Brain pathology on clinical MRI in patients with late-life depression and healthy controls

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Sammendrag

Bakgrunn

Depresjon er en alvorlig psykisk sykdom som rammer 1-5% av den eldre befolkningen (>65 år, depresjon hos eldre, LLD). Man antar at depresjon hos eldre (LLD) øker risikoen for å utvikle mild kognitiv svikt (MCI) eller demens. Funn på MR-bilder av hjernen til eldre, slik som hvit substans hyperintensiteter (WMH), infarkter og hjerneatrofi har blitt knyttet til både LLD, MCI og demens. Målet med denne studien var å undersøke 1. Er det forskjeller på type og frekvens av intrakranielle forandringer på MR-bilder hos LLD pasienter sammenliknet med en gruppe friske eldre? Og 2. har LLD pasienter som konverterer til MCI/demens 3 år etter inklusjon annerledes og/eller flere intrakranielle funn på MR sammenliknet med de LLD pasientene som forblir kognitivt intakte (som ikke får MCI eller demens)?

Materiale og metode

Kognitivt intakte pasienter med LLD ifølge ICD-10 kriteriene (n=95) ble rekruttert fra flere norske alderspsykiatriske avdelinger i den nasjonale, longitudinelle multisenter observasjonsstudien *Prognosis of Depression in the Elderly* (PRODE). Kontrollgruppen (n=111) ble rekruttert fra pasienter henvist til elektiv operasjon på Oslo Universitetssykehus og Diakonhjemmet sykehus i Oslo. Eksklusjonskriteriene til denne studien var demens, kognitiv svikt eller annen organisk hjernesykdom, i tillegg til somatisk sykdom med kort forventet levetid. Ved inklusjon ble detaljert psykiatrisk og medisinsk sykehistorie dokumentert. I tillegg ble det utført kliniske tester, kognitiv vurdering og MR av hjernen hos både pasientene med LLD og kontrollene. Alle MR-bildene ble vurdert av to spesialister i nevroradiologi og dokumentert i henhold til standardiserte metoder for å undersøke de følgende patologiske forandringene: WMH (Fazekas skåring), infarkter (type, størrelse og plassering), frontal, parietal og medial temporallapps atrofi (semikvantitativ gradering), og tilstedeværelse av eventuelt andre patologiske lesjoner. Småkarsykdom i hjernen (SVD) ble definert som tilstedeværelse av ≥1 av disse funnene: lakuner, Fazekas skår ≥2 eller mikroblødninger i hjernen. Ved 3-års oppfølging ble de som var pasienter med LLD ved inklusjon i studien intervjuet og diagnostisert med MCI eller demens etter henholdsvis Winblad kriteriene eller ICD-10, og ble så fordelt i 2 grupper for analysene (kognitiv intakt eller MCI/demens). Signifikante gruppeforskjeller ble utregnet vha uavhengig t-test, Mann-Whitney U test, Fischer's og Pearson Khikvadrattest. Statistisk signifikansnivå ble satt til $p<0.05$.

Resultater

Ved inklusjon var kontrollgruppen yngre, bestod av færre kvinner, hadde høyere utdanningsnivå og fungerte bedre i dagliglivet sammenliknet med LLD pasientene. Ut fra sykehistorien hadde kontrollene

høyere prevalens av kreft ($X^2(2) = 9.518$, $p=0.009$) og signifikant færre hodeskader($X^2(1) = 33.049$, $p<0.001$). På MR-bildene så man at LLD pasientene hadde høyere Fazekas skår ($U=3357$, $p<0.001$) og mer SVD ($X^2(1) = 5.037$, $p=0.025$), men det var ingen signifikante forskjeller med tanke på slag eller semikvantitativt målt atrofi mellom de to gruppene.

Ved 3-års oppfølging hadde mer enn halvparten av LLD pasientene blitt diagnostisert med MCI eller demens (n=45). De LLD pasientene som fortsatt var kognitivt intakte hadde færre infarkter i hvit substans ($p=0.030$, Fischer's Exact Test, FET) og i grå substans ($p=0.030$, FET). Det var ingen andre statistisk signifikante forskjeller ved sammenlikning av funn på MR-bildene mellom de to kognitivt forskjellige gruppene.

Konklusjon

LLD er assosiert med økt mengde WMH og småkarsykdom i hjernen, men ikke hjerneslag, noe som forsterker teorien om at mikrosirkulasjonen i hvit substans er påvirket ved LLD. Det var nesten ingen forskjell i hjernepatologiske forandringer på MR når man sammenliknet LLD pasienter som hadde konvertert til MCI/demens med de som hadde forblitt kognitivt intakte.

Abstract

Background

Depression is a serious mental illness affecting 1-5% of older adults (>65 years, late-life depression, LLD). LLD has been suggested to increase the risk of developing mild cognitive impairment (MCI) or dementia. In older adults, findings on brain MRI such as white matter hyperintensities (WMH), infarction and brain atrophy are linked to both LLD, MCI and dementia. The objectives of this study were to investigate 1. If there were differences in type and frequency of intracranial findings on MRI in the LLD group compared to a group of matched healthy elderly controls, and 2. If participants in the LLD groups who converted to MCI/dementia 3 years after inclusion to the study had different types and/or higher frequency of intracranial findings on MRI compared to participants in the LLD group who remained cognitively intact.

Material and methods

Cognitively intact patients with LLD according to ICD-10 criteria (n=95) were recruited at old-age psychiatry wards in the national, multicenter observational *Prognosis of Depression in the Elderly* (PRODE) study. A control group (n=111) were recruited from patients undergoing elective surgery at Oslo University Hospital and Diakonhjemmet Hospital in Oslo. Exclusion criteria were dementia, cognitive decline or other organic brain disease, as well as serious somatic illness with short life-expectancy. At inclusion, detailed psychiatric and medical history, clinical measures, cognitive assessment and brain MRI were obtained in patients and controls. Two neuroradiologists used standardized methodology to read and score the brain MRIs for the following pathologies: WMH graded according to Fazekas scale, stroke (type, size and location), semi-quantitative grading of frontal, parietal and medial temporal lobe atrophy, and presence of other lesions, which included all other pathological brain lesions. Small vessel disease (SVD) was defined as the presence of $\geq$1 of the following: lacunae, Fazekas score $\geq$2 or cerebral microbleeds. The LLD were interviewed at a 3-year follow-up and diagnosed with MCI or dementia according to ICD-10, and subsequently dichotomized into cognitively intact versus MCI/dementia for the analyzes. Significant group differences regarding demographic, clinical and brain MRI findings at baseline and at 3-year follow-up were assessed using independent samples t-test, Mann-Whitney U test, Fischer's and Pearson Chi-Square test. The statistical significance level was set to $p<0.05$.

Results

At baseline, the participants in the control group were younger, included fewer women, had higher educational level and functioned better in daily life compared to the LLD group. Medically, controls

reported more incidences of cancer ($X^2(2) = 9.518$, $p=0.009$) and significantly less head injuries. On brain MRI, the LLD group had higher Fazekas' score ($U=3357$, $p<0.001$) and more SVD ($X^2(1) = 5.037$, $p=0.025$), but there were no significant differences in frequency of strokes or semi-quantitative atrophy measures between the groups.

