADRS was carried out according to the recommendations for such studies including I) a control group without the target disorder (depression), II) a representative clinical setting where the test (the MADRS) will be used, III) the test (the MADRS) and the reference standard (the DSM-IV criteria for major depressive disorder) were applied to all participants, and IV) independent assessments (“blinded”) (Jaeschke, Guyatt, & Sackett, 1994).

One consultant psychiatrist and one trained nurse examined all included patients from Center 1. Three senior consultant psychiatrists and trained nurses examined the patients from Center 2. All included patients were examined according to the MADRS and the DSM-IV criteria for MDD. The patients from Center 2 were also examined according to the CSDD and the ICD-10 criteria for depressive episode. The trained nurses examined the patients with the MADRS and the CSDD. Within one week of the MADRS and the CSDD examinations, the psychiatrists, who were blinded for the MADRS and the CSDD ratings, carried out the diagnostic interviews independently of the nurses’ examinations. The psychiatrists examined the patients on average of 2.1 days (SD 2.9 days) after the nurses.

### Study 2, Paper II and III:

In the PRODE study, the nine participating departments of old age psychiatry used the same standardized instruments to collect data of the patients on depression and other mental health issues, cognition, physical health, use of medications, functions in activities of daily living, quality of life, and family carer’s situation. Assessors received standardized training in use of the assessment scales prior to the study period and again twice a year during the study period in order to secure reliable data.

Patients were assessed for eligibility and included as early as possible after admission to the department of old age psychiatry at the hospital ( $T_0$ ). Discharge from the hospital ( $T_1$ ) was settled by the individual departments, and the discharge assessment was carried out as near as possible to the date of discharge. Information on prior depressive and psychiatric history, including the number of previous depressive episodes and age at onset of the first lifetime depressive episode, was obtained from case notes and structured interviews with the patients and carers. Patients were diagnosed with depression and dementia according to the ICD-10 criteria. In line with previous studies, we used 60 years as a cut-off age for early versus late onset of the first lifetime depressive episode in the patient’s life (Reynolds et al., 1998). The number of previous depressive episodes was dichotomized into no previous depressive episodes or previous depressive episode(s). Anxiety symptoms were assessed by the seven-item subscale (tension, fear of awful happenings, worrying thoughts, inability to relax, feeling of “butterflies in stomach,” restlessness, and feeling of panic) of the HADS, i.e., the HADS-A (Zigmond & Snaith, 1983). We used the MMSE to evaluate cognitive function. Physical health was assessed with the General Medical Health Rating Scale (GMHR), a four-point scale (excellent, good, fair, and poor) assessing medical comorbidity. The GMHR takes into account each patient’s number of general medical conditions, the severity of those conditions, and the patient’s use of

medications (Lyketsos et al., 1999). We dichotomized the GMHR to good (excellent/good) and poor (fair/poor) for the analyses. We used the Lawton and Brody scale to evaluate the instrumental activities of daily living (IADL). This scale consists of eight items (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances) for females and five items (ability to use telephone, shopping, mode of transportation, responsibility for own medications, and ability to handle finances) for men. We scored the items according to the original publication (0 or 1, where 1 denotes best level of functioning) and then generated a mean score for all patients (Lawton & Brody, 1969). A higher score denotes a higher level of functioning (maximum score is 1 and minimum is 0). Use of medications was classified according to the Anatomical and Therapeutic Chemical (ATC) classification system, and dosages of various psychotropic medications were calculated by using the daily defined dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, 2013).

The included patients underwent an MRI brain scan according to a specific protocol developed for this project. A control group of healthy elderly individuals were recruited for the MRI-study. Furthermore, blood and saliva from the included patients were collected and stored in a Biobank for analyses of pro- and anti-inflammatory cytokines and cortisol. Results from the analyses of these biomarkers are not included in this thesis, but have been reported elsewhere (Lebedeva et al., 2015). Table 7 shows the information collected in the PRODE study.

#### Paper II:

The data collection for Paper II was carried out by health professionals working at the nine participating study centers from December 2009 to July 2013.

The MADRS was used to rate depressive symptoms in detail and was the primary outcome variable in Paper II. In line with results from previous studies and recommendations, we defined remission as a MADRS score of  $\leq 9$  at the time of discharge (Hawley, Gale, Sivakumaran, & Hertfordshire Neuroscience Research, 2002; Rush et al., 2006). Response was defined as a reduction of the MADRS score of at least 50% from time of inclusion to discharge.

#### Paper III:

The data collection for Paper III was carried out by health professionals working at the nine participating study centers from December 2009 to March 2014. The one-year follow-up examination in PRODE ( $T_2$ ) was carried out by health professionals at the individual study center between 11 and 15 months after inclusion to the study. Data were collected from a clinical assessment, case notes, and information from carers. It was not possible to do a clinical examination of 25 patients and for those patients data were collected from all available sources of relevant information including telephone interviews, if possible. These 25 patients were recruited from six different study centers.

The patient's course of depression between  $T_1$  and  $T_2$  was rated using all available information. The rating was based on outcomes in Cole and Bellavance's meta-analysis of longitudinal studies on the prognosis of DLL (Cole & Bellavance, 1997b). We categorized the outcomes into three course groups:

\* Good = no signs of relapse (return of depression within four months of remission) or recurrence (development of a new depressive episode after four months of remission) (Rush et al., 2006)

\* Residual = reports of residual symptoms

\* Poor = rating of continuously ill of depression or reports of relapse or recurrence, which required hospital admission or with suicidal attempt



**Table 7. Information collected in the Prognosis of Depression in the Elderly (PRODE) study at the different time points.**

	At inclusion to the study (T <sub>0</sub> )	During stay in the hospital	At discharge from the hospital (T <sub>1</sub> )	At one-year follow-up (T <sub>2</sub> )
ICD-10 diagnosis of depression		X		X
ICD-10 diagnosis of dementia		X		X
MCI according to Winblad's criteria				X
Depression and psychiatric health: MADRS, CSDD, HADS, NPI-Q	X		X	X
Cognition, including MMSE, Ten Word Recall Test, COWA, TMT A+B, and IQCODE	X		X	X
Activities in daily living including IADL	X			
Physical health including GMHR	X			X
Use of medications	X		X	X
Quality of life (VAS and EQ-5D)	X			X
Coping strategies (LOC and WOC)		X		
Blood tests and blood samples to biobank (ApoE, cytokines)	X			
Saliva to biobank (cortisol)	X			
Brain MRI		X		
Use of health services	X			X
Carers health, including GDS, VAS, EQ-5D and RSS.		X		X

MCI = Mild cognitive impairment; MADRS = the Montgomery and Asberg Depression Rating Scale; CSDD = The Cornell Scale for Depression in Dementia; HADS = The Hospital Anxiety and Depression Scale; NPI-Q = The Neuropsychiatric Inventory Questionnaire; MMSE = Mini Mental State Examination; COWA = The Controlled Oral Word Association Test; TMT = Trail Making Test; IQCODE = The Informant Questionnaire on Cognitive Decline in the Elderly; IADL = Instrumental Activities of daily living according to Lawton and Brody Scale GMHR = General Medical Health Rating; VAS = Visual Analogue Scale; EQ-5D = EuroQol; LOC = Locus of Control; WOC = Ways of Coping; ApoE = Apolipoprotein E; MRI = Magnetic Resonance Imaging; GDS = The Geriatric Depression Scale; RSS = The Relative Stress Scale

### Study 3, Paper IV

Study 3 (Paper IV) was part of a larger longitudinal nursing home study that aimed to describe behavioral and psychological symptoms and particularly depressive symptoms in nursing home residents (Barca, Engedal, Laks, et al., 2010; Selbaek et al., 2014; Selbaek, Kirkevold, & Engedal, 2007, 2008). In this paper, the residents were assessed at baseline, after 12 months, 31 months, 53 months, and 74 months. The mean length of stay in nursing home at the baseline assessment was 941 (standard deviation [SD] = 1014) days.

Sixteen research nurses used a standardized interview and collected data from November 2004 to September 2011. Data were collected from residents' records and interviews with residents' primary carers, who were all registered nurses. All research nurses attended a training program on how to carry out the interview prior to the assessments.

