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Depression in older people with and without dementia

–Non-pharmacological interventions and associations between psychotropic drugs and mortality

Gustaf Boström

Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy
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“Du blir aldrig färdig, och det är som det skall”
Ur *Romanska Bågar* av Tomas Tranströmer

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ABSTRACT

The aim of this thesis was to investigate associations between psychotropic drug use and death, associations between functional capacity, dependency in ADL and depression, and to evaluate a non-pharmacological intervention to reduce depressive symptoms, among older people with and without dementia.

There is limited knowledge about the risk of death associated with psychotropic drug use among those aged ≥85 years, those with dementia, or those living in residential care facilities; groups that have a higher intake of psychotropic drugs and who are also more prone to adverse drug reactions. In a representative sample of people ≥85 years (n = 992), baseline antidepressant use was not associated with an increased 5-year mortality risk when adjusting for confounding factors. A significant interaction between gender and antidepressant use was found, with a higher mortality risk in women, than in men. When analyzing men and women separately, no significant associations were found. In a sample of older people (i.e. ≥65 years) with dementia (n = 1037), there was a significant gender difference in 2-year mortality associated with the baseline use of antidepressant drugs, with a lower mortality risk in men, than in women. In men, the mortality risk was significantly reduced with antidepressant use, while there was no significant association in women. The association between baseline use of benzodiazepines and mortality had a tendency toward an increased risk during the first year of follow-up, although this became non-significant after adjustments. In this time period, the interaction term for sex was significant, with a higher mortality risk among men than women. When the sexes were analyzed separately, no significant associations were found. No significant associations were found between baseline use of antipsychotic drugs and mortality.

Drug treatment for depression seems to have a limited effect in older people and may have no effect in people with dementia. In order to find alternative ways of treating or preventing depression in older age, it is important to increase our knowledge about factors associated with this condition. Functional capacity and dependency in activities of daily living (ADL) are associated with depression in community-dwelling older people. However, it is uncertain whether the same associations are to be found in very old people (i.e. ≥80 years), including those with severe cognitive or physical impairments. In a heterogeneous sample (n = 392) with a high mean age, a large range of cognitive and functional capacity, a wide spectrum of dependency in ADL, and a high prevalence of comorbidities, depressive

symptoms were significantly associated with functional balance capacity, but not with overall dependency in ADL. Among individual ADL tasks, dependency in transfer and dressing were associated with depressive symptoms.

Physical exercise has shown effect sizes similar to those of antidepressants in reducing depressive symptoms among older people without dementia, with moderate–high-intensity exercise being more effective than low-intensity exercise. However, these effects are unclear among older people with dementia. Care-facility residents with dementia (n = 186) were cluster-randomized to a high-intensity functional exercise program or a non-exercise control activity conducted for 45 minutes every other weekday for 4 months. No significant difference between the exercise and control activity was found in depressive symptoms at 4 or 7 months. Among participants with high levels of depressive symptoms, reductions were observed in both the exercise and control groups at 4 and 7 months.

In conclusion, ongoing treatment at baseline with any of the three psychotropic drug classes antidepressants, antipsychotics and benzodiazepines did not increase the risk of mortality in older people with dementia. Neither did antidepressant drugs in very old people. In both samples, gender differences were found in the mortality risk due to antidepressant use. In those with dementia, the mortality risk due to benzodiazepine use also differed by gender. The potential risk from initial treatment and gender differences regarding mortality risk require further investigation in randomized controlled trials or in large cohort studies properly controlled for confounding factors. In older people, living in community and residential care facilities, functional capacity seems to be independently associated with depressive symptoms whereas overall ADL performance may not be associated. Dependency in the individual ADL tasks of transfer and dressing appear to be independently associated with depressive symptoms and may be an important focus for future interdisciplinary multifactorial intervention studies. Among older people with dementia living in residential care facilities, a 4-month high-intensity functional exercise program has no superior effect on depressive symptoms than a control activity. Both exercise and non-exercise group activities may reduce high levels of depressive symptoms. However, this finding must be confirmed in three-armed randomized controlled trials including control groups receiving standard care.

SVENSK SAMMANFATTNING (SUMMARY IN SWEDISH)

Syftet med avhandlingen var att utreda sambandet mellan risken för död och användningen av psykofarmaka (läkemedel som används vid olika psykiatriska tillstånd) och att utforska samband mellan funktionell kapacitet, hjälpberoende i aktiviteter i det dagliga livet (ADL) och depression hos äldre personer med och utan demenssjukdom. Syftet var även att utvärdera effekten av högintensiv funktionell träning på depressiva symtom hos äldre människor med demenssjukdom som bor på särskilt boende.

Kunskapen är begränsad om risken för död vid psykofarmakaanvändning hos de som är 85 år eller äldre, har demenssjukdom eller bor på särskilt boende. Människor i dessa grupper får oftare utskrivet psykofarmaka och är mer benägna att drabbas av biverkningar än yngre och friskare människor. I ett representativt urval av personer som var 85 år eller äldre (n = 992) hade inte antidepressiv medicinering vid baslinjen (d.v.s. studiestarten) något signifikant samband med risken att dö under en uppföljning på 5 år, kontrollerat för störfaktorer. Sambandet mellan risken för död och användningen av antidepressiva läkemedel skiljde sig mellan kvinnor och män, med en relativt högre risk för död hos kvinnor jämfört med män. I separata analyser av män och kvinnor hittades dock inga signifikanta samband. I ett annat urval, där äldre personer med demenssjukdom (n = 1037) följdes i upp till 2 år, hittades också en skillnad mellan män och kvinnor i risken att dö relaterad till antidepressiv användning vid studiestarten. Risken för död var relativt lägre hos män jämfört med kvinnor. När män analyserades separat hittades ett signifikant samband mellan en lägre risk för död och användning av antidepressiva läkemedel, samtidigt som inget samband kunde ses hos kvinnor. Det fanns en tendens mot en ökad risk för död relaterad till användning av bensodiazepiner under det första årets uppföljning. Detta samband försvann dock, när analyserna justerades för störfaktorer. Under det första årets uppföljning fanns det också en könsskillnad i risken för död vid användning av bensodiazepiner. Denna risk var relativt högre hos män jämfört med kvinnor. När män och kvinnor analyserades separat fanns dock inga samband. Inga signifikanta samband hittades heller mellan användning av antipsykotiska läkemedel vid studiestarten och risken för död.

Läkemedelsbehandling vid depression verkar ha en begränsad effekt hos äldre människor och kan möjligtvis sakna effekt hos personer med demens. För att hitta alternativa sätt att behandla eller förebygga depression hos äldre är det därför viktigt att öka kunskapen om faktorer som har samband med depression. Nedsatt funktionell kapacitet och hjälpberoende i ADL är associerat med depression hos relativt friska äldre människor som bor i ordinärt boende. Det är dock osäkert om dessa samband också finns hos

personer som är 80 år eller äldre, inklusive de med gravt nedsatt kognitiv eller fysisk funktion och inklusive de som bor på särskilt boende. I ett heterogent urval (n = 392) med hög medelålder, stor variation av kognitiv och fysisk funktion, mycket varierat hjälpbehov i ADL och hög förekomst av sjukdomar, var depressiva symptom signifikant associerade med nedsatt funktionell balanskapacitet, men inte med övergripande beroende i ADL. Bland enskilda ADL-uppgifter var depressiva symtom relaterade till hjälpberoende i överflyttning och påklädning.

Fysisk träning har haft effekter liknande antidepressiva läkemedel i att minska depressiva symtom hos äldre personer utan demenssjukdom, med bättre effekt av måttlig-högintensiv träning än lågintensiv träning. Hos äldre personer med demenssjukdom är det osäkert om fysisk träning kan minska depressiva symtom. Äldre personer med demenssjukdom (n = 186) som bodde på särskilt boende lottades till att delta i ett högintensivt funktionellt träningsprogram eller till en stillasittande kontrollaktivitet, under 45 minuter varannan vardag i 4 månader. Ingen signifikant skillnad hittades mellan träningen och kontrollaktiviteten i förändring av depressiva symtom vid 4 eller 7 månaders uppföljning. Bland deltagarna med höga nivåer av depressiva symtom sågs signifikanta minskningar i både tränings- och kontrollgruppen vid 4 och 7 månader.

Sammanfattningsvis hittades ingen ökad risk för död hos äldre personer med demens som vid studiestarten behandlades med bensodiazepiner, antidepressiva läkemedel eller antipsykotiska läkemedel. Inte heller hos mycket gamla människor hittades något samband mellan en ökad risk för död och behandling med antidepressiva läkemedel. I båda urvalen hittades könsskillnader i risken för död vid användning av antidepressiva läkemedel. Hos de med demenssjukdom hittades också en könsskillnad i risken för död i samband med användning av bensodiazepiner. Den potentiella risken med initial behandling, samt könsskillnader i risken för död, bör utforskas vidare i randomiserade kontrollerade studier eller i stora kohortstudier med noggranna justeringar för störfaktorer. Hos äldre människor som bor i ordinärt boende eller särskilt boende verkar funktionell kapacitet vara oberoende associerat med depressiva symtom, samtidigt som övergripande ADL-beroende inte verkar vara det. Beroende i de enskilda ADL-uppgifterna överflyttning och påklädning verkar ha oberoende samband med depressiva symtom och kan vara ett viktigt fokus i framtida studier. Bland äldre personer med demenssjukdom som bor på särskilt boende har 4 månaders högintensiv funktionell träning inte bättre effekt på depressiva symtom än en stillasittande aktivitet. Både gruppträning och andra gruppaktiviteter skulle kunna minska höga nivåer av depressiva symtom, men det behöver bekräftas i interventionsstudier som även inkluderar en kontrollgrupp som får sedvanlig vård.

ABBREVIATIONS

ADL	Activities of Daily Living
BBS	Berg Balance Scale
BPSD	Behavioral and Psychological Symptoms of Dementia
CI	Confidence Interaval
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
FOPANU	Frail Older People – Activity and Nutrition
FTD	Frontotemporal Dementia
GDS	Geriatric Depression Scale
GERDA	Gerontological Regional Database
HIFE	High-Intensity Functional Exercise
HR	Hazard Ratio
LBD	Lewy-Body Dementia
MADRS	Montgomery-Åsberg Depression Rating Scale
MMSE	Mini-Mental State Examination
OBS	Organic Brain Syndrome
OSAS	Obstructive Sleep Apnea Syndrome
OT	Occupational Therapist
PGCMS	Philadelphia Geriatric Center Morale Scale
PRN	Pro Re Nata
PT	Physical Therapist
RCT	Randomized Controlled Trial
REMANU	Residential Care Facilities – Mobility, Activity and Nutrition
RM	Repetition Maximum
UMDEX	Umeå Dementia and Exercise

ORIGINAL PAPERS

The thesis is based on the following papers, which will be referred in the text to by their Roman numerals:

I. Boström G, Hörnsten C, Brännström J, Conradsson M, Nordström P, Allard P, Gustafson Y, Littbrand H. Antidepressant use and mortality in very old people. International Psychogeriatrics. 2016; Mar 18:1-10. [Epub ahead of print]

II. Brännström J, Boström G, Rosendahl E, Nordström P, Littbrand H, Lövheim H, Gustafson Y. Psychotropic drug use and mortality in old people with dementia – a gender-sensitive analysis. Manuscript.

III. Boström G, Conradsson M, Rosendahl E, Nordström P, Gustafson Y, Littbrand H. Functional capacity and dependency in transfer and dressing are associated with depressive symptoms in older people. Clinical Interventions in Aging. 2014;9:249-256.

IV. Boström G, Conradsson M, Hörnsten C, Rosendahl E, Lindelöf N, Holmberg H, Nordström P, Gustafson Y, Littbrand H. Effects of a high-intensity functional exercise program on depressive symptoms among people with dementia in residential care: a randomized controlled trial. International Journal of Geriatric Psychiatry. 2015; Dec 7. [Epub ahead of print]

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INTRODUCTION

Depression among older people is a common condition, especially among those with physical and cognitive impairment. It causes emotional suffering, reduces quality of life and is associated with an increased risk of cognitive and physical decline, morbidity, and mortality. All of which make it imperative to find effective treatments. Treatment with antidepressants seems to have only a limited effect in this population, while the use of psychotropic drugs increases the risk of adverse events. This thesis investigates the association between psychotropic drug use and death, associations between functional capacity, dependency in ADL and depression among older people with and without dementia. It also evaluates a non-pharmacological intervention against depressive symptoms, among older people with dementia.

DEPRESSION

Definition

Depression is diagnosed according to sets of criteria based on symptomatology. The symptoms of depression include depressed mood, diminished interest in activities, involuntary weight change, disturbed sleep, psychomotor retardation, fatigue or loss of energy, feelings of guilt or worthlessness, a reduced ability to think or concentrate, and thoughts of death and suicide.[1] Unipolar depressive disorders, has in this thesis been defined by criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR),[1] and include major depression, minor depression, dysthymia, and depression induced by a general medical condition or a substance. The criteria for the different disorders can be found in Appendix 1. For a diagnosis of major depression, minor depression, and dysthymia, the specific symptoms must have been present for two weeks, two weeks, and two years, respectively.[1] Depression is diagnosed in a similar way when using ICD-10 criteria, and may be mild, moderate or severe. Several depression rating scales with a high sensitivity and specificity to depression exist, and may serve as quick, easy, reliable and objective evaluations of depression. However, a rating scale can only serve as an initial screening tool and requires follow-up with a structured clinical interview before a diagnosis of depression can be established.

Prevalence

The World Health Organization (WHO) estimates that 350 million (4.8%) people in the world suffer from depression, including mild, moderate and severe depression as well as bipolar depression,[2] and the lifetime prevalence of depression has been estimated at somewhere between 8-12%.[3] In the 2004 update of the global burden of disease report by WHO, unipolar depressive disorders were ranked as the 3rd leading cause of disability-adjusted life years (DALYs; DALYs = Years Lived with Disability [YLD] + Years of Life Lost [YLL] due to early death), and was estimated to rank 1st by 2030.[4] In the 2010 update, unipolar depressive disorder was redefined to include only major depressive disorder (MDD) and dysthymia, making comparisons with earlier results more difficult, and re-ranking MDD in 11th place.[5]

There is a wide variation reported in the prevalence of depression among older people (i.e. ≥65 years), ranging from 0.4-49%.[6,7] In a systematic review of community-dwelling older people, the weighted average prevalence of major depression was 2%.[7] The corresponding figures for those with minor depression and those with clinically relevant depressive symptoms were 10% and 13%, respectively.[7] In a different review, the prevalence range of major depression in care-facility residents was 14-42%, with the majority of the studies reporting a prevalence of over 30%.[6] In population-based studies of very old people (i.e. ≥80 years), the prevalence range seems to be as wide as among those aged ≥65 years,[6] with the majority of studies reporting a prevalence of 12-17%, using a variety of definitions.[6,8,9] The reported prevalence depends on several factors, such as inclusion/exclusion criteria, the choice of criteria used to identify depression, which depressive disorders are studied, and the assessment methods used to identify depression.[6,7] Exclusion criteria may involve depression-associated comorbidities such as dementia, or care-facility residency. Both of these factors are associated with a higher prevalence of depression if compared with healthy community-dwelling people.[7,8,10] The prevalence of depression may also be influenced by the accuracy of the assessment methods used to identify depression, i.e. whether the methods over- or under-estimate depression prevalence.

Some studies have reported that the prevalence of depression increases with age.[8,11] An age-specific increase in prevalence has also been reported between cohorts, in populations aged ≥77 and ≥85 years.[12,13] Chronological age in itself does not seem to be independently associated with depression, but rather the advanced biological aging process associated with an accumulation of diseases increases the risk of depression.[14-16] Consequently,

the prevalence of depression will be highly dependent on the general health status in the studied population. Thus, if only healthy community-dwelling older people are included in studies about depression, the prevalence will not necessarily be any different from that in studies of younger populations. In addition, research conducted in younger and healthier populations may not be applicable to very old populations that include people with cognitive and physical decline.

Associated factors

Several studies have investigated factors that are associated with depression among older people, including female sex,[16,17] care facility residency,[8] bereavement,[16] cognitive impairment,[10,18] dependency in activities of daily living (ADL) and lower functional capacity,[19-21] visual or hearing impairment,[16] obstructive sleep apnea syndrome (OSAS),[22,23] and multimorbidity.[24] Particular diseases such as dementia,[10,18] preclinical dementia,[25] cardiovascular diseases,[26-28] cancer,[29,30] and inflammatory diseases[31] seem to be linked with depression. Cardiovascular diseases and cardiovascular risk factors that increase the prevalence of depression include elevated blood-pressure,[32] diabetes,[33] a previous stroke,[26] previous myocardial infarction,[34] heart failure[35] and angina pectoris.[36] Furthermore, in longitudinal studies depression has been found to increase the risk of cardiovascular diseases,[27,37] stroke,[38] myocardial infarction,[37] dementia,[39,40] ADL dependency,[19-21] and mortality.[27,37,38]

Stroke and vascular depression

Within the first month after a stroke, depressive disorders may be found in 11-55% of the patients, with major or moderate-to-severe depression ranging from 17-27%.[41] In two systematic reviews, the estimated point prevalence of depression was 29-33% at any time point between the acute stroke to 10 years later,[26,42] with a cumulative incidence of up to 50% within 5 years.[42] The risk of depression after a stroke was increased if depression was present before the stroke, if the stroke was more severe, and if the stroke resulted in cognitive impairment, dependency in ADL, or reduced functional capacity.[28,42] Some studies have found that the location of the stroke is relevant and that the risk of depression may be increased if the stroke is located in the fronto-striatal pathway,[43] or in the left anterior region.[44] A systematic review and meta-analysis from 2000 found that the location was not relevant.[45] However, the authors of a more recent review have proposed a hypothesis in which a stroke located in tracts of certain long association fibers (i.e. the cingulum bundle, uncinate fasciculus or superior longitudinal

fasciculus) may cause depression by disconnecting different parts of the brain.[46] It has been observed that small silent cerebral infarctions may be prevalent in more than 90% of those with an onset of major depression after 65 years of age.[47] A "vascular depression" hypothesis has also been proposed, where MRI findings of white matter lesions is a hallmark which, together with executive dysfunction, may predict poor antidepressant response.[46]

Dependency in ADL and functional capacity

As previously mentioned, depression seems to be more common in those who are dependent in ADL, and/or those who have reduced functional capacity.[19-21] Dependency in ADL and functional capacity can sometimes be regarded as interchangeable measures of functional impairment,[19,21] but although they are highly correlated, they provide different information that may associate differently with depression. An individual's functional capacity is reflected in daily physical activities, such as getting out of a chair, climbing stairs, or walking, and can be measured by the individual's ability to execute such a task in a test situation. In contrast, the degree of dependency in ADL is a measure of disability based on the assistance a person needs in order to perform these activities,[48] and may be more influenced, for example, by cognition, environmental demands, use of assistive devices, and the caregiver's estimation of the need for assistance. Both ADL dependency and a decline in functional capacity may be prevented or ameliorated by intervention programs, which may reduce depressive symptoms. Some factors that might help in mediating a reduction in depression include better self-efficacy, sense of control, self-esteem, the ability to participate in social activities, and an enhanced level of daily physical activity.[20,49-52]

The research that leads to the conclusion that dependency in ADL and/or reduced functional capacity is associated with depression has mainly been conducted among community-dwelling older people.[19-21] Dependency in ADL and lower functional capacity are more common with higher age, cognitive impairment and care-facility residency, but the association between ADL dependency, functional capacity and depression is little explored in these groups. The few studies available[53-55] have limited adjustments, making it difficult to conclude that the associations found are independent. In addition, measures of ADL dependence comprise a wide range of tasks, where depression may be associated with dependency in some tasks, while it may not be associated with dependency in other tasks. To better understand the association between ADL dependency and depression, individual ADL tasks and their relation to depressive symptoms need to be explored.