At 3-year follow-up, more than half of the LLD was diagnosed with MCI or dementia (n=45). The cognitive intact had less infarctions in white matter ($p=0.030$, Fischer's Exact Test, FET) and gray matter ($p=0.030$, FET). No other statistically significant differences were found on brain MRI comparing the two cognitively different groups.

Conclusion

LLD was associated with increased amount of WMH and SVD, but not stroke, suggesting that white matter microcirculation is compromised in LLD and either leading to LLD or co-occurring with LLD. Brain MRI pathology was almost similar in LLD participants who converted to MCI/dementia and those who remained cognitively intact.

1 Introduction

1.1 Background, late-life depression

Late-life depression (LLD) is defined as clinical depression occurring in old age, usually >60 years, and is associated with severe consequences for the patient such as cognitive impairment (Sexton et al., 2012; Thomas and O'Brien, 2008), dementia (Bennett and Thomas, 2014), disability and suicide (Alexopoulos, 2019, 2005). A recent meta-analysis of older adults (aged 50 years and older) in Western countries found a rate of 3.3% for current and 16.5% for lifetime major depression (MD) (Volkert et al., 2013).

1.3 LLD and common MRI findings

White matter hyperintensities (WMHs) appear as hyperintense areas in the brain on T2 weighted MRI scans such as fluid attenuated inversion recovery (FLAIR) MRI images. They are a common finding in the general elderly population and are strongly associated with age (Fazekas et al., 1987; Inzitari et al., 2007; Rhodius-Meester et al., 2017; Ylikoski Ari et al., 1995). However, greater frequency and volume (severity) of the findings are associated with several health-related problems such as functional decline, gait disturbance and mortality (Inzitari et al., 2009, 2007; Rensma et al., 2018; Rosario et al., 2016). The etiology and pathology of WMH are not completely understood, but several studies and reviews have shown associations with cerebrovascular pathology in the smaller vessels. WMH is therefore often used as a surrogate marker for cerebral small vessel disease (SVD) (Farhat et al., 2019; Prins and Scheltens, 2015; Wardlaw et al., 2013). In recent years, studies have proven a link between severity of WMH and LLD creating the hypothesis that LLD might be linked to small vessel disease or white matter disease (Coffey et al., 1989; Farhat et al., 2019; Herrmann et al., 2008; Jorm et al., 2005; O'Brien et al., 2006; Rensma et al., 2018; Salo et al., 2019; Sheline et al., 2008; Tupler et al., 2002; van Uden et al., 2015; Wang et al., 2018).

LLD has been associated with other MRI brain findings besides WMH and other SVD related findings, for instance thinning of gray matter (Andreescu et al., 2008; Lai et al., 2000) and reduction of hippocampal volume (Lebedeva et al., 2015; Sexton et al., 2012; Taylor et al., 2018). Research has also indicated that LLD increases the risk of stroke (Krishnan et al., 2005). More investigation on intracranial lesions and LLD is needed to understand the underlying neurobiology behind this mental illness.

1.4 Dementia and MRI

Dementia pathology in older patients is complex and includes both neurodegenerative and vascular changes in the brain. The current research criteria for diagnosing mild cognitive impairment (MCI) and dementia advise to apply biomarkers such as MRI in addition to the clinical and neuropsychological examination to improve the accuracy of the diagnosis (Dubois et al., 2014; Rhodius-Meester et al., 2017; Wahlund et al., 2016). Structural changes on brain MRI, e.g. atrophy of the medial temporal lobe (MTA), and signs of cerebrovascular abnormalities, e.g. white matter hyperintensities (WMH), have been shown to increase the risk of cognitive decline and dementia in older people (Ferreira et al., 2015; Korf et al., 2004; Mortamais et al., 2013; Scheltens et al., 1992).

1.5 The relationship between dementia and late-life depression

LLD and dementia have many things in common; clinically there is an overlap of symptoms such as apathy, cognitive deficits and memory problems. Studies have showed that LLD patients have an increased risk of developing dementia compared to the general population (Borza et al., 2019; Diniz et al., 2013; Silva et al., 2013). However, there is still no agreement about the causational relationship between the two diseases in the literature (Bennett and Thomas, 2014).

Research into the underlying neurobiological pathways involved in the transition from LLD to dementia could change how we understand these two diseases. New evidence from a longitudinal study using structural MRI data from cognitively intact LLD patients converting to MCI or dementia showed that differences in brain structures, such as the volume of the right ventral diencephalon, exist between the LLD patients who converted to MCI/dementia and those who remained cognitively intact (Lebedeva et al., 2017).

Better understanding of the brain pathologies and which brain structures that are involved in the conversion from cognitively intact LLD patients to MCI or dementia may help to develop neuroradiological tools that can predict development of MCI or dementia in LLD patients.

1.6 Aims

The objectives of this study were to investigate the frequency of different brain pathologies on brain MRI in persons considered to undergo normative brain aging and persons with LLD, and to examine if certain types of brain structural pathologies are more common in cognitively intact LLD patients

converting to MCI/dementia compared to those who remain cognitively intact. We hypothesize that: (1) WMH are more frequent and of greater severity in elderly with LLD compared to mentally healthy controls from a somatic hospital cohort, and (2) Intracranial pathology, especially WMH severity, is greater in elderly with depression who convert from cognitively intact to MCI/dementia 3 years after inclusion in the study.

2 Materials and methods

2.1 Ethics

The PRODE study was approved by the Regional Committee of Medical Research Ethics and Privacy and Data Protection Officer at Oslo University Hospital (2009/1774). The study of the controls was approved by the Regional Committee of Medical Research Ethics with approval number 2011/2052. All the participating controls, patients and caregivers were given oral and written information about the study and provided written consent before entering the study. For patients without the capacity to give consent, their next of kin had to give consent in writing on behalf of the patient according to the declaration of Helsinki. The PRODE study is registered at ClinicalTrials.gov (NCT01952366).

2.2 Study design

The PRODE study is a prospective, observational multicenter study of patients (≥60 years) admitted to departments of old age psychiatry for treatment of depression (n=169). The following centers included patients; Innlandet Hospital Trust (Sanderud and Reinsvoll), Vestre Viken Hospital Trust (Lier), St. Olav's University Hospital (Trondheim), Oslo University Hospital (Ullevaal and Aker), Haukeland University Hospital (Bergen), Diakonhjemmet Hospital (Oslo), and Stavanger University Hospital (Stavanger). Only LLD patients with brain MRI were included in this paper (n=128) (see Figure 1).

All participating centers used the same standardized instruments to collect data and all assessors received standardized training before study start and twice yearly during the study period. Data was collected at admission to the hospital and after three years.