To assess depressive symptoms in detail, we used the CSDD. As many of the residents in this study had dementia with severe aphasia, we did not carry out a clinical interview with the residents, but relied on information provided by the caregivers most familiar with the residents. This procedure has been applied in previous nursing home studies (Gruber-Baldini et al., 2005; Teresi, Abrams, Holmes, Ramirez, & Eimicke, 2001). In line with a factor analysis by Barca et al. we divided the CSDD into a mood and non-mood factor for the analysis (Barca, Selbaek, Laks, & Engedal, 2008). We used the Clinical Dementia Rating (CDR) score to assess the severity of dementia, and in the analysis we also used the CDR sum of boxes score (Hughes et al., 1982; O'Bryant et al., 2008). The Physical Self-Maintenance Scale (PSMS) was used to assess the resident's ability to perform the personal activities of daily living. The PSMS consists of six items (toilet, feeding, dressing, grooming, physical ambulation, and bathing) and a higher score denotes greater impairment (maximum score of 30) (Lawton & Brody, 1969). Physical health was rated by a customized GMHR to nursing home residents, i.e., with ratings of good, fair, poor, or very poor. Use of medication was classified according to the ATC classification system, and we calculated the DDD to analyze the dose of antidepressants.

## Statistics

### Paper I

Data were managed and analyzed with the Statistical Program for Social Science package (SPSS version 18). A Receiver Operating Characteristic (ROC) analysis was carried out. We calculated area under the curve (AUC), the sensitivity, the specificity, the positive and negative likelihood (LR+ and LR-) ratio for the cut-off values on the MADRS, and the CSDD that produced the highest accuracy. Sensitivity is defined as the proportion of the participants with a positive test result that are correctly identified; in our case, the patients with a score on the MADRS or the CSDD higher than the cut-off value who also had depression according to the reference standard, the DSM-IV, or the ICD-10. Specificity is defined as the proportion of negatives that are correctly identified. In our case, we included the participants with a lower score than the cut-off value on the MADRS or the CSDD and who did not have depression according to the reference standard, the DSM-IV or the ICD-10. Accuracy was defined as the proportion of the study group correctly classified as positive or negative.

## Paper II

Data were analyzed with the SPSS version 22 and Statistical Analysis System (SAS) version 9.3. Results with p-values below 0.05 were considered statistically significant. We used independent samples t-test or  $\chi^2$ -test to assess differences in age and gender between the patients who refused to participate and the included patients in PRODE and to compare the clinical and demographic characteristics between the excluded and included patients in the analyses of this paper. To assess the change in use of psychotropic medications from inclusion to discharge, we used McNemar's test. The paired sample t-test was applied to assess change in DDD and MADRS score from inclusion to discharge.

We calculated effect size (Cohen's d) to determine how the MADRS symptoms changed during stay in hospital. This was done by dividing the mean change in score for each MADRS symptom by the SD (Leon et al., 1993). The SD was adjusted for cluster effect due to sampling from several study centers.

Predictors for change in the MADRS score and for remission and response were assessed by regression models adjusting for possible cluster effect due to center. A linear mixed model with random intercepts (SAS MIXED procedure) was estimated for change in MADRS score, and logistic regression models for hierarchical data with random effects for intercepts were fitted to dichotomous outcomes (response and remission) (SAS GLIMMIX procedure).

The results with p-values below 0.05 were considered statistically significant.

We imputed missing values on IADL items for patients with less than 50% missing values in the IADL scale by drawing one random number per missing value from the empirical distribution of a specific item, estimated on the available data.

## Paper III

Statistical analyses were performed in STATA version 14 and SPSS version 22. Demographic and clinical characteristics at inclusion ( $T_0$ ), discharge from the hospital ( $T_1$ ), and at the one-year follow-up ( $T_2$ ) are presented as means, SDs, and percentages, as appropriate. The independent groups (e.g., completers versus non-completers) were compared by independent samples t-test or  $\chi^2$ -test. The comparison of dichotomous variables at different assessment points was carried out using McNemar's test.

Trend in the MADRS score through the three assessment points was assessed by a linear mixed model with fixed effects for the time component up to second-order and random effects for study centers and patients nested within the center. Such a model correctly accounts for possible intra-class correlations due to both repeated measurements and center-belonging.

Next, a growth mixture model was estimated with an attempt to identify two or more unobserved classes of patients, each following a distinct trajectory. Akaike's Information Criterion (AIC) was applied when identifying trajectories. In addition, we aimed at an average class probability larger than 0.7 and non-overlapping 95% confidence intervals (CI) for trajectories. A logistic regression model with class membership as its outcome was estimated to identify characteristics of the patients describing the classes.

The course of depression from  $T_1$  to  $T_2$  was defined as a categorical variable with categories good, residual, and poor. An ordinal regression model was estimated to assess possible predictors for the course of depression from  $T_1$  to  $T_2$ .

For both regression models the covariates (GMHR, MMSE, diagnosis of dementia, age at onset of the first lifetime depressive episode, remission, depression with psychosis, bipolar disorder, age, sex, marital status, years of education and length of hospital stay/follow-up days between  $T_1$  and  $T_2$ ) were selected based on previous studies, their clinical value, the uniqueness of the present dataset, and the number of variables our regression models could handle. Correlation analysis among relevant covariates and between each covariate and the dependent variables was performed. Age (higher) at onset of the first depressive episode correlated strongly with (no) previous depressive episode(s) (Pearson's correlation coefficient = 0.63). The effects of previous depressive episode(s) and age at onset of the first depressive episode can thus be similar, and in the present analyses we used only age at onset of the first depressive episode, as this variable correlated strongest with both outcomes.

No intra-center correlation was present in the outcomes. The parallel odds assumption in the ordinal regression model was assessed by a test of parallel lines, and no violations were detected. Both regression models were reduced by applying the AIC, where a smaller value implies a better model. The results were presented as odds ratios (OR) with the corresponding 95% CI. Trajectories were presented graphically. The results with p-values below 0.05 were considered statistically significant.

Among patients with less than 50% missing values on the MMSE scale, missing values on MMSE items were imputed with a randomly drawn number from empirical distribution for each relevant item. Subsequently, we imputed MMSE items for three patients at  $T_0$ , two patients at  $T_1$ , and five patients at  $T_2$ .

#### Paper IV

Data were analyzed with the SPSS version 22 and SAS version 9.3. In the analyses we used the following definitions: prevalence (point prevalence) was the proportion of residents with the symptom present at an individual assessment; cumulative prevalence was the proportion of residents with the symptom present at least at one of the five assessments; incidence rate was the ratio of residents who presented the symptom at one assessment to those who were symptom free at the preceding assessment; persistence rate was the ratio of residents who presented the symptom at one assessment to those who presented the symptom at the preceding assessment.

We used independent sample t-test to analyze differences in clinical and demographic characteristics between completers and non-completers. Days of stay in a nursing home was symmetrized by a logarithmic transformation before applying the t-test. We used  $\chi^2$ -test for categorical data. Results with p-values below 0.05 were considered statistically significant.

At baseline ( $T_0$ ), 256 of the 1158 residents (22%) had the rating "unable to evaluate" on one or more items on the CSDD, and at the last follow-up ( $T_4$ ), the corresponding numbers were 29 of the 98 completers (30%). To calculate the CSDD sum score we first imputed items "unable to evaluate" with a score of 0 (Leontjevas et al., 2012), and then calculated the sum score only to those where at most 20% of the CSDD items had the rating "unable to evaluate". With this method we were able to calculate a sum score for 1087 of the 1158 residents (94%) at  $T_0$ , 743 of the 786 residents (95%) at  $T_1$ , 342 of the 394 residents (87%) at  $T_2$ , 180 of the 209 residents (86%) at  $T_3$ , and for 83 of the 98 completers (85%) at  $T_4$ . To assess time trend in the 19 depressive symptoms on the CSDD, we first dichotomized them to present (score of 1 or 2) or absent (score of 0). Then, a logistic regression

model adjusting estimates for repeated measures and hierarchical structure in the data (SAS GLIMMIX procedure) was estimated. The odds ratios (OR) were further adjusted for the CDR sum of boxes score observed simultaneously with depressive symptoms.  $T_0$  was chosen as the reference time point.

We fitted a three-level linear mixed model with random intercepts for residents nested within wards nested within nursing homes (SAS MIXED procedure) to assess time trend in CSDD scores (total CSDD, mood CSDD, and non-CSDD). Dummies for each time point were included in the model as fixed effects with the baseline as reference. Time trend estimates were further adjusted for age, days of stay in the nursing home, education, marital status, physical health, CDR sum of boxes score, PSMS score, use of antidepressants, and number of medications.

