Frequency and prognostic implications of orthostatic hypotension and white matter hyperintensities in older people with mild dementia

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"Everything is connected to everything else"

Barry Commoner, *The Closing Circle*, 1971

Contents

Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
APOEε4	Apolipoprotein E ε (epsilon) 4
BP	Blood pressure
CDR	Clinical dementia rating scale
CDR-SB	Clinical dementia rating scale – sum of boxes
CIRS	Cumulative illness rating scale
CVD	Cerebrovascular disease
DLB	Dementia with Lewy bodies
ECG	Electrocardiogram
FTD	Frontotemporal dementia
LBD	Lewy body dementia
MADRS	Montgomery and Aasberg depression rating scale
MMSE	Mini mental status examination
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NPI	Neuropsychiatric inventory
NPId	Neuropsychiatric inventory depression subscale
OH	Orthostatic hypotension
PD	Parkinson's disease

PDD	Parkinson's disease with dementia
SPECT	Single photon emission computed tomography
QTc	Frequency corrected QT interval
VaD	Vascular dementia
WMH	White matter hyperintensities

Scientific environment

This thesis is the result of work performed primarily at the Centre for Age-Related Medicine, Stavanger University Hospital, but also at the Department of Internal Medicine, Stavanger University Hospital. I am a member of the DemVest study group, as well as the Regional Research Network on Mood Disorders (MoodNet), and for almost three years I have been affiliated with the Department of Clinical Science at the University of Bergen. During the entire period I have been working, mostly part-time, as a consultant at the Section for Geriatric Medicine, Department of Internal Medicine at Stavanger University Hospital.

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First of all, I would like to thank my main supervisor, Professor Dag Aarsland, without whom this thesis never would have been written. From the very beginning, back in 2007, he has involved me, encouraged me and given me valuable advice and quick responses, always with a positive and optimistic attitude.

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The Western Norway Regional Health Authority, after some unsuccessful applications, finally provided me with a Ph.D. scholarship, and thus has been my main source of financial support during the past three years.

The Regional Research Network on Mood Disorders (MoodNet) kindly supported me financially for a total of six months at the beginning of this project, and thus, crucially, allowed me to lay the foundations of my Ph.D. project.

I also would like to thank Stavanger Health Research, from which I received funding for a brief period.

My thesis is based on data collected as part of the DemVest Study. I therefore will express my sincere gratitude towards all the doctors, nurses and other personnel involved in the inclusion and follow-ups of patients in the DemVest study, and of course the patients and their carers, as well as the patients included in the convenience sample. Furthermore, I would like to thank the ParkWest study group for permission to use controls from the ParkWest study.

My co-authors not mentioned previously (please see list of publications below) also should be given credit for their many valuable contributions and helpful suggestions.

Not to be forgotten is the Centre for Age-Related Medicine, Stavanger University Hospital, led by Ingelin Testad, which has provided an inspiring and friendly environment for my research activities.

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1. Abstract

Background: In addition to cognitive impairments, dementia sufferers may have other problems as well, such as depression and orthostatic hypotension (OH), both of which according to previous studies may be associated with white matter hyperintensities (WMH). WMH are a common finding on magnetic resonance imaging (MRI) scans of the brains of older people. Aims: To study the frequency and some potential prognostic implications of OH and WMH in a sample of older people with mild to moderate dementia. Materials and methods: The subjects of the four substudies are participants in the DemVest study; a prospective cohort study which from March 2005 to April 2007 included consecutive referrals to secondary care outpatient clinics in old age psychiatry and geriatric medicine in western Norway with mild dementia. Dementia and dementia subtypes were diagnosed according to standardised criteria. The comprehensive baseline assessment included brain MRI, blood tests and orthostatic blood pressure measurements, followed by annual examinations. Results: OH was found to be significantly more common in patients with mild dementia than in normal controls (41 % vs. 14%), and dementia was an independent predictor of OH. From baseline to the 4-year follow-up, 30 to 45% had OH. Having persistent OH did not seem to predict a less favourable course with respect to cognition, daily functioning, or survival. No association was found between OH and WMH load. Baseline WMH load was positively correlated with baseline severity of depressive symptoms, and appeared to be associated with persistent and incident depression at 1 year. Conclusions and implications: OH was common in mild dementia, but was not associated with an unfavourable course or a higher WMH load. However, depressive symptoms were positively associated with the WMH load. Nevertheless, due to its association with falls, and potential for treatment, OH should be actively looked for. The potential prognostic implications of WMH for depression and the etiology of WMH in dementia deserve further attention in future studies.

2. List of publications

Paper I Sonnesyn H, Nilsen DW, Rongve A, Nore S, Ballard C, Tysnes OB, Aarsland D. High prevalence of orthostatic hypotension in mild dementia. Dement Geriatr Cogn Disord 2009;28:307-313

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Paper II Soennesyn H, Oppedal K, Greve OJ, Fritze F, Auestad BH, Nore SP, Beyer MK, Aarsland D. White matter hyperintensities and the course of depressive symptoms in elderly people with mild dementia. Dement Geriatr Cogn Disord EXTRA 2012;2:97-111

Paper III Soennesyn H, Nilsen DW, Oppedal K, Greve OJ, Beyer MK, Aarsland D. Relationship between orthostatic hypotension and white matter hyperintensity load in older patients with mild dementia. PLoS One 2012; 7(12):e52196

Paper IV Hogne Soennesyn, Ingvild Dalen, Dag Aarsland. Persistence and prognostic implications of orthostatic hypotension in older people with mild to moderate dementia**. Submitted**

3. Introduction

Dementia is a syndrome that can be caused by a number of illnesses that affect the brain, resulting in deterioration of memory, thinking, behaviour and the ability to perform everyday activities (1). Alzheimer's disease is the most common type of dementia (AD; 50-75%), other common types include vascular dementia (VaD; 20-30%), dementia with Lewy bodies (DLB; <5%) and frontotemporal dementia (FTD; 5-10%) (2). Some studies, however, have found a higher prevalence of DLB (3, 4) and a lower prevalence of VaD (4); this could be due to both sample characteristics and the diagnostic criteria employed. Most types of dementia, e.g. AD and DLB, are nonreversible; these dementias are often termed "degenerative" (5).

Of note, DLB was only rather recently formally recognised as a separate diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders (DSM)(6).

Dementia is prevalent among older people, in particular the oldest-old, and the number of people afflicted with dementia is expected to increase steeply in the coming decades, due to increasing numbers of people surviving into their old age (7-9). The burden of dementia at the societal level is already tremendous (1). In Norway, the number of older people suffering from dementia is expected to increase from approximately 60 000 in 2010 to around 142 000 in 2050 (10).

Most types of dementia are progressive, leading to increasing impairment of daily function (11), as well as emotional and behavioural disturbances (12), all of which lead to reduced quality of life, affect the carers adversely (13) and result in increased health-related societal costs (14). Dementia also is associated with decreased life expectancy (15).

3.1 Autonomic dysfunction

In addition to the characteristic cognitive deficits associated with dementia, subjects afflicted with dementia may have other types of dysfunction as well. Notably, some

studies (16, 17) have found various types of autonomic dysfunction to be prevalent in older persons with dementia, and more so than in older people without dementia, particularly in those with DLB and Parkinson's disease with dementia (PDD) (18, 19). Autonomic dysfunction is associated with a number of bothersome or even dangerous symptoms, such as falls and syncope (20). In non-AD dementias, it is associated with poorer outcomes in measures of physical activity, activities of daily living, depression and quality of life (21).

3.1.1 Orthostatic hypotension

One common manifestation of autonomic dysfunction is orthostatic hypotension (OH, i.e. an abnormally large blood pressure drop when rising from the supine to the standing position) (22), which also, generally and in a particular older patient, may have other causes, including age-related changes in the cardiovascular system (23), medications (24), and acute illness with volume reduction (23). The prevalence of OH increases with advancing age (25), and OH is a common and clinically important problem, particularly in older people, in whom it may be a marker of frailty (26). In most cases it is asymptomatic (25). Potential symptoms of OH include dizziness, syncope, weakness, fatigue, visual blurring, vertigo, suboccipital and paracervical pain, chest pain, headaches, palpitations, low back pain and dyspnoea (27). OH seems to be even more common in older people with dementia (16, 28) than in those not having dementia. In prospective cohort studies, OH has been associated with increased all-cause mortality and risk of coronary heart disease (29), and it may also be a risk factor for incident heart failure (30). In a large, longitudinal, population-based study, OH was found to be independently predictive of stroke (31). Furthermore, in older adults with dementia, symptomatic OH has been prospectively associated with falls (20), which are an important cause of morbidity and mortality in this group. This may partly be related to the fact that older people with dementia are at increased risk of sustaining fall-related hip fractures (32), which are a powerful independent predictor of long-term excess mortality (33) in older people. Moreover, older people with

dementia have an even higher relative mortality rate after fall-related hip fractures than those without dementia (32). Falls in persons with AD also has been found to be associated with an increased rate of institutionalisation (34).

OH is potentially amenable to amelioration, treatment or even prevention (35-38), thus justifying screening for this condition, particularly in groups with a known or suspected high prevalence.

Prior to 2008, when this project was being planned, no studies had explored the prevalence of OH in mild dementia in general. Passant and coworkers (39), in a cross-sectional study published in 1997 of patients with AD, VaD and FTD of undisclosed severity, found OH to be common in organic dementia. Thaisetthawatkul and collaborators, in a small study published in 2004 (18), found OH in 10/20 patients with DLB of undisclosed severity, intermediate between multiple system atrophy (worst) and PD. In a larger, cross-sectional study of patients with AD, VaD, DLB and PDD of moderate severity, compared with elderly controls, Allan and coworkers (17) found the prevalence of OH to be significantly higher in all these types of dementia than in controls. Andersson and collaborators, in a comparatively large study published online in 2007 (28), compared older controls with patients with AD and DLB having mean MMSE scores of 21-22. OH occurred in 69% of the DLB patients and in 42% of the AD patients, but in only 13% of the controls.

A related question is whether OH is reproducible, i.e. whether it is diagnosed also on repeated measurements, in older persons with mild dementia. Apart from being of theoretical interest, this is important because reproducibility of OH for a given person or group may be associated with a higher susceptibility to the potential adverse consequences of OH (40). The reproducibility of OH has been explored in a number of studies (41) (42, 43) (44, 45) in various settings, using both supine-stand measurements and head-up tilt testing, with inconsistent results (27). However, most of these studies were performed in well-functioning older adults, with measurements being repeated one year later at most (46). To my knowledge, the only study to date (9 January, 2014) exploring the long term reproducibility of OH in older persons with dementia was

published in 2012 by Stubendorff and coworkers (47), who measured blood pressures at baseline and after 12 and 24 weeks, in 30 patients with mild to moderate DLB or PDD. However, according to my understanding of their definition of "persistent orthostatic hypotension", it would be possible to receive a diagnosis of "persistent OH" based on the measurements from only one, out of a total of 3 visits (5 measurements of diastolic and systolic standing BP on each occasion, with "persistent OH" defined as ≥5 orthostatic values (BP drop ≥20 mm Hg systolic or ≥10 mm diastolic)).