2.3 Patient group

Patients aged 60 years or more and diagnosed with late-life depression (LLD) according to the Tenth Revision of the International Classification of Diseases and Health Related Problems (ICD-10) criteria (World Health Organization, 1993) based on a semi structured clinical interview performed by a research clinician specialized in old-age psychiatry, were assessed for eligibility and included to the PRODE study as early as possible after admission. Recruitment was between December 2009 and January 2013. There was no difference with regard to age or sex between those who agreed and those who declined to participate in the study (n=38) (Borza et al., 2019, 2015). Exclusion criteria for this particular study were (1) dementia, mild cognitive impairment (MCI, ICD-10: F06.7) or other organic psychiatric diagnosis (ICD-10: F00-F09), (2) severe somatic diseases, (3) life-threatening disease with short life-expectancy. In addition, LLD with any MRI contraindications were excluded from MRI scanning.

The LLD excluded due to a F00-F09 diagnosis either at inclusion or during the hospital stay (n=21) did not differ from the other LLD patients (n=107) in sex nor age ($X^2_{sex}(1)=1.235$, $p_{sex}=0.266$, $t_{age}(126)=0.490$ $p_{age}=0.625$). But they had a significant lower MADRS score than their counterpart ($t(124)=2.211$, $p=0.029$).

2.4 Control group

Control participants (n=111) were recruited at Oslo University Hospital and Diakonhjemmet Hospital in Oslo from patients scheduled for elective orthopedic, gynecological or urological surgery in spinal anesthesia (Idland et al., 2017; Lebedeva et al., 2015) (See Figure 1). Exclusion criteria to this particular study were the same as for the LLD group, and in addition; current use of antidepressants, diagnosis of recurrent depressive disorder, previous treatment in specialist health care service in psychiatry, and Montgomery-Asberg Depression Rating Scale (MADRS) score ≥8 (Montgomery and Åsberg, 1979; Hawley et al., 2002; Rush et al., 2006).

No controls were diagnosed with MCI/dementia at baseline, but some had a history of clinical depression or with suspected depression at inclusion (n=18). These were excluded. There were no significant differences regarding sex nor age in the excluded persons compared to the control group included ($X^2_{sex}(1)=0.110$, $p_{sex}=0.741$, $U_{age}=994.0$, $p_{age}=0.973$).

2.5 Characteristics of the excluded

Out of the 257 included participants (128 LLD and 129 hospital controls), only 206 were included in the analysis at baseline. 51 participants from both cohorts were excluded from MRI analysis due to dementia, MCI, depression (in the control group), motion artefacts on MRI, technical difficulties and severe brain pathology (see Figure 1). There were no difference in sex distribution or age in the excluded compared to included participants ($X^2_{sex}(1)=0.217$, $p_{sex}=0.641$, $U_{age}=5183.5$, $p_{age}=0.884$). But there was a significantly higher number of LLD patients who were excluded from analyzes than controls (33 LLD vs 18 controls, $X^2(1)=5.651$, $p=0.017$).

2.6 Demographics and lifestyle

Total years of education was stratified into three levels according to Norwegian school reforms during the 20th century (Thune, 2019): level 1: ≤ 7 years of education, level 2: 8-12 years of education, and level 3: > 12 years of education.

Living conditions and marital status were calculated based on participants' reports.

Marital status was dichotomized to "not-single" (including married or living together) and "single" (including widow [er], divorced or living apart).

The instrumental activities of daily living (IADL) was used at inclusion to assess everyday functioning (Lawton and Brody, 1969). The scale contains five items for males and eight for females. We generated a sum score by adding the IADL-scores together. Calculations for male and females were done separately. A higher score denotes a lower level of functioning (max score for women 32 and for men 20).

History of smoking and/or harmful alcohol consumption was obtained using a structured interview and case notes. Alcohol consumption data from the LLD group were collected as a yes/no/previously variable, in comparison to the controls who gave their alcohol consumption as units per week (only current use). Cut-off limits for the controls were based on Furtwængler and Visser's suggestions (Furtwængler and Visser, 2013).

2.7 Psychiatric health

Information on psychiatric history and prior depressive episodes, including number of previous depressive episodes and age at onset of the first lifetime depressive episode, was obtained from case

notes and semi-/structured clinical interviews, including Montgomery and Asberg Depression Rating Scale (MADRS) with LLD patients and their next of kin.

MADRS consists of 10 items, each rated from 0 points (no symptoms) to 6 points (severe symptoms), with higher score denoting more severe depression.

Cognitive function was evaluated at baseline by MMSE (score range 0-30). A higher score indicates better cognition (Folstein et al., 1975).

MCI or dementia was diagnosed at inclusion (both groups) or during the hospital stay (for LLD) according to the ICD-10 criteria (World Health Organization, 1993). At 3-year follow-up (≥ 3 years after inclusion), MCI was diagnosed according to the Winblad criteria (Winblad et al., 2004) and dementia was diagnosed according to the ICD-10 criteria. This was done by psychiatrists specialized in old-age psychiatry based on 1-year clinical follow-up data, and telephone interviews ≥ 3 years after inclusion with patient and their next of kin and/or health care workers.

2.8 Somatic health

Medical history was collected by interview with a medical doctor at inclusion and scored according to the ICD-10 criteria.

Head injury includes concussion, unspecified head injury and cranial fracture.

Cerebrovascular incident includes “transient cerebral ischemic attacks and related syndromes” (ICD-10 code: G45) and stroke.

2.9 Magnetic resonance imaging (MRI)

2.9.1 MRI parameters

Brain MRI were acquired across sites using a harmonized standard MRI PRODE protocol (Nakken, 2011) on 1.5-Tesla and 3-Tesla scanners from GE, Philips and Siemens.

The protocol was based on the 1.5 T ADNI protocol (Jack et al., 2008) and consisted of a T1 weighted volume, axial FLAIR, T2* and dual echo scans. Scan parameters across sites are presented in Table 1. For a detailed overview per center see Supplementary Table 1.

Table 1. *Overview of the harmonized MRI scan parameters across all nine 1.5T and one 3T scanners used in the PRODE multicenter study ("PRODE protocol")*

	T1	Dual echo	T2 FLAIR	T2*
Sequence type	3D MP-RAGE	TSE	IR TSE	GRE/EPI
Imaging time	~7:30 min	~5:30 min	~4-6 min	~5-6 min
Repetition time (TR)	2400 ms	3 000-3 030 ms	9 000-10 000 ms	683-835 ms
Echo time (TE) 1	2.88-3.79 ms	11-13 ms	107-121 ms	21-26 ms
TE 2	-	96-102 ms	-	-
Inversion time (TI)	1000 ms	-	2 500 ms	-
Flip angle	8°	150°-180°	150°-180°	20°-30°
No. echoes	-	7-16	15-34	-
Receiver bandwidth	162-200 Hz/px	161-165 Hz/px	174-305 Hz/px	80-122 Hz/px (EPI: 770 Hz/px)
No. of slices	160-170	44-48		
Slice thickness	1.2 mm	3 mm		
Slice gap	0 mm	0 mm		
Field of view (FOV)	240x240 mm	230x230 mm		
Matrix size	192x192 px	256x256 px		
Voxel size	1x1x1.2 mm	0.9x0.9x3.0 mm		

Abbreviations: FLAIR, fluid-attenuated inversion recovery; MP-RAGE, Magnetization Prepared – RApid Gradient Echo; TSE, turbo spin echo; IR, inversion recovery; GRE, gradient echo; EPI, echo-planar imaging; TE 2, time to the second echo (in a dual echo sequence).