A three-level growth model with random intercepts for residents nested within wards and wards nested within nursing homes was also estimated to assess the time change in CDR sum of boxes score.

## **Ethical and legal considerations**

### **Study 1**

The participants provided informed consent in writing to participate in the study. The study was approved by the Regional Committee of Medical Research Ethics and the Data Inspectorate (File number: S-08099dd; 2008/70581 and 2009/379).

### **Study 2**

All the participating patients and caregivers were given oral and written information about the study, and they subsequently gave consent to participate in writing. For patients without the capacity to give consent, their next of kin had to give consent in writing on behalf of the patient. The study was approved by the Regional Committee of Medical Research Ethics (File number: 2009/1774) and Data Protection Officer at Oslo University Hospital. The PRODE study has been registered at Clinical-Trials.gov: NCT01952366.

### **Study 3**

Information about the study was given to the residents and their family members. At the time this study was carried out, an explicit consent to participate was not required. However, the residents, and in case of impaired capacity for consent, their next of kin, were informed that they could refuse to participate at any stage of the study. The Regional Committee of Medical Research Ethics (File number: 2009/2012 and 2010/1894) and the Data Inspectorate and the Directorate for Health Social Affairs approved this procedure.

## Abstract of the papers with additional results

### **Paper I: The validity of the Montgomery–Aasberg depression rating scale as a screening tool for depression in later life**

**Background:** The aims of the study were to examine the validity of the MADRS and to compare it with the validity of the Cornell Scale for Depression in Dementia (CSDD).

**Methods:** We included 140 patients without dementia, with a mean age of 81.5 (SD 7.7) years. Trained psychiatric nurses interviewed all participants using the MADRS. In addition, for 70 patients caregivers were interviewed using the CSDD. A psychiatrist who had no access to the MADRS or the CSDD results made a diagnosis of depression according to the DSM-IV criteria for major depression, and the ICD-10 criteria was also applied for the 70 patients assessed with the CSDD.

**Results:** Twenty-two out of the 140 had depression according to the DSM IV criteria, whereas 25 out of 70 had depression according to the ICD-10 criteria. The area under the curve (AUC) in a receiver operating characteristic analysis (ROC) was 0.86 (95% CI 0.79–0.93) for the MADRS using the DSM-IV criteria. The best cut-off point was 16/17 with sensitivity of 0.80 and specificity of 0.82. The AUC for the CSDD was 0.83 (95% CI 0.71–0.95). The recommended cut-off score on the CSDD of 7/8 was valid but not the best in this study.

**Limitations:** The patients were diagnosed with depression by only one psychiatrist and the procedures in the two centers were not exactly the same.

**Conclusions:** The MADRS has good discriminating power to detect depression in elderly people and should be preferred to the CSDD for use with persons without dementia.

## **Paper II: The course of depression in later life as measured by the Montgomery and Asberg Depression Rating Scale in an observational study of hospitalized patients**

**Background:** Depression and depressive symptoms are highly prevalent in old people but are potentially reversible. Full recovery is the main goal in the treatment of depressive episodes. Compared to clinical trials, observational studies of patients with depression in later life (DLL) show poorer prognoses in terms of response and remission. However, observational studies on the course of DLL are scarce. The aims of this study were to examine the course of DLL in terms of response, remission and symptom-specific changes as measured by the Montgomery and Asberg Depression Rating Scale (MADRS), and to explore which clinical variables were associated with the response and remission.

**Methods:** This is an observational, multicenter and prospective study of patients aged 60 years and older who were referred to treatment of depression in the department of old age psychiatry at specialist health care services in Norway. The patients were evaluated with the MADRS at admission to and discharge from the hospital. The mean, median, minimum and maximum values for days stayed in the hospital were 68, 53, 16 and 301, respectively. Effect size (ES) was calculated to determine which MADRS symptoms changed most during the treatment. To assess the predictors for change in the MADRS score (continuous variable) and for remission and response (both dichotomous variables), regression models adjusting for cluster effects within center were estimated.

**Results:** Of 145 inpatients, 99 (68.3%) had a response to treatment (50 % or more improvement of the MADRS score). Remission (MADRS score  $\leq 9$  at discharge) was experienced in 74 (51.0 %) of the patients. Of the individual MADRS items, "reported sadness" (ES =0.88) and "lassitude" (ES = 0.80) showed the greatest amount of improvement, and "concentration difficulties" (ES = 0.50) showed the least amount of improvement during treatment. Having a diagnosis of dementia was associated with a lower remission rate and less improvement in the MADRS score during the treatment. Poorer physical health was associated with a lower response rate. Having experienced previous episode(s) of depression was associated with a lower remission rate.

**Conclusions:** Recurrent episodes of depression, poor physical health, and a diagnosis of dementia were found to be negative prognostic factors for the course of DLL. Clinicians should therefore pay close attention to these factors when evaluating treatment.

### Paper III: Clinical prognostic factors and trajectories of depression in late life

**Background:** Depression in late life (DLL) can have a chronic or relapsing course. More longitudinal studies, including ones with patients with cognitive impairments, are needed in order to help with better treatment plans.

**Methods:** This study was an observational, multicenter and longitudinal study of 160 patients, 60 or older and with or without dementia, and who were admitted to inpatient treatment of DLL at specialist health care services. The patients were followed with three assessments: at inclusion ( $T_0$ ), at discharge from the hospital ( $T_1$ ), and after one year ( $T_2$ ). We applied growth mixture modeling to identify trajectories. Two regression models were estimated to investigate clinically important factors: one based on the trajectories and one on a clinical assessment of the depression course between  $T_1$  and  $T_2$ .

**Results:** Two distinct trajectory classes were identified: one with higher and one with lower MADRS (Montgomery and Asberg Depression Rating Scale) scores. About one-third of the patients had a clinically poor depression course between  $T_1$  and  $T_2$ . Not being in remission at  $T_1$  and a longer stay in the hospital were associated with higher odds of being in the trajectory class with a poorer outcome. Early onset of first lifetime depression (EOD) was associated with higher odds of being in a group with a poorer course between  $T_1$  and  $T_2$ .

**Conclusion:** EOD and not being in remission at discharge from the hospital were important negative prognostic factors for the course of DLL. Clinicians should be attentive to these factors when planning and assessing treatment.



## Additional results and relevant figures the from the one-year follow-up examination in the Prognosis of Depression in the Elderly (PRODE) study

To assess the trend in the MADRS score at the PRODE's junctures we carried out a linear mixed model with fixed effects for the time component up to second-order and random effects for study centers and patients nested within the center.

**Figure 2. Trend in Montgomery and Asberg Depression Rating Scale (MADRS) score at the three assessment points ( $T_0$  = at inclusion,  $T_1$  = at discharge from the hospital, and  $T_2$  = one-year follow-up) in the PRODE study assessed by a linear mixed model.**

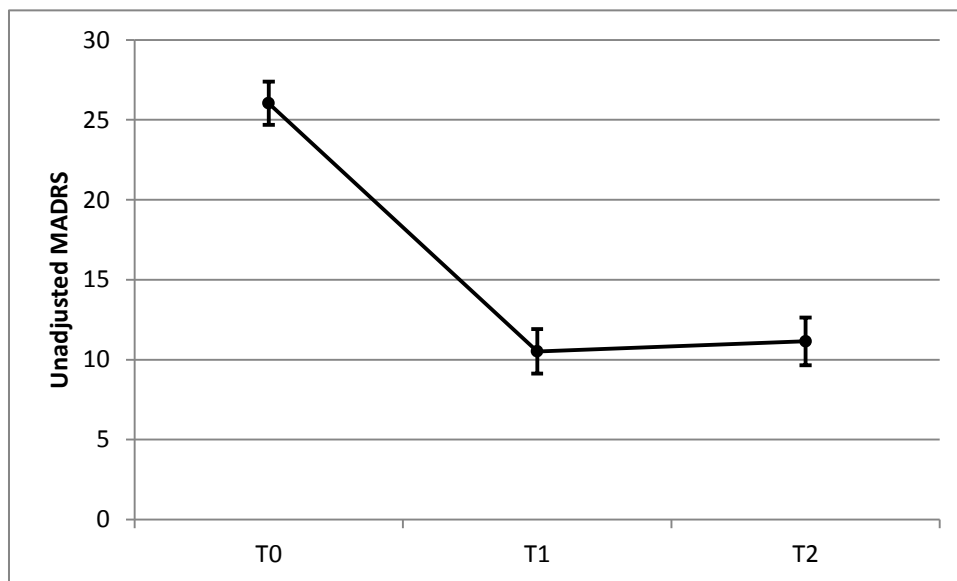


Figure 2 shows that the MADRS score was 26.0 with 95% CI (24.7-27.4) at  $T_0$  ( $n=157$ ). There was a decrease in MADRS score to 10.5 (8.8-12.3) at  $T_1$  ( $p<0.001$ ) ( $n=147$ ), and no significant change from  $T_1$  to  $T_2$  ( $p=0.503$ ), with mean MADRS score at  $T_2$  equal to 11.2 (9.3-13.0) ( $n=126$ ).