Few studies have explored the potential longitudinal implications of OH in dementia, with respect to cognitive and daily function, and mortality. Over a period of 2.5 years, Viramo and coworkers (48) found no longitudinal association between OH and cognition; the only predictors of cognitive decline were old age and a low level of formal education. Concerning the potential association between OH and activities of daily living (ADL), a previous study (21) found that in non-Alzheimer's dementias higher autonomic symptom scores and postural dizziness were associated with poorer outcomes. In the previously mentioned study by Stubendorff and co-workers (47), it was found that in patients with DLB and PDD, those having persistent OH had a significantly shorter survival than those without persistent OH.

3.1.2 QTc

Prolongation of the heart rate-corrected QT interval (QTc) on the electrocardiogram (Figure 1)

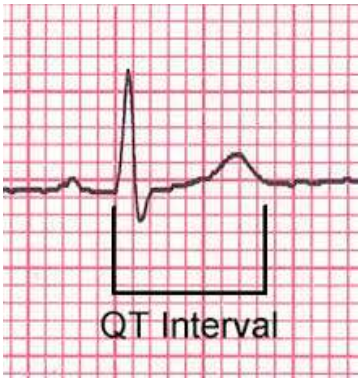

Figure 1. The QT interval (http://www.shortqtsyndrome.org/what_is_a_qt.htm)

is, like OH, a potential marker of autonomic dysfunction in dementia (49). QTc prolongation has previously been found in primary disorders of autonomic failure, such as multiple system atrophy (50) and Parkinson's disease (51-53), but also in patients with diabetes (54). As Parkinson's disease and DLB are closely related conditions (55), this might also apply to the latter condition. In prospective population-based studies, prolongation of QTc has predicted increased cardiac and all-cause mortality (56, 57). QTc prolongation is an established risk factor for torsades de pointes (TdP) (58), which is a potentially life-threatening arrhythmia. Importantly, many psychotropic medications, in particular certain antidepressants (59) and many neuroleptics (60), both of which are frequently administered to older people with dementia (61), may prolong this interval (62). Several other drugs belonging to other drug classes may also induce prolongation of the QT interval (63).

3.2 White matter hyperintensities

White matter hyperintensities (WMH), also called leukoaraiosis , white matter lesions or white matter changes (these terms may, however, not always describe identical phenomena) are a common finding on MRI scans of the brains of older people (64, 65). On these images, WMH appear as bright areas in the more gray-appearing normal brain tissue (Figure 2).

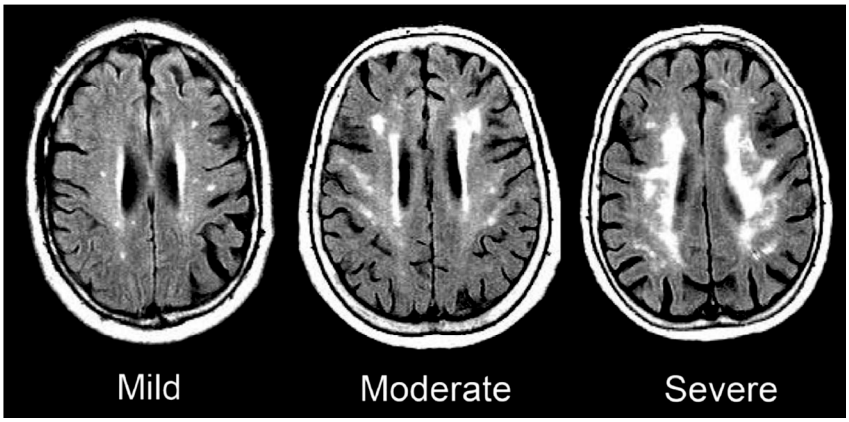

Figure 2. White matter hyperintensities (66)

In population-based studies, the prevalence of WMH varies between 45% and 95% (67). The prevalence and severity of these changes increase with age (64). WMH are best seen on T2-weighted MRI sequences; combination with Fluid Attenuated Inversion Recovery (FLAIR) sequences reduces the number of false positives (68) . Evidence of these changes has been found even in regions of "normal appearing white matter" (69), by means of new quantitative MRI techniques, such as diffusion tensor imaging (DTI) and magnetisation transfer imaging (MTI). Notably, age-related small vessel disease of the brain (please see below) seems to be a diffuse process, affecting the whole brain, and the white matter lesions may be only the tip of the iceberg (70).

WMH predict an increased risk of stroke, dementia and death (71), and also have been associated with depressive symptoms in older people, both cross-sectionally (72) and

longitudinally (73, 74). According to the LADIS study, both baseline severity of white matter changes and lesion progression were predictive of depressive symptoms in a community sample of non-disabled older adults (75). In elderly patients with major depressive disorder, severe white matter changes were associated with poor outcome (76). WMH are common across both degenerative and vascular dementias (77, 78). The WMH load has been found to be higher in many dementia groups (i.e. AD, DLB and VaD) than in normal controls, and in all patients with dementia, frontal WMH were associated with higher depression scores (79, 80). In a longitudinal study WMH burden predicted functional decline in bladder voiding, mobility and cognition in older people (81). Cross-sectionally, a significant association between WMH severity and falls has been demonstrated (82). In a recent study including subjects with mild cognitive impairment, increased WMH volume at baseline conferred risk for a future diagnosis of AD (83). According to the results of the LADIS study, the severity of white matter changes is a strong and independent predictor of the transition from an autonomous status to disability (75).

WMH are generally subdivided into periventricular and deep WMH. Periventricular WMH are those seen around the cerebral ventricles, and deep WMH are those seen in the subcortical cerebral white matter (72). Various methods for classification and quantification of these changes have been devised. Among the most well-known and utilised are the Fazekas scale (84) and the Scheltens scale (85) , both of which are so-called semi-quantitative scales, which employ visual rating. Limitations of visual rating scales include lack of sensitivity to small changes and susceptibility to ceiling effects (68, 86). The other main method of assessment is volumetry, which can be manual, semi-automated or automated (86-88).

The spatial distribution of WMH has been compared in a number of studies, between subjects with healthy ageing and various disease groups, including AD, cerebral amyloid angiopathy and vascular dementia. The distribution has often (89, 90), but not in all studies (91) been found to be similar, regardless of the underlying diagnosis. One important exception to this may be late-life depression, where the WMH pattern in

depressed subjects seems to differ from that of normal subjects, in that the depressed have greater WMH in brain regions associated with emotional and cognitive function (92, 93). This could indicate that WMH in a specific location in the brain might impair e.g. cognitive, motor or emotional functions associated with that location (75, 94, 95), possibly due to disruption of white matter tracts and subsequent disconnection of cortical-cortical and cortical-subcortical connections (96, 97).

The pathological correlates and potential etiologies of WMH have been explored in numerous studies, the results of which generally indicate considerable heterogeneity. One main point seems to be that the etiology may differ between various locations of WMH, and also between the shapes and sizes, as visualised on MRI, of these lesions. According to a recent review (70), smooth periventricular and punctate deep WMH most likely are of non-vascular origin, the former probably caused by increased fluid accumulation related to the proximity to the ventricles, and the latter most likely being of mixed origin. Confluent WMH and non-punctate deep WMH, on the other hand, are probably ischemic lesions, characterised by rarefaction of periventricular myelin, fiber loss and gliosis, with focal transitions to true infarcts, according to the same review. However, in a neuropathological study comparing elderly subjects with and without a history of major depression, all the deep WMH in the depressed group were found to be ischemic, compared with less than a third in the control group (98). In depression, interestingly, the results of a recent study (99) suggested that in men, but not in women, WMH may be a consequence of depressed mood. WMH and depression may conceivably in some instances be linked by e.g. autonomic dysfunction or inflammation (100).

Deep WMH are often seen together with vessels affected by small vessel disease (71), other probable expressions of which are lacunes and microbleeds (101). Particularly when WMH arise in the absence of strong cardiovascular risk factors, potential etiologies include cerebral amyloid angiopathy (CAA) (102, 103) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

(CADASIL) (104, 105). Both conditions are, however, radiographically and pathologically also associated with (micro)hemorrhages.

Increased blood-brain barrier permeability, possibly related to endothelial dysfunction, could also be involved in a proportion of WMH (69).

Interestingly, the heritability of WMH has been found to be consistently high in various populations (67). Several candidate genes have been found, which might indicate possible new mechanisms leading to these lesions. Apolipoprotein E, including the ApoEe4 allele, which is the most robust genetic risk factor for late-onset AD (106) may also be associated with WMH (70, 107).

On a more general level, WMH have been associated etiologically, although only modestly (108), with classic cardiovascular risk factors (64, 109), including hypertension (110, 111). In addition to hypertension, age and lacunar strokes have been found to be major determinants of these changes (112, 113). They are generally considered to be a consequence of cerebrovascular disease, more specifically small vessel disease (114, 115). Recently, aortic arch pulse wave pressure has been found to be a highly significant independent predictor of subsequent WMH volume (116, 117).

However, some studies have found indications that hypotension, including orthostatic hypotension, might be implicated in the development of WMH associated with depression (118-120) and dementia (121). In a review on the pathogenesis of leukoaraiosis, performed prior to the above-mentioned studies, Pantoni suggested that some types of these changes might be caused by repeated moderate drops in regional blood flow (122). In a study of carotid sinus hypersensitivity in patients with DLB and AD, Kenny and collaborators found a significant positive correlation between magnitude of drop in systolic blood pressure during carotid sinus massage and severity of deep white matter changes (123).

3.2.1 WMH and AD

In AD, a recent cross-sectional study found that WMH were independently associated with age, hypertension, current smoking and lacune presence (124). From another perspective, Grimmer et al. (125) found indications that baseline WMH, considered to reflect small vessel disease, were significantly associated with the progression of amyloid load. In the same vein, Provenzano and coworkers (83) recently found that WMH, in the context of significant amyloid deposition, may provide a "second hit" necessary for the clinical manifestation of AD. According to the results of a recent longitudinal neuropathologic and imaging study, ischemia may lead to both vascular brain injury, including WMH, and the neurodegenerative changes of AD (115).

3.3 Depression

Depression (major-) is a syndrome characterised by depressed mood or loss of interest in almost all activities (or both) for at least 2 weeks, accompanied by at least 3 or 4 of the following symptoms: insomnia or hypersomnia, feelings of worthlessness or excessive guilt, fatigue or loss of energy, diminished ability to think or concentrate, substantial change in appetite or weight, psychomotor agitation or retardation, and recurrent thoughts of death or suicide (126).

Depression is a highly prevalent disorder, and a leading cause of disability in all age groups from young adulthood and above. It occurs more frequently among women, but, interestingly, the prevalence of *major* depressive episodes may be lower in people older than 65 years (127, 128). However, within the group of older people, both the incidence and prevalence of depression increase with age (129). Depressed older people are less likely than younger adults to display affective symptoms such as depressed mood, and more likely to display somatic symptoms, cognitive changes and loss of interest (130). The syndrome of depression mainly affects those with chronic medical illnesses and cognitive impairment. Both ageing-related and disease-related

processes and psychosocial adversity, as well as hereditary factors, may increase vulnerability for depression (131).

According to DSM-IV (126) and ICD-10 (132) several sub-categories of depressive disorders exist, including bipolar disorder and unipolar depression, and major and minor depression episodes can be identified, often subdivided into early- and late-onset depression (131, 133) .

3.3.1 Depression in dementia

In dementia, symptoms or syndromes of depression are common (134), and such symptoms may be more common and severe in DLB compared to AD (135).