Inflammation

Depression among older people has been associated with inflammation,[56] and many of the diseases associated with depression present increased inflammatory activity.[31,57] For instance, in Alzheimer's disease, there is increased inflammatory activity in the pathological regions of the brain;[58,59] in cardiovascular disease, it appears in the atherosclerotic vessel wall;[27,60] in autoimmune diseases, there is a systemic inflammatory process;[31] and in many types of cancer, tumor progression is driven by inflammation.[61]

There are several potential pathways linking inflammation and depression.[56] For example, according to the monoamine depletion theory, major depression is associated with low levels of serotonin, norepinephrine or dopamine in the brain.[62] In the human body, serotonin is synthesized from the essential amino acid tryptophan. In inflammatory processes, tryptophan is redirected to inflammatory pathways, reducing the amount available to become serotonin, or even depleting it.[63] In the process, the risk of depression may increase.[64]

DEMENTIA

Dementia is an irreversible, major neurocognitive disorder causing progressive cognitive impairment. It is associated with depression, dependence in ADL, institutionalization and premature death.[10,65] Just as in depression among older people without dementia, depression among older people with dementia seems to be associated with increased morbidity and mortality, a higher susceptibility to cognitive and physical decline, and poorer outcomes for rehabilitation and physical illness.[66] Antidepressant use is very common in this group,[67] despite very limited evidence to support its efficacy,[68] and alternative ways of treating depression need evaluation.

Definition and prevalence

Dementia as a diagnosis is usually defined by DSM or ICD criteria, including memory impairment and aphasia/apraxia/agnosia or disturbance in executive functioning, causing significant impairment of social and occupational functioning compared to a previous state, and should not be explained by delirium.[1] The prevalence of dementia increases exponentially with higher age, and is roughly 1.5% in those aged 60-69 years, and 40% in those aged 90-99 years.[65,69] The global prevalence of dementia is expected to almost double every 20 years from 46.8 million in 2015 to 74.7 million in 2030, reaching 131.5 million in 2050.[69,70] The large increase in dementia prevalence is driven by an aging world population, primarily in low- and

middle-income countries. Some studies have found a decrease in the age-specific prevalence of dementia,[71,72] while others have found an age-specific increase.[73,74]

Types of dementia

The two most common types of dementia are Alzheimer's disease and vascular dementia. Alzheimer's disease is characterized by a gradual onset and a continuous cognitive decline, while the course of vascular dementia may vary over time with the cognitive decline occuring stepwise. Alzheimer's disease is the most common type of dementia, constituting 50-70% of all those with dementia; vascular dementia is estimated to account for 15-25%.[65,70,75] Mixed dementia, with a coexistant pathology of Alzheimer's disease and vascular dementia, is probably common and underdiagnosed,[75] and has been estimated to comprise 20-40% of dementia cases.[76] With age and comorbidities, vascular brain pathology increases in prevalence, making mixed dementia more common.[77] Of the other dementia types, Frontotemporal dementia (FTD) and Lewy body dementia (LBD) are thought to be relatively common accounting for 5-10% and <5% respectively.[75] FTD is characterized by personality changes, mood changes, and disinhibition, while LBD shows a marked fluctuation in cognitive ability, visual hallucinations and Parkinsonism. High alcohol consumption as well as neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and Huntington's disease, may also eventually lead to dementia, if the disease progresses over a long period of time.

Dementia and depression

Approximately 20-30% of those who have Alzheimer's disease also have depression.[18] The prevalence is higher in those with vascular dementia or Lewy Body dementia, where approximately 30-45% are depressed.[18] The level of depression has been reported to remain relatively persistent over time, but also to decrease with increasing cognitive impairment.[18,78-80] Depression among older people with dementia seems to increase the risk of morbidity, mortality, and cognitive and physical decline.[66] It may also reduce the effect of rehabilitation and the recovery rate from physical illness.[66]

It can be difficult to differentiate between depression and dementia among older people, since many symptoms overlap, and depression is often underdiagnosed in dementia. Dementia can include depressive symptoms such as apathy, lack of interest and motivation, anxiety, loss of energy, sleep

disorders, reduced appetite, and concentration difficulties. At the same time, depression in older people may cause temporary cognitive impairment, known as pseudodementia.[81] However, a large proportion of those who have temporary memory impairment as part of depression may also eventually develop dementia.[81]

It may be difficult to perform a psychiatric interview with someone who has advanced cognitive impairment. Modified DSM-IV-TR criteria for depression in Alzheimer's disease have been suggested,[82] and different depression rating scales for people with dementia have also been developed, where interviews with caregivers play a central role.[83,84] However, some studies have found a low correlation between proxy assessments and self-reports of depressive symptoms,[85,86] with underestimation of depressive symptoms reported from caregivers, and more valid results from self-reports in those with minor or advanced cognitive impairment.[86,87]

Depression in midlife has been linked to dementia, and depression in late life may be both a risk factor and a prodromal symptom of dementia.[39,40,75,88] Joint risk factors for depression and dementia in old age[88,89] include cardiovascular diseases and inflammatory processes.[63,88] When evaluating risk factors for Alzheimer's disease, the time lapse between the start of the pathological processes and the possible diagnosis of dementia based on symptoms needs to be taken into account. Studies have estimated that the pathological process of Alzheimer's disease starts at least 10 years, and possibly 20-30 years, before dementia can be diagnosed in a clinical setting.[75,90,91] Risk factors for a clinical Alzheimer's disease diagnosis in studies with a follow-up time of less than 10 years may thus be factors associated with the progress of the disease, rather than true risk factors.

TREATMENT OF DEPRESSION

Antidepressants

Antidepressant drug therapy is the most common form of treatment for depression among people aged ≥65 years. Antidepressant treatment is more common among women, people with dementia, and those living in nursing homes.[67,92]

The evidence for treating older people with antidepressants is so far limited,[93,94] and among older people with dementia, antidepressant drugs may have no effect on depression.[18,68,95] Furthermore, adverse drug reactions and the risk of harmful effects increase with age, especially among women, people with multi-morbidities, and those with dementia.[96-100] Studies examining the association between antidepressants and mortality have found both positive and negative associations. A reduced risk of mortality was found in a randomized controlled trial among people with post-stroke depression being treated with antidepressants,[101] and in an observational study the mortality rate after a myocardial infarction was lower among patients using antidepressants.[102] However, a large cohort study found that all antidepressant drug classes (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], and other) were associated with higher risks of falls, fractures, upper gastrointestinal bleeding, attempted suicide, and all-cause mortality, after adjusting for confounders and depression severity, in depressed community-dwelling older people.[103] In addition, SSRIs and other antidepressants were associated with increased risks of stroke and epilepsy.[103] Increased risks of stroke (SSRI) and all-cause mortality (SSRI and TCA) were also found in a large sample of postmenopausal women.[104] Two other studies found independent associations between antidepressants and death among community-dwelling men.[105,106] The risk of cardiovascular death in particular was elevated among antidepressant users in one of the studies.[106] The other study found the risk to be particularly elevated among antidepressant users with more severe depression.[105] The association between antidepressants and mortality has not been evaluated in representative samples of very old people, among whom dementia, multimorbidity, and disability are common.

Physical exercise

As antidepressant drug therapy seems to have limited and possibly harmful effects in older people, alternative ways of treating depression need to be evaluated. Physical exercise is another possible method that may reduce

depressive symptoms, for example, by providing social contacts, increasing self-efficacy and self-esteem, by changing endorphin and monoamine levels, reducing cortisol levels, and stimulating nerve cell growth.[107] Other positive effects of physical activity that may impact on depression include a reduction in cardiovascular risk factors and inflammation, improved brain perfusion and synaptic function, increased neurogenesis, and reduced amyloid burden.[75,108] Among older people without dementia, physical exercise has had an effect comparable to that of antidepressants in reducing mild-moderate depressive symptoms.[109-111] Using progressive resistance training, moderate- to high-intensity exercise has been more effective in reducing depressive symptoms than low-intensity exercise.[112] Among older people with dementia, knowledge in this field is limited and it is uncertain whether or not physical exercise can reduce depressive symptoms.[113] The number of randomized controlled trials evaluating the effects of physical exercise on depressive symptoms is limited[114-118] and none have demonstrated an effect on depressive symptoms. However, the average number of participants in the studies is low, the exercise intensity is rarely registered, and the attention given to the control group and the intervention group is seldom comparable. Comparable attention is particularly important among people with physical and cognitive impairment, who generally have few social contacts,[119,120] and among whom incomparable amounts of attention could introduce bias affecting the observed effects of exercise.[121]

Other treatments

The Swedish Council on Health Technology Assessment published a report in January 2015 where they evaluated the available evidence for various treatments of depression among older people.[93] The evidence for using cognitive behavioral therapy (CBT), reminiscence therapy, interpersonal psychotherapy, light therapy and electroconvulsive therapy (ECT) was found to be insufficient.[93] Problem-solving therapy seemed to have a possible effect, but the number of studies and participants was limited.[93] When evaluating any psychological treatment against treatment as usual, a Cochrane review found moderate evidence for a small effect in a limited sample with dementia.[122] Another method, with limited evidence and a possible effect, is to reduce depressive symptoms among those with a previous stroke and sleep apnea by using nasal continuous positive airway pressure.[123,124]

PSYCHOTROPIC DRUGS IN PEOPLE WITH DEMENTIA

Psychotropic drugs are used to alter the mind, emotions or behavior of the patient for whom they are prescribed. Three of the major groups are antipsychotics, antidepressants, and benzodiazepines, with the last mentioned occasionally being presented as anxiolytics and hypnotics/sedatives. These drugs are often used among older people with dementia to treat behavioral and psychological symptoms of dementia (BPSD),[125] such as delusions, hallucinations, aggression, depressive symptoms, anxiety, disinhibition, and irritability. Despite the widespread use of psychotropic drugs among people with dementia,[126-129] the evidence for their efficacy in this group is limited,[68,95,130-133] and the risk of adverse events is increased.[98] In addition, gender differences may exist as men and women seem to exhibit different BPSD,[134] are prescribed different psychotropic drugs,[127,134,135] and may experience different adverse effects from these drugs.[136]

Prevalence

In a population-based study among very old people ≥85 years, the prevalence of psychotropic drug use was 48%; 60% among those with dementia, and 38% among those without dementia.[126] Among people with dementia, 37% used benzodiazepines, 34% antidepressants, and 22% antipsychotics. Among people without dementia, the corresponding figures were 31%, 11% and 3% respectively.

In studies of nursing-home residents around the world, the prevalence of psychotropic drug use varies between 49-82%.[127,129,137] Studies with higher prevalences may also include anti-dementia drugs. In studies among nursing-home residents with dementia in the Nordic countries, 26-43% used antipsychotics, 39-54% antidepressants, 23-38% hypnotics and sedatives, and 15-25% anxiolytics.[127,129,137]

ATC codes and subgroups

Psychotropic drugs are included under N05 and N06 in the Anatomical Therapeutic Chemical (ATC) classification system, where N stands for "Nervous system" and N05 represents Psycholeptic drugs (i.e. drugs with calming effects), and N06 Psychoanaleptic drugs (i.e. drugs with stimulating effects). Each psychotropic drug class contains subgroups, based on active substance, effect, or generation of development.

Antipsychotics

Antipsychotics (ATC code: N05A) are drugs used to treat psychosis. They are divided into typical and atypical antipsychotics, corresponding to the first and second generation of antipsychotics, where the latter is thought to cause fewer extrapyramidal side effects (i.e. Parkinsonism, rigidity, and tremors). Some drugs (i.e. Hydroxyzine/Atarax [N05BB01], Propiomazin/Propavan [N05CM06] and Phenothiazine derivatives [R06AD]) are closely related to antipsychotic drugs, with similar mechanisms of action and causing similar adverse events. In some studies these drugs are included in the group of antipsychotics.

Antipsychotic drugs are often prescribed for older people with dementia to treat delusions, hallucinations, agitation and aggression. Despite the fact that antipsychotics should be considered a short term, second-line treatment option, after non-pharmacological approaches and pain treatment,[130] they are frequently administered to people with dementia, and inappropriate long-term use is common.[129,130,138] An increased risk of death has been found in short-term use of antipsychotics[139] and the risk of hospitalization and death seem to increase with prolonged treatment.[130,140] A meta-analysis of randomized controlled trials found 50% higher odds of death among those taking atypical antipsychotics compared with a placebo.[141] Increased mortality has been found in studies with both typical and atypical antipsychotic drugs, although studies comparing the two have shown a higher relative risk with typical antipsychotics.[130] Other serious side effects include QTc-prolongation, increased risk of cerebrovascular events, extrapyramidal symptoms, Parkinsonism, and anticholinergic side-effects causing delirium.[130,142] To my knowledge, no study among people with dementia has evaluated whether the risk of death associated with antipsychotics differs between men and women.

Antidepressants

Antidepressants (ATC code: N06A) are used to treat depressive disorders and anxiety disorders. They are often divided into tricyclic antidepressants (TCAs; N06AA), selective serotonin reuptake inhibitors (SSRIs; N06AB), and other antidepressants (N06AX or N06A excluding N06AA and N06AB), with SSRIs being the most commonly used class of antidepressants. Monoaminoxidas-inhibitors (N06A F/G) are sometimes included in the group of other antidepressants, due to its relatively limited prescription, and sometimes reported as a subgroup on its own. Other antidepressants (N06AX) include substances such as tetracyclic antidepressants (TeCAs; N06AX03+N06AX11), norepinephrine-dopamine reuptake inhibitors

(NDRIs; N06AX12), and serotonin-norepinephrine reuptake inhibitors (SNRIs; N06AX16+N06AX21).

Although antidepressants may have no effect in reducing depressive symptoms in people with dementia,[18,68,95] such symptoms may increase if the therapy is discontinued.[143] Two reviews found few studies evaluating the effect of antidepressants on BPSD in people with dementia.[131,144] However, a third and more recent review evaluated 19 trials, of which 11 showed positive effects, indicating that antidepressants may be effective and well tolerated when treating BPSD.[145]

Despite that antidepressant use has been associated with an increased risk of all-cause mortality in community-dwelling older people,[103-106] few studies have evaluated the mortality risk in people with dementia. In a register-based study, Jennum *et al.* found an increased risk of death associated with serotonergic antidepressant use, although significantly lower than among controls without dementia.[146] Another large register-based study found a small increased risk of death associated with antidepressant use, excluding TCAs and MAO-inhibitors.[147] As the studies were based on register data, their ability to control for potentially confounding factors was limited, and their result may have been affected by confounding by indication.

Benzodiazepines

Benzodiazepines and benzodiazepine-like drugs are used for their anxiolytic (N05B), hypnotic (N05C) and sedative effects (N05C). They also have muscle relaxing and anticonvulsant properties. Benzodiazepines are used to reduce anxiety, restlessness and sleeping disorders, although evidence of the results of treating people with dementia is scarce.[131-133] To avoid the development of tolerance, short-term or intermittent treatment is recommended.[131] Benzodiazepines are contra-indicated with sleep apnea syndrome,[148] which is very prevalent in those with dementia.[149] In addition, treatment with benzodiazepines has been associated with increased risk for falls, delirium, impaired cognition, depression and mortality.[131,150-152] However, to my knowledge, the only study evaluating the risk of death associated with benzodiazepine use in people with dementia is one register-based study[146] which found no association, but did not investigate gender differences.

RATIONALE FOR THE THESIS

Depression is a common and serious health issue among older people, especially among very old people, and those with cognitive and physical impairment. There is limited knowledge available about effective interventions against depression in older people, with and without dementia. Antidepressants seem to have a limited effect in older people and may have no effect in people with dementia. In addition, there may be an increased risk of harm when treating older people with antidepressants, as adverse drug reactions become more common with age, especially among women, people with multimorbidities, and those with dementia. The association between antidepressants and mortality has not been evaluated in representative samples of very old people, among whom dementia, multimorbidity, and disability are common.

Treatment with psychotropic drugs is very common among older people with dementia, despite the limited evidence regarding its effect, and is associated with an increased risk of adverse events. Apart from that concerning antipsychotics, associations between psychotropic drugs and mortality are little explored among older people with dementia. Men and women seem to exhibit different BPSD, are prescribed psychotropic drugs differently, and may experience different adverse effects from psychotropic drugs. However, no study has reported gender-specific analyses or investigated whether there might be sex-dependent interactions in the association between psychotropic drug use and mortality.

In order to find alternative ways of treating or preventing depression in older people, it is important to increase knowledge about the factors associated with this condition. It has not yet been determined whether functional capacity and dependency in ADL are associated with depression in very old people, including those with severe cognitive or physical impairments. Both ADL dependency and a decline in functional capacity may be prevented or ameliorated by intervention programs, in turn affecting depressive symptoms positively. Dependency in some tasks included in measures of ADL dependence may be associated with depression while dependency in other tasks may not be associated. To better understand the association between ADL dependency and depression, individual ADL tasks and their relation to depressive symptoms need to be explored.