2.9.2 Neuroradiological MRI reading

Two consultants in neuroradiology read all images independently. They were blinded for participants' clinical status but had access to participants' sex and age. Subsequently, the two neuroradiologists came to consensus with regard to the reading. All images were evaluated on overall scan quality, classifications of intracranial pathology, normal variants and age-related changes using standard neuroradiological criteria, and scored using several semi-quantitative assessment tools.

Naming of different cerebral findings followed the STRIVE nomenclature (Wardlaw et al., 2013).

Brain infarctions were registered with regard to anatomical location (cortical, subcortical nuclei, white matter and hemispheric lobe, cerebellum and brain stem) and dichotomized into ≥ or < 10 mm in largest diameter. Cerebral microbleeds were dichotomized into present or not. Other structural lesions (i.e. meningioma, hypophyseal lesion, perivascular space[s], arachnoid cyst, hemosiderin, tumor, cavernoma, subdural hemorrhage/hematoma, choroid fissure, cyst, cerebellar lacuna, falx meningioma) were dichotomized into present or not.

2.9.2.1 Semiquantitative MRI reading

White matter hyperintensities (WMH) were assessed using Fazekas scale: a 4 point rating scale (0-3) where a higher score denotes more severe load (volume, confluency, frequency)(Fazekas et al., 1987). For some of the calculations Fazekas were dichotomized into "low" (score 0-1) and "high" (score 2-3).

Brain atrophy was semiquantitatively assessed in various regions of the brain (medial temporal lobe atrophy [MTA], global cortical atrophy-frontal subscale [GCA-f] and posterior atrophy [PA]) using visual rating scales.

MTA rating uses a 5-point rating scale (0-4) where a higher score denotes more severe atrophy (Scheltens et al., 1992). A score of 2 or more in a <75 year old and a score of 3 or more in ≥75 years was considered abnormal on the left and right, as MTA has been associated with age (Duara et al., 2013; Rhodius-Meester et al., 2017). MTA was dichotomized into abnormal or normal for the analyzes based on the participants' age.

PA and GCA-f were scored independently, both using a 4-point rating scale (0-3) where a higher score denotes a higher grade of atrophy (Ferreira et al., 2015; Koedam et al., 2011; Pasquier et al., 1996).

Small vessel disease (SVD) was defined by having ≥1 of any of these lesions: lacunae of presumed vascular origin, white matter hyperintensities (Fazekas score of ≥ 2) or cerebral microbleeds, after the STRIVE criteria (Wardlaw et al., 2013).

2.9 Statistics

Data were analyzed in SPSS version 25.

Demographic and clinical characteristics at inclusion and at 3-year follow-up are presented as mean with SD, and percentages. For group comparisons between LLD and controls at baseline and between those in the LLD who remained cognitively intact versus those that converted to MCI/dementia at 3-year follow-up, independent samples t-test or Mann-Whitney U-test was used for continuous and ordinal variables as suitable, and Chi-Square-test or Fisher's exact test were used for categorical variables.

The statistical significance threshold was set to $p < 0.05$.

3 RESULTS

3.1 Demographic and clinical characteristics of the LLD and control groups

Figure 1 displays inclusion into the study and selection of participants with MRI scans of sufficient quality for neuroradiological reading.

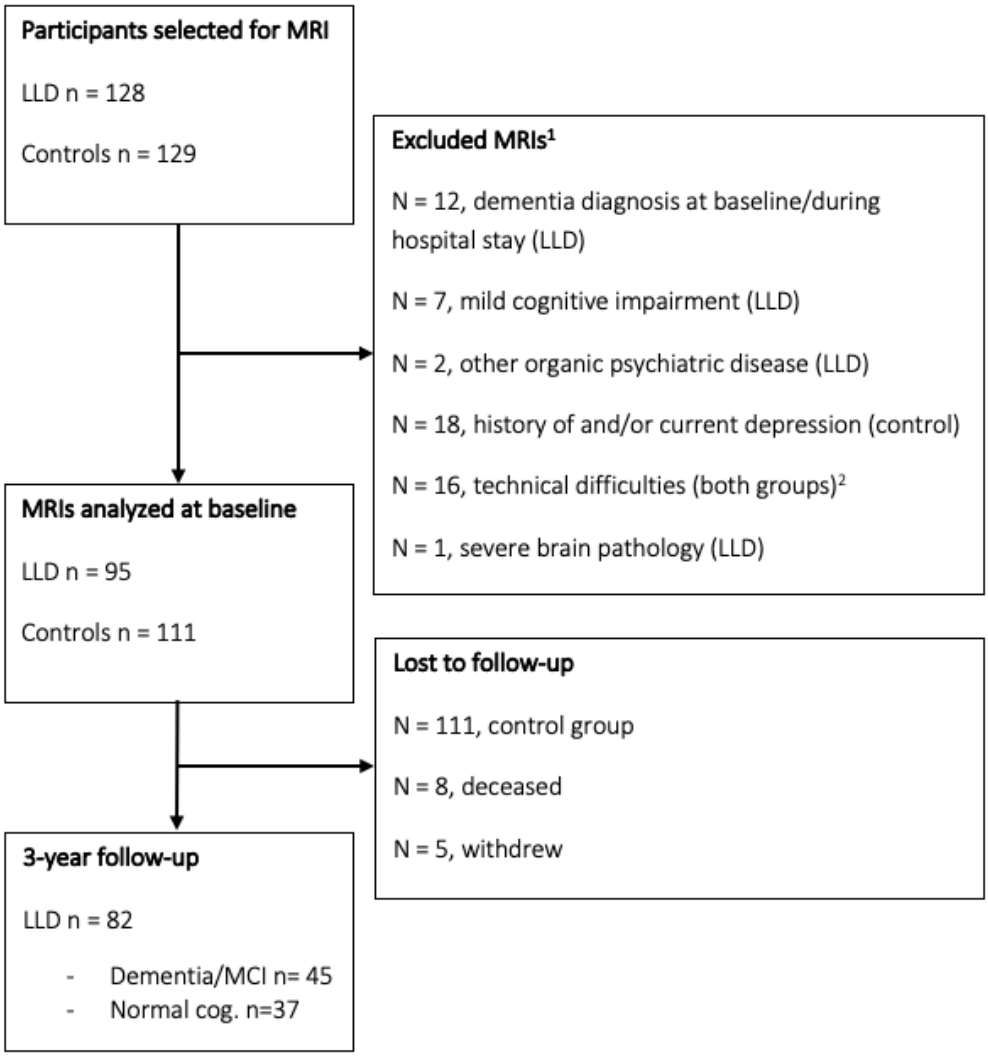

Figure 1. Flow chart displaying participant-selection

Abbreviations: LLD, Late life depression; MCI, mild cognitive impairment.