The association of pre-morbid depression with dementia has been explored in several studies (136), and pre-morbid depression has been found to approximately double the risk of subsequent dementia (137). Thus, depression may be regarded as a risk factor for AD (and VaD)(138), in addition to being an accompanying symptom (139). Potential explanations for the association between depression and AD include depression being an initial manifestation of AD, as well as the vascular depression hypothesis (140), according to which brain vascular disease can predispose to both dementia and depression. However, the results of a recent longitudinal cohort study suggested that depression accompanies cognitive impairment, but does not precede it (141). With regard to depression in the context of cognitive impairment associated with cerebrovascular disease (CVD), there is emerging evidence of a bi-directional relationship, meaning that depression may cause CVD, and subcortical CVD may increase the risk for depression (142).

Depression in dementia is associated with functional impairment (143), accelerated cognitive decline (144), lower carer ratings of quality of life (145), and nursing home admission (146, 147).

Several studies of treatment with antidepressants for depression in dementia have been performed (148, 149), the results of which suggest that antidepressants may not be more beneficial than placebo (139).

3.4 WMH and depression in dementia

The vascular depression hypothesis, mentioned above (140), postulates that cerebrovascular disease can predispose, precipitate and perpetuate depression in late-onset depression. This hypothesis has been challenged in a number of recent studies. For instance, in a large, prospective population-based study, Newson and collaborators (150) concluded that atherosclerosis does not appear to increase the risk of incident depression in older adults. Rather, depression might contribute to the vascular burden, or both might result from an (unknown) biological substrate. Commenting on this and other studies, Jellinger, in a critical update on organic bases of late-life depression (151), states that there exists "a significant gap in our understanding of the pathobiology of late-life depression". However, according to the results of the LADIS study, baseline severity of white matter changes is predictive of depressive symptoms, thus supporting the vascular depression hypothesis (75). As to the potential role of WMH, considered as a manifestation of cerebral small vessel disease, for depression in the subgroup of older people with dementia, the knowledge at present is limited.

3.5 Concluding remarks

Above, I have attempted to provide some background for my project, pointing out some topics about which limited knowledge exists (and even more so as of 2008, when this project was being planned). These topics include the frequency of OH in mild dementia (and its predictors and reproducibility) (*3.1.1*), the frequency of QTc prolongation in mild dementia (*3.1.2*) the potential role of OH in the development of WMH in dementia (*3.2*), the potential role of WMH for depression in dementia (*3.4*),

and the potential prognostic implications of OH for functioning and mortality in dementia (*3.1.1*).

Literature searches were generally performed in PubMed and in many cases also in Embase, using identical search terms and combinations of search terms. Google Scholar was also searched in some cases. The last literature search was performed 9 January 2014.

4 Aims and hypotheses

General aim: To study the frequency and prognostic implications of OH and WMH in a sample of older people with mild dementia

Specific aims:

1) To study the frequency of OH and QTc prolongation in mild dementia, and also in relation to various types of dementia.
2) To explore whether OH in mild dementia is associated with WMH, and if so, also after adjustment for some classic vascular risk factors.
3) To explore the relationship between WMH load and the longitudinal course of depressive symptoms in patients with mild dementia.
4) a) To study the reproducibility and longitudinal course of OH in the stages of mild to moderate dementia.
   b) To explore whether persistent OH is associated with a more rapid cognitive and functional decline, and shorter survival.

   According to the original project plan, we also intended to explore the relationship between OH and falls, but due to a low number of falls registered in the database, we refrained from this.

We hypothesised that

1) autonomic dysfunction, as manifested by OH and QTc prolongation, is more prevalent in older people with mild dementia than in normal controls, and more prevalent in patients with DLB and PDD than in other dementias.
2) older people with mild dementia and OH have more severe WMH than those without OH.
3) frequency and prognosis of depressive symptoms in mild dementia are related to the severity of WMH, and frontal deep WMH in particular.

4) older people with mild dementia and persistent OH will have a more unfavourable course with respect to cognitive and daily function and survival than those without persistent OH.

5 Materials and methods

5.1 Subjects and samples

The subjects of the studies comprising this project were, with two exceptions (please see *5.6*) participants of the DemVest study. This is a still ongoing, prospective, clinico-pathological cohort study of patients with a first time diagnosis of mild dementia, with a particular focus on DLB. From March 2005 to March/April 2007 all referrals to outpatient clinics in geriatric medicine and old age psychiatry in the counties of Rogaland and Hordaland in western Norway were screened for patients with a first time diagnosis of mild dementia. In addition, the three neurology outpatient clinics in the region agreed to refer new cases of dementia to one of the participating centres. The investigators aimed to include all patients with a first time diagnosis of mild dementia in the region, until at least 20 patients with DLB had been included. This was, pragmatically considered, the minimum number of DLB patients required for achieving sufficient statistical power, assuming a prevalence of DLB of 10-15% (152). The last patient diagnosed with dementia not being DLB was included 19 April 2007; thereafter the intention has been to include patients with DLB (and normal controls) only.

5.2 Dementia diagnoses

The diagnosis of dementia was made according to the DSM-IV criteria (126). The diagnoses of dementia subtypes were made according to consensus criteria (153-156). Two of the investigators, both of whom are old age psychiatrists, independently applied the diagnostic criteria after baseline and two years later. In cases of disagreement, and in patients fulfilling more than one set of operationalised diagnostic criteria, the final diagnosis was made based on consensus. In the diagnostic work-up, standardised instruments, including the Informant Questionnaire on Cognitive Decline in the Elderly **(**IQCODE) (157), the Clinical Dementia Rating (CDR) scale (158) and

the Hachinski ischemia scale (159) were employed, in addition to a battery of neuropsychological and psychiatric tests (please see ref (4) for more details). Patients have been followed annually with the same assessment battery for the first two years, thereafter with a simplified test battery, i.e. without neuropsychological tests beyond the MMSE.

5.3 Exclusion criteria

Patients without dementia, or with acute delirium, terminal illness, previous bipolar disorder or psychotic disorder, and those recently diagnosed with life-threatening or severe somatic illness were excluded (4).

5.4 Ethical considerations

The DemVest study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway (167.04) and the Norwegian authorities for collection of medical data. The patients provided written consent to participate, after the study procedures had been explained in detail to the patient and a caregiver, usually the spouse or offspring.

The subjects of the convenience sample (please see below) of paper I also provided written consent to participate, after having been explained the details and purpose of the study (please see Appendix). The Regional Committee previously had given their approval of the recruitment of cognitively healthy persons for the DemVest study (please see Appendix), an approval that we considered applicable also to this particular group of healthy controls.

5.5 Overview of the samples of the various papers

For various reasons, the samples included in the various substudies of this project differ. The background and details of this are rather complex; therefore I will firstly give a brief overview, before proceeding to a more detailed account below.

The samples of paper I included the initial consecutively recruited baseline sample of older people with mild dementia (n=196), plus two comparison groups of n=81 and n=23, respectively.

The sample of paper II included n=206 consecutively recruited persons with mild dementia, constituting a more complete baseline database than that used for paper I.

The sample of paper III included a total of n=246 subjects with mild dementia. Importantly, these n=246 also encompassed all the subjects with possible or probable DLB selectively included after April 2007.

The sample of paper IV included the n=211 consecutively recruited subjects with mild dementia in the most recent and updated database version available at the start of this substudy.

5.6 Sample of paper I

The sample of paper I initially included all the 196 patients with (mild) dementia in the most recent DemVest database version available at the time. These were divided into an AD group (n=128/196, 65%), a PDD group (n=11/196, 6%), a DLB group (n=39/196, 20%), and a mixed group (vascular dementia n=11, frontotemporal dementia n=4, and alcoholic dementia n=3, adding up to 9% of the 196). Possible and probable cases were merged in their respective dementia categories.

A total of 158 of these 196 had complete orthostatic systolic and diastolic BP measurements, 113 had ECGs that could be analysed with respect to QTc prolongation, and 86 had both, leaving 27 with neither. In addition, two comparison

groups were recruited. For control data regarding OH, we were kindly given permission to use controls from the ParkWest study (160), more specifically spouses or friends of patients with Parkinson's disease, who were at least 70 years of age (NC-OH, n=81). ECG was not available for this group. Therefore, for control data of QTc values, a convenience sample of non-demented elderly (65 years or older) patients from non-cardiological medical wards and orthopaedic wards (mainly electively admitted) at Stavanger University Hospital (NC-ECG, n=23) was recruited. Exclusion criteria for this group were treatment with QT interval prolonging drugs (i.e. amiodarone, sotalol, phenothiazines (chlorpromazine, levomepromazine, perphenazine, flupentixol, prometazine, alimetazine) and tricyclic antidepressants (TCA)), chronic atrial fibrillation (AF), or suspected or documented dementia according to the nurses in charge of the respective wards or the medical records.

Thus, a total of 262 (158+81+23) subjects were included in this substudy.

5.7 Sample of paper II

A total of 215 patients with mild dementia had been entered into the most recent database version available for this substudy. Among these, 9 were later excluded; 5 were re-diagnosed as MCI (mild cognitive impairment), 2 withdrew from the study and 2 were excluded due to lack of complete data. At the time, I was under the impression that selective inclusion of DLB patients started from April 2007, therefore the patients included in the DemVest study in April 2007 or later (n=3) were excluded from the database used for this paper, since our aim was to explore the relationship between WMH and the course of depressive symptoms in consecutively and not selectively included older patients with mild dementia.

5.8 Sample of paper III

For this substudy, we included all subjects with dementia entered into the most recent version of the database available (version 18 April 2011), i.e. also those included after 27 April 2007, yielding at total of 246 patients.

Of these 246, 82 patients had both OH measurements and available baseline MRI scans that could be analysed volumetrically for WMH, and 139 had both OH measurements and available baseline MRI scans that could be evaluated semi-quantitatively according to the Scheltens scale. The scans of 61 patients could be analysed with both methods, finding a Spearman correlation coefficient of 0.791 ($p<0.001$) between the scores of these methods.

5.9 Sample of paper IV

The sample of paper IV included all subjects with dementia included from 2005 until (and including) 19 April 2007, i.e. 211 patients.

5.10 Clinical assessments

At baseline, the patients were examined by a board-certified specialist in psychiatry, geriatric medicine or neurology, and a research nurse. Prior to the study, both study clinicians and study nurses had participated in several training sessions concerning the use of relevant diagnostic and clinical rating scales. The patients underwent a comprehensive assessment, including a detailed history, using a semi- structured interview encompassing demographics, previous diseases and drug history, as well as clinical examination and the neuropsychiatric assessment mentioned above (*5.2*). Blood tests, electrocardiogram (ECG) and MRI of the brain (please see below) were performed. The assessments took place during normal office hours (8 a.m. to 4 p.m.).

5.10.1 Blood pressure measurements and OH

Blood pressure was measured using an analogue sphygmomanometer available in the respective outpatient clinic, once with the subject in the supine position, and then at least once within 3 minutes after standing up. Orthostatic hypotension (OH) was defined according to the consensus definition (22) as a reduction of systolic blood pressure by at least 20 mm Hg or by a drop in diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing.

"Persistent OH" was defined as having OH at both baseline and at the 1-year follow-up, and "never OH" as not having OH at either of these examinations.