Physical exercise has been found to have positive effects on depressive symptoms among older people without dementia, with moderate- to high-intensity exercise having better effects. Among older people with dementia,

there is insufficient evidence concerning whether physical exercise may reduce depressive symptoms or not. More large studies evaluating the effects of high-intensity exercise against control activities giving a comparable amount of attention are needed.

AIMS OF THE THESIS

The overall aim of this thesis was to investigate associations between psychotropic drug use and death, associations between functional capacity, dependency in ADL and depression, and to evaluate a non-pharmacological intervention against depressive symptoms, among older people with and without dementia.

Specific aims
Paper I - to evaluate the risk of death associated with antidepressant use in a population-based cohort of very old people, and to determine whether depressive symptom level, sex, dementia, heart failure, or stroke moderate this association.

Paper II - to study the association between psychotropic drug use and two-year mortality in old people with dementia, and to investigate possible gender differences in outcome.

Paper III - to examine associations between depressive symptoms and functional capacity, overall dependency in ADL, and dependency in individual ADL tasks, respectively, in people with a high mean age, a large range of functional capacity, and a wide spectrum of dependency in ADL.

Paper IV - to evaluate the effect of a high-intensity, functional exercise program on depressive symptoms compared with a control activity, and to determine whether the effect differs in subgroups of dementia type or depressive symptom level, among older people with dementia living in residential care facilities.

METHODS

This thesis is based on data from four studies; the population-based cohort study Umeå 85+/Gerontological Regional Database (GERDA) study;[153] the randomized, controlled, exercise intervention trial Frail Older People – Activity and Nutrition (FOPANU) study;[154] the cohort study Residential Care Facilities – Mobility, Activity, and Nutrition (REMANU) study;[155] and the randomized, controlled, exercise intervention trial Umeå Dementia and Exercise (UMDEX) study.[156] An overview of the papers comprising the thesis is shown in Table 1.

Table 1 Overview of the papers comprising the thesis

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Studies included	Umeå85+/GERDA[153]	Umeå85+/GERDA, FOPANU,[154] REMANU,[155] UMDEX[156]	Umeå85+/GERDA, FOPANU, REMANU	UMDEX
Year of data collection	2000, 2002, 2005, 2007, 2010, 2012	2000, 2002, 2004, 2005, 2007, 2010, 2011, 2012	2000, 2002, 2004	2011, 2012
Design	Longitudinal	Longitudinal	Cross-sectional	RCT
Aim	Associations antidepressants and 5-year mortality	Associations psychotropic drugs and 2-year mortality	Associations depressive symptoms, functional capacity, ADL dependency	Exercise effects on depressive symptoms
Sample size, n	992	1037	392	186
Population characteristics	A representative sample of very old people	A sample of very old people with dementia and older people with dementia	A sample of old and very old people	A sample of older people with dementia, living in residential care facilities
Age, mean ± SD (range)	89.1 ± 4.5 (85-103)	89.4 ± 6.2 (65-104)	86.2 ± 6.0 (65-103)	85.1 ± 7.1 (65-105)
Women, %	65	74	72	76
Dementia, %	27	100	39	100
Depressive disorders, %	34	51	42	58
Dependent in p-ADL, %	51	92	75	100
Previous stroke, %	20	25	24	31
Heart failure, %	29	35	25	30
Antidepressants, %	16	37	34	55
Barthel ADL Index, mean ± SD (range)	17.6 ± 4.1 (0-20)	12.0 ± 6.1 (0-20)	15.4 ± 4.8 (0-20)	10.8 ± 4.4 (2–18)
MMSE, mean ± SD (range)	22.9 ± 5.4 (5-30)	13.8 ± 6.7 (0-29)	20.5 ± 6.0 (8-30)	14.9 ± 3.5 (10-26)
GDS, mean ± SD (range)	3.8 ± 2.7 (0–14)	4.2 ± 3.0 (0-14)	3.9 ± 2.8 (0-14)	3.8 ± 3.2 (0-13)
GDS ≥ 5, %	31	36	31	30

Note: p-ADL = Personal Activities of Daily Living; MMSE = Mini-Mental State Examination; GDS = 15-item Geriatric Depression Scale; RCT = Randomized Controlled Trial.

STUDIES INCLUDED IN THE THESIS

Umeå 85+/GERDA (Papers I, II, and III)

The population-based cohort study, Umeå 85+[153] was initiated by Umeå University in 2000, and succeeded by the GERDA study in 2003 when the study was prepared for an expansion to Finland and a collaboration was established between Umeå University, Åbo Akademi, University of Vaasa, and the Novia University of Applied Sciences. The objectives of the Umeå 85+/GERDA study were to increase knowledge about the health, quality of life, and living conditions of very old people, and to provide data for use in the planning and support of their care. The first collection of data started in 2000 in the municipality of Umeå. Population data were acquired from the Swedish Tax Agency, and every second 85-year-old, every 90-year-old and every 95-year-old and older were invited to participate. The procedure was repeated in Umeå in 2005 and 2010; in the rural municipalities Storuman, Sorsele, Malå, Vilhelmina, and Dorotea in 2002, 2007 and 2012; in Vasa/Vaasa and Korsholm/Mustasaari in Finland in 2005 and 2010; and in Korsnäs/Ristitaipale and Malax/Maalahti in Finland in 2010.

Those who were eligible to participate in each round were contacted by post. A few days later, they were telephoned and asked if they were willing to participate. Different levels of participation were offered; a participant could, for example, agree to a home visit, grant access to medical charts, or let the assessor interview caregivers and a next of kin.

FOPANU (Papers II and III)

The FOPANU Study[154] was a randomized controlled exercise intervention trial conducted in nine residential care facilities in Umeå, 2002. The facilities comprised private apartments with access to dining facilities, alarms and on-site nursing and care, specialized units for people with dementia, with private rooms and staff on hand, and nonspecialized units where both people with and without dementia were living. The objectives of the study were to evaluate the effects of an exercise intervention and a nutritional supplement in older people living in residential care facilities. The inclusion criteria were: living in a residential care facility, age ≥ 65 years, dependency in personal ADL, ability to rise from a chair with armrests with help from no more than one person, Mini-Mental State Examination (MMSE) score[157] ≥ 10, and approval from the resident's physician. Only baseline data from FOPANU were used in this thesis.

REMANU (Papers II and III)

The REMANU Study[155] was an observational cohort study, conducted in three residential care facilities in Umeå, 2004. The facilities comprised private apartments with access to dining facilities, alarms and on-site nursing and care, and specialized units with private rooms and staff on hand for people with dementia. The objectives of the study were to monitor changes in mobility, activity, and nutrition over a period of six months, and to evaluate a number of measures regarding physical function in older people, dependent in ADL and living in residential care facilities. REMANU used the same inclusion criteria as the FOPANU study. Only baseline data from REMANU were used in this thesis.

UMDEX (Papers II and IV)

The UMDEX Study[156] was a randomized controlled exercise intervention trial conducted in 16 residential care facilities in Umeå, 2011–2012. The facilities comprised specialized and non-specialized units for people with dementia. In 14 facilities there were units with private rooms and staff on hand and 5 facilities had units where residents lived in private apartments and had access to dining facilities, alarms, and on-site nursing and care. The objective of the study was to evaluate the effects of an exercise intervention in older people with dementia living in residential care facilities. The inclusion criteria were the same as in the FOPANU and REMANU studies with the addition of having a diagnosis of dementia according to DSM-IV-TR-criteria,[1] and the ability to hear and understand Swedish sufficiently well to participate in assessments. Physical therapists (PTs) and physicians assessed the eligibility of all residents. A team of physicians, including a specialist in geriatric medicine, established dementia diagnoses according to DSM-IV-TR criteria using medical records, MMSE scores, assessment of temporary states of confusion, and information about visual and hearing impairment. In Paper II, only baseline data from UMDEX were used.

Clusters and randomization

The participants were divided into 36 clusters/activity groups comprising residents of the same wing, unit, or floor of a facility. The mean number of participants in a cluster was 5 (range: 3–8). Researchers not involved in the study performed the concealed randomization (using sealed, opaque envelopes), which started with the order of the cluster allocation, and was followed by the allocation to intervention or control group. The randomization was performed after participant enrollment and baseline assessment.

Exercise intervention

Two PTs supervised every exercise session. The exercise intervention was based on the High-Intensity Functional Exercise (HIFE) program, which has been described in detail elsewhere.[156,158,159] The purpose of the HIFE program is to improve lower limb strength, balance, and mobility in older people. It comprises 39 exercises, intended to be performed at high intensity and designed to imitate daily functional movements. The strength exercises were defined as high-intensive when 8-12 repetitions maximum (RM)[160] were performed, and the balance exercises when they were performed near the limit for maintaining postural stability. The load in strength exercises and the difficulty in balance exercises were increased gradually as participants progressed. All participants were individually supervised and each participant had a personalized exercise program. Throughout the intervention period, the PTs chose and adapted exercises and intensity for each participant based on his/her current physical and functional capacity, cognitive function, BPSD, and health status. Participants were encouraged to exercise at moderate intensity (i.e. 13-15 RM for strength exercises) in the first two weeks and at high intensity thereafter. After each session, PTs evaluated the exercise intensity achieved by each participant (high, moderate or low), according to a predefined scale.[158]

Control activity

The control activity was a non-exercise activity program developed for the study by occupational therapists (OTs) and an OT assistant. Each session comprised seated activities (e.g., conversing, singing, picture viewing, listening to readings or music), under the guidance of one OT or OT assistant. Sessions included topics such as the seasons, wildlife, cooking, authors, and famous artists.

SAMPLE

Paper I

Participants from the following areas and data collections of the Umeå85+/GERDA study were included in the paper; Umeå (2000, 2005, 2010), Storuman, Sorsele, Malå, Vilhelmina, and Dorotea (2002, 2007, 2012), and Vasa/Vaasa and Korsholm/Mustasaari (2005), which represented all available data collections at the time. Only participants who had answered 10 or more questions on the 15-item Geriatric Depression Scale (GDS) were allowed to participate in this paper. From the 1694 people invited to participate, 992 (59%) were included (Figure 1). Those who

declined home visits (n = 512) or failed to answer ≥10 GDS items (n = 190) were more likely to be older (90.1 vs. 89.1 years, P < 0.001) and female (76% vs. 65%, P < 0.001) compared with those included in the analyses.

Paper II

Participants with a dementia diagnosis and information about prescribed drugs from the Umeå85+/GERDA, FOPANU, REMANU and UMDEX studies were included in this paper. In addition to the data collections from Umeå85+/GERDA included in Paper I, the data collected in Vasa/Vaasa, Korsholm/Mustasaari, Korsnäs/Ristitaipale and Malax/Maalahti in 2010 were included in this study. No criterion based on GDS was used in this paper. Of the 2498 participants in the four original studies, 1037 met the inclusion criteria. Of those not included, 1378 persons did not have a dementia diagnosis, and data on prescribed drugs were missing for 8. Data from 75 test subjects were excluded since they were already participating with data from one of the previously conducted studies. The inclusion procedure is described further in Figure 2.

Paper III

This paper included datasets where the Berg Balance Scale (BBS) had been applied. These were the Umeå85+/GERDA, FOPANU and REMANU studies. For Umeå85+/GERDA, BBS was only applied to data collected in Umeå 2000. Only participants with a BBS score who answered 14 questions or more on the GDS were included in this paper. Of 507 persons participating in the respective studies, 392 were included in this paper. Of the excluded participants, 46 were missing a BBS score, 39 answered less than 14 questions on GDS, and 30 had been included in a previous study (Figure 3).

Paper IV

This paper included the participants from the UMDEX study. Of the 241 persons who met the inclusion criteria, 186 (77%) agreed to participate. There was no difference in age and MMSE score between the 186 study participants and the 55 residents who declined to participate. A higher proportion of men than women declined to participate (34% vs 18%, P = 0.008; Figure 4).

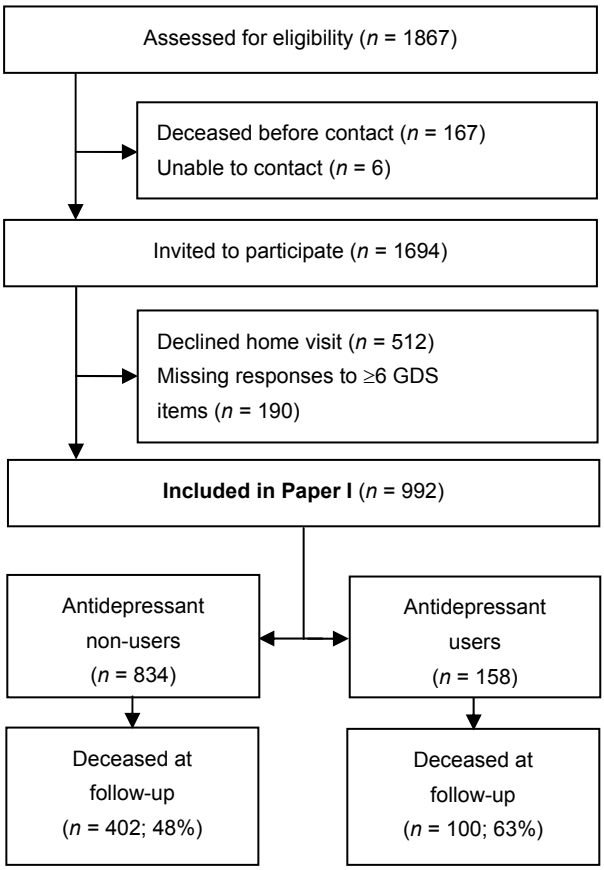

Figure 1 Flowchart of the inclusion process in Paper I.

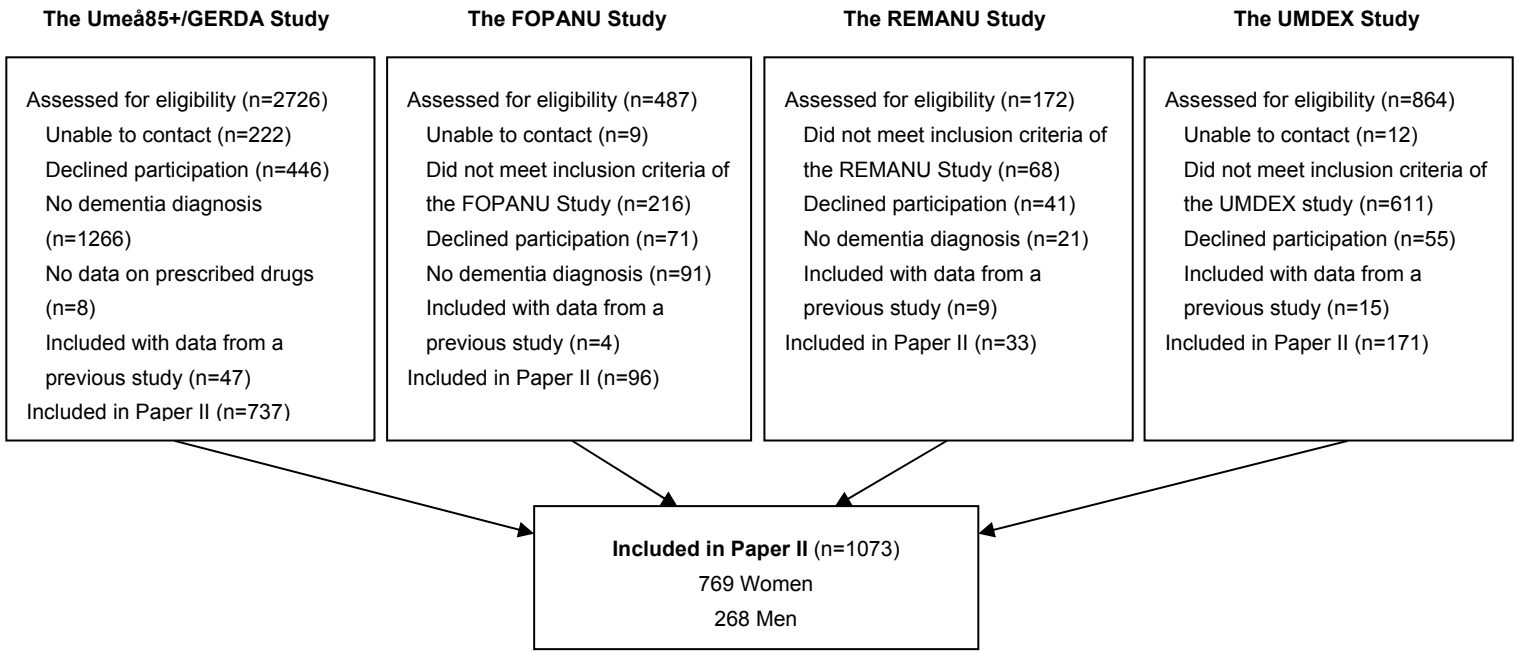

Figure 2 Flowchart of the inclusion process in Paper II.