[1]Some participants had both technical difficulties and dementia (and/or depression in the control group). [2]Technical difficulties: center did not follow the correct scan protocol.

The LLD patient and control groups' demographic and clinical characteristics are shown in Table 2.

Table 2 *Demographic and clinical characteristics of the sample at baseline (n=206, if not specified)*

Group	Control (n=111)	LLD (n=95)	p-value[1]
Demographics and lifestyle			
Age in years, mean (SD)	73.8 (6.6)	75.8 (6.8)	**0.040**
Sex, n (male/female)	54 (48.6%)/57 (51.4%)	26 (27.4%)/69 (72.6%)	**0.002**
Education in groups 1/2/3[2], n (controls: n= 110, LLD: n=91)	3 (2.7%)/33 (29.7%)/ 74 (66.7%)	21 (22.1%)/ 54 (48.6%)/16 (16.8%)	**<0.001**
Marital status: single, n (%)	39 (35.1%)	51 (53.7%)	**0.007**
Living conditions[3], n (%)			
- Living alone	39 (35.1%)	49 (51.6%)	**0.017**
- Home nursing (LLD: n=92)	0 (0%)	31 (33.7%)	*NA*
- Housing with all-day care	0 (0%)	0 (0%)	*NA*
IADL[4] score, male/female, mean (SD) (controls: n=46, LLD: n=18/controls: n=52, LLD: n=66)	8.4 (0.98)/ 8.4 (1.1)	13.6 (5.3)/ 15.2 (6.4)	**<0.001/** **<0.001**
Harmful alcohol consumption, n (%) male/female (LLD: n=24/66)	4 (7.4%)/ 3 (5.3%)	0 (0.0%)/ 4 (6.1%)	0.306/ 1.000
Tobacco use, n (%) previous/current use (LLD: n=92)	69 (62.2%) 57/12	43 (46.8%) 26/17	**0.004**
Psychiatric health			
MADRS-score, mean (SD) (LLD: n=94)	2.0 (2.3)	27.4 (8.3)	**<0.001**

MMSE score, mean (SD) (controls: n=110, LLD: n=90)	29.0 (1.4)	26.7 (2.8)	**<0.001**
Somatic Health			
Hypertension from questionnaire, n (%)	43 (38.7%)	40 (42.1%)	0.340
Diabetes type 1 and type 2, n (%)	8 (7.2%)	8 (8.4%)	0.746
Cancer, n (%) previous history/current	37 (33.3%) 17/20	27 (19.3%) 16/4	**0.009**
Cerebrovascular incident, n (%) previous history/current	6 (5.4%) 6/0	13 (13.7%) 10/3	0.062
Heart disease[5], n (%)	34 (30.6%)	29 (30.5%)	0.987
COPD[6], n (%) previous history/current	7 (6.3%) 0/7	13 (13.7%) 2/11	0.108
Head injury, n (%) (patients: n=92)	3 (2.7%)	30 (32.6%)	**<0.001**

Abbreviations: LLD, Late life depression; NA, not applicable; IADL, Instrumental activities of daily living; MADRS, Montgomery and Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; COPD, chronic obstructive pulmonary disease

[1]t-test, Mann-Whitney U test, chi-square test or Fisher's exact test as appropriate. [2]Education: level 1: ≤7 years of education, level 2: 8-12 years of education, level 3: >12 years of education. [3]Living in his or her private home if not specified otherwise. [4]after Lawton & Brody's scale. [5]Heart disease: previous or current coronary heart disease and/or heart failure and/or rhythm disorder. [6]COPD: including asthma and/or emphysema. Previous history includes childhood asthma and bronchiectasis

The LLD patients were on average 2 years older (U=4396.5, p=0.040), were more likely women ($X^2(1)$=9.759, p=0.002), had lower educational level ($X^2(2)$=54.64, p<0.001) and were more likely to be single and living alone ($X^2_{single}(1)$=7.159, p_{single}=0.007, $X^2_{living\ alone}(1)$=5.657, $p_{living\ alone}$ =0.017).

Their living situation also differed, as about 33% of the LLD patients received home nursing compared to 0% in the control group, and their mean IADL score were significantly higher (denoting more difficulties in daily activities) than the control group (U_{males}=126.5, $U_{females}$=431.5, p<0.001 in both sexes).

Current harmful alcohol consumption was similarly low in the two cohorts (p_{male}=0.306, p_{female}=1.000), but 4 LLD patients (4.2%) did record earlier history of harmful use. The control group had smoked significantly more than the LLD group ($X^2(2)$ =11.3, p=0.004), but there were more current smokers amongst LLD (current smokers: 12 controls vs 17 LLD).

Unsurprisingly, LLD had a significantly higher MADRS score (more depressed) (U=20.5, p<0.001). They also scored worse on the MMSE (U=2502, p<0.001).

Somatic report from both groups showed no significant difference in common cardiovascular risk factors (hypertension, diabetes, cerebrovascular incidents, heart disease, COPD) (see Table 2). The control group reported more current cancer than LLD ($X^2(2)$ =9.518, p=0.009) while the LLD patients reported a significant higher incidence of head injuries ($X^2(1)$ =33.049, p<0.001).

3.2 Brain MRI findings in LLD and control groups

The LLD patients and control groups' brain MRI findings are shown in Table 3.

Table 3. *Frequency of intracranial findings in the two groups*

	Control group (n=111)	LLD group (n=95)	P value[1]
Infarction (present), n (%)	7 (6.3%)	11 (11.6%)	0.182
- Frontal	2 (1.8%)	6 (6.3%)	0.147
- Parietal	2 (1.8%)	1 (1.1%)	1.000

- Occipital	2 (1.8%)	5 (5.3%)	0.252
- Temporal	0	0	*NA*
- Cerebellum	2 (1.8%)	3 (3.2%)	0.664
Cortical infarction (present): n (%)	7 (6.3%)	11 (11.6%)	0.182
Lacunae of presumed vascular origin (present): n (%) (LLD: n=92)	29 (26.1%)	28 (30.4%)	0.496
Fazekas: n (%) (LLD: n=91)			
- Grade 1	48 (43.2%)	33 (36.3%)	
- Grade 2	22 (19.8%)	28 (30.8%)	**<0.001**
- Grade 3	13 (11.7%)	24 (26.4%)	
Cerebral microbleeds: n (%) (LLD: n=63)	10 (9.0%)	11 (17.5%)	0.100
Small vessel disease[2], n (%) (LLD: n=61)	53 (47.7%)	40 (65,6%)	**0.025**
Global cortical atrophy, frontal subscale: n (%) (controls: n=109)			
- Score = 0	11 (10.1%)	18 (18.9%)	
- Score = 1	50 (45.9%)	54 (56.8%)	**0.002**
- Score = 2	43 (39.4%)	21 (22.1%)	
- Score = 3	5 (4.6%)	2 (2.1%)	
Abnormal total MTA: n (%) (controls: n=109)	43 (39.4%)	37 (38.9%)	0.942
- Abnormal MTA right, n (%)	29 (26.6%)	30 (31.6%)	0.434
- Abnormal MTA left, n (%)	35 (32.1%)	24 (25.3%)	0.282
PA average, mean (SD) (controls: n=109)	1.16 (0.83)	0.97 (0.90)	0.086
Other structural findings[3]	12 (10,8%)	20 (21,1%)	**0.043**

Abbreviations: LLD, late life depression; MTA, medial temporal lobe atrophy; PA, posterior atrophy; NA, not applicable.