5.11 ECG and QTc

At baseline, the patients had a resting 12-lead surface ECG taken, at a paper speed of 50 mm/s, using the ECG recorder available in the respective outpatient clinic. The QTc was calculated according to Bazett's formula (161); for details of the procedure, please see the Methods section of paper I.

5.12 MRI and WMH

The patients were scanned at three different sites; Stavanger University Hospital (Stavanger), Haugesund Hospital (Haugesund), and Haraldsplass Deaconess Hospital (Bergen). A 1.5 T scanner was used in all three centres; Philips Intera in Stavanger and Haugesund, and in Bergen a 1.5T GE Signa Excite scanner. MRI scanning was performed on the same scanner in each centre during the entire study period, and a common study imaging protocol was to be used. Unfortunately, one of the centres used the wrong protocol, resulting in a substantial reduction (n=61) (78) of the number of usable scans.

WMH were assessed volumetrically, according to a method developed and previously published by Firbank et al. (92) and modified as previously described (162). This method requires sets of 3D T1-weighted scans and axial FLAIR images. WMH were segmented on a slice-by slice basis from the FLAIR image. Due to variability in image quality from the different centres, a threshold level for WMH was chosen that overestimated the WMH load in all subjects, thereafter manual editing was done to correct for this. The manually edited scans were then used in the further analyses of volumes of total and regional WMH. In order to compensate for interindividual differences in total brain volumes, the ratios of volumes of WMH to total brain volumes were calculated, and these ratios were used in the statistical analyses.

WMH load also was rated visually, according to the Scheltens scale (85). This scale accounts separately for periventricular WMH and deep WMH, evaluating the presence and extent of these changes in a number of different anatomic regions with a 0 to 6 point scale (163).

For further details, please see the Methods section of paper II.

5.13 Depression

Depression was assessed using the depression sub-item of the Neuropsychiatric Inventory (NPId), and the Montgomery and Aasberg Depression Rating Scale (MADRS).

The NPI was designed to assess psychiatric symptoms in patients with dementia, based on a structured interview of a caregiver (164). The Norwegian version has been validated (165). The NPI consists of 12 items, including a depression (dysphoria) item (NPId) with a maximum score of 12. A cut-off score of $\geq$1 was used to detect any depression, and a cut-off score of $\geq$4 was used for clinically relevant depression (166).

The MADRS (167) is a clinical interview with 10 items, each scored 0-6. Scoring was performed by an experienced geriatrician, neurologist or psychiatrist, after a training

procedure. A cut-off score of ≥ 7 was used to detect at least mild depression (168), and a cut-off score of ≥15 was used for clinically significant depression (169). The raters met bi-annually to ensure similar administration of the instruments.

5.14 Cognitive and daily function

The Mini-Mental State Examination (MMSE) (170) was used as a measure of cognitive function in all the papers of this project. In addition, in paper IV, the Clinical Dementia Rating sum-of-boxes (158) (CDR-SB) was employed as a measure of cognitive as well as of general function (171, 172).

5.15 Physical comorbidity

On the basis of information gained from the history and available medical records, we used the ”Cumulative Illness Rating Scale” (CIRS) in order to get a quantitative measure of physical comorbidity. This instrument measures the chronic medical illness burden, while at the same time taking into account the severity of chronic diseases. Scoring was done by an experienced geriatrician, in accordance with guidelines (173).

5.16 Design

Paper I and paper III employed a cross-sectional design, while paper II and paper IV are both cross-sectional (regarding baseline status) and cohort studies.

5.17 Statistics

For comparisons between groups, the Mann-Whitney U test, the Kruskal-Wallis test or the independent samples t-test were used, as appropriate, for continuous variables, and the Chi-square test for independence or Fisher's exact test were used for categorical variables, as appropriate. For determination of Normality status of continuous variables, the Kolmogorov-Smirnov test (available in the IBM SPSS Statistics) was used. For bivariate correlations, the Spearman rank order correlation was used. For calculation of confidence intervals of proportions, and for calculation of the significance of the difference between two independent proportions, calculators available at http://vassarstats.net/ were used. In paper II, analysis of covariance (ANCOVA) was performed, to control for effects of centre affiliation and other potential confounders.

For analysis of potential predictors of WMH load and depression measures, stepwise multiple logistic regression models were employed. Survival analysis was performed with Kaplan-Meier plots and Cox proportional hazards modelling. Analyses of the longitudinal outcomes in paper IV were performed using Generalised Estimating Equations (GEE) in IBM SPSS Statistics, as well as the function joineR in R (Revolution Analytics).

Unless otherwise stated, the statistical analyses were performed using the most recent IBM SPSS Statistics version available.

P-values <0.05 (two tailed) were considered statistically significant.

Further details of the statistical procedures are given in the respective papers. For comments, corrections and supplementary analyses; please see Discussion.

6 Results

The various papers will in the remainder of this thesis be presented and discussed not in a strictly chronological order, but in a more logical order, i.e. according to the order of the hypotheses (i.e. paper I, paper III, paper II and paper IV; please see **4**).

6.1 Paper I (High prevalence of orthostatic hypotension in mild dementia)

OH was significantly more prevalent among older people with mild dementia than in older people without dementia (41% vs 14 %, p=0.0002). In post-hoc pairwise comparisons, OH was significantly ($p<0.05$) more common both in DLB, PDD and AD patients than in normal controls. Furthermore, the median systolic BP drop from supine to standing was significantly larger in the DLB group and the mixed group than in normal controls. We found no significant differences between AD and DLB with respect to either systolic or diastolic blood pressure drops.

When comparing the QTc values of the normal controls (n=23) with those of AD patients (n=81) and DLB patients (n=22), we found no significant differences in the prevalence of QTc prolongation (defined as QTc > 420 ms or >450 ms (57, 174)) or in terms of mean QTc values, also after exclusion of those taking QT interval prolonging drugs.

6.2 Paper III (Relationship between orthostatic hypotension and white matter hyperintensity load in older patients with mild dementia)

When comparing the clinical characteristics of patients in the highest and lowest total WMH volumetry quartiles, the only significant difference was a lower proportion among those in the highest WMH volumetry quartile having at least one APOEε4 allele (Fisher's exact test, p=0.030). In the semi-quantitative group, patients in the highest deep WMH quartile were significantly older (Mann-Whitney U test, p=0.002),

and the proportion with a history of stroke was significantly higher (Fisher's exact test, p=0.016), than in the lowest deep WMH quartile.

In stepwise multiple logistic regression analyses, only APOEε4 status (≥1 APOEε4 allele yes or no) remained a significant predictor of being in the highest WMH volumetry quartile (OR 0.075, 95% CI 0.007-0.851, p=0.037). With respect to the Scheltens deep WMH scores, only age remained a significant predictor of being in the highest, as opposed to the lowest quartile (OR 1.119, 95% CI 1.018-1.230, p=0.019).

6.3 Paper II (White matter hyperintensities and the course of depressive symptoms in elderly people with mild dementia)

6.3.1 Baseline analyses

A total of 206 patients with mild dementia were included in the database version used for this substudy (please see *5.7*). Of these, 77 patients had baseline MRI scans of sufficient quality for volumetric analysis of WMH, 137 had MRI scans that could be rated semiquantitatively for WMH according to the Scheltens scale, and the scans of 63 patients were analysed using both methods. The correlations between WMH ratios (i.e. WMH volume/total brain volume) and Scheltens scores, both total and frontal, were highly significant (Spearman's rho 0.838 and 0.839, respectively, p<0.001). Using MADRS cut-offs of ≥7 and ≥15, 33/77 and 14/77 were depressed, respectively.

With respect to the *volumetric* WMH analysis, the ratios of both total and frontal deep WMH were significantly and positively, but rather weakly correlated with the baseline severity of depressive symptoms, as measured with the MADRS (Spearman's rho 0.274, p=0.016, and Spearman's rho 0.238, p=0.037, respectively). Furthermore, depressed patients, defined both as having MADRS scores of ≥7 and ≥15, or NPId ≥4, had significantly higher total and frontal deep WMH ratios than non-depressed patients. In contrast, no significant differences were found using an NPId cut-off of ≥1.

We found no significant associations between *Scheltens* total scores or deep frontal scores and depression measures at baseline, except that patients having an NPId score of ≥4 had significantly (p=0.034) higher deep frontal scores than those with a NPId score of <4.

In multiple logistic regression analyses, performed separately for total and frontal deep WMH ratios (*volumetry*) due to high correlation (Spearman's rho 0.797, p<0.001) between these, we found both total and frontal deep WMH ratios, in addition to prior depression and having non-AD dementia, to be significant predictors of having a baseline MADRS score of ≥7. Similarly, total and frontal deep WMH ratios, and prior depression were significant predictors of a baseline MADRS score of ≥15.

In corresponding analyses, using a baseline NPId score of ≥4 as the response variable, prior depression, as well as the total and frontal deep WMH ratios (*volumetry*), emerged as significant predictors.

6.3.2 Longitudinal analyses

Volumetric WMH analysis

Patients having MADRS scores of ≥15 at follow-up (i.e. those with persistent or incident depression) had significantly higher baseline total and frontal deep WMH ratios (p=0.012 and p=0.006, respectively) than those having a MADRS score of <15 at follow-up (i.e. those "never" depressed or "in remission" (175)).

Patients with NPId scores of ≥4 at follow-up (i.e. those with persistent or incident depression) had significantly higher frontal deep WMH ratios (p=0.047), but not higher total WMH ratios than those never depressed or in remission. There were no significant differences in terms of WMH ratios between patients in remission and patients with persistent depression. When comparing those never depressed and those having persistent depression, the only difference of statistical significance was that

patients with persistent depression had higher frontal deep WMH volume ratios (p=0.031).

Using MADRS and NPId cut-offs of ≥7 and ≥1, respectively, there were no significant differences in WMH ratios between patients with favourable (i.e. remission or never depressed) and unfavourable (i.e. persistent or incident depression) courses, between remission and persistence, or between never depressed and persistently depressed patients.

The median change in MADRS scores from baseline to the one-year follow-up was +1.0. Of the 206 patients, 47% had a MADRS score of ≥7 and 12% ≥15 at the one-year follow-up. Employing a MADRS cut-off of ≥15, 57% (20/35) had recovered and 5% (8/170) had incident depression. There were no significant correlations between one-year MADRS or NPId scores and baseline total or frontal deep WMH ratios.

Semiquantitative WMH analysis

We found no significant associations between the Scheltens total and deep frontal WMH scores and the course of depression variables.

6.4 Paper IV (Persistence and prognostic implications of orthostatic hypotension in older people with mild to moderate dementia)

Of the 211 patients available at baseline, 133 had OH measurements at both baseline and the 1-year follow-up, 29 of whom were OH-positive on both occasions and were classified as “persistent OH” (OH+), whereas 57 were OH-negative at both examinations and were classified as “never OH” (OH-). These 133 patients had slightly longer education and somewhat higher cognitive performance than the remaining 78 patients. Among the 211 patients, a total of 67 patients died prior to the expected 4-year follow-up time.

Point prevalence of OH from baseline to the 4-year follow-up varied in the range of 30-45%. Persistence of OH from one annual examination to the next varied in the

range of 44-58% during this period. Among the 85 patients having OH measurements at both baseline, 1-year follow-up and 2-year follow-up, 32 (38%) “never” had OH, 18 (21%) had OH once, 27 (32%) twice, and 8 (9%) had OH at all three examinations.