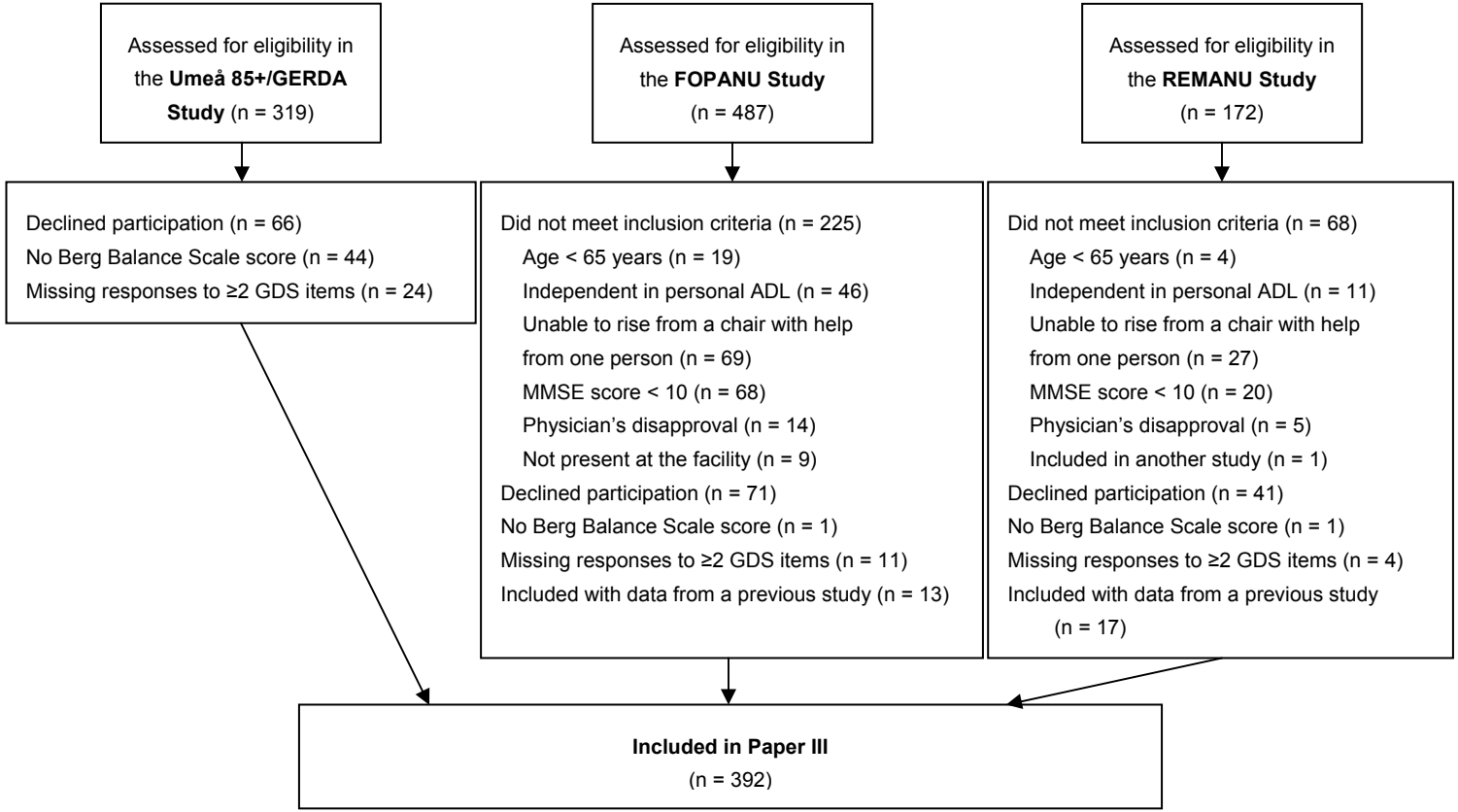

Figure 3 Flowchart of the inclusion process in Paper III.

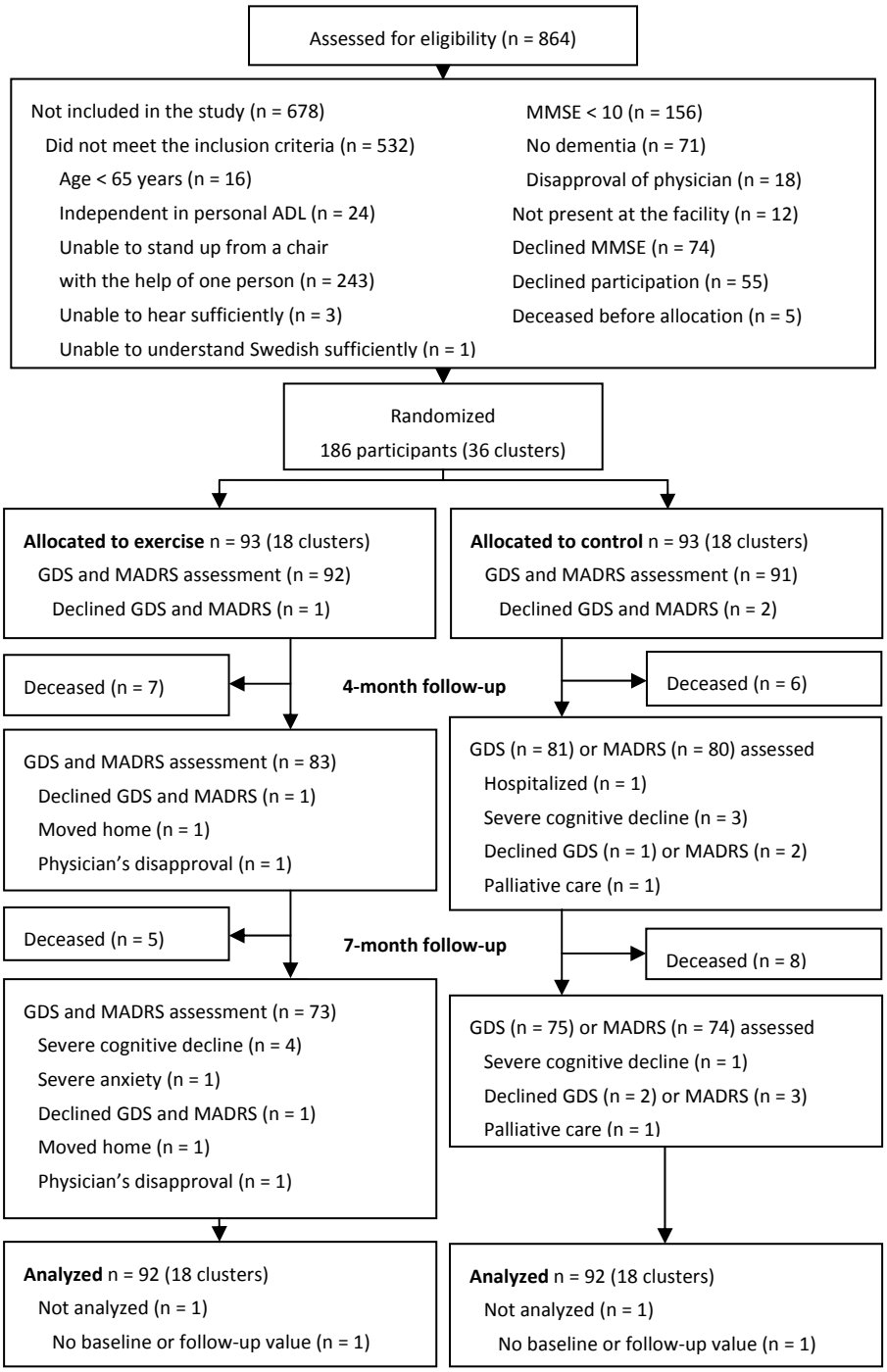

Figure 4 Flowchart of Paper IV.

ETHICS

In the Umeå85+/GERDA study, informed consent was obtained over the telephone and confirmed during a subsequent home visit. In cases of severe cognitive or hearing impairment, contact was established via a next of kin or a caregiver. In addition, a next of kin was asked to provide informed consent in cases of cognitive impairment. The study was approved by the Regional Ethics Review Board in Umeå (registration nos. 99-326, 05-063M, 09-178M and 2015/296-31) and the Ethics Committee of Vaasa Central Hospital (registration nos. 05-87 and 10-54).

In the FOPANU and REMANU studies, PTs screened all residents available at the care facilities of the respective studies, and obtained informed consent from eligible participants. A close relative was also asked to provide informed consent in cases of cognitive impairment. The studies were approved by the Regional Ethics Review Board in Umeå (registration nos. 391/01 and 439/03 respectively). The study protocol of FOPANU (ISRCTN31631302) is available at http://www.isrctn.com/.

In the UMDEX study, physicians and PTs screened all available care facility residents. Eligible residents gave their informed oral consent to participation, which was confirmed by their next of kin. The Regional Ethics Review Board in Umeå approved the study in August 2011 (2011-205-31M). The study protocol (ISRCTN31767087) is available at http://www.isrctn.com/.

DATA COLLECTIONS AND ASSESSMENTS

In all four studies, trained assessors (nurses, PTs, physicians, and medical students) visited and interviewed consenting participants in their homes or in the living areas of the residential care facilities.

Baseline characteristics

Structured interviews included sociodemographic questions and the application of rating scales, assessments, and various tests. MMSE was used to measure cognitive function (range 0–30; mild cognitive impairment, 18–23; severe impairment, <18).[157,161] Nutritional status was assessed using the Mini Nutritional Assessment (range 0–30).[162] Measured height and weight were used to calculate body mass index (kg/m^2). Visual impairment was considered to be present when a participant was unable to read a sentence printed in 5-mm capital letters, with visual aids if needed. Hearing

impairment was defined as the inability to hear a normal conversational tone, with hearing aids if needed. The second part of the Organic Brain Syndrome (OBS) scale[163] was used in Umeå85+/GERDA to evaluate disturbances in awareness, orientation, emotional reactions, psychotic symptoms, and time variations in confusional state. Only the confusion subscale of the OBS scale was used in UMDEX. The Philadelphia Geriatric Centre Morale Scale (PGCMS) was used to assess morale.[164]

In UMDEX, behavioral and psychological symptoms of dementia (BPSD) were measured using the Neuropsychiatric Inventory (range 0–144).[83] Self-reported presence of pain during a walking test was recorded. Self-reported health was extracted from the first item of the 36-item short-form questionnaire.[165]

Diagnoses

In the Umeå 85+/GERDA study, information about diagnoses and prescribed drugs was collected from participants and their medical records. When appropriate, relatives and/or caregivers were contacted to confirm certain diagnoses. In the FOPANU and REMANU studies, residential care facility nurses obtained this information from medical records, and in the UMDEX study, the information was acquired by the study's physicians from medical records. An experienced specialist in geriatric medicine checked and verified diagnoses in all four studies. Dementia, depressive disorders and delirium were diagnosed or verified according to DSM-IV-TR criteria,[1] based on all available information, including medical records, MMSE scores, the OBS scale,[163] information about visual and hearing impairment, the GDS,[166] the PGCMS,[164] the Montgomery-Åsberg Depression Rating Scale (MADRS) (UMDEX and GERDA only),[167] and indications for prescribed drugs. Participants receiving ongoing antidepressant treatment (indicated for a depressive disorder) were classified as having a depressive disorder, regardless of the baseline assessments' results.

Outcome and target variables

The Geriatric Depression Scale

The 15-item version of the Geriatric Depression Scale (GDS) was used to assess depressive symptoms and to screen for depression.[166] The scale comprises 15 yes/no questions, with each answered question graded 0 or 1. A total score of 0-4 is considered normal, 5-9 indicates mild depression, and 10-15 moderate to severe depression.[166,168] The GDS has been shown to detect clinical depression with high sensitivity and specificity in people aged

≥85 years,[169] and in people living in residential care facilities.[170] In addition, it has been validated and judged useful in older people with severe cognitive impairment.[170,171] The GDS was administered in interviews to make it easier for people with cognitive decline or functional impairment to complete the test. In Papers I and III, participants answering fewer than 10 and fewer than 14 GDS questions, respectively, were not included in the respective papers.

The Montgomery-Åsberg Depression Rating Scale

The Montgomery-Åsberg Depression Rating Scale (MADRS) was constructed to detect changes in depressive symptoms and has been used widely in clinical trials involving antidepressants.[167] It is based on a clinical interview where 10 depressive symptoms are rated on a scale of 0 to 6, with higher scores reflecting greater severity. Total scores range from 0 to 60, with a score ≥ 7 indicating clinically relevant depressive symptoms.[172] The MADRS was used in the UMDEX and the GERDA studies. In the UMDEX study, all participants were interviewed with GDS and MADRS by physicians, blinded to group allocation and previous test results. In the GERDA study, MADRS was applied when the assessor was a physician, which was the case in approximately 30% of the interviews.

The Berg Balance Scale

Functional balance capacity was assessed in Paper III using the Berg Balance Scale (BBS),[173] a well-established, valid, and reliable scale for use with older people, including those with cognitive impairment.[155,174] The BBS measures functional balance capacity in 14 common everyday tasks of varying difficulty, including standing up from a seated position, transferring from one chair to another, standing and reaching forward, standing and turning 360°, and placing one foot at a time onto a step while standing. Thus, the scale reflects aspects of physical function other than balance, such as lower-limb strength and gait. Item scores range from 0 to 4 and total scores range from 0 to 56, with higher scores indicating better balance/functional capacity.[174] People who exceed specified time limits or require supervision or physical or verbal guidance are given lower scores. The unavailability of a BBS score resulted in the exclusion of a participant's data from Paper III.

The Barthel ADL Index

Dependency in ADL was assessed in all papers using the 10-item version of the Barthel ADL Index, a well-established and valid measure of dependency in personal care and mobility[175] that has demonstrated

reliability among older people with impaired function.[176] The Barthel ADL Index measures what a person does, rather than what he or she is able to do. Scores range from 0 to 20, with higher scores indicating a greater level of independence. In the FOPANU, REMANU and UMDEX studies, licensed practical nurses or nurse's aides who knew the participants well were interviewed about dependency in ADL. In the Umeå 85+/GERDA Study, participants were interviewed and in cases of cognitive impairment, relatives and caregivers were contacted to confirm the scores.

Antidepressants, Antipsychotics, and Benzodiazepines

Prescribed drugs were categorized according to the Anatomical Therapeutical Chemical (ATC) index. Antidepressant drugs were defined as all drugs within ATC-code N06A. The definition of antipsychotic drugs included drugs bearing a close similarity to conventional antipsychotics, resulting in the inclusion of N05A (but not N05AN01, Lithium), N05BB01, N05CM06 and R06AD. Benzodiazepines included bensodiazepine-like drugs, i.e. all drugs classified as N05BA, N05CD, N05CF or N03AE were included. Scheduled medications, as well as those used pro re nata (PRN)/as needed, were included.

Mortality

Data on mortality were collected from population registers (in Sweden provided by the Swedish Tax Agency and in Finland by the Population Register Centre), death certificates (the Swedish National Board of Health and Welfare's register of death certificates), and medical records (mortality dates specifying the time and place of death, registered within two weeks after death). In Paper I, the date of death up to 5 years after the date of study inclusion of each participant, or the last date of data collection (1 September 2014) was used as the termination date for analyses. In Paper II, 2-year mortality was used.

STATISTICAL ANALYSES

Paper I

Participant characteristics were considered potential confounders when associated significantly ($P < 0.05$) with both death and antidepressant use in independent samples *t*-tests or χ^2 tests. When 10–14 of the 15 GDS questions were answered, total GDS scores were imputed using the fraction of the answered score extrapolated to 15 questions and rounded up to an integer.[177] Of the 139 participants with imputed GDS scores, the majority (n=94) had only 1 missing answer. The covariates care facility resident and MMSE score were not included in the final model due to high correlation ($r > 0.5$) with Barthel ADL Index scores and dementia, respectively.

Cox proportional hazard regression models were used to estimate hazard ratios (HRs) for death among antidepressant users compared with non-users. HRs were calculated in three models: model 1, adjusted for age and sex; model 2, adjusted for age, sex, and GDS score; and model 3, adjusted for age, sex, GDS score, and potential confounders (living alone, dementia, neuroleptics, heart failure, Barthel ADL index). The three models were applied to the total sample and to those with GDS scores ≥ 5 and < 5, respectively. Sensitivity analyses of participants without imputed GDS scores were performed in model 3, giving essentially the same results as in the total sample (data not shown).

Interaction effects between antidepressant use and sex, dementia, heart failure, and stroke, respectively, were analyzed in model 3. In case of significant interactions, HRs for death due to antidepressant use were investigated further in subgroups. Schoenfeld residuals were used to test the proportional hazard assumption. As model 3 indicated that age was time-dependent in the total sample and in men, an extended Cox regression model including an age × follow-up time interaction term was used in these analyses and in interaction analyses based on model 3. IBM SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. All statistical tests were two tailed and $P < 0.05$ was considered to indicate statistical significance.

Paper II

Cox proportional hazards regression models were used to estimate HRs for death among psychotropic drug users, compared with non-users, investigating each of the three drug classes separately. For each drug class,

unadjusted and adjusted analyses were performed. In the adjusted analyses, adjustments for age, sex and potential confounders were included. Characteristics included as potential confounders were those that associated with both the usage of the investigated drug ($P \leq 0.15$, analyzed using the chi-2 test and student's t-test) and with mortality ($P \leq 0.15$, analyzed using Cox proportional hazards regression models). Separate potential confounders were produced in the total sample and among men and women. GDS was included in the models investigating the risk of death associated with antidepressant use, irrespective of association with antidepressant use or death. Some variables were excluded due to singularity or due to multicollinearity (correlations coefficient, $r \geq 0.6$). MNA was excluded in all analyses due to singularity caused by the variable "number of drugs". Similarly, opioids were removed in some analyses due to singularity with analgesics. PGCMS was not included in any analysis due to high correlation ($r \geq 0.6$) with GDS. GDS was chosen before depressive disorders due to high correlation in some analyses. Angina pectoris was chosen before organic nitrates due to high correlation in some other analyses. If the selection process resulted in more potential confounders for a model than one tenth of the number of events in the subgroup,[178] a stepwise backwards removal was conducted. In addition, interaction analyses were used to investigate possible gender differences, using a sex × drug variable, in the total sample of all adjusted psychotropic drug analyses.

Several potential confounders had missing data associated with higher morbidity and lower scores on several scales. Thus, the missing data was considered to be missing at random (MAR; in contrast to missing completely at random [MCAR] or missing not at random [MNAR])[179] and multiple imputation (20 sets) was used to complete the variables GDS (35% imputed), MMSE (14% imputed), BMI (15% imputed), Barthel ADL Index (6.5% imputed), and having had a myocardial infarction (12% imputed). Variables used as predictors in the imputation model were (1) the potential confounders in the Cox regression models, (2) variables correlating with the variables to be imputed ($r \geq 0.3$), (3) the variables associated with missing values in the variables to be imputed, and (4) the outcome variables and mortality data.[180] No restrictions were set for the imputed values. All analyses were conducted on the original data as well as the data completed through imputation. The two sets of results were close to identical, concerning the main outcomes. The results presented in Paper II come from the imputed data set. All statistical analyses and calculations were performed using IBM SPSS Statistics, version 23 (IBM Corporation, Armonk, NY, USA). All statistical tests were two tailed and $P < 0.05$ was considered to indicate statistical significance.