[1]t-test, Mann-Whitney U test, chi-square test or Fisher's exact test as appropriate (significance level: $p<0.05$). [2]Presence of white matter hyperintensities and/or lacunae of presumed vascular origin and/or cerebral microbleed. [3]Other structural findings: any other finding/lesions on brain MRI not already mentioned

The two cohorts showed no significant difference regarding infarction, not in frequency nor in location (see Table 3).

For lesions associated with SVD, no difference in number/location of lacunae or cerebral microbleeds were uncovered between the LLD and hospital controls, but Fazekas scores were significantly higher in the LLD patient group (U=3357, $p<0.001$). Also, when grouping these three lesions together into the possible SVD score there was a significantly higher prevalence of SVD amongst the LLD patients ($X^2(1)=5.037$, p=0.025).

Global cortical atrophy-frontal subscale (GCA-f) was significantly more prominent in the control than the LLD group ($U_{GCA\text{-}f}$=3988.5, $p_{GCA\text{-}f}$=0.002). There was no difference in the occurrence of medial temporal lobe atrophy nor posterior atrophy (see Table 3).

The LLD patient group had significantly more structural lesions than the control group ($X^2(1)=4.092$, p=0.043).

3.3 Associations between conversion to MCI or dementia and MRI findings in the LLD group

Out of the 95 LLD patients included at baseline with intact cognition, 82 (86%) were interviewed three years after inclusion. Of these, more than half (n=45, 54.9%) were diagnosed with either MCI (n=25) or dementia diagnosis (n=20) (see Figure 1).

The MRI findings at baseline in those who remained cognitively intact (not developing MCI or dementia) and those who received a MCI or dementia diagnosis three years after inclusion are shown in Table 4.

Table 4. *Comparison of baseline MRI from LLD patients with normal cognition or MCI/dementia at 3-year follow-up*

	Normal cognition (n=37)	MCI/dementia (n=45)	P value[1]

Infarction (present), n (%)	0 (0%)	6 (13.3%)	**0.030**
- Frontal	0 (0%)	2 (4.4 %)	0.499
- Parietal	0 (0%)	0 (0%)	*NA*
- Occipital	0 (0%)	2 (4.4 %)	0.499
- Temporal	0 (0%)	0 (0%)	*NA*
- Cerebellum	0 (0%)	2 (4.4 %)	0.499
Cortical infarction (present): n (%)	0 (0%)	6 (13.3%)	**0.030**
Lacunae of presumed vascular origin (present): n (%) (MCI/Dem.: n=42)	7 (18.9%)	13 (31.0%)	0.220
Fazekas: n (%) (Norm. Cog.: n=36, MCI/Dem.: n=43)			
- Grade 1	18 (50.0%)	13 (30.2%)	0.112
- Grade 2	12 (33.3%)	13 (30.2%)	
- Grade 3	4 (11.1%)	13 (30.2%)	
Cerebral microbleeds: n (%) (Norm. Cog.: n=24, MCI/Dem.: n=30)	3 (12.5%)	5 (16.7%)	0.720
Small vessel disease[2], n (%) (Norm. Cog.: n= 24, MCI/Dem.: n=28)	12 (50.0%)	20 (71.4%)	0.113
Global cortical atrophy, frontal subscale: n (%)			
- Score = 0	11 (29.7%)	6 (13.3%)	0.092
- Score = 1	20 (54.1%)	28 (62.2%)	
- Score = 2	5 (13.5%)	10 (22.2%)	
- Score = 3	1 (2.7%)	1 (2.2%)	
Abnormal total MTA: n (%)	13 (35.1%)	18 (40.0%)	0.651

- Abnormal MTA right, n (%)	10 (27.0%)	14 (31.1%)	0.686
- Abnormal MTA left, n (%)	7 (18.9%)	13 (28.9%)	0.295
PA average, mean (SD)	0.87 (0.83)	0.96 (0.88)	0.661
Other structural findings[3]	8 (21.6%)	9 (20.0%)	0.857

Abbreviations: LLD, late life depression; MTA, medial temporal lobe atrophy; PA, posterior atrophy; NA, not applicable.

[1]t-test, Mann-Whitney U test, chi-square test or Fisher's exact test as appropriate (significance level: $p<0.05$). [2]Presence of white matter hyperintensities and/or lacunae of presumed vascular origin and/or cerebral microbleed. [3]Other structural findings: any other finding/lesions on brain MRI not already mentioned

Infarctions were only present in the MCI/dementia conversion group which was significantly different from the group that remained cognitively intact (p=0.030, Fisher's Exact Test, FET). There was no significant difference regarding infarction in the white matter, but the MCI/dementia group reported a significantly higher incidence of cortical infarction (p=0.030, FET).

No other MRI findings differed significantly between the cognitively intact and the MCI/dementia conversion groups (see Table 4).

4 Discussion

4.1 General

This study demonstrated that the severity of white matter hyperintensities on brain MRI was significantly greater in cognitively intact patients with LLD compared to a control group of elderly hospitalized patients with no history of mood disorders. SVD and presence of other structural lesions were also more frequent in the LLD group. Surprisingly, the LLD patients had less frontal cortical atrophy than the control group, even though they were significantly older, had worse cognitive scores and reported more instances of previous head injury. In the LLD patients who converted from cognitively intact to MCI/dementia 3 years after inclusion, WMH severity was not greater than in those who remained cognitively intact, but they had more cortical infarctions.

4.2 The differences on brain MRI between the LLD and control group

The LLD group had significantly more severe WMH, SVD and structural findings on brain MRI than the control group.

Previous studies also report more severe WMH in late-life depression (Coffey et al., 1989; Herrmann et al., 2008; Jorm et al., 2005; O'Brien et al., 2006; Salo et al., 2019; Sheline et al., 2008; Thomas and O'Brien, 2008; Tupler et al., 2002; Wang et al., 2018). There are few studies on WMH in patients younger than 65 years of age, but one recent study found associations between WMH severity and depression in adults (30-65 years) with type 1 diabetes (Nunley et al., 2019). To our knowledge there are no studies proving against this association between WMH severity and clinical depression. This study confirms previous findings associating WMH severity and depression.

The presence of SVD was also higher in the LLD group. A study in the Netherlands found that elderly with depressive symptoms had lower white matter integrity (van Uden et al., 2015). However, as WMH is a marker of SVD, the difference found between LLD patients and controls in our study is probably driven by the already discussed difference in WMH.