Cox regression models, adjusted for relevant baseline characteristics, did not show any significant effect of OH status (OH+ vs. OH-) on survival from baseline until 1 October, 2012.

General and cognitive function declined as expected, as measured with the CDR-SB and the MMSE. No significant differences were found at any point from baseline to the 4-year follow-up regarding CDR-SB scores or MMSE scores between those with and without OH.

In multivariable analyses, no clear evidence of differential longitudinal development of CDR-SB scores or MMSE scores for the OH+ and OH- groups was found.

7 Discussion

7.1 Introduction

The *main concepts* of this thesis and their probable or potential associations are illustrated in Figure 3. Only some of these potential associations have been explored in this thesis (i.e. dementia vs. OH, OH vs. WMH, and WMH vs. depression) and will be discussed below, whereas some of the remaining associations briefly mentioned in the Introduction section will not be discussed any further. Moreover, the time course aspect has not been included, as it does not fit readily into this model.

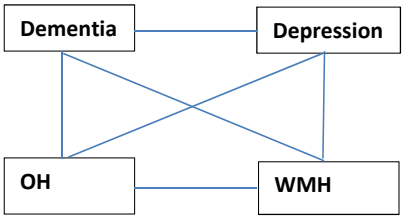

Figure 3. Probable and potential associations between the main concepts of this thesis

The *main hypotheses* explored in this thesis are, briefly, that OH is particularly common in dementia; that OH might be a cause of WMH, and that WMH in turn might be associated with increased prevalence and incidence of depressive symptoms; and, finally, that having OH might be associated with an unfavourable course with respect to cognition, function and mortality.

The *main findings* of the studies included in this thesis are, summarily, that OH was significantly more common in patients with mild dementia than in normal controls (41 % vs. 14%), and dementia was an independent predictor of OH. From baseline to the 4-year follow-up, 30 to 45% had OH at each examination. Having persistent OH did

not seem to predict a less favourable course with respect to cognition, function or survival. No association was found between OH and WMH load. However, baseline WMH load was positively correlated with baseline severity of depressive symptoms, and appeared to be associated with persistent and incident depression at 1 year.

7.1.1 Comments on the structure of the Discussion

As the methods and results of the various substudies already have been presented in the respective sections, I have chosen to start the Discussion with some general methodological considerations, which are relevant to some or all of the substudies. Thereafter, I shall discuss the substudies in what I consider the most logical order, namely paper I, paper III, paper II and paper IV (please see section **6**), discussing methodological considerations specific to each paper in connection with the respective paper.

7.2 Some general methodological considerations

7.2.1 Dementia diagnoses and categories

As explained in the Methods section (*5.1*), the DemVest study sample is not population-based, but rather a referral-based sample. This of course has several implications, including potential issues of representativity and generalisability. One important aspect of this is the distribution of dementia diagnoses in the sample, particularly the proportions having DLB and VaD. This has been discussed at some length in a previous paper from the DemVest study group (4), using the same baseline sample of 196 patients. Compared to some other studies (3, 176-178), the proportion of AD (65%) in our study is intermediate, the proportion of VaD (6%) is lower and the proportion with possible or probable DLB (20%) is in the upper range. The high proportion of DLB patients in our sample might conceivably be a consequence of a special interest in DLB at the outpatient clinics involved, i.e.; an ascertainment bias

(179). On the other hand, patients screened for inclusion were consecutive referrals, and underwent a comprehensive assessment employing standardised clinical instruments and diagnostic criteria (4). However, as the care and treatment of patients with DLB may be more demanding for both primary care providers and the patients' carers than that of some other types of dementia (180), a referral bias also cannot be excluded. Alternatively, this could be due to chance variation, related to the moderate size of the sample. This explanation might apply to the rather low percentage of patients with vascular dementia as well, which also could be related to our use of rather strict criteria for a diagnosis of probable vascular dementia, requiring both focal neurologic signs, evidence from brain imaging and a defined relationship between dementia and these findings(155). On the other hand, we also included possible cases of VaD, subject to less strict criteria.

Dementia diagnoses were made after a detailed baseline assessment, including dopamine transporter Single Photon Emission Computed Tomography (SPECT) scan for most patients with suspected DLB (181). Diagnostic criteria were re-applied 2 years later, and also at 5 years, thus ensuring a high standard of diagnostic precision. Importantly, there was a high degree of agreement between the clinical consensus diagnoses at 5 years and the provisional neuropathological diagnoses (n=22, unpublished data).

Both possible and probable cases of AD, DLB and VaD were included, and merged in their respective categories. Including both possible and probable cases would increase the sensitivity, at the price of reducing the specificity of these diagnoses (182). Furthermore, this may have reduced the reproducibility of findings concerning specific dementia subtypes, but it was considered necessary for statistical reasons, in view of the comparatively limited size of our sample, and acceptable for the purposes of the project.

7.2.2 DLB and PDD

A related issue is whether DLB and PDD, both being disorders of alpha-synuclein metabolism (183), are sufficiently similar for combining them into one DLB/PDD group, as was done in all the papers except paper I. According to Aarsland et al. (55), although important differences exist, such as the additional cortical amyloid beta deposition in DLB, these disorders might best be seen as parts of a spectrum. However, despite global similarities concerning cognitive performance and white matter pathology, patients with DLB, in a study employing voxel-based diffusion tensor imaging, were found to have more severe impairments in certain cognitive subsets and more severe white matter pathology in temporal and visual association fibres, suggesting differences in their underlying nature (184). With respect to autonomic dysfunction, patients with PDD may generally be more severely affected, but in terms of prevalence and severity of OH, which is the main measure of autonomic dysfunction in this thesis, PDD and DLB appear to be comparable (17). Furthermore, the neuropsychological profiles may also be sufficiently similar for combining these conditions into one group (185).

7.2.3 Inclusion of all common types of dementia

From March 2005 to April 2007, the DemVest study consecutively included cases of mild dementia referred to the relevant outpatient clinics in the region, ideally yielding a representative mixture of the most common types of dementia. As discussed above, this may not be the case. Furthermore, the papers on which this thesis is based have generally used all the patients available in the database, as opposed to focusing on some dementia subtypes only. This approach has the advantage of increasing the power of the statistical analyses, as well as to some (limited) extent perhaps allowing generalisation of findings to the "average" older patient with mild dementia. On the other hand, important differences between dementia subtypes may have been obscured, or not explored. However, due to rather small numbers of patients in most of

the various dementia categories, analyses studying associations of dementia subtypes may not have been statistically feasible or advisable.

7.2.4 OH measurement

The DemVest study was not specifically designed to assess OH in dementia. This fact may, at least partly, explain the existence of certain methodological weaknesses. Firstly, no period of rest in the supine position was explicitly required. This may have led to an underestimation of the orthostatic blood pressure drop in some cases. In a recent study, it was found that in the diagnosis of OH, a period of 4 minutes of supine rest was required for the initially falling BP to stabilise (186). Secondly, the case report form employed at baseline required the BP to be measured once during the first 3 minutes in the standing position. As the systolic and diastolic blood pressure as a physiologically normal response may fall more than the 20/10 mm Hg required according to the consensus definition (22) of OH during the first 30 seconds in the standing position (187), this may have led to a falsely positive OH measurement in cases where the BP was measured shortly after rising to the standing position. Furthermore, at baseline, in some 40% of the cases (please see paper IV), the non-standing measurement was made in the sitting, instead of the lying position. As previously shown (188), and repeatedly stated in the papers, this may have led to an underestimation of the "real" prevalence of OH. Of note, some recent, similar studies (189, 190) have used sit-stand measurements exclusively. Restricting OH measurement to the first 3 minutes in the standing position may also have led to underestimation of the prevalence of OH. According to a previous study including patients with dementia, in 20-30% of cases the maximum BP drop occurs after 5 minutes of standing or later (39). However, in this project we chose to use the consensus definition of OH; whether or not this definition is fruitful or reasonable is a different discussion (please see section **9**). According to this definition, concurrent measurement of pulse (i.e. heart rate) is not required, and therefore pulse measurement in the lying and standing position was not systematically performed, at least not at

baseline, although this might have provided useful information on the etiology of any orthostatic hypotension (187). Related issues are our employment of the sphygmomanometers being available in each outpatient clinic, and the lack of training and standardisation with respect to orthostatic BP measurements, both of which may have reduced the accuracy and reproducibility of the measurements.

7.2.5 Power

In hypothesis testing, i.e. using the "p" to make a decision, two possible errors can be made (191). Firstly, the null hypothesis (i.e. "no difference or relationship exists") may be rejected, when it is in fact true. This is called a Type I error, and the probability of committing this error ("false positive") is called alpha (α). Secondly, a non-significant result may be obtained, when the null hypothesis is *not* true ("false negative"). This is called a Type II error, and the probability of committing this error is called beta (β). The probability of a test to detect an effect or a difference of a given size, assuming that it exists in the population, is called the power of the test (192). The power equals 1- β (or 100(1- β)%). A power of 80% is usually considered adequate. The value of alpha is determined in advance, usually as 5%. The power depends on both the size of the effect being studied and the size of the sample. When the effect size and/or the sample size increase, so does the power. To illustrate this, I will use QTc data from Table 3 of paper I, employing the calculator available at https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx (using two-tail test). The power to detect the observed difference in mean QTc values between DLB (429.5 $\pm$ 39.5, n=22) and AD (424.2$\pm$28.2, n=81) is calculated at 9.1%. In order to achieve a power of 80%, one would have to increase the sample size to e.g. n=658+ n=658. If the mean QTc value of the DLB group had been e.g. 439.5, instead of 429.5, keeping the other values constant (as given in the table), the power would increase to a still inadequate 39.9%.

As stated in section *5.1*, the DemVest investigators aimed to include all patients with a first time diagnosis of mild dementia in the region, until at least 20 patients with DLB had been included; according to the protocol this was the minimum number of DLB patients required for achieving sufficient statistical power (with respect to what effect, one might ask), assuming a prevalence of DLB of 10-15%. However, the final number of patients included at baseline (n=196-246, depending on database version and inclusion criteria) may still have been insufficient with respect to some of the topics explored in the various papers, and even more so in view of the incompleteness of data on some variables. This of course would increase the probability of type II errors ("false negatives"), and lower the reliability of our conclusions (193).

7.2.6 Additional comments on methodology

All the substudies were naturalistic, implying that the investigators had no control over factors such as drug treatment which might have an influence on the outcomes of interest. Also, data on changes in drug treatment after baseline, and intercurrent and incident disease were not entered into the analyses of the substudies employing longitudinal analysis.

7.3 Discussion paper I

The main findings of paper I were, firstly, that the point prevalence of OH was significantly higher in a sample of older people with mild dementia than in a similar group without dementia, and secondly, that QTc values were not significantly different between patients with AD or DLB and normal controls. More specifically, OH was found to be significantly more common in AD, DLB and PDD, but not in the mixed group, than in normal controls. Furthermore, the systolic blood pressure drop from supine to standing position was significantly larger in DLB and the mixed group than in normal controls.

According to the conclusion of the abstract, "OH occurs even in patients with mild dementia, in particular in dementia with Lewy bodies". This statement is not entirely correct, as OH was *not* more prevalent in DLB than in AD and in particular PDD (see Table 2 in the paper), even if the systolic blood pressure drop was significantly larger than in normal controls only in DLB (*and* the mixed group).