Paper III

Descriptive characteristics were chosen in advance of analysis, based on previous associations in the literature of these characteristics with depression. These associations were tested in univariate linear regression analyses, with GDS score serving as the dependent variable. To further investigate each task in the Barthel ADL Index, they were each dichotomized as independent (maximum task score) or dependent (at least one point deducted). Differences in GDS scores between these groups were evaluated using independent samples t-test.

Univariate and multivariate linear regression analyses were used to investigate associations between GDS and BBS, GDS and Barthel ADL Index, and GDS and each individual ADL task of Barthel ADL Index, separately. In every model, the dependent variable was GDS score, and in the respective models, independent variables were BBS score, overall Barthel ADL Index score, and the dichotomized Barthel ADL tasks, respectively. Age, sex, and descriptive characteristics associated with the GDS score ($P \leq 0.15$) in univariate analyses were added to the multivariate linear regression models, after controlling for multicollinearity ($r \geq 0.7$). Given the high correlation ($r = -0.74$) between dependency in the ADL task of bathing and living in a residential care facility, the latter was not controlled for when analyzing the former. In addition, depressive disorders, MMSE score, benzodiazepine use, and antidepressant use were not included in any multivariate regression model; depressive disorders since the dependent variable (GDS score) was measuring depressive symptoms; MMSE score since dementia diagnosis has been associated more consistently with depression in the literature and MMSE scores can be falsely low among depressed older people; benzodiazepine and antidepressant use were considered to be effects, rather than causes, of depression and were not included in the analyses. Interaction effects between BBS score and Barthel ADL Index score, respectively, and sex, dementia, and living in a residential care facility were also evaluated in multivariate linear regression analyses. IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY), was used for statistical analyses. All statistical tests were two tailed and $P < 0.05$ was considered to indicate statistical significance.

Paper IV

Differences in baseline characteristics between exercise and control, and between high and low GDS scores were examined using the independent samples t-test or χ^2 test. High and low GDS scores were separated based

on the cut-off at 4/5 points. Scores were considered missing when <10/15 questions were answered. For incomplete scores with ≥10/15 answered GDS items or ≥8/10 answered MADRS items, a total score was imputed by dividing the score by the number of questions answered and multiplying by 15 for GDS and 10 for MADRS (with rounding up to an integer).[177] The number of participants with imputed GDS and MADRS total scores, respectively, were 3 and 0 at baseline; 3 and 2 at 4 months; and 17 and 4 at 7 months. The only attribute that differed significantly ($P < 0.05$) between activity groups was antidepressant use, which was adjusted for in subsequent analyses.

Longitudinal changes in GDS and MADRS scores over 4 and 7 months were analyzed using linear mixed models, with baseline and follow-up values as the outcome variables. Analyses were adjusted for cluster and test-subject as random effects, and age, sex, and antidepressant use as fixed effects. Between-group differences were estimated using an activity × timepoint interaction term, and within-group differences (follow-up – baseline values) were estimated using least square means (LSMs). Adjusted intention-to-treat (ITT) analyses included all participants with at least one (baseline or follow-up) outcome measurement, and were performed according to group allocation, irrespective of activity adherence. Intracluster correlation coefficients were calculated as the proportions of total variance attributed to cluster variance in GDS and MADRS scores in the total sample. Because previous studies included only participants with Alzheimer's disease, dementia type was dichotomized as Alzheimer and non-Alzheimer (including mixed) dementia. Within-group LSM analyses were performed according to dementia type, GDS score (≥5 and <5), and MADRS score (≥7 and <7) following the same procedure as in the whole sample. Between-group analyses compared within-group LSM changes using the independent samples t-test with 50% fewer degrees of freedom to obtain conservative *P*-values. Activity × timepoint interaction terms and subgroup divisions (dementia type, GDS score, MADRS score) were also tested using linear mixed models in the total sample. R version 3.0.1,[181] (R Core Team, 2014) with the LME4 package,[182] and SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA) were used to perform statistical analyses. All statistical tests were two tailed and $P < .05$ was considered to indicate significance.

RESULTS

PAPER I – ANTIDEPRESSANT USE AND MORTALITY IN VERY OLD PEOPLE

Table 2 shows the baseline characteristics of the sample in Paper I according to survival status and antidepressant use. The mean age of the participants was 89 years and 271 (27%) were diagnosed with dementia. A total of 158 (16%) participants used antidepressants, most commonly citalopram (91 users), mirtazapine (20 users), and sertraline (11 users). SSRIs were used by 121 participants, TCAs by 16, and other antidepressants by 35 (14 participants used two antidepressant drug classes). The mean GDS score (± standard deviation) was 3.8 ± 2.7 and 310 (31%) participants had GDS scores ≥5, of whom 76 (25%) were being treated with antidepressants. During the follow-up period (mean 3.3 years), death rates were 51% (502/992) in the total sample and 63% (100/158) among antidepressant users. Mortality and antidepressant use were associated with living alone, neuroleptic use, dementia, heart failure, lower MMSE scores, lower Barthel ADL Index scores, and higher GDS scores. Among women, mortality rate was lower and antidepressant use higher than in men (Table 2).

In the initial age- and sex-adjusted model (model 1), antidepressant use was associated with a 76% increased risk of death (HR = 1.76, 95% confidence interval [CI], 1.41–2.19). In model 2, additionally adjusted for continuous GDS score, antidepressant use remained associated with an increased risk of death (HR = 1.62, 95% CI, 1.29–2.03). In model 3, additionally adjusted for factors associated with both mortality status and antidepressant use (Table 2), this association was no longer significant (Table 3; Figure 5). In particular, adjustment for dementia, heart failure, and ADL dependency attenuated the associations found in models 1 and 2 (data not shown). In subgroups of participants with high and low GDS scores, antidepressant use was associated with an increased risk of death in models 1 and 2, but not in model 3 (Table 3).

Interaction analyses in model 3 revealed a higher mortality risk with antidepressant use among women, compared with men (HR: 1.76; 95% CI, 1.05– 2.94). The HRs for death among antidepressant users in model 3 were 0.76 (95% CI, 0.47–1.24) among men and 1.28 (95% CI, 0.97–1.70) among women (Table 3; Figure 5). Interaction effects in model 3 were not significant for dementia (HR: 0.69; 95% CI, 0.44–1.09), heart failure (HR: 0.79; 95% CI, 0.50–1.24), or previous stroke (HR: 0.80; 95% CI, 0.45–1.41).

Table 2 Baseline characteristics of the sample in Paper I

CHARACTERISTIC	TOTAL (*N* = 992)	ALIVE (*N* = 490)	DEAD (*N* = 502)	*P*	NO ANTIDEPRESSANT USE (*N* = 834)	ANTIDEPRESSANT USE (*N* = 158)	*P*
Age (years)	89.1 ± 4.5 (84–103)	87.5 ± 3.6 (84–102)	90.6 ± 4.7 (84–103)	<0.001	89.1 ± 4.5 (84–103)	89.1 ± 4.3 (84–101)	0.86
Sex (female)	645 (65)	339 (69)	306 (61)	<0.01	524 (63)	121 (77)	0.001
Living alone	770 (78)	363 (74)	407 (81)	<0.01	633 (76)	137 (87)	<0.01
Care facility residents	304 (31)	83 (17)	221 (44)	<0.001	215 (26)	89 (56)	<0.001
Diagnoses and medical conditions							
Dementia	271 (27)	74 (15)	197 (39)	<0.001	189 (23)	82 (52)	<0.001
Previous stroke	194 (20)	90 (18)	104 (21)	0.35	151 (18)	43 (27)	0.01
Heart failure	289 (29)	87 (18)	202 (40)	<0.001	227 (27)	62 (39)	<0.01
Angina pectoris	342 (34)	144 (29)	198 (39)	<0.001	277 (33)	65 (41)	0.054
Atrial fibrillation	212 (21)	70 (14)	142 (28)	<0.001	173 (21)	39 (25)	0.32
Cancer, current/last 5 years	132 (13)	57 (12)	75 (15)	0.13	107 (13)	25 (16)	0.31
Regular use of drugs							
Antidepressants	158 (16)	58 (12)	100 (20)	<0.001	-	158 (100)	
Neuroleptics	87 (9)	26 (5)	61 (12)	<0.001	58 (7)	29 (18)	<0.001
ASA	430 (43)	198 (40)	232 (46)	0.07	358 (43)	72 (46)	0.60
Warfarin	86 (9)	38 (8)	48 (10)	0.31	71 (9)	15 (9)	0.42
NSAID	64 (6)	34 (7)	30 (6)	0.54	53 (6)	11 (7)	0.91
Assessments							
MMSE (0–30)*	22.9 ± 5.4 (5–30)	24.7 ± 4.2 (5–30)	21.1 ± 5.8 (5–30)	<0.001	23.5 ± 5.0 (5–30)	19.8 ± 6.2 (5–30)	<0.001
Barthel ADL Index (0–20)*	17.6 ± 4.1 (0–20)	18.9 ± 2.5 (0–20)	16.2 ± 4.9 (0–20)	<0.001	18.0 ± 3.6 (0–20)	15.0 ± 5.3 (0–20)	<0.001
GDS (0–15)	3.8 ± 2.7 (0–14)	3.3 ± 2.4 (0–14)	4.2 ± 2.9 (0–14)	<0.001	3.6 ± 2.6 (0–14)	4.9 ± 3.0 (0–14)	<0.001
GDS ≥ 5	310 (31)	121 (25)	189 (38)	<0.001	234 (28)	76 (48)	<0.001

Note: ASA = acetylsalicylic acid; NSAID = nonsteroidal anti-inflammatory drug; MMSE = Mini-Mental State Examination; ADL = activities of daily living; GDS = 15-item Geriatric Depression Scale. Data are presented as mean ± standard deviation (range) or *n* (%). For all assessment scales except GDS, higher scores indicate higher function. Differences between living and deceased participants and between antidepressant users and non-users were analyzed using the χ^2 test or independent-samples *t*-test, as appropriate. *Indicates some individuals had missing data.

Table 3 Hazard ratios for death among antidepressant users compared with non-users

MODEL	TOTAL SAMPLE (*N* = 992)		GDS < 5 (*N* = 682)		GDS ≥ 5 (*N* = 310)		MEN (*N* = 347)		WOMEN (*N* = 645)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	(HR 95% CI)	*P*	HR (95% CI)	*P*
1	1.76 (1.41, 2.19)	<0.001	1.85 (1.37, 2.50)	<0.001	1.48 (1.05, 2.07)	0.02	1.34 (0.87, 2.08)	0.18	1.97 (1.52, 2.56)	<0.001
2	1.62 (1.29, 2.03)	<0.001	1.84 (1.36, 2.48)	<0.001	1.42 (1.01, 1.99)	0.04	1.22 (0.79, 1.90)	0.38	1.84 (1.41, 2.40)	<0.001
3	1.08 (0.85, 1.38)	0.51	1.10 (0.79, 1.53)	0.58	1.02 (0.72, 1.46)	0.90	0.76 (0.47, 1.24)	0.27	1.28 (0.97, 1.70)	0.08

Note: HR = hazard ratio; CI = confidence interval; GDS = 15-item Geriatric Depression Scale. Analyses were performed using Cox proportional hazard regression models. Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, and continuous GDS score; and model 3 was adjusted for age, sex, continuous GDS score, living alone, dementia, neuroleptics, heart failure, and Barthel ADL Index. In the total sample and among men, model 3 was also adjusted for age × follow-up time.

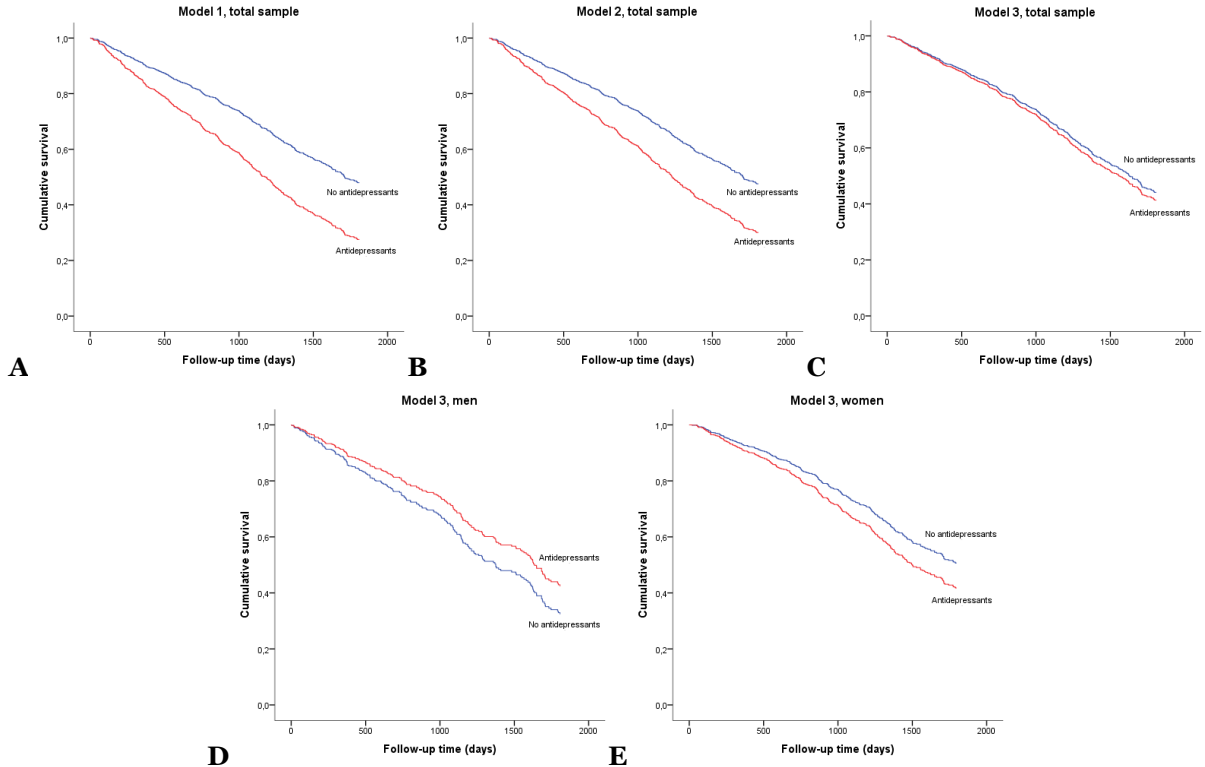

Figure 5 Survival curves based on Cox proportional hazard regression models of antidepressant users *vs*. non-users in the total sample (A–C) and in subgroups of men (D) and women (E). Model 1 (A): adjusted for age and sex; Model 2 (B): adjusted for age, sex, and continuous GDS score; Model 3 (C–E): adjusted for age, sex, continuous GDS score, living alone, dementia, neuroleptics, heart failure, and Barthel ADL index.

PAPER II – PSYCHOTROPIC DRUG USE AND MORTALITY IN OLD PEOPLE WITH DEMENTIA

Table 4 shows a detailed description of the participants' characteristics at baseline.

Paper II included 1037 older people with dementia. Their mean age was 89.4 years, 769 (74%) were women, and 488 (47%) died during the two-year follow-up. Alzheimer's disease was the most common type of dementia (52%), followed by vascular dementia (38%). Depressive disorders were diagnosed in 525 (51%) participants and delirium during the last month in 494 (48%). Antidepressants were used by 37% of the participants, antipsychotics by 22%, and benzodiazepines by 39% (Table 4). At least one of the three psychotropic drugs was used by 64% of the participants.

Those who died during the follow-up were older, had more depressive symptoms, worse cognition, were more dependent in ADL, used more analgesics and were prescribed more drugs. They also had a lower frequency of Alzheimer's disease, were more delirious in the last month, and had more heart diseases, compared with those who survived for two years. Women, compared to men, were older, had worse cognition, were more dependent in ADL, and were prescribed more drugs; benzodiazepines and analgesics in particular (Table 4).

Among the antidepressant users, women used more other antidepressants (N06AX) than men (12% vs. 7%, $P<0.05$). Gender differences were seen in most of the different benzodiazepines, with a higher total use among women (41% vs. 32%, $P<0.05$), a higher use of anxiolytics (N05BA, 18% vs. 10%, $P<0.05$), and benzodiazepine related hypnotics (N05CF, 25% vs. 19%, $P<0.05$). No gender differences were seen in antipsychotic use.

The adjusting factors qualified for each multiple regression model of respective psychotropic drug and sample are shown in Table 5. The results from the Cox proportional hazard regression models are shown in Table 6.

Antidepressants

No association was seen between antidepressant drug use and mortality among all participants. The interaction for gender was significant ($P=0.047$), with a higher mortality risk for women than for men. When studying men and women separately, a significant association between antidepressant use

and lower two-year mortality was found in men (HR: 0.61, 95% CI: 0.40-0.92), whereas no association was seen in women (Table 6).

Antipsychotics

No associations were seen between baseline use of antipsychotics and mortality in any of the analyses. The interaction for gender was non-significant (*P*=0.962; Table 6). No significant differences in association with mortality were seen between typical and atypical antipsychotics for men, women or in the total sample (data not shown).

Benzodiazepines

Benzodiazepine use at baseline was associated with increased mortality during the first year in the unadjusted analysis (HR: 1.38, 95% CI: 1.08-1.77), but not in the fully adjusted model. During the second year no mortality risk was seen in the unadjusted analysis, whereas an association between benzodiazepines and reduced mortality appeared when fully adjusting (HR: 0.72, 95% CI: 0.54-0.96). The interaction for gender was significant (*P*=0.029), with a higher mortality risk for men, compared with women during the first year, but not the second year after baseline. First year mortality associated with benzodiazepine use was elevated in men, in the univariate analysis (HR: 2.07, 95% CI: 1.29-3.32), but not with full adjustment. No significant associations were seen for men during the second year, or for women in any of the analyses (Table 6).