**Figure 3. The Montgomery and Asberg Depression Rating Scale (MADRS) sum scores by trajectory classes**

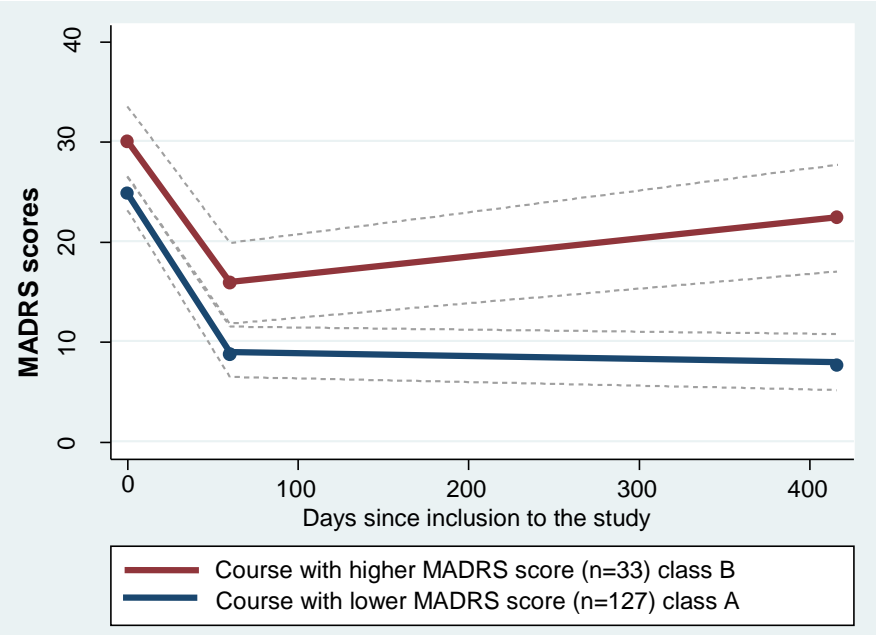


Figure 3 shows that the growth mixture modeling of the MADRS scores resulted in two trajectory classes: class A and class B. Class A had a high MADRS score at inclusion ( $T_0$ ), which decreased by the discharge from the hospital ( $T_1$ ), and stayed low at the one-year follow-up ( $T_2$ ). For class B, the MADRS score was higher at  $T_0$  than it was among class A. The score among class B also declined between  $T_0$  and  $T_1$ , but to a lesser extent, and had increased at  $T_2$ . The confidence intervals of the trajectory curves did not overlap, and the average class probabilities were above 0.70, indicating well-separated classes.

At the one-year follow-up, the patients were assessed according to the Winblad's criteria (Winblad et al., 2004) for mild cognitive impairment (MCI) and the ICD-10 criteria for dementia and additionally according to the Neary's criteria (Neary et al., 1998) for frontotemporal lobe dementia (FTD) and the McKeith's criteria for dementia of probable Lewy Body type (DLB) (The third report of the DLB consortium)(McKeith et al., 2005). Table 8 presents the results from the assessment and the results are discussed later in the thesis.

**Table 8. Subtypes of dementia and mild cognitive impairment (MCI) at the one-year follow-up in PRODE**

	<b>n=146</b>	<b>n=23</b>
No dementia or MCI <sup>1</sup>	85 (58.2)	
Mild cognitive impairment (MCI) (Winblad's criteria) <sup>1</sup>	38 (26.0)	
Diagnosis of dementia <sup>1</sup>	23 (15.8)	
Dementia in Alzheimer's disease (F00.0/1) <sup>2</sup>		4 (17.4)
Dementia in Alzheimer's disease, atypical or mixed type (F00.2) <sup>2</sup>		6 (26.1)
Vascular dementia (F01.x) <sup>2</sup>		4 (17.4)
Frontotemporal lobe dementia (Neary's criteria) <sup>2</sup>		3 (13.0)
Dementia in Parkinson's disease (F02.3) <sup>2</sup>		1 (4.3)
Dementia of probable Lewy Body type (McKeith's criteria) <sup>2</sup>		1 (4.3)
Unspecified dementia (F03) <sup>2</sup>		4 (17.4)
<b>Total</b>	<b>146 =100%</b>	<b>23 =100%</b>

<sup>1</sup> = n and % of 146 (patients assessed at one-year follow-up)

<sup>2</sup> = n and % of 23 (patients with dementia at one-year follow-up)

## **Paper IV: The course of depressive symptoms as measured by the Cornell Scale for Depression in Dementia over 74 months in 1158 nursing home residents**

**Background:** Depressive symptoms and depression are common in nursing home residents. However, longitudinal studies of depression in nursing home residents are scarce and the sample sizes are small. This study aimed to investigate the course of depressive symptoms as measured by the Cornell Scale for Depression in Dementia (CSDD) and associated explanatory demographic and clinical variables.

**Methods:** A longitudinal study over 74 months of 1158 nursing home residents aged 50 years and older from 26 nursing homes in Norway where data was collected at five time points.

**Results:** "Irritability" was the most prevalent, incident and persistent CSDD symptom. Compared with the baseline assessment, the likelihood of the mood symptoms "suicidal ideation," "pessimism" and "delusions" being present was lower at all subsequent assessments. This persisted after adjusting for the severity of dementia. The severity of depression as measured by CSDD decreased over 74 months when adjusting for relevant resident variables. Poorer physical health, higher number of medications, more severe dementia and use of antidepressants were associated with higher depression scores.

**Limitations:** Depression and dementia were not diagnosed according to standardized diagnostic criteria. The use of CSDD did not include a clinician's interview with the patient. This could have implications for the generalization of the results.

**Conclusion:** This study adds important knowledge about the long-term course of depressive symptoms and depression for residents in nursing homes, and underlines the importance of paying close attention to the overlap between depression and dementia symptoms when evaluating depression in this setting.

## Discussion

### Discussion of the main results

All four papers included in this thesis are clinical studies of DLL. In the first paper, we investigated the psychometric properties of the MADRS in elderly participants without dementia. The MADRS was originally not designed as a screening aid, but as a scale sensitive to treatments effects. However, use of depression scales can increase case finding and we found the MADRS to have good discriminatory power to detect depression in elderly persons. We reported an AUC of 0.86 in the ROC analysis when the DSM-IV was used as a reference standard. The optimal cut-off point was 16/17 with sensitivity of 0.80 and specificity of 0.82. When the ICD-10 was used as reference standard, we found the best cut-off value to be 13/14 with sensitivity of 0.88 and specificity of 0.88. A lower cut-off on the MADRS when ICD-10 was the reference standard makes sense, as the ICD-10 criteria for depression are less strict (Barca, Engedal, & Selbaek, 2010; Knapskog et al., 2011).