As stated in the introduction, no studies had explored the prevalence of OH in "unselected" mild dementia prior to 2008. The results of our study generally are in line with previous studies including patients with moderate dementia and/or specific types of dementia, except that patients with DLB were found to have a higher point prevalence of OH than in our study in all three studies including DLB patients (17, 18, 28). This may, at least in part, be due to differences in measurement methods, particularly the duration of the OH measurement period (more on this later; please see section **9**).

From 2008 on, only a few similar studies have been published. In a Polish study (194) including patients with AD (n=54), orthostatic hypotension was found in 34.5%, but in a Brazilian study including patients with AD and mixed dementia (n=54, mean MMSE score 16.4 points), OH was found in only 16.6% of the patients (195). In a much larger study from Singapore including 2321 community-living older adults (mean age 65.5 years), an identical percentage (16.6%) had OH (196). With the exception of the Brazilian study, these point prevalences are in line with those found in our study, as well as the earlier studies.

To my knowledge, no studies exploring QTc (prolongation) in dementia have been published after 2008, only some case reports. Thus, our finding of no significant difference in QTc values between patients with mild dementia, including DLB patients, and normal controls has not been challenged. As can be seen from the Introduction, I have not been able to find any previous studies exploring this topic.

7.3.1 Supplementary analyses

In paper I, only bivariate analyses were performed, thus no conclusions could be drawn with respect to whether dementia is an independent predictor of having OH. Therefore, I have later performed multiple logistic regression analyses exploring this question. Dementia yes/no, age, sex, prevalent hypertension yes/no, OH drugs yes/no (please see paper I) and diabetes mellitus yes/no were entered as potential predictors, and OH yes/no as response. Using both forced entry, backward and forward likelihood ratio modes, having dementia emerged as an independent predictor of having OH (OR 3.990, 95% CI 1.882-8.461, p<0.0005) (see Table 1).

Table 1. Multiple logistic regression analysis of predictors of having OH (forced entry mode)

								95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Bl_DemYN(1)	1,384	,383	13,022	1	**,000**	**3,990**	**1,882**	**8,461**
	OHDrugsBl(1)	,197	,398	,245	1	,621	1,217	,559	2,653
	agebaseline	,027	,023	1,365	1	,243	1,027	,982	1,074
	SEX(1)	,359	,311	1,332	1	,248	1,432	,778	2,635
	DiaYN(1)	-1,814	,769	5,565	1	**,018**	**,163**	**,036**	**,736**
	HTyesno(1)	-,296	,368	,647	1	,421	,744	,361	1,531
	Constant	-3,894	1,725	5,092	1	,024	,020		

a. Variable(s) entered on step 1: Bl_DemYN, OHDrugsBl, agebaseline, SEX, DiaYN, HTyesno.

In addition to dementia, diabetes mellitus emerged as a significant predictor, but, surprisingly, having diabetes *reduced* the odds of having OH. This is contrary to what might be expected from previous studies and the pathophysiology of OH, and I have no plausible explanation for this finding.

Similar models, but substituting AD vs. DLB/PDD for dementia yes/no did not perform well (poor goodness of fit; all Omnibus tests of model coefficients p>0.05), and were not pursued any further.

7.4 Methodological considerations paper I

7.4.1 NC-QT sample

As explained in section *5.6*, we recruited a rather small (n=23) convenience sample of older non-demented patients in order to have a control group for comparisons of QTc values. This was a pragmatic solution, under constraints of time and other resources, to this problem, with potential for various biases, and limited information on clinical characteristics. However, the convenience sample did not differ significantly from the dementia groups with respect to the available data (i.e., age, sex and use of QT interval prolonging drugs), and we considered it likely to be sufficiently representative for our purposes. Ideally, we would have liked to have had a larger sample, and more information on medical history and status, including cognitive function.

7.4.2 ECG/QTc

According to a review published in 2003(197), optimal measurement of the QT interval is problematic, due to lack of standardisation and lack of data on the best method to adjust for heart rate. In our paper, we employed Bazett's formula (161), using manually obtained ECG intervals for the calculation of QTc. Our method mainly is in accordance with expert guidelines (198), except for not generally averaging the QT interval over 3-5 beats. We did however average the QT interval over 2-3 beats in patients with sinus arrhythmia. Furthermore, we did have data on relevant drugs, as well as some data on electrolyte values, allowing us to take these factors into account.

As only 113 of the 196 patients (58%) with mild dementia had ECG's that could be analysed in terms of QTc, there is a possibility of selection bias. Notably, only 3 out of 43 (7%) of the patients from one of the participating old age psychiatry outpatients clinics had valid ECG's, compared with between 58% and 81% of those from the 4 other centres. As can be read in paper I, only a minority (n=8) of the included patients with dementia were using potentially QTc-prolonging medications, and these 8 were distributed between 3 different centres (data not shown). Thus, any selection bias is

unlikely to have influenced the results through uneven distribution of use of QTc medications. Furthermore, the proportion of females, who have significantly higher mean values of QTc derived from Bazett's formula (199, 200), did not differ significantly between the participating centres (Fisher's Exact Test 3.695, p=0.453).

7.5 Discussion paper III

The main findings of this study were that in the present sample of older people with mild dementia, only age and APOEε4 status, but not OH or low standing systolic blood pressure were associated with having a higher WMH load.

As stated in the paper, in contrast to some previous studies we did not find any association between OH and WMH. Importantly, these studies were performed either in older people with major depression (118, 119, 201) or in samples including a higher percentage of DLB patients (121, 123), i.e. differing clearly from our study with regard to the samples. Furthermore, in the two last studies, blood pressures were measured partly or only during carotid sinus massage, whereas in our study blood pressures were measured only in the supine (or sitting) and standing positions. With respect to the potential relationship between OH and WMH load in DLB/PDD, we found no associations. However, our rather small sample in combination with missing values for the relevant variables did not permit any multivariable exploration of these potential relationships.

A tentative conclusion might be that WMH load may be related to OH in major late life depression, which seems to be associated with significant autonomic dysfunction (202), but not in dementia, with the possible exception of DLB/PDD. However, as OH and WMH share some risk factors, including age and hypertension (25, 124), any apparent association between OH and WMH might conceivably be due to residual confounding (203), i.e. even if this fact of shared risk factors has been taken into account and attempts have been made to adjust for it in the statistical models.

When comparing the clinical characteristics of patients in the highest and lowest WMH volumetry quartiles, the only significant difference found was a *lower* proportion in the former group with at least one APOEε4 allele, suggesting that other alleles (i.e., ε2 or ε3) might be associated with an increased risk of having a high WMH load. As stated in the paper, this finding was in accordance with at least two previous studies (204, 205). Also, patients having the ε4 allele, which is a major risk factor for AD (206), might have more neurodegenerative damage and therefore develop dementia (the entry criterion of our study) with a lower WMH load. According to a recent systematic review and meta-analysis (207), both the ε2 and the ε4 alleles generally are associated with increasing burdens of WMH, while the ε2 allele, in contrast to the ε4 allele, seems to have a protective effect on the occurrence of AD. Taken together, the results of the above-mentioned studies appear to provide a possible explanation regarding the lack of an association between APOEε4 positivity and a high WMH load in our study.

To my knowledge, no similar studies have been published after our study (as of 25 November, 2013).

7.6 Methodological considerations paper III.

One major limitation of this study is its cross-sectional design. If any significant associations between OH and WMH had been found, no conclusions regarding causality could have been made. Also, if there does exist any causal relationship between OH and WMH load in mild dementia, one would expect OH to have exerted its effect over an extended period *prior to* the diagnosis of dementia.

Another potentially important limitation is the use of only one OH measurement as the basis of the diagnosis of OH. This of course is in agreement with the consensus definition of OH, which does not require more than one measurement. However, as shown in both this project (paper IV), and in previous studies (please see section 3.1.1), the reproducibility of OH probably is moderate, at best. Having OH at baseline

therefore may not give a reliable indication of whether OH is persistent, frequently recurrent or only transient. This would tend to obscure any potential relationship between (persistent) OH and WMH load, assuming that any persistence of OH also applies to the past.

One minor comment regarding the abstract: In the "Results" section, the term "multivariate" is used. Strictly speaking, the term "multivariable" should have been used instead (208).

7.6.1 Volumetric assessment of WMH

In order to compensate for interindividual differences in brain volumes, we calculated the ratios of volumes of WMH to total brain volumes. As discussed in a paper using largely the same material (78), this could be a potential limitation, because both ageing and dementia are associated with atrophy in gray and white matter (209), and the extent of this atrophy is likely to differ between individuals and types of dementia (210). A possibly better alternative would have been to use the total intracranial volume as a reference, as has been done in some studies (81).

7.6.2 Visual assessment of WMH

For various reasons, including lack of adherence to the MRI protocol, a rather large number of MRI scans could not be analysed volumetrically. Primarily in order to be able to increase sample size and thereby power, we therefore also used a visual assessment method, namely the Scheltens scale (85). However, due to certain weaknesses of visual scoring methods, such as susceptibility to ceiling effects and poor discrimination of WMH lesion volumes, resulting in lower sensitivity (86), the use of such a method may not have been optimal for the purposes of our study.

7.6.3 Dichotomisation of WMH measures

As far as we know, no reference ranges for WMH volumes or Scheltens scores exist. For the multivariable analyses, we therefore chose to dichotomise these variables into highest vs. lowest quartiles, as has been done in some other studies (211). An alternative approach might have been to use total WMH volume ratios and deep WMH Scheltens scores as continuous dependent variables in multiple regression analyses, thereby avoiding the loss of information resulting from dichotomisation. However, due to a rather limited sample size and skewed distribution of values and scores this was not considered to be a good alternative. Notably, in a paper studying essentially the same sample, log transformation of the WMH volumes was attempted. However, these data did not become more normally distributed after a log transformation (78).

7.6.4 Total vs. regional WMH

Another potential issue concerns the choice of WMH regions used in the analyses. With respect to volumetric assessment of WMH, a number of studies have found a high correlation between regional and total WMH volumes (81, 212). Therefore, using only total WMH volumes appears to be a reasonable choice.

As to the visually rated WMH, we chose using the deep WMH scores, because these had been found to be associated with OH in previous studies employing the Scheltens scale (121, 123). According to a review on classification of white matter lesions in elderly persons (68), there may however be a dissimilarity in pathogenetic mechanisms between (irregular) periventricular and deep white matter lesions, with the former more likely determined by chronic hemodynamic insufficiency, and the latter by small vessel disease, suggesting that the periventricular lesions might be more relevant, as a potential consequence of OH. Still, I consider the association of OH with deep WMH in previous studies to be a sufficiently good reason for choosing deep WMH, instead of periventricular WMH.

7.6.5 Differences between scanners/centres and raters

Not being a radiologist, I shall not discuss the technical details of MRI acquisition and WMH segmentation, some of which have been described in the papers employing WMH quantification (i.e. papers II and III). However, some issues concerning potential significant differences between MRI scanners and between raters should be mentioned. With respect to the former issue, a phantom study was performed, the results of which indicated excellent inter- and intrascanner reliabilities (all Cronbach's alpha values >0.95)(78). Concerning the latter issue, for the volumetric assessment intraclass correlation coefficients (ICCs) of 0.998 and 0.964 were found for inter-rater and intra-rater reliabilities, respectively, and for the visual assessment an inter-rater reliability ICC of 0.923 was found, all of which indicating excellent reproducibility.