Table 4 Baseline characteristics of the sample in Paper II

Characteristic	Total (n=1037)	Men (n=268)	Women (n=769)		Alive (n=549)	Dead (n=488)	
Age	89.4 ± 6.2	88.0 ± 5.9	89.9 ± 6.3	*	87.9 ± 6.4	91.0 ± 5.5	*
Sex, female	769 (74)	0 (0)	769 (100)	*	412 (75)	357 (73)	
Death ≤ 2 years	488 (47)	131 (49)	375 (46)		0 (0)	488 (100)	*
Medical conditions and diagnoses							
Alzheimer's disease	536 (52)	135 (50)	401 (52)		309 (56)	227 (47)	*
Vascular dementia	398 (38)	121 (45)	277 (36)		196 (36)	202 (41)	
Depressive disorders	525 (51)	129 (48)	396 (51)		276 (50)	249 (51)	
Stroke, ever	257 (25)	78 (29)	179 (23)		124 (23)	133 (27)	
Delirium, in last month	494 (48)	126 (47)	368 (48)		221 (40)	273 (56)	*
Malignant disease, ever	196 (19)	71 (26)	125 (16)	*	100 (18)	96 (20)	
Diabetes mellitus	165 (16)	55 (21)	110 (14)	*	86 (16)	76 (16)	
Atrial fibrillation	213 (21)	66 (25)	147 (19)		98 (18)	115 (24)	*
Angina pectoris	370 (36)	104 (39)	266 (35)		171 (31)	199 (41)	*
Congestive heart failure	359 (35)	87 (32)	272 (35)		150 (27)	209 (43)	*
Myocardial infarction, ever (12.2% imputed)	198 (19)	61 (23)	137 (18)		86 (16)	112 (23)	*
Hip fracture, ever	187 (18)	32 (12)	155 (20)	*	96 (17)	91 (19)	
Prescribed drugs							
Analgesics	691 (67)	154 (57)	537 (70)	*	332 (60)	359 (74)	*
Antiepileptics	47 (4)	13 (5)	34 (4)		27 (5)	20 (4)	
Antidepressants	388 (37)	94 (35)	294 (38)		203 (37)	185 (38)	
Antipsychotics	230 (22)	54 (20)	176 (23)		113 (21)	117 (24)	
Benzodiazepines	404 (39)	87 (32)	317 (41)	*	205 (37)	199 (41)	
Cholinesterase inhibitors	163 (16)	52 (19)	111 (14)		100 (18)	63 (13)	*
Ebixa	38 (4)	11 (4)	27 (4)		22 (4)	16 (3)	
Number of prescribed drugs	7.7 ± 3.8	7.2 ± 3.9	7.9 ± 3.8	*	7.1 ± 3.6	8.4 ± 4.0	*
Scales and measurements							
MMSE (14.2% imputed)	13.8 ± 6.7	15.3 ± 6.0	13.2 ± 6.8	*	15.5 ± 6.1	11.8 ± 6.8	*
Barthel ADL index (6.5% imputed)	12.0 ± 6.1	13.2 ± 5.9	11.6 ± 6.2	*	13.8 ± 5.5	9.9 ± 6.2	*
BMI (14.9% imputed)	25.2 ± 4.9	25.4 ± 4.3	25.1 ± 5.1		26.0 ± 4.9	24.3 ± 4.8	*
GDS (35.1% imputed)	4.2 ± 3.0	4.1 ± 3.1	4.2 ± 2.9		4.0 ± 2.9	4.4 ± 3.1	*

Note: Group differences marked with * are statistically significant ($P < 0.05$). MMSE = Mini-Mental State Examination; ADL = Activities of Daily Living; BMI = Body Mass Index; GDS = 15-item Geriatric Depression Scale. Data are presented as mean ± standard deviation or %.

Table 5 Variables qualified for the adjusted analyses of each psychotropic drug in the total sample and in subgroups of men and women

Characteristic	Antidepressants			Antipsychotics			Benzodiazepines		
	All	Male	Female	All	Male	Female	All	Male	Female
Age	X	X	X	X	X	X	X	X	X
Sex	X			X			X		
Medical conditions									
Alzheimer's disease		X					X		X
Vascular dementia		X							
Delirium, in the last month	X	X	X	X	X	X	X		X
Depressive disorder								(X)	
Angina Pectoris							X	X	
Congestive heart failure							X		X
Diabetes mellitus		X							
Myocardial infarction				X		X			
Stroke, ever	X								
Chronic lung disease			X	X		X	X		X
Sleeping disorder		X			X			X	
Prescribed drugs									
Antipsychotics				X	X	X			
Antidepressants	X	X	X						
Benzodiazepines	X	X		X	X		X	X	X
Analgesics	X	X	X				X	(X)	X
Cholinesterase inhibitors	X		X			X			
Organic nitrates		X		X					X
Antibiotics	X	X			X		X	(X)	
ASA						X			
Digoxin	X		X						
Agents acting on RAAS	X								
Diuretics							X	X	X
Number of prescribed drugs	X	X	X	X	X	X	X	(X)	X
Scales and measurements									
Barthel ADL index	X	X		X	X	X	X	X	X
BMI	X	X	X				X		
GDS	X	X	X	X	X		X	X*	
MMSE				X		X			
Included variables (n)	15	15	10	12	9	10	15	7(11)	11

Note: ASA = acetylsalicylic acid; RAAS = renin-angiotensin-aldosterone-system; ADL = Activities of Daily Living; BMI = body mass index; GDS = 15-item Geriatric Depression Scale; MMSE = Mini-Mental State Examination.

Variables qualified for the adjusted analyses were associated ($P < 0.15$) with mortality and use of respective drug in the total sample and in subgroups of men and women, respectively. Adjustment for age and sex were included in all models. GDS was included in the models with antidepressant use without any required association with mortality or drug use. Variables marked as (X) were included in the model but were removed in a backwards selection process due to a low number of events in relation to the number of included variables. *GDS was removed in the backwards selection process from the model analyzing second-year mortality associated with benzodiazepine use in men.

Table 6 Results from Cox proportional hazards regression models

	Unadjusted analyses		Adjusted analyses		Interaction term[a]
	HR	95% CI	HR	95% CI	
Antidepressants (2-year mortality)					Sex × antidepressants
All participants	1.01	0.84, 1.21	0.96	0.78, 1.17	HR: 1.55 (95% CI: 1.01-2.39)
Male participants	0.96	0.67, 1.37	0.61	0.40, 0.92	*P*=0.047
Female participants	1.03	0.84, 1.28	1.09	0.87, 1.38	
Antipsychotics (2-year mortality)					Sex × antipsychotics
All participants	1.16	0.94, 1.43	0.91	0.73, 1.14	HR: 0.99 (95% CI: 0.61-1.60)
Male participants	1.24	0.82, 1.87	0.79	0.51, 1.24	*P*=0.962
Female participants	1.15	0.90, 1.46	0.90	0.70, 1.15	
Bensodiazepines (first-year mortality)					Sex × benzodiazepines
All participants	1.38	1.08, 1.77	1.13	0.86, 1.47	HR: 0.54 (95% CI: 0.31-0.94)
Male participants	2.07	1.29, 3.32	1.37	0.77, 2.45	*P*=0.029
Female participants	1.21	0.91, 1.62	0.96	0.71, 1.31	
Bensodiazepines (second-year mortality)					Sex × benzodiazepines
All participants	0.95	0.73, 1.24	0.72	0.54, 0.96	HR: 0.99 (95% CI: 0.51-1.90)
Male participants	0.90	0.51, 1.59	0.81	0.45, 1.45	*P*=0.964
Female participants	0.98	0.72, 1.33	0.73	0.53, 1.02	

Note: HR=Hazard ratio. CI=Confidence interval. The adjusted analyses are adjusted for age, sex, and all available confounders associated ($P < 0.15$) with mortality and use of respective drug in respective subgroup. In the interaction analyses, sex is defined as 0 for men and 1 for women.

[a]The interaction terms were tested in the adjusted analyses only.

PAPER III – FACTORS ASSOCIATED WITH DEPRESSIVE SYMPTOMS IN OLDER PEOPLE

The 392 participants' characteristics of Paper III are shown in Table 7. The mean age was 86.2 years, 282 (72%) participants were women, and 264 (67%) were living in residential care facilities. Depression was diagnosed in 166 (42%) participants, the mean ± SD GDS score was 3.9 ± 2.8, and 132 (34%) were using antidepressants. The mean ± SD MMSE score was 20.5 ± 6.0 and 153 (39%) participants were diagnosed with dementia.

The mean ± SD GDS score of the participants with and without depressive disorders was 5.3 ± 3.2 and 3.0 ± 1.9, respectively ($P < 0.001$). Of the 166 participants with depressive disorders, 129 (78%) were using antidepressants, and of those 77 (60%) had a GDS score below 5. The mean ± SD Barthel ADL Index and BBS scores were 15.4 ± 4.8 and 33.3 ± 16.8, respectively, and 293 (75%) participants were dependent in ADL (Barthel ADL Index < 20).

Among the individual ADL tasks of the Barthel ADL Index, the highest rate of dependency was found in bathing (70%) and the lowest in bowel continence (13%). There was a significant difference in GDS scores between independence and dependency in all ADL tasks except bowel continence, bladder continence and bathing (data not shown). The largest differences in mean ± SD GDS scores between the participants independent and dependent in individual ADL tasks were found for transfer (3.6 ± 2.5 vs 5.4 ± 3.5, $P < 0.001$), mobility (3.7 ± 2.5 vs 4.8 ± 3.4, $P = 0.004$), and toilet use (3.7 ± 2.5 vs 4.8 ± 3.4, $P = 0.009$).

In univariate linear regression analyses, BBS score, Barthel ADL Index score, and dependency in all ADL tasks except bowel continence, bladder continence and bathing, were significantly and inversely associated with the GDS score (Table 8). In the multivariate linear regression analyses, the BBS score was found to be significantly and inversely associated with the GDS score (unstandardized b = –0.03, $P = 0.008$), but the Barthel ADL Index score was not (unstandardized b = –0.07, $P = 0.068$). No significant interaction effect was found between the BBS score and the Barthel ADL Index score, respectively, and sex ($P = 0.48$ and $P = 0.91$, respectively), dementia ($P = 0.99$ and $P = 0.72$, respectively), or living in a residential care facility ($P = 0.33$ and $P = 0.20$, respectively).

Multivariate regression analyses examining associations between GDS score and dependency in each individual ADL task, separately, revealed that

dependency in transfer and dressing were significantly and inversely associated with the GDS score (unstandardized b = −1.03, P = 0.007 and unstandardized b = −0.70, P = 0.035, respectively; Table 8). In additional analyses, comparing differences in BBS scores between participants independent or dependent in the ADL tasks of transfer and dressing, the mean ± SD scores were 38.7 ± 12.8 vs 9.71 ± 10.6 (P < 0.001) and 41.9 ± 11.4 vs 21.7 ± 16.0 (P < 0.001), respectively.

Table 7 Participant characteristics and their association with the 15-item Geriatric Depression Scale[a]

Characteristic	Total (n=392)	Unstandardized β (95% CI)	*P*
Age	86.2 ± 6.0 (65–103)	0.03 (–0.02, 0.08)	0.20
Female sex	282 (72)	0.27 (–0.35, 0.88)	0.39
Living in residential care facility	264 (67)	0.67 (0.09, 1.26)	0.024
Diagnoses and medical conditions			
Depression	166 (42)	2.27 (1.76, 2.78)	<0.001
Dementia	153 (39)	–0.49 (–1.06, 0.07)	0.088
Previous stroke	94 (24)	0.66 (0.01, 1.30)	0.045
Urinary tract infection, current	44 (11)	0.75 (–0.12, 1.62)	0.091
Diabetes mellitus	59 (15)	0.54 (–0.23, 1.31)	0.17
Heart failure	96 (25)	0.21 (–0.43, 0.85)	0.52
Angina pectoris	127 (32)	0.44 (–0.15, 1.03)	0.14
Malignancy, in the last 5 years	47 (12)	–0.76 (–1.61, 0.09)	0.078
Constipation	173 (44)	1.37 (0.83, 1.91)	<0.001
Osteoporosis	125 (32)	0.37 (–0.23, 0.95)	0.23
Rheumatic disease	45 (12)	1.67 (0.82, 2.52)	<0.001
Regular use of drugs			
Diuretics	200 (51)	0.52 (–0.03, 1.07)	0.065
Analgesics (not ASA)	213 (54)	0.61 (0.06, 1.16)	0.03
Benzodiazepines	132 (34)	0.96 (0.38, 1.54)	0.001
Antidepressants	132 (34)	1.05 (0.48, 1.63)	<0.001
Neuroleptics	72 (18)	0.20 (–0.51, 0.92)	0.58
Acetylcholinesterase inhibitors	37 (9)	–1.08 (–2.01, –0.14)	0.025
Number of drugs used regularly	7.9 ± 4.4 (0–24)	0.17 (0.11, 0.23)	<0.001
Assessments			
Visual impairment*	82 (21)	0.71 (0.04, 1.39)	0.039
Hearing impairment	65 (17)	0.45 (–0.29, 1.19)	0.23
Mini-Mental State Examination*	20.5 ± 6.0 (8–30)	–0.06 (–0.10, –0.01)	0.015
Body mass index*	25.0 ± 4.4 (12.6–41.4)	–0.02 (–0.08, 0.04)	0.53

Note: CI = confidence interval; ASA = acetylsalicylic acid. Data are presented as mean ± standard deviation (range) or n (%).

[a]Associations were tested with linear regression using 15-item Geriatric Depression Scale as the dependent variable.

*Indicates some individuals had missing data.

Table 8 Univariate and multivariate linear regression analyses for associations between GDS and BBS, GDS and Barthel ADL Index, and GDS and each individual ADL task of Barthel ADL Index, separately[a]

Characteristic	**Univariate linear regression analyses** (n = 392)		**Multivariate linear regression analyses** (n = 391)	
	Unstandardized β (95% CI)	***P***	**Unstandardized β (95% CI)**	***P***
Berg Balance Scale	–0.04 (–0.06, –0.03)	<0.001	–0.03 (–0.05, –0.01)	0.008
Barthel ADL Index	–0.12 (–0.18, –0.06)	<0.001	–0.07 (–0.14, 0.004)	0.068
Dependency in individual tasks of Barthel ADL Index				
Bowel continence	–0.39 (–0.88, 0.11)	0.12	–0.02 (–0.83, 0.79)	0.96
Bladder continence	–0.27 (–0.62, 0.08)	0.13	0.09 (–0.54, 0.71)	0.79
Grooming	–0.79 (–1.42, –0.16)	0.015	–0.41 (–1.06, 0.25)	0.22
Toilet use	–0.66 (–1.05, –0.28)	<0.001	–0.47 (–1.17, 0.24)	0.19
Feeding	–1.01 (–1.69, –0.33)	0.004	–0.36 (–1.14, 0.42)	0.36
Transfer	–0.95 (–1.36, –0.54)	<0.001	–1.03 (–1.77, –0.29)	0.007
Mobility	–0.55 (–0.87, –0.23)	<0.001	–0.57 (–1.26, 0.13)	0.11
Dressing	–0.79 (–1.15, –0.44)	<0.001	–0.70 (–1.35, –0.05)	0.035
Stairs	–0.50 (–0.79, –0.20)	<0.001	0.05 (–0.76, 0.86)	0.90
Bathing	–0.43 (1.03, 0.17)	0.16	0.03 (–0.67, 0.74)	0.93

Note: GDS = 15-item Geriatric Depression Scale; BBS = Berg Balance Scale; ADL = Activities of Daily Living; CI = confidence interval. Each multivariate linear regression analysis was adjusted for age, sex and baseline characteristics associated ($P \leq 0.15$) with GDS in univariate analysis (dementia, previous stroke, current urinary tract infection, angina pectoris, malignancy in the last 5 years, constipation, rheumatic disease, diuretics, analgesics, acetylcholinesterase inhibitors, number of drugs used regularly and visual impairment). Living in residential care facility was adjusted for in all multivariate analyses except for that of the ADL item bathing.

[a]GDS was used as dependent variable.

PAPER IV – EFFECTS OF EXERCISE ON DEPRESSIVE SYMPTOMS

Depressive disorders were diagnosed in 107 (58%) participants. Antidepressants were used by 102 (55%) participants, with a higher usage in the exercise group than in the control group (62% vs 47%, $P = 0.04$; Table 9). The 55 (30%) participants with GDS scores ≥ 5 were more likely to have angina pectoris (38% vs 22%, $P = 0.02$) and constipation (78% vs 59%, $P = 0.01$), and had a lower average BBS score (23.0 ± 14.8 vs 31.6 ± 13.7, $P < .001$). Dementia type ratios differed according to GDS score, with a higher ratio of vascular dementia and lower ratio of Alzheimer's disease among those with GDS scores ≥ 5 ($P = 0.03$).

Rates of adherence to the exercise and control activities were 73% and 70%, respectively. Participants reached high intensity during strength exercises at a median of 47% of attended sessions, and moderate–high intensity at a median of 76% of sessions.

No significant difference in effect on GDS or MADRS score at 4 or 7 months was observed between the exercise and control activities (Table 10). In addition, no difference in effect between the exercise and control activities was found in subgroups of dementia type or depressive symptom level (data not shown). Furthermore, no interaction effect was found in the subgroup analyses of depressive symptoms level (Table 11), or dementia type (data not shown).

Among participants with GDS scores ≥ 5, adjusted within-group analyses showed similar significant reductions in GDS score at 4 months in the exercise and control groups (–1.58, $P = 0.001$ and –1.54, $P = 0.004$, respectively; Table 11, Figure 6). At 7 months, the GDS scores in both groups were still improved compared with baseline (exercise: –1.25, $P = 0.01$; control: –1.45, $P = 0.007$; Table 11, Figure 6). Among participants with MADRS scores ≥ 7, significant reductions in MADRS score were observed at 4 months in the control group (–2.80, $P = 0.009$) and at 7 months in the exercise and control groups, compared with baseline (–3.17, P = 0.003 and –3.34, $P = 0.002$; Table 11, Figure 6).