Other validity studies of the MADRS in elderly persons have shown different results than ours in terms of optimal cut-off value (see Table 2). One possible explanation for different results is the use of different methods. For instance, Mottram et al. used the GMS/AGECAT, which is based on a semi-structured interview, as the reference standard (Copeland, Dewey, & Griffiths-Jones, 1986; Mottram et al., 2000). In the study by Sagen et al. the diagnostic interview (Structured Clinical Interview for DSM-IV [SCID]) and the MADRS were carried out by the same person in the same sequence (not blinded). Another possible explanation for inconsistent results is different study samples. Our study sample constituted a heterogeneous population of elderly individuals without dementia who were in need of health care. Several previous validity studies of the MADRS in elderly samples have been carried out on patients with Parkinson's disease without dementia (Leentjens et al., 2000; Reijnders et al., 2010; Silberman et al., 2006). These studies all report different optimal cut-off values, and our optimal DSM-IV cut-off value was generally somewhat higher. This could partly be related to the fact that the participants in our study were more than ten years older than those in the other studies. In a study on the validity of the MADRS in memory clinic patients Knapskog et al. found lower optimal cut-off values than we did. Knapskog et al. reported a prevalence of DSM-IV- depression of 27.2% but the main focus in the memory clinic setting was probably memory and other cognitive impairments rather than depressive symptoms, and this could have influenced the cut-off value (Knapskog et al., 2011). Studies on the validity of MADRS in samples with dementia generally have reported lower AUCs and lower ability of the MADRS to discriminate between depressed and non-depressed individuals than in our study (Portugal Mda et al., 2012). One study found that MADRS had good properties to detect depression in patients with Alzheimer's disease, independently of the severity of dementia, but the study did not validate the MADRS against a clinical diagnosis of depression (Muller-Thomsen, Arlt, Mann, Mass, & Ganzer, 2005). The MADRS is usually scored during an interview with the patient. Studies have also investigated the validity of a proxy-based MADRS in samples with dementia, and have reported that this provides a good distinction between depressed and non-depressed participants (Leontjevas et al., 2012; Leontjevas et al., 2009).

As only half of the participants were examined by the use of the CSDD, we defined to compare the validity of the MADRS with the CSDD as a secondary aim. However, we found the MADRS to have

better discriminatory power in distinguishing non-depressed and depressed patients as compared to the CSDD. This was consistent with findings from other validity studies of proxy-based CSDD in samples without or with mild dementia (Knapskog et al., 2011). One possible explanation may be that the CSDD, more than the MADRS measures behavioral symptoms that are not specific for depression. Later studies have described a weak correlation between the MADRS and proxy-based CSDD (Knapskog, Barca, & Engedal, 2013). This underlines the importance of collecting information from the patient and from the carer when evaluating depression in elderly patients, particularly in those with cognitive impairments.

### *Paper II*

In the second paper of this thesis, we used the MADRS to evaluate the prognosis of depression during a stay in the hospital at the department of old age psychiatry in specialist health services. As documented, the MADRS has been found to be a valid scale for measuring treatments effects in DLL (Cipriani et al., 2011; Heo et al., 2007; Kok et al., 2012; Montgomery & Asberg, 1979). Of 145 patients with complete MADRS records, 68.3% had a response to treatment and 51.0% experienced a remission at discharge from the hospital. The mean MADRS score decreased from 26.1 (SD=8.6) at inclusion to 10.7 (SD=7.9) at discharge. These results are comparable to those reported in similar studies, although definitions of outcomes vary (Table 3). The prognosis in our study was somewhat better than in a similar study from the Netherlands, which also used the MADRS as an outcome measure and with the same definitions of response and remission. The Dutch study reported a remission rate of 40% and response rate of 53%. One possible explanation for better figures in our study may be the more frequent use of ECT in our study, 26%, as compared to 4% in the Dutch study. Furthermore, the patients in the Dutch study had a higher median MADRS score at inclusion; 34, range 8-56 as opposed to 26, range 3-52 in our study (previously unreported figures) (Heeren et al., 1997). Studies have shown that more severe depression can be associated with worse clinical outcomes (Alexopoulos et al., 1996; Comijs et al., 2015; Dew et al., 1997; Katon, Unutzer, & Russo, 2010).

The main goal in treatment of depressive episodes is remission and then full recovery, so the definition of remission is a key issue. According to a report on response and remission in MDD by the American College of Neuropsychopharmacology (ANCP) from 2006, remission should be based on absence of the diagnostic criteria for depression, but cut-off values on various depression rating scales have also been used (Rush et al., 2006). Searching the literature, we found various MADRS-based definitions of remission. The ANCP-report described that a MADRS score < 10 and a MADRS score < 6 have been used to estimate remission. The lowest cut-off value was based on a narrow definition of remission, as in completely free of clinically significant depressive symptoms (Rush et al., 2006; Zimmerman, Chelminski, & Posternak, 2004). Hawley et al. investigated which cut-off value on the MADRS was the optimal value for remission as defined by the Clinical Global Impression Scale for Severity (CGI-S) in 684 major depressed patients with a mean age of 45 years. The report found that the optimal definitions of remission for a MADRS score < 9 and <10, and recommended MADRS <10 as a reasonable target for remission (Hawley et al., 2002). None of these reports have specific recommendations for elderly patients. In a one-year follow-up of 166 patients aged 60 years or older with unipolar depression at baseline, Bosworth et al. used a MADRS score of 7 or higher as indicative of non-remission (Bosworth et al., 2002). This cut-off value was based on Snaith's work to establish grade scores of the MADRS carried out in a population with an age range from 20 to 70 years and

without severe physical illness and organic disorder (Snaith et al., 1986). In line with the ANCP-report, the study from Hawley et al., and the analogous observational study of elderly depressed inpatients from the Netherlands, we chose MADRS < 10 as a cut-off value for remission.

Although comparable to other similar studies, we considered a remission rate of 51% at discharge from the hospital as low. There could be several explanations to why we and other similar studies find low remission rates. Firstly, it can be related to the nature of DLL. Many inpatients have depression that is difficult to treat according to a defined remission. Patients with DLL often have comorbidities and can present unspecific symptoms like reduced sleep and reduced appetite, or symptoms of cognitive impairment like concentration difficulties. The MADRS can tap these symptoms as depressive, rather than as symptoms of comorbidities, and it can be harder to attain remission according to a cut-off value of the MADRS. Secondly, low remission rates can be related to the treatment offered. The treatment was perhaps not intensive or long enough for all patients. In Norway, several patients will be offered treatment at a lower level of care after discharge from the department of old age psychiatry. Some patients in our study may have reached remission after discharge. Thirdly, our definition of remission could have been a conservative measure in DLL patients. Some validity studies of the MADRS among elderly patients have indicated higher optimal cut-off values to distinguish between depressed and non-depressed individuals (Leontjevas et al., 2009; Mottram et al., 2000). In the first paper of this thesis we also reported a higher optimal cut-off value on the MADRS; 13/14 with the ICD-10 as reference standard, and 16/17 with the DSM-IV.

The multivariable regression model showed that dementia and previous depressive episode(s) were associated with a lower remission rate. Other studies have also found recurrent depressive episodes of DLL to be more difficult to treat (Driscoll et al., 2005). The number of previous depressive episodes is highly linked to the age at onset of the first depressive episode in one's lifetime, and it can be clinically difficult to distinguish between the effects attributable to the number of depressive episodes and those attributable to age at the first depressive episode (Reynolds et al., 1998). Several studies have investigated how EOD versus LOD were related to the prognosis of DLL episodes. Reynolds et al. described a longer time to remission and more suicide attempts in patients with EOD (Reynolds et al., 1998). Kozel et al. found no difference in remission rates between EOD and LOD participants treated with citalopram (Kozel et al., 2008). Alexopoulos et al. reported that LOD predicted slow recovery in a naturalistic study of 63 elderly depressed patients treated with antidepressants. The study included both in- and outpatients; age at the onset of first depression was treated as a continuous variable; and the group with no previous depressive episodes consisted of only 15 patients (Alexopoulos et al., 1996). This may partly explain why these results differed from our study. Taken from these studies, we can conclude that there is no clear consensus of how a patient's age at the onset of the first lifetime depression is related to outcome in depressive episodes.

Although only 9% of our sample had dementia, we found having a diagnosis of dementia to be associated with a lower remission rate. Many of the similar studies in Table 3 have excluded patients with dementia. However, Zubenko et al. found better cognitive performance at admission (MMSE-score) to predict remission in their naturalistic study of 205 (194 for this particular analysis) elderly inpatients (Zubenko et al., 1994). Our findings correspond with studies indicating lower treatment response in patients with depression and dementia (Nelson et al., 2008) and in subgroups with cognitive impairments (Sneed et al., 2011). Another explanation could be that patients with

dementia score higher on the MADRS due to the overlap of symptoms between depression and dementia (Leontjevas et al., 2009).

*Paper III and additional results from the one-year follow-up examination in the PRODE study*

The third paper of this thesis picks up on the second and we present results from the one-year follow-up examination in the PRODE study. During the year after inclusion, more patients had been diagnosed with dementia; more patients had worse physical health; and more patients resided in nursing home.