7.6.6 CIRS vs. other comorbidity indexes

The patients included in the DemVest study are old, and thus belong to a group generally suffering from other conditions in addition to dementia. These other conditions, for which the term "comorbidity" often is used, are of interest for several reasons, including issues of confounding and also for purely descriptive purposes. So-called comorbidity indexes reduce coexisting illnesses and their severity to a single numerical score, which allows comparison with scores from other patients (213). For this paper, as well as paper II and IV, the Cumulative Illness Rating Score (CIRS)(214) was employed. Several other methods are available, the most well-known probably being the Charlson Index (215). However, according to a 1993 critical review of available methods, the CIRS is one of a few valid and reliable methods that can be used in clinical research (216).

7.7 Discussion paper II

The main findings of this paper were, firstly, that in older people with mild dementia volumes of both total and particularly deep frontal WMH were positively correlated with baseline severity of depressive symptoms, and that depressed patients had significantly higher WMH volumes than non-depressed at baseline. Secondly, in multivariable analyses, both total and deep frontal WMH volumes, in addition to a history of depression or having non-AD dementia, were significant predictors of having depressive symptoms or clinically significant depression at baseline. Thirdly, patients with an unfavourable course of depression from baseline to the 1-year follow-up had significantly higher baseline frontal deep (and total) WMH volumes than those with a favourable course.

Our baseline findings are in agreement with those of Barber et al. (79) and O'Brien et al. (80)(these studies appear to use identical materials and methods), who found a cross-sectional association between frontal WMH burden and higher depression scores in patients with DLB (n=27), AD (n=28) and VaD (n=25) of moderate severity, using the Scheltens scale and the MADRS. In a small retrospective study (n=31), including both early- and late-onset AD, and employing the MADRS and a modified version of the Fazekas scale (113), clinician-rated depressive symptoms were higher in subjects with large anterior hyperintensities (217). By contrast, in a cross-sectional study, including only patients with mild to moderate AD (n=51) (218), no correlation was found between WMH load, as measured with the Wahlund scale (219), and clinical scales, including the NPI (164). Taken together, these results suggest that there may be an association between WMH load, and in particular frontal WMH, and depression in patients with mild to moderate dementia. However, a potential causal relationship between WMH and depression might in principle go in either direction (or be bidirectional) (202), or both conditions could result from an underlying biological substrate (150) .

With respect to the relationship between baseline WMH load and the course of depressive symptoms, I am not aware of any directly comparable studies. The studies

that have been performed have mainly included subjects *without* dementia. Most of these have, however, like us, found higher baseline WMH load to be associated with poor outcome in those having depression or depressive symptoms at baseline (76, 220), and/or that higher baseline WMH load is a predictor of developing depression during follow-up (73, 74, 221). Interestingly, in one of these studies (Teodorczuk et al. 2010), the association disappeared after adjustment for transition to disability.

In the multivariable analyses, prior depression and having non-AD dementia emerged as predictors of being depressed at baseline, in addition to WMH load. This is in line with the findings of previous research.Depression is often recurrent (222, 223), and prior depression appears to be an important risk factor for depression in older people. (224, 225). However, little seems to be known about prior depression as a potential predictor of depression in older people with dementia. Also, previous studies suggest that depression is more common and severe in DLB patients, who constitute the majority of our "non-AD" category, than in AD patients (226).

In contrast to a previous study (79, 121), we found no significant associations between Scheltens scores and baseline measures of depression (or course of depression variables). This scoring was, as stated in the paper, performed by an experienced neuroradiologist, and the interrater reliability with another neuroradiologist was good; therefore I consider poor quality of the rating an unlikely explanation. Instead, it could be due to visual rating scales' displaying ceiling effects and poor discrimination of lesion volumes (86), or differences between the samples studied, e.g. in terms of dementia types and stages of dementia.

I have not been able to find more recent studies than ours dealing with this subject matter.

7.8 Methodological considerations paper II

Although a rather small study in absolute terms, our study is among the largest in this field, and one of a limited number of longitudinal studies. Furthermore, we employed both semiquantitative rating of WMH load, which has been used in most previous studies, and volumetry, which is more sensitive (86), and measured both total and frontal WMH. We also used both a carer-based measure of depression (the NPId), and an observer-based measure (the MADRS), employing cut-offs for both mild depression and clinically significant depression for both tests. The downside of this is that the paper may have become unnecessarily long and complex. In retrospect, a better, or at least a simpler, solution might have been to use only frontal WMH values, and use the MADRS only as the measure of depression, employing only the higher cut-off. Originally, we had intended to use the lower cut-offs only, but added the higher cut-offs in response to a reviewer who commented that using the former would not properly capture depression, to which we agreed. However, the title of the paper does not mention "depression", only "depressive symptoms".

Concerning the use of both total and frontal deep WMH measurements, this was a consequence of one of our hypotheses being that depressive symptoms would be more strongly related to the latter. Although the frontal deep WMH volumes were associated with higher odds ratios in the multivariable analyses, the total WMH volumes also emerged as significant predictors in the corresponding analyses. From a practical point of view, total WMH volumes may be easier to establish, and appear to predict important functional measures almost as well as regional volumes (81).

Some other issues concerning the evaluation of WMH have been discussed previously; please see "Methodological considerations paper III", sections *7.6.1, 7.6.2, 7.6.4* and *7.6.5*.

Despite being a relatively large study, it was not large enough for performing multivariable analyses concerning the potential association between baseline WMH and the risk of being clinically depressed at the 1-year follow-up. Corresponding

analyses using the lower MADRS cut-off value of ≥7 were not performed for the paper, due to absence of significant differences in the bivariate analyses using this cut-off (see page 107 of paper II). I have later performed a multiple logistic regression analysis (forced entry mode), entering MADRS≥7 yes (n=25) or no at the 1-year follow-up as response, and history of depression yes or no, AD vs. non-AD dementia and deep frontal WMH (volumetric) as predictors. The resulting model did not perform well (Omnibus tests of model coefficients p=0.082) and no significant predictors emerged (data not shown). Moreover, when entering only one of these potential predictors at a time, together with deep frontal WMH, in the model, similar results emerged (data not shown), thus supporting our previous conclusion.

As stated in the paper, the changes regarding depression status were relatively small. This could at least partly be due to the rather short study period, but irrespective of possible explanations, this fact also limits the statistical power to detect potential associations between WMH burden and the course of depression.

The issues of generalisability and combination of DLB and PDD into one LBD group have been discussed elsewhere in this thesis (sections 7.2.1 and 7.2.2, respectively). The question of depression scale scores versus structured psychiatric interview has, at least briefly, been discussed in the paper (p. 108). Not being a psychiatrist, I shall not venture into any further discussion of the relative merits of these approaches. However, according to Pellegrino and coworkers (137), caregiver reports (e.g. the NPId) may over-report symptoms and patient reports (e.g. the MADRS) may under-report symptoms, thus using both may give a more balanced view of the mood symptoms of patients with cognitive impairment (227). In the present paper, however, we used the scores on only one of these scales at a time, but in clinical practice using both might be useful. Regarding the various cut-offs for any vs. clinically relevant depression and the corresponding potential relationships with WMH load, the lower NPId cut-off (i.e. ≥1), as opposed to the other cut-offs, appears to be less relevant.

7.9 Discussion paper IV

The main findings of this paper were, firstly, that OH was "moderately" (an imprecise and relative term) prevalent and persistent from baseline to the 4-year follow up. However, only a minority had OH at all three measurements from baseline to the 2-year follow-up. Secondly, having persistent OH, defined as having OH at both baseline and the 1-year follow-up, did not seem to predict a less favourable course with respect to cognitive or daily function, or survival, when compared to those without OH at the same follow-ups.

Few, if any, previous studies have explored the course of OH over a period as long as 4 years in older people with dementia. The only somewhat comparable study that I am aware of concerns the effect of comprehensive geriatric assessment on the prevalence and incidence of OH in older persons, of whom only about 11% had dementia, over a period of 3 years (37). A total of 10.9% (25/228) patients remained OH-positive during all the 4 measurements of the study, as compared to 9% (8/85) during 3 measurements in our study. Taken together, this suggests that OH may be an unstable diagnosis in older people in general, and that OH may not be more persistent in older people having dementia than in those without dementia. This could be different in older people with particular types of dementia, e.g. DLB/PDD, but our study was neither designed nor powered to explore this question. Contrary to what might have been expected if assuming that the prevalence and/or the severity of autonomic dysfunction increases with age and the duration of the dementing illness, we found rather stable point prevalences of OH (with overlapping 95% confidence intervals) from baseline to the 4-year follow-up. As discussed in the paper, this finding could have a number of explanations. One of these, namely the possibility that having OH is associated with a higher mortality rate, and thus that those having OH, and those with persistent OH in particular die at an earlier stage, is not in accord with other results from our study. It could also be related to the moderate length of our OH follow-up period. This is, however, purely speculative, in view of the paucity of relevant studies. What appears to be the most likely explanation would be that the prevalence of OH

really may be relatively constant, at least in mild to moderate dementia. But then again, this might differ between various types of dementia.

Our finding of no prognostic consequences of OH for the cognitive function of older people with mild to moderate dementia is in line with the only comparable (although studying older people in general) study that I know of (48). However, as noted in the paper, our Cox regression models weakly suggest that there might be an association between OH-status (i.e. persistent vs. never OH) and the course of MMSE, although in the opposite direction of what was hypothesised. This should be explored in a larger sample. On the other hand, when comparing the MMSE and CDR-SB scores of those *with* and *without* OH at each examination (please see box plots), no indication of differences emerged.

In contrast to a previous cross-sectional study, which employed autonomic symptom scores and used other measures of ADL (21), we found no implications of having OH (a potential measure of autonomic dysfunction) for performance in ADL, at least not to the extent that this is measured by means of the CDR-SB. This could be due to differences in study design, sample characteristics and outcome measures. However, in contrast to the above-mentioned study, the longitudinal design of our study, disregarding issues of power, might in principle enable us to discover potential causal relationships.

We found no association between OH status (i.e. persistent vs. never) and survival. This is in contrast to the only similar study that I am aware of (47). However, as stated in the paper, the studies differ both in terms of types of dementia studied and the definition of "persistent" OH, as well as the length of the follow-up period and the number of patients included. Of note, our study had a somewhat higher power to discover potential differences in mortality between these groups. Thus, the lack of an association in our study might indicate that the prognostic consequences of OH differ between various types of dementia, e.g. AD, which constituted the majority of our sample (59/86, vs. 14/86 with LBD) and LBD, which was the only category of dementia in Stubendorff and coworkers' study (47).

The issue of power may also be relevant when comparing our negative results to the positive results of large population based studies exploring the prognostic implications of OH (measured on one occasion only) in elderly people, such as the Rotterdam Study (29) and the Honolulu Heart Program (228). Both studies found OH to be a significant independent predictor of all-cause mortality in elderly people.

7.10 Methodological considerations paper IV

As stated both in the paper and previously in this thesis, our study may not have had the power to discover potential prognostic correlates of OH.