Table 9 Baseline characteristics of study participants

Characteristic	Total (n = 186)	Exercise (n = 93)	Control (n = 93)	*P*
Age (years)	85.1 ± 7.1 (65–105)	84.4 ± 6.2 (67–97)	85.9 ± 7.8 (65–105)	0.15
Female sex	141 (76)	70 (75)	71 (76)	0.86
Diagnoses and medical conditions				
Dementia type				0.86
Vascular	77 (41)	36 (39)	41 (44)	
Alzheimer	67 (36)	34 (37)	33 (35)	
Mixed Alzheimer/vascular	15 (8)	8 (9)	7 (8)	
Other	27 (15)	14 (16)	12 (13)	
Depressive disorder	107 (58)	53 (57)	54 (58)	0.88
Delirium in the last week	102 (55)	48 (52)	54 (58)	0.38
Previous stroke	57 (31)	33 (35)	24 (26)	0.15
Diabetes mellitus	29 (16)	18 (19)	11 (12)	0.16
Heart failure	55 (30)	24 (26)	31 (33)	0.26
Angina pectoris	49 (26)	21 (23)	28 (30)	0.24
Cancer, in the last 5 years	20 (11)	13 (14)	7 (8)	0.16
Constipation	121 (65)	60 (65)	61 (66)	0.88
Rheumatic disease	28 (15)	14 (15)	14 (15)	1.00
Regular use of drugs				
Diuretics	88 (47)	41 (44)	47 (51)	0.38
Analgesics (not ASA)	112 (60)	55 (59)	57 (61)	0.76
Benzodiazepines	40 (22)	19 (20)	21 (23)	0.72
Antidepressants	102 (55)	58 (62)	44 (47)	0.04
Neuroleptics	31 (17)	11 (12)	20 (22)	0.08
Anti-dementia drugs[a]	47 (25)	28 (30)	19 (20)	0.13
Number of drugs used regularly	8.3 ± 3.8 (0–22)	8.4 ± 4.0 (0–22)	8.2 ± 3.7 (0–20)	0.75
Assessments				
Visual impairment	26 (14)	10 (11)	16 (17)	0.20
Hearing impairment	32 (17)	12 (13)	20 (22)	0.12
MMSE (0–30)	14.9 ± 3.5 (10–26)	15.4 ± 3.4 (10–23)	14.4 ± 3.5 (10–26)	0.06
Mini Nutritional Assessment (0–30)	21.0 ± 2.7 (12.5–26)	21.2 ± 2.7 (12.5–26.0)	20.9 ± 2.6 (14.5–26.0)	0.35
Barthel ADL Index (0–20)	10.8 ± 4.4 (2–18)	10.7 ± 4.5 (2–17)	11.0 ± 4.4 (2–18)	0.66
Berg Balance Scale (0–56)	28.9 ± 14.5 (2–54)	28.6 ± 14.3 (2–52)	29.3 ± 14.7 (3–54)	0.71
NPI (0–144)	14.8 ± 14.2 (0–82)	15.2 ± 15.8 (0–82)	14.4 ± 12.6 (0–42)	0.68
Pain when walking (n = 185)	35 (20)	15 (16) (n=92)	20 (22)	0.37
Self-reported health as good, very good, or excellent	119 (64)	60 (65)	59 (63)	0.88
Outcomes				
MADRS (0–60, n = 183)	5.7 ± 6.3 (0-31)	5.6 ± 6.5 (0-31) (n=92)	5.9 ± 6.1 (0-27) (n=91)	0.80
GDS (0–15, n = 183)	3.8 ± 3.2 (0-13)	4.0 ± 3.4 (0-13) (n=92)	3.6 ± 2.9 (0-13) (n=91)	0.37

Note: ASA = acetylsalicylic acid; MMSE = Mini-Mental State Examination; ADL = Activities of Daily Living; NPI = Neuropsychiatric Inventory; MADRS = Montgomery-Åsberg Depression Rating Scale; GDS = 15-item Geriatric Depression Scale. Data are presented as mean ± standard deviation (range) or n (%). For all assessment scales except Neuropsychiatric Inventory, MADRS and GDS, higher scores indicate higher function.

[a]Anti-dementia drugs include acetylcholinesterase inhibitors and memantine.

Table 10 Within- and between-group differences in GDS and MADRS scores at 4 and 7 months

Test	N[c]	Month	Adjusted within-group[a]						Adjusted between-group[b]		
			Exercise			Control					
			N[d]	Mean (95% CI)	*P*	N[d]	Mean (95% CI)	*P*	Mean (95% CI)	*P*	ICC[e]
GDS	183	4	83	0.03 (–0.53, 0.59)	0.91	81	0.08 (–0.49, 0.64)	0.78	–0.05 (–0.84, 0.75)	0.91	0.032
	184	7	73	–0.03 (–0.61, 0.56)	0.92	75	0.03 (–0.55, 0.61)	0.91	–0.06 (–0.89, 0.76)	0.88	
MADRS	183	4	83	0.40 (–0.77, 1.57)	0.50	80	0.33 (–0.85, 1.52)	0.58	0.06 (–1.60, 1.73)	0.94	<0.001
	184	7	73	–0.08 (–1.30, 1.15)	0.90	74	–0.24 (–1.47, 0.99)	0.70	0.16 (–1.57, 1.89)	0.86	

Note: GDS = 15-item Geriatric Depression Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; CI = confidence interval; ICC = intracluster correlation coefficient.

[a]Performed using linear mixed models with least square means (follow-up – baseline values), adjusted for age, sex, antidepressant use, cluster and test-subject.

[b]Three-way interactions of activity, time, and subgroup were analyzed in the total sample using linear mixed models adjusting for cluster and test-subject as random effects and age, sex, and antidepressant use as fixed effects.

[c]Number of participants in analyses with baseline or follow-up outcome measurement.

[d]Number of participants in subgroup with complete before-and-after measurement.

[e]Calculated as the proportion of the total variance attributed to cluster variance in GDS and MADRS scores in the total sample.

Table 11 Within-group differences and interaction effects of GDS and MADRS scores in subgroups of participants with high and low levels of depressive symptoms

Test	N[b]	Month	Group	Adjusted within-group[a]						Interaction[c]	
				Exercise			Control				
				N[d]	Mean (95% CI)	*P*	N[d]	Mean (95% CI)	*P*	Mean (95% CI)	*P*
GDS	183	4	GDS ≥ 5	26	–1.58 (–2.53, –0.63)	0.001	21	–1.54 (–2.56, –0.50)	0.004	–0.09 (–1.76, 1.57)	0.91
			GDS < 5	57	0.78 (0.14, 1.42)	0.02	60	0.72 (0.10, 1.35)	0.02		
	184	7	GDS ≥ 5	23	–1.25 (–2.23, –0.26)	0.01	21	–1.45 (–2.49, –0.41)	0.007	0.26 (–1.45, 1.98)	0.76
			GDS < 5	50	0.53 (–0.14, 1.21)	0.12	53	0.59 (–0.06, 1.25)	0.08		
MADRS	183	4	MADRS ≥ 7	27	–1.69 (–3.66, 0.27)	0.09	23	–2.80 (–4.90, –0.71)	0.009	1.54 (–1.90, 4.99)	0.38
			MADRS < 7	56	1.31 (–.05, 2.67)	0.06	57	1.74 (0.40, 3.09)	0.01		
	184	7	MADRS ≥ 7	22	–3.17 (–5.28, –1.06)	0.003	22	–3.34 (–5.47, –1.21)	0.002	–0.08 (–3.67, 3.51)	0.97
			MADRS < 7	51	1.32 (–0.08, 2.72)	0.07	51	1.07 (–0.33, 2.47)	0.13		

Note: GDS = 15-item Geriatric Depression Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; CI = confidence interval.

[a]Performed using linear mixed models with least square means (follow-up – baseline values), adjusted for age, sex, antidepressant use, cluster and test-subject.

[b]Number of participants in analyses with baseline or follow-up outcome measurement.

[c]Three-way interactions of activity, time, and subgroup were analyzed in the total sample using linear mixed models adjusted for cluster and test-subject as random effects and age, sex, and antidepressant use as fixed effects.

[d]Number of participants in subgroup with complete before-and-after measurement.

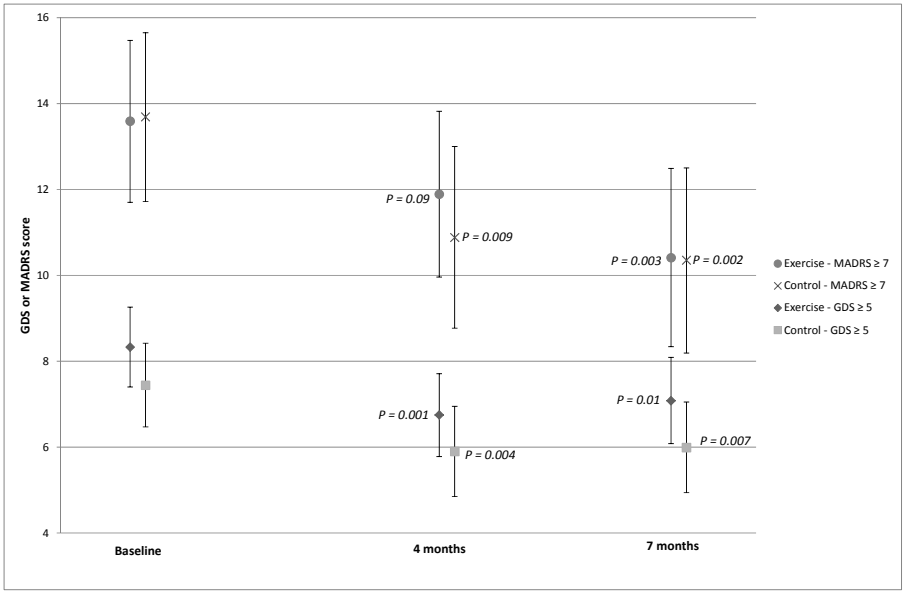

Figure 6 Adjusted GDS and MADRS scores of participants with high levels of depressive symptoms by activity and follow-up timepoint.
Note: GDS = 15-item Geriatric Depression Scale; MADRS = Montgomery-Åsberg Depression Rating Scale. *P*-values represent comparisons of follow-up values at 4 and 7 months with baseline values using least square means, adjusted for age, sex, antidepressant use, cluster, and test-subject. Lower scores represent lower levels of depressive symptoms.

DISCUSSION

MAIN FINDINGS

Ongoing antidepressant treatment at baseline was not associated with increased mortality in very old people or in older people with dementia. In both investigated samples, gender was found to interact with the mortality risk associated with antidepressant use, with a tendency to an increased mortality risk among very old women, and a significantly decreased mortality risk among older men with dementia. In the sample of older people with dementia, no significant associations with mortality were found among baseline users of antipsychotic drugs. During the first year of follow-up, the mortality risk with baseline use of benzodiazepines was significantly higher in men than in women.

Among older people living in the community and in residential care facilities, reduced functional capacity and dependency in transfer and dressing were independently associated with the presence of more depressive symptoms. Overall dependency in ADL was not associated with depressive symptoms after comprehensive adjustment.

Among older people with dementia living in residential care facilities, no difference was found between a 4-month high-intensity functional exercise program and a non-exercise activity regarding the effects on depressive symptoms, irrespective of dementia type or depressive symptom level. In those with high levels of depressive symptoms, both the exercise and the non-exercise group activities reduced depressive symptoms.

PSYCHOTROPIC DRUG USE AND MORTALITY

Antidepressants

In Papers I and II, antidepressant use was not associated with an increased risk of death in the fully adjusted models. These results contrast with those of other large cohort studies conducted in younger and healthier populations.[103-106,146] In Paper I, dementia, heart failure, and ADL dependency were the main confounding factors explaining the association between antidepressant use and mortality. These conditions are more common among very old people than among younger old people and seem to be associated with both a higher prescription rate of antidepressants and a higher rate of mortality.

In Paper II, among those with dementia, antidepressant use was not associated with an increased risk of death even in unadjusted analyses. Two register-based studies have previously found increased mortality risks among people with dementia.[146,147] However, in one of them, the risk was lower than in participants without dementia,[146] and in the other the risk of death was only slightly increased.[147] In contrast, a large randomized controlled trial and a randomized withdrawal study found no increased mortality risk related to antidepressant use in older people with dementia.[68,143]

Mortality risk due to antidepressant use differed between men and women in both of the present papers, with a higher mortality risk among women than men. Among men with dementia, the mortality risk was significantly decreased with antidepressant use. To my knowledge, gender differences have not previously been explored in the mortality risk due to antidepressant use among people with dementia. However, in older people without dementia, earlier studies have found men to have a higher mortality risk associated with antidepressant use than women,[105] although increased mortality risks have been found both in samples of postmenopausal women and older men.[104,106] One factor that may have contributed to the sex difference in mortality in the present papers is the increased risk among women of QTc prolongation and torsade de pointes, an adverse drug reaction that can be found among antidepressant and antipsychotic users.[99,136,142,183,184] However, no increased risk of death associated with baseline antidepressant treatment was seen among participants with heart failure in Paper I, suggesting that adverse drug reactions affecting the heart may be limited after the initial phase of antidepressant usage. Furthermore, the stronger association observed between mortality and antidepressant use among women compared with men in Paper I could have been confounded by preclinical dementia, which has been associated with depressive disorders,[25,88,185] mortality,[25] and female sex[186] in the very old. However, the gender difference was also present in Paper II, among those with dementia. In Paper II, the antidepressants mirtazapine and venlafaxine, which have previously had a stronger association with mortality,[103,142] were used more frequently by women. If the stronger association also applies to older people with dementia, it could help explain the gender difference in the observed mortality risk due to antidepressant use. Nevertheless, gender differences need to be further explored in future studies.

Coupland *et al.* in their study used a crude measure to adjust for depression severity (mild, moderate or severe depression) but recognized the need for a more sensitive measurement.[103] Both Papers I and II used GDS as a more sensitive adjustment for depression severity. However, adjustment for

depression severity hardly affected the mortality risk due to antidepressant use. In addition, no tendency toward an increased mortality risk was observed among antidepressant users with GDS scores ≥ 5 compared to those with GDS scores < 5 in Paper I.

Antipsychotics

Antipsychotic use was not associated with any risk of death and no gender difference was found among people with dementia. This was unexpected since an increased risk of death due to antipsychotic use has been shown in several previous studies, including observational studies,[139,142,187,188] randomized withdrawal studies,[140] and a meta-analysis of randomized controlled trials using atypical antipsychotic drugs.[141] However, it is worth noting that none of the randomized controlled trials included in the meta-analysis found an association between antipsychotic use and mortality risk on its own, and that the meta-analysis itself was barely significant. This may indicate that it is difficult to reach sufficient statistical power in individual studies. However, evidence from previous studies supports the view that antipsychotic use is associated with an increased mortality risk, and that antipsychotic drugs should only be prescribed in minimal doses for a minimum amount of time.

Benzodiazepines

The relation between benzodiazepine use at baseline and mortality was found to be time-dependent, with a tendency for the risk of mortality to be increased during the first year and significantly decreased during the second year. There was also a gender-difference with a higher risk among male users compared to female users. Few studies have evaluated the mortality risk of benzodiazepine use among older people with dementia. In a register-based study, benzodiazepine or benzodiazepine-like drug use was associated with an increased risk of death among participants without dementia, but not in participants with dementia.[146] However, gender differences were not evaluated. In a systematic review and meta-analysis of 2.35 million patients aged 18-102 years, anxiolytic and hypnotic drugs were found to increase the risk of death similarly in men and women.[151] However, lower risks were observed in high quality studies, population-based studies, and studies with participants aged > 50 years. The gender difference in the association between benzodiazepine use and mortality may possibly be moderated by prolonged sleep apnea events with benzodiazepine use,[148] which has been shown to increase the risk of ischemic events, such as stroke, in men particularly.[189]

If frailer participants have a higher susceptibility to adverse events from taking benzodiazepines, they may have died to a higher extent during the first year of follow-up in Paper II. Thus, the remaining participants may have constituted a healthier subgroup of the sample with a better chance of survival during the second year. The increased risk during the first year, compared to the second, may also be related to a higher prescription rate of anxiolytics during palliative care.[190]

Common traits

Compared with previous studies, the lack of increased mortality risk associated with psychotropic drug use in Papers I and II may partly be explained by differences in the timing of prescribed medication in relation to data collection. Data on prescribed drug use were gathered during home visits, rather than at the time of treatment initiation. Thus, some individuals who received psychotropic drugs may have died or discontinued treatment due to serious side effects before inclusion in the present studies. The participants that used psychotropic drugs at baseline may therefore be less prone to adverse drug reactions, resulting in a healthy user bias. In addition, non-users at baseline may have become users with a higher susceptibility to serious side effects during the follow-up. However, in longitudinal studies, psychotropic drug use, especially the use of antidepressants and antipsychotics, has typically been long-term among older people with dementia.[129,138]

Coupland *et al.* observed the highest risks of mortality in community-dwelling older people within 28 days after antidepressant initiation and 28 days after discontinuation.[103] Furthermore, the risk of death diminished over time and was lower among antidepressant users 85 days after treatment initiation than among those who never received an antidepressant.[103] Similar observations have been made among people with dementia using antipsychotic drugs, where the risk of mortality may be highest in the first 30-40 days of treatment, decrease over time, and fade when the treatment has stopped.[188,191] In Paper II, the risk of mortality associated with benzodiazepine use was higher in the first year of follow-up, and diminished during the second year. To my knowledge, no previous study has found a time-dependent mortality risk with benzodiazepine use among older people with dementia.

Jennum *et al.* found increased mortality risks among people with dementia using antidepressants or antipsychotics, but not among those using benzodiazepines.[146] Interestingly, the risks were significantly higher among controls without dementia for all three psychotropic drug groups. This points

to a big flaw associated with register-based and observational studies; residual confounding.[192] There is an increased likelihood that psychotropic drugs are being prescribed because a (possibly undetected) disease is causing depressive symptoms, psychotic symptoms, anxiety, or sleeping disorders. Dementia or preclinical dementia are examples of such diseases.[185,193] Other examples might include cardiovascular diseases such as heart failure and stroke.[27,47] In Paper I, antidepressant users with any of these diseases had a tendency to a lower risk of mortality than antidepressant users without these diseases. However, the power may have been insufficient to detect significant interactions. Among people with dementia, BPSD resulting in treatment with psychotropic drugs may be symptoms of diseases,[194] and BPSD have also been associated with higher rates of mortality.[195,196]

FUNCTIONAL CAPACITY, DEPENDENCY IN ADL AND DEPRESSIVE SYMPTOMS

In Paper III, reduced functional capacity, but not overall dependency in ADL, was associated with depressive symptoms. This is in contrast to the majority of previous observational studies performed among very old people in which overall ADL dependency has been independently associated with depressive symptoms.[9,53-55] Previous studies have performed less extensive adjustments for potential confounders, which may possibly have been insufficient to investigate appropriately the association between overall dependency in ADL and depressive symptoms.