A diagnosis of dementia was present in 1.9% of the 160 patients at inclusion to the study ( $T_0$ ). At discharge from the hospital ( $T_1$ ), 8.8% were diagnosed with dementia. The most likely explanation for this increase is that health professionals working in departments of old age psychiatry are more aware of the link between DLL and dementia and have recognized the depressive symptoms as part of a dementia syndrome. At the one-year follow-up ( $T_2$ ), 15.8% of the patients had a diagnosis of dementia. The symptoms of dementia may have become more evident in a substantial proportion of the patients in our study or these patients may have been particularly vulnerable for developing dementia. Other studies have shown that the following patient groups with DLL may have an increased risk of developing dementia: I) those needing ECT-treatment (Brodaty et al., 2000), II) those with pseudodementia (Alexopoulos et al., 1993), III) those with DLL as part of a bipolar disorder (da Silva et al., 2013), and IV) those with cerebrovascular diseases or a severe load of WML (Alexopoulos, 2006; Pantoni, Fierini, & Poggesi, 2015; Verdelho et al., 2013).

Additionally, 26% of the patients in our study had a diagnosis of mild cognitive impairment (MCI) according to the Winblad's criteria at the one-year follow-up. The patients were not assessed according to these criteria for MCI during their stay in the hospital, so we were not able to tell when the MCI was established. However, our results show that dementia and MCI frequently played an important role in the clinical picture among DLL patients admitted to specialist health care services.

At the one-year follow-up, patients with dementia were subtyped (presented as additional results in Table 8). Previous reports on the distribution of dementia subtypes vary according to the study sample and which criteria have been used for the different dementia subtypes. There is general agreement that dementia in Alzheimer's disease (AD) is the most prevalent dementia subtype, often constituting 50-70% of patients with dementia (Brunnstrom, Gustafson, Passant, & Englund, 2009; Calvo-Perxas et al., 2015; Tola-Arribas et al., 2013; "www.alzheimers.org.uk/site/scripts/documents\_info.php?documentID=412," 2014).

In our study, 43.5% of the patients with dementia at the one-year follow-up had AD. Of those patients with AD, 60% had an atypical or mixed type (including mixed Alzheimer's and vascular dementia). Additionally, 17% had a pure vascular dementia (VD). Our results are in line with previous reports showing that DLL is frequently associated with VD, and even more so than AD (Ballard et al., 2000; Brunnstrom, Passant, Englund, & Gustafson, 2013; Diniz et al., 2013). Patients with VD and patients with frontotemporal lobe dementia (FTD) were overrepresented in our sample, as might be expected in patients admitted to specialist health care services (Alexopoulos, 2006; Brunnstrom et al., 2013; Neary et al., 1998; Rascovsky et al., 2011). With respect to dementia with Lewy Bodies (DLB), we may have expected the number of patients to be higher (Auning et al., 2011; Vann Jones & O'Brien, 2014). However, the number of patients with dementia was small, particularly with respect to the subtyping (see Table 8), making it hard to draw a firm conclusion.



In our study, we used a definition of relapse and recurrence with high clinical relevance in that relapse and recurrence had to include admission to a hospital or a suicide attempt. Even though our definition was stringent, more than one-third of the patients had evidence of a relapse or recurrence or were rated as continuously ill during  $T_1$  and  $T_2$ , highlighting the poor prognosis of DLL (Beekman et al., 2002; Cole & Bellavance, 1997b; Comijs et al., 2015).

Based on the MADRS scores over the course of the study period, we identified two distinct trajectory classes: one with lower MADRS scores (class A) and one with higher MADRS scores (class B)(Figure 3).

Not being in remission at discharge from the hospital was the factor most strongly associated with belonging to the trajectory class with worst outcome; it was also a significant predictor for being in a worse course group between  $T_1$  and  $T_2$  in the bivariate ordinal analysis, though not in the multivariate analysis. Our findings concur with that of others, highlighting the importance of remission for further outcomes during the course of depression (Alexopoulos et al., 2005; Frank et al., 1991; Rush et al., 2006). It can be challenging for patients with DLL to attain remission due to psychiatric and medical comorbidity, and an inability to attain remission from DLL has been associated with a greater risk for relapse and recurrence, more functional disability, and worse quality of life ((Alexopoulos et al., 2005; Azar, Chopra, Cho, Coakley, & Rudolph, 2011; Cui et al., 2008; Kiosses & Alexopoulos, 2013). As discussed (page 81-82), there has been debate in the literature over the most appropriate way to define remission. According to some authors, remission should be based on the absence of the diagnostic criteria for depression, but cut-off values on various depression rating scales are also used (Azar et al., 2011; Hawley et al., 2002; Rush et al., 2006). Using our definition (MADRS<10), approximately 50% of the patients we studied were in remission at discharge from the hospital. A broader or narrower definition might have an impact on our results, but it is not clear as to how, particularly as remission was a covariate and not an outcome variable in this paper.

We used the same clinical covariates in the ordinal regression model with course group of depression during  $T_1$  and  $T_2$  as outcome, as in the regression model for characteristics of the trajectory classes. The former analysis showed that age at onset of the first lifetime depressive episode before 60 years was associated with a poorer course between  $T_1$  and  $T_2$ . This finding is in concordance with the results reported in Paper II and other studies reporting poorer outcomes in elderly patients with EOD (Comijs et al., 2015; Hybels et al., 2015; Reynolds et al., 1998). As discussed (page 82), other papers have found that the association between age at onset of the first lifetime depression and outcome is less straightforward. Patients with LOD have also been linked to more medical comorbidity, which further complicates the picture (Mitchell & Subramaniam, 2005).

Age at first lifetime onset of depression was not significantly associated with trajectory class membership. Possible explanations for the inconsistent findings of age at first lifetime onset of depression as a covariate may include differences in the observation period and estimation of different regression models. The trajectory analysis was based on the MADRS scores, and we found no significant differences in the mean MADRS scores at the three time points between the LOD and the EOD groups. The ordinal model may have identified and put more emphasis on different aspects of the depression course than the trajectory class model. Some EOD patients might have had a more complicated and severe depression in terms of suicidality than the MADRS score itself indicated. Only one of the ten items on the MADRS assesses suicidality. Other studies have found EOD to be

associated with a more severe depression course including more suicidality (Reynolds et al., 1998; Sachs-Ericsson et al., 2013).

Dementia was not found to be a significant covariate in the regression models in this paper. However, there was a trend in the model with trajectory class as outcome, so the sample size could have been too small to show any significant effect of dementia.

#### *Paper IV*

The fourth paper of the thesis was a longitudinal study of 1158 nursing residents. We measured the depressive symptom by the CSDD at five time points over 74 months. In the PRODE cohort, around 9% of the patients had a diagnosis of dementia established during their stay in the hospital, and in our nursing home study, 81% of the residents had dementia as evaluated by the CDR at baseline. As discussed previously in the thesis, the CSDD has been validated for patients with or without dementia, and is widely used in clinical practice and research. The CSDD is thus a useful depression scale for residents in nursing homes, but some research has indicated that the scale might be sensitive to comorbid conditions in frail institutionalized elderly persons, potentially not tapping the core depressive features (Kurlowicz et al., 2002). We will argue that the CSDD still is the best and most validated clinical depression scale for use in nursing homes where the prevalence rates of dementia are high (Lavretsky et al., 2013; Mayer et al., 2006).

A striking finding in our nursing home study was that compared to baseline, the likelihood of the CSDD-items “suicidal ideation,” “pessimism,” and “delusions” being present decreased throughout the study period, and this persisted even after adjusting for the severity of dementia. We found the severity of dementia to increase non-linearly during the study period. The described CSDD-items are all defined as mood symptoms according to an exploratory factor analysis of the CSDD in Norwegian nursing homes (Barca et al., 2008) and a later confirmatory factor analysis (Barca et al., 2015). The latest analysis stressed that clinicians should focus more on the mood symptoms of the CSDD when assessing depression among patients with dementia. Interestingly, we found the sum score of the mood factors on the CSDD (both unadjusted and adjusted for control variables) to decrease at the latest assessment, compared to baseline. Taken together, we can argue that “survivors” or residents staying for many years in nursing home seem less prone to develop depression (Boorsma et al., 2012).