There was no group difference between LLD and the controls in the frequency of strokes, implying that the LLD group did not have more pathology related to the larger blood vessels in the brain. There was no evidence for differences in the frequency of infarctions related to the posterior circulation either, which could imply an increased risk of embolic infarction in one of the groups (Markus et al., 2013). Taken together, our results suggest that LLD is a condition associated with the smaller vessels in the brain.

The LLD group had more structural lesions on brain MRI (described in Methods and Materials section). To our knowledge no previous study has examined this.

Surprisingly, frontal cortical atrophy (GCA-f) was more common in the control group compared to the LLD group. Studies using automated quantitative methods to assess frontal gray-matter volume have reported reduced volume in the orbitofrontal and ventromerdial frontal cortex in patients with LLD (Andreescu et al., 2008; Boccia et al., 2015; Sexton et al., 2013). Previous structural MRI-analyses of our data using Freesurfer found thinning in the left parahippocampal fusiform and inferior-parietal cortex in the LLD group compared to the controls. Cortical thinning in the control group correlated with age, however the same correlation could not be found in the LLD group (Lebedeva et al., 2015). We could not find previous reports on a difference in frontal cortical atrophy between LLD and control groups in the literature. Semi-quantitative methods, such as the visual rating scales we have used in this study, gives an assessment of changes in both area and thickness in the gray matter and is therefore not completely comparable with most quantitative methods. This could explain why our

results did not match previous literature on gray matter atrophy in the frontal region of the brain and LLD.

Several of the results in this study could be related to demographic or somatic differences between the LLD and the controls. The higher mean age of the LLD group could in part explain the difference in WMH severity, as age is known to be the strongest risk factor for WMH (Rhodius-Meester et al., 2017). Since the mean age difference was less than 2 years, it seems unlikely that differences in WMH severity stems from the age distribution. Age is also known to greatly increase the risk of ischemic stroke (Sacco, 1995), but we did not find such difference between the two groups. The control group smoked significantly more than the LLD group, which according to the literature can lead to more severe WMH (Vangberg et al., 2019), the opposite of what we found. This could mean that depression has a stronger influence on WMH severity than smoking or age.

The lower level of education in the LLD group compared to the control group might have affected some of the results in this study as it has been associated with higher risk of dementia (Xu et al., 2016). Lower education can also cause considerable bias to MMSE scores (Lancu and Olmer, 2006). This difference in educational level could therefore partly explain the significantly lower MMSE score in the LLD group.

More than 30% of the LLD patients reported a previous history of head injuries compared to only about 3% in the control group. Traumatic brain injury (TBI) is known to lead to cortical atrophy (Brezova et al., 2014). However, in our study the LLD patients had less frontal cortical atrophy than the controls. TBI is also known to increase the risk of depression (Perry et al., 2016), however most studies base their results on short follow-up periods after the TBI. To our knowledge there has not been studies examining the associations between TBI and LLD. There are some limitations to our results as the two different cohorts used different questionnaires to report medical history (information bias). Also, we do not know the temporal relationship between TBI and age of first depression onset in our cohorts, making it difficult to determine any relationship. To our knowledge, this is the first study to show that a previous TBI is more common in LLD than controls.

There are several structural differences in the brain comparing a group of hospitalized LLD patients with a control group. In line with previous studies, we found an increased severity of WMH and SVD in the LLD patients compared to the controls. The groups showed no difference in stroke and atrophy, except for the surprisingly less frontal cortical atrophy in the LLD group. This finding has not been reported before. Several of these MRI findings might have been influenced by demographic factors, especially since the LLD and control group proved to be different in some respects (see Table 2).

4.3 LLD conversion to MCI/dementia (3-year follow-up)

In this study we found that more than 50% of those LLD patients without cognitive impairment at baseline developed MCI/dementia over a 3-year period. A high conversion rate in LLD patients has been previously reported (Barnes et al., 2012; Bennett and Thomas, 2014; Diniz et al., 2013; Silva et al., 2013; Thomas and O'Brien, 2008). The fact that the LLD group consisted of more women than men might have affected the results, as women have an increased risk of AD (Beam et al., 2018). The risk of converting to MCI or dementia was substantial in the LLD compared to previous reports.

4.3.1 MRI findings and conversion to MCI/dementia

The increased frequency of SVD differentiating the LLD and control group, was not found to be related to conversion to MCI/Dementia which was characterized by increased frequency of cortical infarctions.

Common MRI biomarkers of MCI/dementia risk such as MTA (Dubois et al., 2014; Korf et al., 2004; Scheltens et al., 1992; Wahlund et al., 2016), PA (Koedam et al., 2011), GCA (Pasquier et al., 1996), WMH (Mortamais et al., 2013) and SVD (Bos et al., 2018; Rensma et al., 2018), did not differ between the converters and non-converters in the LLD group. Some of these biomarkers are better known for their association with Alzheimer's disease (AD) rather than unspecified dementia. Since we merged MCI and dementia (including Alzheimer's) into one group in our analyses, this might have affected the results. Most of the LLD patients were older than 60 years at time of the MRI scanning, which according to a recent publication decreases the diagnostic value of visual rating scales on atrophy (Rhodius-Meester et al., 2017). In our study, we could not confirm any of the common MRI biomarkers for MCI/dementia as a risk factor for converting to MCI/dementia in a group of LLD patients.

In the MCI/dementia converters, cortical infarctions were more frequent compared to the cognitively intact LLD group. Cortical infarctions and LLD conversion to MCI/dementia is an unusual combination in the literature, but cortical infarctions have been associated with cerebral amyloid angiopathy (van den Brink Hilde et al., 2018) and vascular cognitive impairment (Ferro et al., 2017). To our knowledge, no other study has reported more cortical infarction at baseline in people with LLD who convert to MCI/dementia.

4.4 Clinical implications

This study shows that there are differences in type and frequency of MRI findings between LLD and controls and in LLD patients who convert to MCI/dementia versus those who remain cognitively stable/intact. These findings suggest that neuropathology plays a role in LLD and increases the risk of MCI/dementia conversion. This could have clinical implications as a subgroup of LLD patients with cortical infarctions on brain MRI will be at increased risk of MCI/dementia and could therefore be targeted as a group for future therapeutic treatments against cognitive decline. However, the Norwegian Directorate of Health does not recommend MRI/CT as a criterion for dementia diagnosis dementia in the new guidelines of 2019, but rather to exclude other organic disease or to decide subtype of dementia, "due to lack of research based evidence" (Helsedirektoratet, 2019). The results from this study indicate that brain MRI may have a clinical role in the diagnosis and prognostication in certain subgroups of patients at risk of dementia.

4.5 Limitations to this study

4.5.1 Study design

This study has several limitations, one of them being the study design. As this is an observational study, there is a high risk for possible unknown confounding factors interfering with the results.

There were several differences when it comes to the data collection between the LLD and control group as they were recruited in two independent projects. During examination, the two groups were not examined with the exact same clinical variables nor questionnaires making some of the results prone to information bias. Therefore, we chose to exclude several interesting variables from the study because they could not be compared without probably interfering with the results.