Functional capacity, rather than ADL dependency, was found to be associated with depressive symptoms. This finding is in accord with the results of an observational study conducted among very old community-dwelling people, in which comprehensive adjustments were performed.[197] The study showed that low performance in tests of balance, lower-limb strength, and gait speed was independently associated with depression, whereas overall dependency in ADL was not. Together with the results from Paper III, this may indicate that overall dependency in ADL is not related to depressive symptoms, whereas lower functional capacity resulting in a higher rate of dependency is. The present study did not measure possible mediators of this association, such as physical activity, self-esteem, and self-efficacy.[20,49-52] These factors may be more affected by a low level of functional capacity than a high rate of dependency in ADL. For example, knowing that one is able to perform a task might be more important for self-esteem and self-efficacy than accepting being helped in relation to depression. It is also possible that the association between balance and depression have a common denominator in the vascular depression hypothesis, where white

matter lesions in specific areas of the brain could affect both balance and depressive symptoms.[46,198]

In Paper III, dependency in transfer and dressing was associated with depressive symptoms. Previous studies of ADL dependency have not investigated the impact of individual ADL tasks on depression. One possible explanation for the associations of transfer and dressing with depressive symptoms in Paper III may be that dependency in these ADL tasks particularly lowers self-esteem, self-efficacy, sense of control, and physical activity.[20,49-52]

Balance, lower-limb strength and depressive symptoms

Generally, higher functional capacity, which depends on balance and lower-limb strength, appears to be associated with the presence of fewer depressive symptoms in older populations with a high prevalence of disability. Balance and lower-limb strength are important prerequisites for transfer and dressing. Not being able to dress or transfer (e.g. from bed to chair) independently seems to be an important threshold, prompting more depressive symptoms. The small unstandardized *b* values of the BBS in relation to GDS indicate that a change in BBS score of 20-30 points seems to be required to change the GDS score approximately one point. Thus, a large improvement in functional capacity seems to be necessary to reduce depressive symptoms. The unstandardized *b* values of dressing and transfer indicate that a change from independent to dependent, or vice versa, in one of these activities might change the GDS score approximately one point.

Exercise interventions conducted in residential care facilities have so far failed in their attempts to reduce depressive symptoms.[115,199-201] These interventions may have had insufficient effect on functional capacity, or an insufficient number of participants may have managed to become independent in dressing or transfer.

NON-PHARMACOLOGICAL INTERVENTIONS IN DEPRESSION

In Paper IV, physical exercise had no superior effect on depressive symptoms than a non-exercise control activity. This finding is in line with previous research in older people with dementia.[114,116,117] However, it contrasts with the finding that 3–4 months of moderate–high-intensity physical exercise seems to reduce depressive symptoms in older people without dementia.[109] The contrasting results may be explained by differences in the etiology of depression, which may in turn be related to organic brain disorders in people with dementia.[18,46] It has been suggested that physical exercise may prevent

or reduce depressive symptoms via different pathways, such as changes in endorphin and monoamine levels,[107] reduced ADL dependency, or improved functional capacity.[20,51] As presented by Toots et al.,[156] the HIFE program reduced ADL decline in the present trial among participants with non-Alzheimer dementia and improved functional balance capacity in the total sample in comparison with the control activity. Balance was also improved in a similar study that employed the HIFE program.[114] The lack of a better effect from exercise on depressive symptoms despite these positive results may be due to insufficient improvement in functional capacity. In Paper III, the results indicated that an improvement of 20-30 points in BBS would be needed to reduce the GDS by 1 point. However, the improvement in BBS in UMDEX was only 2.39 points.[156] Another possibility may be that changes over time in functional capacity are not related to changes in GDS among older people living in residential care facilities,[202] including those with dementia.

A similar study also demonstrated that both exercise and non-exercise activities reduced high levels of depressive symptoms in older people with dementia in residential care facilities.[116] These results are of particular interest, as antidepressants seem to have little or no effect in this population.[68,95] That the exercise per se did not seem to reduce depressive symptoms in the present study suggests that the social interactions mediated in both group activities could partly explain the positive effects found in participants with high levels of depressive symptoms.[20,52,203] However, as the exercise and control interventions were not compared with usual care in the present study, we cannot disregard the possibility that the observed effects reflect the natural course of depressive symptoms in this group. In studies of the natural course of depressive symptoms in people with dementia, it has been found that they may remain the same, decrease, or vary over time.[18,78-80] The results may also have been influenced by regression towards the mean, considering that participants with low baseline levels of depressive symptoms tended to have more depressive symptoms at 4 and 7 months.

ETHICAL CONSIDERATIONS

All the studies included in this thesis, conducted in Sweden and Finland, were approved by the Regional Ethics Review Board in Umeå and the Ethics Committee of Vaasa Central Hospital, respectively.

Depression among older people is an under-researched subject, especially among very old people, those with dementia and those living in residential care facilities. The etiology of depression seems to be different in these groups in that it is more multifaceted and possibly related to structural brain

damage, in contrast to depression in younger people. In order to gain the necessary knowledge about depression and how to treat it successfully in very old people, people with dementia, and people living in residential care facilities, it is important to include these groups in research. However, important concerns associated with doing research in these groups need to be addressed.

Very old people and older people with cognitive and physical impairments are considered to be vulnerable populations of older people that should only be included in research from which they benefit, directly or as a group. It is also important that they are not harmed and that they are approached respectfully.

As neurodegenerative diseases are progressive, it may be difficult to know how much information a test subject is able to process, whether or not informed consent can be understood, whether a risk/benefit argument may be conducted, and whether or not the autonomy of the test subject is intact. In all the studies included in this thesis, a next of kin, in addition to the test subject, was asked to provide informed consent, if cognitive impairment was present. In addition, participants and their next of kin were allowed to withdraw their consent and end their participation at any time without giving any reason.

The participants in the Umeå 85+/GERDA study may not live long enough to experience the potential benefit from the results of the study. However, other benefits for them include that of being visited by a medically trained investigator who, in addition to asking health related questions, was able to engage in social conversations, give advice regarding health-related issues, or contact local caregivers if needed (with the permission of the participant).

Previous research indicates that physical exercise may be beneficial for older people living in residential care facilities, and that medium to high intensity may be better than low intensity.[158,204] The inclusion criteria applied in the FOPANU, REMANU and UMDEX studies were used to increase potential benefit, limit potential harm, and facilitate the evaluation of the exercise interventions. For example the requirement to have a MMSE score ≥ 10 was applied in order to be sure that the participants included would understand instructions throughout the intervention period and be able to answer questions in the respective protocols. The participants also had to have the approval of their physician to ensure that adverse events during the exercise activities were kept to a minimum. All participants were approached by trained investigators with previous experience of working with people with cognitive impairment. The participants randomized to the control activities

of the respective studies were, naturally, given less exercise and thus received less rehabilitation but a control group is necessary in order to evaluate the effects of an intervention. In addition, the control activities were developed with the aim and expectation that they would be interesting and stimulating for older people with and without dementia, living in residential care facilities.

METHODOLOGICAL CONSIDERATIONS

All Papers included in this thesis have some strengths and limitations that should be considered. Papers I, II and III were observational studies so no causal inference can be drawn from the associations. In Papers I and II, the limited number of users of the respective psychotropic drugs and the uneven distribution of drug classes prevented the analysis of mortality risk in the respective subgroups of antidepressants, antipsychotics and benzodiazepines. As the risk of death due to baseline psychotropic drug use was investigated, data on time since treatment initiation or discontinuation were not available. Likewise, data regarding the number of non-users at baseline who became users during the follow-up period was missing. Although baseline treatment did not seem to increase the risk of death among very old people, or among older people with dementia, the initiation and discontinuation phases of treatment may require further examination.

Paper I is based on the population based study Umeå 85+/GERDA, making the results representative of very old people. The sample in Paper II did not include community-dwelling people with dementia aged 65-85 years, but is otherwise fairly representative of older people with dementia. Multiple imputation enabled participants with all stages of dementia to be included in Paper II, but the inclusion criterion of 10 and 14 answers on the GDS in Papers I and III, respectively, led to the exclusion of some of the most cognitively impaired participants. Home visits were made in all of the included studies, enabling an extensive collection of participants' characteristics and diseases and enabling even the frailest people to participate. Although proper adjustments were performed, residual confounding may still be present and additional factors might have influenced the associations found in the respective papers. Patterns and preferences regarding prescribed drugs and dosages may change over time as new drugs become available and new evidence emerges, thus changing the mortality risk associated with various drug classes. These potential cohort effects may have influenced the results in Papers I and II but have not been evaluated.

The cross-sectional design in Paper III excludes the possibility of drawing conclusions concerning whether a reduction in functional balance capacity causes depressive symptoms, or depressive symptoms cause a decline in balance, or if these traits develop simultaneously. However, longitudinal studies among people aged < 80 have shown both that depression is a risk factor for ADL dependency and that ADL dependency is a risk factor for depression.[19-21] By merging data from three studies, a heterogeneous sample was obtained, including subjects living in the community and residents living in care facilities. This sample is neither representative of the very old population or of care facility populations, which may limit the external validity of the results. However, the sample represented the entire range of the BBS and the Barthel ADL Index, and a large variation in MMSE scores, which should be important in studies intending to thoroughly investigate the associations between depression and functional capacity or ADL dependency.

The UMDEX study included both people with high and low levels of depressive symptoms. Those with low levels may have had limited ability to reduce their depressive symptoms. However, it is of great interest to evaluate whether physical exercise can prevent, as well as reduce, depressive symptoms among people with dementia, where reduced functional capacity and dependency in ADL may be risk factors for depressive symptoms,[20] as was discussed in Paper III. A limitation in Paper IV is that the power calculation was not based on depressive symptoms. However, the sample size in the present study was relatively large, and the between-group changes found were small, indicating that there were no clinically relevant effects.[205] Positive effects on depressive symptoms were found in participants with high levels of depressive symptoms in both the exercise and the non-exercise group. The inclusion of a third group receiving usual care would have helped to determine whether these reductions were the effects of the activities rather than the natural course of depressive symptoms in this group. However, limited resources prevented the implementation of this study design in the UMDEX study.

The strengths of Paper IV are that it involved the inclusion of participants with non-Alzheimer dementia, exercise intensity was assessed at each session, and assessors were blinded. In addition, the inclusion criteria were wide, the proportion of people who declined to participate in the study was comparably low (23%),[115,118] and ITT analyses were used, enabling the results to be applied to many older people with dementia living in residential care facilities. The assessment of intensity makes comparison easier between the HIFE intervention and exercise trials where effects have been shown on depressive symptoms in people without dementia. Furthermore, the study

included an attention control activity with adherence comparable to the exercise activity, allowing evaluation of the effects of exercise per se.

CLINICAL IMPLICATIONS

Depression in older people with cognitive and physical impairments may be difficult to treat. This is possibly because of the increased prevalence of structural brain damage in this group. However, other factors, such as cardiovascular diseases, dementia, inflammation, and cognitive and physical impairments, may also contribute to the increased prevalence of depression and the difficulty in treating it in older people.

When depressive disorders are identified and antidepressant treatment is considered among older people with and without dementia, it is important to reflect over potential risks associated with treatment in relation to potential benefits. In Papers I and II of this thesis, ongoing antidepressant treatment was not associated with an increased mortality risk. As this does not agree with previous studies conducted in younger and healthier samples, where increased mortality risks have been found, no recommendation regarding the mortality risk can be made until more studies have been conducted. If treatment is initiated, any effects and side-effects of the prescribed drug should be evaluated regularly, with more careful monitoring during the initial and discontinuation phases. In addition, the potentially higher mortality risk among women compared with men should be considered.

Among older people with dementia, treatment with antipsychotic drugs has an established association with an increased mortality risk, both in the initial phase and with prolonged treatment.[130,139,140] Even though ongoing treatment with antipsychotics did not seem to increase the mortality risk among people with dementia in Paper II, treatment should only be considered after nonpharmacological, psychosocial interventions and pain treatment have failed.[130] If initiated, dosages should be kept to a minimum for a minimal amount of time (maximum 6-12 weeks).[130]

It may not be appropriate to prescribe benzodiazepines for older people with dementia, a group in whom obstructive sleep apnea syndrome is common.[149] If treatment is considered, short-term application with short-acting benzodiazepines may have less effect on OSAS.[148] Although there is a potentially higher mortality risk associated with benzodiazepine use in men than in women, more studies are needed to establish this finding and also whether or not benzodiazepine use is associated with an increased mortality risk among older people with dementia.

Physical impairments affecting lower limb strength and balance, and the ability to dress and transfer independently seem to be associated with a higher level of depressive symptoms. If these impairments could be prevented or reversed, e.g. by means of a rehabilitation program, depressive symptoms could possibly be prevented or reduced.

Older people with dementia and high levels of depressive symptoms, living in residential care facilities, may have their depressive symptoms reduced through exercise or non-exercise group activities, possibly through increased social interaction. However, studies with a second control group receiving usual care are needed to confirm this result.

IMPLICATIONS FOR FUTURE RESEARCH

The etiology of depression among older people is not fully understood, but associated factors include bereavement, cognitive and physical decline, cardiovascular diseases, structural brain damage, and inflammatory diseases. More research is needed to fit these pieces of the puzzle together in order to fully understand depression in older people with and without dementia.

Among older people the evidence to support various treatments for depression, including antidepressant drug treatment, is currently limited and larger studies using high quality study designs are needed to determine which treatments may be the most effective against depression in this group.

Larger cohort studies of very old people or older people with dementia, properly controlled for confounding factors, could help to increase knowledge about the associations between antidepressants, benzodiazepines, and mortality. However, randomized controlled trials and randomized withdrawal studies would be more effective in this context, and would at the same time reduce the risk of residual confounding. Ultimately, meta-analyses of randomized controlled trials evaluating the risk of death in connection with antidepressant or benzodiazepine use would be needed to establish a final verdict concerning the associations between mortality and antidepressants or benzodiazepines. This has to my knowledge only been done for antipsychotic drugs.[141]

As depression may be difficult to treat, it is also important to prevent its occurrence among older people. Targeting cardiovascular risk factors may bring about a decline in the incidence of diseases such as stroke, heart failure and dementia, which in turn might affect the incidence of depression. Among those who are already depressed, it may also be of interest to

evaluate the effects on the depressive symptoms of interdisciplinary multifactorial rehabilitation programs combining physical exercise, specific skill training, the assessment and fitting of appropriate assistive devices, and targeting dependency in transfer and dressing.

Among older people with dementia living in residential care facilities, it is possible that both exercise and non-exercise activities may reduce high levels of depressive symptoms. Future studies evaluating the effectiveness of exercise and non-exercise activities should include both an attention control group and a control group receiving standard care.

CONCLUSIONS

None of the three psychotropic drug classes (antidepressants, antipsychotics or benzodiazepines) investigated were independently associated with mortality in the total sample of older people with dementia. In very old people, the association between mortality and ongoing antidepressant treatment at baseline was dependent on confounding factors; in particular, dementia, heart failure, and ADL dependency. Gender may moderate the association between antidepressant use and mortality, both in very old people and in older people with dementia. Among very old people, antidepressant use might be associated with an increased mortality risk in women, compared with men, while in people with dementia, antidepressant use might be associated with a better survival in men. Gender may also moderate the association between benzodiazepine use and mortality in older people with dementia, where men might have a higher mortality risk than women. Randomized controlled trials or large cohort studies with proper control for confounding factors are needed to further investigate the gender differences in mortality risks with psychotropic drug use and with the initial treatment.

Functional capacity seems to be independently associated with depressive symptoms in older people, both living in the community and in residential care facilities. However, overall ADL performance may not be associated with depressive symptoms. Dependency in the individual ADL tasks of transfer and dressing appear to be independently associated with depressive symptoms and may be an important focus of future interdisciplinary, multifactorial intervention studies.

Among older people with dementia living in residential care facilities, a high-intensity functional exercise program has no superior effect on depressive symptoms than a control activity. Both exercise and non-exercise group activities may reduce high levels of depressive symptoms. However, three-armed randomized controlled trials, including control groups receiving usual care, are needed to confirm this finding.

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APPENDIX, DSM-IV-TR CRITERIA FOR DEPRESSIVE DISORDERS

DSM-IV-TR criteria for major depressive disorder

A. Five (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 first two symptoms is present.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day.
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet the criteria for a 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 the direct physiological effect of a substance or a general medical condition.

E. The symptoms are not better accounted for by bereavement.

DSM-IV-TR criteria for minor depressive disorder

A. Two to four 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 first two symptoms is present.

B. There has never been a major depressive episode and criteria are not met for dysthymic disorder.

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 the direct physiological effect of a substance or a general medical condition.

E. The symptoms are not better accounted for by bereavement.

F. There has never been a manic, mixed or hypomanic episode and criteria are not met for cyclothymic disorder.

G. The mood disturbance does not occur exclusively during schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or psychotic disorder not otherwise specified.

DSM-IV-TR criteria for dysthymic disorder

A. Depressed mood, for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least two years.

B. Presence, while depressed, of two or more of the following:

1. Poor appetite or overeating.
2. Insomnia or hypersomnia.
3. Low energy or fatigue.
4. Low self-esteem.
5. Poor concentration or difficulty making decisions.
6. Feelings of hopelessness.

C. During the two-year period of the disturbance, the person has never been without the symptoms in criteria A and B for more than two months at a time.

D. No major depressive episode has been present during the first two years of the disturbance.

E. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.

G. The symptoms are not due to the direct physiological effects of a substance or a general medical condition.

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

DSM-IV-TR criteria for mood disorder due to general medical condition

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either or both of the following:

1. Depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.
2. Elevated, expansive, or irritable mood.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder.

D. The disturbance does not occur exclusively during the course of a delirium.

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

DSM-IV-TR criteria for substance-induced mood disorder

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:

1. Depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.

2. Elevated, expansive or irritable mood.

B. There is evidence from the history, physical examination, or laboratory findings of either 1. or 2:

1. The symptoms in criterion A. developed during, or within a month of, substance intoxication or withdrawal.

2. Medication use is etiologically related to the disturbance.

C. The disturbance is not better accounted for by a mood disorder that is not substance induced. Evidence that the symptoms are better accounted for by a mood disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced mood disorder.

D. The disturbance does not occur exclusively during the course of a delirium.

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