As previously indicated, the CSDD can tap symptoms as depressive in frail nursing home residents that are not necessarily due to a depressive disorder (Kurlowicz et al., 2002). Thus, a high score on the CSDD is not equal to depression. However, we found a strong association with worse physical health and a higher CSDD score, both mood and non-mood CSDD scores. This corresponds with Hoover’s large-scale study of nursing home residents in the USA, where physical comorbidity was associated with persistent depression over one year (Hoover et al., 2010). Rozzini et al. reported that the number of clinical problems was independently associated with higher GDS scores in a 12 month study of 56 nursing home residents (Rozzini et al., 1996). Other longitudinal studies have contrasted these findings, e.g., Smallbrugge et al. found no association between persistence of depressive symptoms as measured by the GDS and physical comorbidity in a six-month study of 350 nursing home residents (Smallbrugge et al., 2006). Additionally, in a one-year longitudinal study of 868 residents of nursing homes or congregate apartments, Parmelee et al. described that those residents with remitted depression as measured by the GDS and the DSM-III-R, showed greater decline of

physical health as measured by the Cumulative Illness Rating Scale (CIRS) compared to residents with persistent depression, incident depression, or no depression (Parmelee et al., 1992b). Taken together, many longitudinal nursing home studies have described an association between physical health and depression, but findings are inconclusive. This seems related to different study samples, different assessment scales of physical health and depression, and different study methods. Thus, it is not clear how well the documented link between physical health and depression is displayed for nursing home residents.

We found that a higher CDR sum of boxes score was associated with higher CSDD scores (both mood and non-mood symptoms). Other longitudinal nursing home studies have investigated how the severity of dementia was associated with depression, and although several studies have reported associations, findings are somewhat mixed. For instance, Boorsma et al. found dementia to be a risk factor for incident depression in a six-month study of nursing home residents with a minimum stay of more than 90 days at baseline (Boorsma et al., 2012). A large scale American nursing home study reported that dementia/Alzheimer's disease was a predictor for depression both at admission to the nursing home and after a 10 to 12-month stay. However, residents with very severe cognitive impairment, as measured by the MDS Cognition, had reduced odds of having a diagnosis of depression during the same year (Hoover et al., 2010). Barca et al. reported a higher CDR score at baseline to be associated with incident depression, but not persistent depression in the 12-month follow-up examination of the same study sample as the one in the present paper (Barca, Engedal, Laks, et al., 2010). In a smaller study of 51 newly admitted nursing home residents, McSweeney and O'Connor reported that clinical depression most often occurred in cognitively impaired residents (McSweeney & O'Connor, 2008). It is hard to draw firm conclusions on how the severity of dementia relates to the development and persistence of DLL in nursing homes from these studies. Verkaik et al. have in a systematic review indicated evidence for a lack of association between the severity of Alzheimer's disease and the prevalence of comorbid depressive symptoms or diagnosed depression. However, none of the included studies in the review were from a nursing home setting (Verkaik, Nuyen, Schellevis, & Francke, 2007).

In our study use of antidepressants was associated with higher depression scores on the CSDD. The design of our study only allowed us to describe and discuss an association and not address causality to a great extent. There may be several explanations for this finding. As debated previously in this thesis, there is evidence for less effect of antidepressants in patients with depression and dementia (Bains, Birks, & Denning, 2002; Nelson & Devanand, 2011). Recent studies have, in addition, documented that up to half of the nursing home residents received antidepressants for indications other than depression and that use of antidepressants was often persistent (Iden, Engedal, Hjørleifsson, & Ruths, 2014; Midlov, Andersson, Ostgren, & Molstad, 2014). About one-third of the residents in the present study used antidepressants, and a significant proportion could be non-responders. Another possible explanation is that residents taking antidepressants in nursing homes can have depression that is difficult to treat (Bergh et al., 2012).

Further findings of the different studies are described and discussed in the enclosed Papers I-IV.

## Issues related to the methods

### Study 1

Participants were recruited from different clinical settings for the MADRS validation study, which was in line with the recommendations for validity studies according to Jaeschke et al (Jaeschke et al., 1994). The patients were assessed by different nurses and different doctors in different settings, which may have influenced the results. For example, the nurses in departments of old age psychiatry, where depression is more prevalent, could have been more familiar with and aware of depressive symptom and that could have influenced the results. However, there were no differences in the AUCs when we compared the results from subsamples with or without participants from the department of old age psychiatry.

Patients with dementia were excluded from the study. In the assessment of cognition, different versions of the MMSE (20-item and 12-item versions) were used (Braekhus, Laake, & Engedal, 1992). We do not see this as a major problem, as we also gathered information on dementia from the medical records and the patients were assessed by experienced senior consultants. In addition, dementia was not an outcome variable in this study, just an exclusion criterion.

The assessors were instructed not to take use of medication into account when the patients were evaluated for depression. Many of the patients received antidepressants at the time of the evaluation, which could have influenced the results.

Only half of the participants were assessed according to the ICD-10 and the CSDD. This is a weakness for validity comparisons, and we therefore defined comparisons including the ICD 10 and the CSDD as secondary aims of the study.

### Study 2

The PRODE study is a multicenter, observational, and prospective study of depressed inpatients aged 60 years or older. The inclusion criteria in PRODE were broader than comparable studies in that patients with dementia, bipolar disorder, and depression linked to physical disorders, such as cancer or medications, were also included. Other observational studies have often included patients with MDD, either with or without mild cognitive impairments, and have thus had more homogenous patient groups with depression. This is an advantage in order to more purely study MDD in elderly patients. In everyday practice the clinical picture of DLL is often more heterogeneous, and we wanted to carry out a study with high clinical relevance. The study sample in the PRODE study was recruited in order to be representative of patients referred to treatment of depression at hospitals in specialist health care services of old age psychiatry in Norway. Most health regions in the country were represented in the study.

There could be a selection bias in that severely depressed patients may be more difficult to include, and, accordingly, be underrepresented.

In the PRODE study data of the baseline stay in the hospital were collected from December 2009 to July 2013, and on the one-year follow-up examination from January 2011 to August 2014. The collection of data to the study was more or less financed by voluntary work by the participating study

centers. Some centers ran into difficulties recruiting patients due to reorganization of health services and one center had to stop recruiting patients because the department had to prioritize ordinary daily clinical activity. Summer vacations and periods with absence of key staff were vulnerable phases to recruit new patients and to collect complete data. We were also confronted by “Lasagna’s law on patient recruitment:” how eligible patients for clinical studies decreases once you have started a study (Lasagna, 1979). Accordingly, the study period was prolonged in order to increase the number of included patients.

It was not possible to carry out a clinical examination of 25 of the 146 patients at the one-year follow-up examination, due to various patient factors and/or organizational matters. For these patients, if possible, data were collected from relevant case notes at the local study center, telephone interviews with the patients, and supplemental information from carers and caregivers. This may have influenced the results of clinical scales like the MADRS and the MMSE, as it is not unlikely that some of the patients with missing data might have high MADRS scores and low MMSE scores. However, we were able to collect valid data for all 25 patients, as described, for the clinical assessment of the course of depression between discharge and the one-year follow-up.

The assessors were health professionals who worked in the participating study centers. In order to secure valid data, assessors received standardized training prior to the study period, and twice a year during the study period. The assessors were involved in the clinical management of the included patients, and thus not blinded or independent. This may have affected the validity of the collected data. We further experienced that two centers recruited proportionally more patients. There was a hierarchical structure in the scoring of the MADRS symptoms to Paper II; a cluster effect due to different centers. Accordingly, in the analyses of symptom-specific changes we adjusted for the cluster effect. No intra-center correlation was present in the outcomes for paper III.

DLL symptoms can fluctuate, and the study could have assessed them more often, particularly after discharge from the hospital and to the one-year follow-up examination. The mean follow-up days between these two assessments were 356 days (SD=59). However, the methods of the PRODE study allowed us to have the three described assessments.

The sample size may have been too small to show any significant effect of having a diagnosis of dementia, depression with psychosis, or bipolar disorder in Paper III.

### Study 3

In Study 3 we experienced that for some residents it was not possible to rate all of the items on the CSDD. At baseline, the residents with one or more missing items on the CSDD (n=256, 22%) were younger, more cognitively impaired, had poorer physical health, had stayed longer in the nursing home, had higher imputed CSDD sum scores, and performed more poorly in personal activities of daily living, compared to the residents without missing item(s). With our method to impute missing scores and calculate the CSDD score for those with at most 20% of the CSDD items missing, we were able to calculate a sum score for 1087 of the 1158 residents (94%) at baseline. Correspondingly, among the completers, 70% had complete records of the CSDD, and we were able to calculate the CSDD score for 85% of the residents. The completers with incomplete records of the CSDD were more cognitively impaired and performed more poorly in personal activities of daily living, compared

to those with complete CSDD-records. Like several other nursing home studies using the CSDD, we experienced that the CSDD items most often “unable to evaluate” were pessimism (n=151 missing at baseline), self-esteem (n=128 missing at baseline), and suicidal ideation (n=123 missing at baseline) (Snowdon, 2010).