Originally, we had intended to use the RDRS-2 (229) as a measure of ADL functioning. Regrettably, two different versions of this scale had been used in the DemVest study; therefore we chose to use the CDR-SB as a measure of both cognitive and functional impairment. This may not have been optimal, but we considered it a reasonable and acceptable alternative, with the advantage of the CDR-SB giving a good measure of stage and outcome in dementia (171, 172).

Although the neuropsychological impairments, and thus the MMSE subscores of patients with DLB differ from those of AD patients (230), the rates of longitudinal decline in MMSE scores seem to be equivalent (231). Of note, MMSE score loss in pure DLB (i.e. autopsy proven) may be less severe than in cases with significant AD pathology (232). For our study, however, including patients with clinically diagnosed dementias, the MMSE was considered an adequate measure of cognitive function.

However, both CDR-SB scores and MMSE scores are rather unspecific outcome measures, and the use of more specific and sensitive instruments might have yielded different results. Even so, with respect to the MMSE a study of cognitive functions in patients with neurogenic OH found OH to be associated with impairment of global cognitive functioning, as well as more specific tasks, mainly related to executive functions (233). Furthermore, both of these instruments have been used to follow the course of both AD, DLB and VaD in previous studies (231, 234, 235)

Our method of OH measurement, which had some clear weaknesses, has been discussed in section *7.2.4*. For various reasons, OH measurements were not performed in all and not in the same patients at each examination. Therefore, our estimates of point prevalence and reproducibility are less precise than what would have been the case if such measurements had been available for all patients (alive) at each visit. This also limits the number of patients eligible for the longitudinal analyses, and thus the power of these analyses.

When planning the study, we chose to use "persistent" OH (baseline and 1-year follow-up), instead of a single positive baseline OH measurement as a potential predictor of an unfavourable course of dementia. This choice was based on previous reports' finding the reproducibility of OH to be inconsistent at best (27), in combination with the idea that patients having two consecutive positive OH measurements might be more exposed to the potential adverse consequences and correlates of OH than those without any positive measurements during the same period, and possibly expressing an underlying disposition toward OH. Interestingly, a large longitudinal study including middle-aged men found that participants with OH at both baseline and at re-screening (5.6±1.0 years later) showed the highest risk of any adverse event, including all-cause mortality (40).

To my knowledge, no established definition of "persistent OH" exists, only definitions of various types of (potentially) momentary or acute OH (236). Except for the study by Stubendorff and coworkers (47), in which a diagnosis of persistent OH was based on 3 (x5) measurements over a period of 6 months, the studies of which I am aware have defined it on the basis of measurements during a single day (44, 237). These studies have defined "persistent OH" as at least 50% ($\geq$2/3, $\geq$4/8) of the measurements being positive.

Our approach of comparing the "persistent OH" group with the "never OH" group in the multivariable longitudinal analyses of course excluded patients having OH *once* (baseline and 1-year follow-up), thus conceivably reducing the statistical power of these analyses. However, *all* patients having OH measurements were included in the

analyses comparing the MMSE and CDR-SB scores of those with and without OH at each annual examination from baseline to the 4-year follow-up. These analyses essentially yielded the same result as the multivariable longitudinal analyses, i.e., no association between OH and course.

8 Conclusions

8.1 Paper I

The main findings of paper I were, firstly, that the point prevalence of OH was significantly higher among older people with mild dementia than in a comparison group without dementia, and, secondly, that QTc values were not significantly different between patients with AD or DLB and normal controls. More specifically, OH was found to be significantly more common in AD, DLB and PDD, but not in the mixed group, than in normal controls. Furthermore, the systolic blood pressure drop from supine to standing position was significantly larger in DLB and the mixed group, but not the AD group, than in normal controls.

Thus, although hypothesis no.1 was only partly supported (please see discussion), we were able to shed some light on the prevalence of OH in mild dementia, which appears to be relatively high, and probably higher than in older people without dementia. Prolongation of QTc in dementia has been even less studied, and even though no difference was found between QTc values in those with and without dementia, this is a subject of definite clinical interest and relevance, particularly with respect to the use of psychotrophic medications in dementia.

8.2 Paper III

The main findings of paper III were that age and APOEε4 status, but not OH or low standing systolic blood pressure were associated with having a higher WMH load. Hence our hypothesis no. 2 was not supported. However, this may not be the final word on this matter, as larger studies employing a longitudinal design might yield a different conclusion.

8.3 Paper II

The main findings of paper II were, firstly, that volumes of both total and particularly deep frontal WMH were positively correlated with baseline severity of depressive symptoms, and that depressed patients had significantly higher WMH volumes than non-depressed at baseline. Secondly, in multivariable analyses, both total and deep frontal WMH volumes, in addition to a history of depression or having non-AD dementia, were significant predictors of having depressive symptoms or clinically significant depression at baseline. Thirdly, patients with an unfavourable course of depression from baseline to the 1-year follow-up had significantly higher baseline frontal deep (and total) WMH volumes than those with a favourable course.

Briefly, this suggests that in mild dementia, having severe WMH is independently associated with having depression or depressive symptoms at baseline, and that having high WMH volumes at baseline is associated with a more unfavourable course with respect to clinically significant depression. Thus, our results provide some support for our hypotheses.

8.4 Paper IV

The main findings of paper IV were, firstly, that from baseline to the 4-year follow up 30-45% had OH at each examination, and that 44-58% of those having OH at a given examination had OH at the next follow-up. However, only 8/85 (9%) had OH at all 3 measurements from baseline to the 2-year follow-up. Secondly, having persistent OH, defined as having OH at both baseline and the 1-year follow-up, did not seem to predict a less favourable course with respect to cognitive or daily function, or survival, when compared to those without OH at the same follow-ups.

The results of this study provide a relatively clear answer to some of our research questions. However, due to some limitations of our study, the potential longitudinal implications of having (persistent) OH for function and survival still are less than clear.

9 Future perspectives

As shown in paper IV, the reproducibility of OH in mild to moderate general dementia was moderate at best, and over the longer term it seemed to be poor. This is in accordance with the results of several previous studies, as reviewed by Naschitz and Rosner (27). In their excellent paper, for a variety of reasons they call for a revision of the present OH criteria (22), a call that later has been repeated by others (238), with subsequent prospective comparisons of the prognostic impact of old vs. new criteria. Here, I shall discuss briefly only one aspect of this topic, namely the differentiation of acute OH (i.e. measured on one occasion only) from chronic or persistent OH. Even though several studies have found single measurement-based OH to be associated with a number of longitudinal adverse outcomes (please see *3.1.1*), there are indications that persistent OH (i.e. multiple measurements-based OH) may be a more powerful predictor of some adverse outcomes (40, 47, 239). However, I am not aware of any generally accepted definition of "persistent OH". Keeping the blood pressure drop criteria and the time limit of the consensus definition (22) unchanged, a possible definition of "persistent OH" might be "-at least 2 out of 3 sequential measurements performed with an interval of at least 1 month being positive ". The interval requirement would reduce the impact of intercurrent disease. Future studies should explore the prognostic implications of these criteria.

Furthermore, OH measurements should be performed in the morning, preferentially before or alternatively at least 1hour after breakfast (27). Importantly, the first measurement in the standing position on each occasion should be made at 1 minute, in order to avoid "false positives" due to the initial physiological blood pressure drop (187). This provision should be stated clearly also with respect to the consensus definition of OH.

So-called "initial orthostatic hypotension", defined as a transient systolic blood pressure drop of more than 40 mm Hg or a greater than 20 mm Hg transient diastolic drop within 15 seconds after standing with symptoms of cerebral hypoperfusion (240,

241) can only be measured with continuous noninvasive monitoring. This is a different phenomenon from OH defined according to the consensus definition, and the prognostic implications of this phenomenon remain to be explored (242).

A standing measurement period of 3 minutes may be sufficient in many cases (243), but in people having dementia with Lewy bodies a measurement period of 10 minutes should be used (28), if feasible.

We were not able to confirm the potential association between OH and WMH in dementia in our cross-sectional study. Future studies should employ a longitudinal design, measuring OH at baseline and comparing baseline WMH volumes with those at e.g. 3 years, adjusting for potential confounders. Comparing patients with persistent OH with those without (persistent) OH would probably be preferable.

In addition, future studies of the potential prognostic implications of OH in dementia need to be sufficiently powered.

Regarding the potential association between WMH and depression in early dementia, our study only provides tentative conclusions. Therefore, larger longitudinal studies, preferably employing volumetric quantification of WMH and using a longer study period should be performed. Volumetric assessment of WMH is, for reasons mentioned previously, superior to semi-quantitative assessment. As non-automated methods for WMH volumetry may be very time-consuming, such studies would be much easier to perform using fully automated methods, the development of which should be a priority, preferably resulting in standardised methods. Consensus on grading or even reference ranges of WMH volumes also would be desirable. However, when volumetry is not available, established semi-quantitative measures appear to be preferable to the non-formalised and non-quantified evaluations provided by individual radiologists (86, 244), and should be implemented in the evaluation of people with cognitive complaints. Moreover, consensus criteria for depression in

people with dementia need to be developed and validated (245). Additionally, the pathobiology (please see *3.4*) and predictors of depression in older people with dementia seem to merit further study.

The most important clinical implication of our findings may be that, as OH seems to be rather common among older people with mild to moderate dementia, and has been associated with a number of adverse outcomes in other studies, it should be actively looked for, and treated or ameliorated, if possible. Another clinically important point is that WMH, which are a common finding on brain MRI scans of older people (please see *3.2*), are not to be considered as a chance finding of small or unclear clinical significance. Rather, particularly when severe, they should be regarded as a harbinger of a possibly unfavourable prognosis, including potential development of depression.

10 Appendix

Informed consent form, convenience sample

Samtykkeerklæring

Tidligere undersøkelser kan gi mistanke om at eldre med demens oftere har visse forandringer på EKG enn ikke-demente. Overlege Hogne Sønnesyn er i samarbeid med professor Dag Aarsland i ferd med å undersøke dette. Vi trenger da kopi av EKG fra ikke-demente eldre som deg, og må i tillegg se igjennom medikamentlisten din med tanke på medikamenter som kan gi EKG-forandringer. Kopi av EKG vil bli lagret anonymt, ingen andre opplysninger utenom kjønn og alder vil bli registrert, og disse opplysningene vil ikke bli brukt i andre sammenhenger.

Jeg gir med dette samtykke til at det kan bli tatt kopi av mitt EKG, og at legen kan se gjennom medikamentlisten min.

Stavanger/SUS, den……. Underskrift

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Sak nr. 167.04 – 06/329

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Ad prosjekt: Ad prosjekt: Demensprosjektet på Vestlandet – DEMVEST (REK Vest nr. (167.04)

Det vises til din endringssøknad datert 07.09.06 vedrørende ønske om å rekruttere kognitivt friske personer til studien.

REK Vest v/leder har vurdert saken og en har noen mindre merknad til forespørselen om deltakelse. Det bør sies eksplisitt at det er frivillig å delta og at det ikke gi noen negative konsekvenser dersom en ikke gir sitt samtykke. En forutsetter også at det foreligger en standard samtykkeerklæring ("Jeg har mottatt skriftlig og muntlig informasjon om studien og sier meg villig til å delta") med plass for dato og pasientens underskrift. Skriftstørrelsen bør også økes.

Klarering opprettholdes.

Vennlig hilsen

Jon Lekven
leder

Arne Salbu
sekretær

11 References

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