Moreover, the controls were recruited from only two hospitals in the same health region in Norway, compared to 9 different hospitals and all health regions in the LLD group. This could have affected socioeconomic background or other demographic variables and hence the results. As the controls were selected from patients hospitalized for elective surgery, some could argue that they were not fit as a control group for participants with depression as they had other health issues as reason for their hospital stay. A recent study found that popular screening tools for depression in the hospitals did not perform well in patients with geriatric cancer (Saracino et al., 2017). If patients in the control group were depressed, but this was not uncovered, this might imply that depression due to somatic disease and LLD is differently linked to brain pathology.

Depression affects cognition, however there are no validated cognitive assessment tools to use in a depressed population (Bakkour et al., 2014). A recent study reported that The Montreal Cognitive Assessment (MoCA), a screening tool for assessing global cognitive performance, could also be used for depressed patients (Srisurapanont et al., 2017). Still, insights into the role of depression on MMSE could not be found when searching through the literature.

Late-life depression is often divided into early onset depression (EOD) and late onset depression (LOD), but we did not differentiate between these two groups in this study. Several studies on LLD and conversion to dementia have found clear evidence that there are differences in the risk of developing dementia related to the age of onset of the first depressive episode (Bennett and Thomas, 2014; Lebedeva et al., 2015; Silva et al., 2013). This temporal difference also affects frequency of WMH severity (Salo et al., 2019). Not distinguishing between EOD and LOD might have affected the results related to MRI findings in the LLD compared to the control group, and in the MCI/dementia conversion analysis.

4.5.2 MRI

As this is a multi-center study, our MRI data were collected with scanners from different vendors and with different field strengths. In comparison, every participant in the control group was scanned with the same MRI machine at one of the MRI centers, resulting in homogenous MRI-scan data from this group. To harmonize the LLD patients' scans between sites, the MRI parameters varied (see Supplementary Table 1). Image quality did also vary (Nakken, 2011), making specific findings impossible to report from some individuals (see Table 3 & 4). This problem is common to most multi-center MRI studies.

The use of visual rating scales to assess atrophy and WMH is debated (Rhodius-Meester et al., 2017). They are subjective and affected by the readers' experience and should be interpreted with reference to a patient's gender and age. However, it is an accessible and fast method used in daily practice that can be used on even suboptimal images, making it preferable in studies with different scanners, image quality and field strength such as the PRODE study.

4.5.3 3-year follow-up

At 3-year follow-up, all diagnoses concerning cognitive impairment and dementia were grouped into one single variable, MCI/dementia. This was mostly due to the assessment of dementia subtype being

difficult to do by phone interview, resulting in several patients with the diagnosis "unspecified dementia". The relationship between depression and dementia has been considered to be different depending on the dementia subtype (Barnes et al., 2012; Diniz et al., 2013). The merging of different dementia subtypes might have interfered with our results.

4.6 Strengths

The study design had several strengths such as few exclusion criteria (avoiding selection bias), a rather large cohort from several different regions in Norway and long follow-up period (3 years). The LLD group is believed to be representative for LLD patients admitted to specialist health care (Borza, 2016). The results from this study could therefore reflect the actual situation for depressed elderly in old-age psychiatric wards in Norway.

The MRI readings were of high quality. All MRI images were harmonized before they were scored by two neuroradiologists independently before reaching consensus. Inter-site reliability for the centers was estimated using intra-class correlation coefficient (ICC) and were found to be high across the centers (Lebedeva et al., 2017).

The questionnaires and visual rating scales used in this study are widely used in the field and well validated (see above).

The diagnosis of MCI/dementia at 3-year follow-up was carefully performed. Three specialists in old-age psychiatry independently diagnosed the patients before reaching a consensus together.

5 Conclusion

In this study we found using clinically validated visual rating scales, that there are specific neuroanatomical MRI findings which are more common in people with LLD compared to controls with somatic disease, and one finding that are more common in those who convert to MCI/dementia compared to those who remain cognitively intact. Firstly, WMH, an expression of cerebral small vessel disease, proved to be more frequent in LLD, in line with existing literature and our first hypothesis. Atrophy and stroke were not more common in LLD. Indeed, frontal cortical atrophy was significantly more prominent in the control group. This was an unexpected result. Secondly, cerebral small vessel disease was not more common in the LLD patients who converted to MCI/dementia compared to in

those who stayed cognitively intact which was contrary to our prediction (see chapter 1.6). The MCI/dementia converters did however have a higher presence of cortical infarctions. More frequent cortical infarctions in people with LLD who convert to MCI/dementia has not been reported before and future research is needed to prove if this association is a coincidence or not.

Having LLD is a serious health risk in many ways, and greatly increases the risk of developing dementia. In this study, 50% of the LLD participants had MCI/Dementia after 3 years. By today's knowledge, an MRI scan of every patient with LLD to predict conversion to MCI or dementia would not be reasonable. There is still no agreement into which neuroanatomical changes and/or neuroradiological assessment tools, that would be the best to use in LLD patients to predict conversion to MCI/dementia. The current findings suggest that clinical readings uncovering standard neurobiological findings such as cortical infarctions may be more relevant than previously thought. To understand the pathological mechanisms behind MCI/dementia conversion, insights into what differentiates the brain in people with LLD from normal aging, and on the pathology and physiology preceding conversion in people with LLD versus those in other older adults is needed. Studies implementing PET (e.g. amyloid, glucose metabolism), SPECT (e.g. regional blood flow), fMRI and/or cerebrovascular spinal fluid samples could provide such data.

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7 Supplementary table

Supplementary Table 1 *MRI scan parameters for each center included in the PRODE study*

Center N	Location	Scanner	Antenna type	Patients (n) Total = 95	Controls (n) Total = 111	MFS (Tesla)	TR[1] (ms)	TE[1] (ms)
1	Ullevål universitetssykehus	Siemens Avanto	12-channel headcoil	12	111	1.5	2400	3.79
2	Diakonhjemmet	GE Signa	8-channel headcoil	1	0	1.5	7.61	3.32
3	Hukommelsesklinikken	Siemens Avanto	12-channel headcoil	3	0	1.5	1900	3.1
4	Elverum	Siemens Symphony	8-channel headcoil	21	0	1.5	2010	3.93
5	Gjøvik	Siemens Avanto	12-channel headcoil	3	0	1.5	2400	3.79
6	Drammen sykehus (Vestre Viken)	Siemens Avanto	12-channel headcoil	35	0	1.5	1900	2.91
7	Stavanger	Philips Intera	6-channel headcoil	3	0	1.5	6.94-8.58	3.18-3.99
9	St. Olav's Hospital	Siemens Avanto	12-channel headcoil	14	0	1.5	2400	3.61
11	Haukeland	Siemens Symphony Vision	CP headcoil	5	0	1.5	2400	2.88
12	St. Olav's Hospital	Phillips Intera	8-channel headcoil	7	0	3	6.73	3.11

Abbreviations: GE, general electric; CP, circular polarized; MFS, magnetic field strength; TR, Repetition time; TE, Echo time.
[1]TR and TE is for the T1 3D sequence

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