Other studies using the CSDD have excluded patients with severe dementia or patients with incomplete records of the CSDD (Ballard, Bannister, Solis, Oyebode, & Wilcock, 1996; Payne et al., 2002). Thus, direct comparisons with these studies must be interpreted with caution. We believe our study sample is representative of Norwegian nursing homes. As described in the methods section, the nursing homes were selected from four Norwegian counties to assure representativeness.

Some of the longitudinal studies in the nursing homes presented in Table 5 were carried out in newly admitted nursing home residents. Our study differed from these studies in that the residents had on average stayed 941 days in the nursing home before inclusion to the study. The period around transitioning to the nursing home might have impacted the course of depressive symptom (Barca, Engedal, Laks, et al., 2010; Giebel et al., 2015; Iden et al., 2014; Luppá et al., 2010; Snowdon & Donnelly, 1986) and should be kept in mind when comparing longitudinal nursing home studies.

The original paper by Alexopoulos et al. described that the CSDD includes an interview with the patients (Alexopoulos, Abrams, et al., 1988). It can be hard to obtain valid information in a short interview with residents with severe dementia, and 34% of the residents in our study had severe dementia at baseline as evaluated by the CDR. In our study the CSDD was based on information solely provided by professional caregivers, which has also been the case in other nursing home studies (Barca, Engedal, & Selbaek, 2010; Barca et al., 2015; Gruber-Baldini et al., 2005). Towsley et al. investigated the potential discrepancy between how patients and caregivers rate the depressive symptoms on the CSDD. The authors reported that nurses scored facility residents as more depressed than the residents scored themselves. Most residents in that study had MCI, as compared to more than 80% with dementia in our sample (Towsley, Neradilek, Snow, & Ersek, 2012).

### **General considerations related to the methods**

We have used different cut-offs ages to define later life in this thesis. As previously described, there is no clear consensus on which cut-off age to use, and we have used the most common ones, in Study 1: 65 years and Study 2: 60 years. In Study 3 we used 50 years, but residents in nursing homes are often older than their biological age would imply. Additionally, the mean age in our nursing home study (84.5 at baseline) is comparable to other nursing home studies in Norway (Kirkevold & Engedal, 2004) and was comparable to what was reported in national statistics ("[www.ssb.no/a/kortnavn/pleie/arkiv/tab-2010-07-08-02.html](http://www.ssb.no/a/kortnavn/pleie/arkiv/tab-2010-07-08-02.html)," 2010). The study sample should be representative of Norwegian nursing homes at the time the study was carried out.

This thesis has included two longitudinal studies (PRODE and PSIN), and has generally discussed how clinical factors can be associated with DLL, and how DLL and dementia can be linked. The heterogeneity of the patients and methods of both these studies have not allowed us to discuss the findings in terms of causality (Hill, 1965; Lucas & McMichael, 2005).

Some of the major strengths of the studies included in this thesis are the use of well validated scales such as the MADRS, the CSDD, the HADS, the MMSE, the CDR, and the Lawton and Brody scales for IADL and physical self-maintenance. We have used statistical methods that have allowed for drop-outs and adjusted for possible clustering effects due to a multicenter design.

## Implications

In the thesis we have discussed the MADRS and how it is used in elderly individuals without dementia. We report that the MADRS can be a useful scale for clinicians to detect DLL. Our documented optimal cut-off values of 13/14 and 16/17 on the MADRS according to the ICD-10 and the DSM-IV, respectively, suggest that clinicians should consider higher cut-off values for elderly persons than the previous recommendations of lower cut-off values when discriminating between depressed and non-depressed individuals.

The longitudinal studies of DLL in this thesis have illustrated that DLL often has a poor prognosis. We found recurrent episodes of depression, poor physical health, and a diagnosis of dementia to be negative prognostic factors for the course of depressive episodes. We, therefore, recommend that clinicians pay attention to these factors when evaluating treatment of DLL episodes.

When treating depressive episodes, the clinicians should aim for remission. At discharge from the hospital, about half of the patients were in remission. Not being in remission at discharge and experiencing the first lifetime depressive episode before age 60 were negative prognostic factors for the longer term course of depression. We, therefore, further recommend that clinicians pay attention to these factors when planning and evaluating treatment of DLL.

The longitudinal study of depressive symptoms in nursing home residents has shown the need for clinicians to focus on the overlap between depression and dementia when evaluating DLL in this setting. The fact that use of antidepressants was associated with higher CSDD scores also highlights the need for clinicians and research to focus on other treatments options for patients with depression and dementia.

## Future research

In the beginning of the 1980s Milliard argued that the 30 years before had produced little in terms of positive treatment effects of DLL, and he postulated a “rule of three” for hospital treatment of DLL: “No matter what is done, a third get better, a third stay the same and a third get worse” (Millard, 1983). In an editorial on the history of DLL research in 2014, Blazer put forward that in the past 30 years, the research of DLL had exploded both in quantity and quality (Blazer, 2014). Although the knowledge base of DLL has expanded greatly over the past 30 years, there still are barriers to cross in order to implement what we know about DLL into clinical practice (Aakhus, Granlund, Odgaard-Jensen, Oxman, & Flottorp, 2016; Aakhus, Granlund, Oxman, & Flottorp, 2015). We need more implementation research for DLL.

As previously described, there is no definite biomarker of DLL, but several genetic factors, inflammatory markers, and findings on imaging can be associated with the development and prognosis for at least subgroups of DLL patients. There is a need to investigate further how these biological and clinical factors of DLL interact longitudinally.

Taken from the presentation of treatment studies in the present thesis (page 45-48) and elsewhere (Thomas, 2013a), high-quality studies of non-pharmacological treatment of DLL, such as various psychotherapeutic interventions and physical exercise, should be carried out to a greater extent. Also, with regard to further treatment studies, some research on the effect of personalized interventions has emerged, but this field needs to be studied more. The concept of remission is crucial in treatment studies of DLL, and warrants further investigation. What kind of remission is for frail, elderly patients, and what treatments can/should be given to patients with residual symptoms in order to obtain remission and recovery over time? (Kiosses & Alexopoulos, 2013)

Patients with severe dementia and depression can have an altered neurobiology of their depression, and it can be challenging to carry out studies in these patients. However, depression in the context of severe dementia needs clarification. Longitudinal studies and treatment studies of DLL where patients are subdivided according to dementia type are further needed. Also, more studies on the depressive trajectories from admission to nursing home to death should be carried out. Furthermore, there is a need for intervention studies for depressed residents in nursing homes, partly due to the reduced efficacy of medications, but this field of medicine has been understudied (Stewart, 2013). Additional treatments that can alleviate the burden of depression are necessary. More studies on how to implement treatments in nursing homes and for nursing home residents should also be carried out.



## Pusteøvelse

Hvis du kommer langt nok ut  
får du se solen bare som en gnist  
i et sluknende bål  
hvis du kommer langt nok ut.

Hvis du kommer langt nok ut  
får du se hele Melkeveiens hjul  
rulle bort på veier av natt  
hvis du kommer langt nok ut.

Hvis du kommer langt nok ut  
får du se Universet selv,  
alle lysår-milliardenes summer av tid,  
bare som et lysglimt, like ensomt, like fjernt  
som juninattens stjerne  
hvis du kommer langt nok ut

Og ennå, min venn, hvis du kommer langt nok ut  
er du bare ved begynnelsen

– til deg selv

*Rolf Jacobsen, Pusteøvelse*

## Breathing exercise

If you go far enough out  
you can only see the sun as a spark  
in a dying fire  
if you go far enough out.

If you go far enough out  
you can see the entire wheel of the MilkyWay  
roll away on roads of night  
if you go far enough out.

If you far enough out  
you can see the Universe itself,  
all the billion light years summed up time  
only as a flash, just as lonely, as distant  
as a star on a June night  
if you go far enough out.

And still, my friend, if you go far enough out  
you are only at the beginning

-of yourself

*Rolf Jacobsen, Breathing exercise  
from "Night Open – selected poems of Rolf  
Jacobsen" - translated by Olav Grinde.*

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