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Research paper

The course of depressive symptoms in Lewy body dementia and Alzheimer's disease

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ABSTRACT

Background: Depressive symptoms frequently affect patients with neurocognitive disorders. In cross-sectional studies, patients with Lewy body dementia (DLB) showed higher levels of depressive symptoms than those with Alzheimer's disease (AD). We here describe the 5 year course of depressive symptoms in patients with DLB and AD.
Methods: Secondary analysis of a dementia study in Western Norway (DemVest) longitudinal cohort study.
Setting: This multicenter study was conducted in memory clinics in Western Norway. 187 patients newly diagnosed with AD ($n = 111$) and DLB ($n = 76$) were followed up annually for 5 years. Depressive symptoms were assessed using the Montgomery Åsberg Depression Rating Scale (MADRS). MADRS subclusters dysphoria, retardation, vegetative, anhedonia were analyzed. The impact of proximity of death and the role of risk factors for depression and dementia on the course of depressive symptoms were evaluated.
Results: We observed continuously increasing mean levels of depressive symptoms in DLB, while patients with AD showed a delayed increase at later follow-up visits. Increase in MADRS total score was mainly driven by increases in the anhedonia and retardation subclusters. Proximity to death was associated with an increase in depressive symptoms in DLB, while it tended to decrease in AD. Previous smoking and hearing loss were associated with higher MADRS scores during follow-up in the total sample.
Limitations: Yearly assessment of depressive symptoms might be too infrequent.
Conclusion: Depressive symptom load was consistently higher in DLB compared to AD during five years after diagnosis, but tended to become more similar at later stages.

1. Introduction

Emotional, cognitive, physical, and behavioral symptoms of depression are more frequent in patients with dementia than in the general population (Leung et al., 2021). Depressive symptoms can have a significant clinical impact. In addition to its negative effects on emotional wellbeing, even a subclinical trajectory of symptoms is associated with poor health-related outcomes, such as low quality of life and disability (de la Torre-Luque et al., 2019; van de Beek et al., 2019). Depressive symptoms also accelerate cognitive deterioration (Ly et al., 2021; Piras et al., 2021) and increase morbidity and mortality risk (Schulz et al., 2002).

Depression in the context of neurodegenerative diseases is a heterogeneous clinical syndrome, and psychosocial and biological processes contributing to depressive symptoms are varied and complex. There is an overlap between affective disorders and age-related and dementia-related symptoms. Several overlapping pathophysiological substrates explain comorbidities (Linnemann and Lang, 2020).

The prevalence of depressive symptoms differs among neurodegenerative diseases. In a recent meta-analysis, the mean prevalence of depression in people with different types of dementia was 20 % in Alzheimer's disease (AD) and 28 % in dementia with Lewy bodies (DLB) compared to 13 % in the general community (Kuring et al., 2018).

A higher prevalence of depressive symptoms has also been shown in

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studies directly comparing DLB and AD (Andreasen et al., 2014; Chiu et al., 2017; Fritze et al., 2011b). As disease progression in neurodegenerative diseases is heterogeneous and neuropsychiatric symptoms tend to fluctuate (Vik-Mo et al., 2020), longitudinal studies offer advantages for assessing symptom development over time.

Few longitudinal studies of depression in dementia exist, in particular in DLB. Our group previously reported a 1-year follow-up of a patient sample (included in the DemVest study) and comparison of depressive symptoms between AD and combined DLB/PD with dementia (PDD) groups (Fritze et al., 2011a). At baseline, depression was more common and more severe in DLB than in AD (Fritze et al., 2011b). At follow-up, the proportion of patients with persistent depression (defined by a score above 6 on the MADRS was higher in the combined DLB/PDD group (45.5 %) than in the AD group (28 %) (Fritze et al., 2011a).

Survival after diagnosis of dementia varies between individuals. Though DLB is associated with faster disease progression and shorter survival compared to AD (Liang et al., 2021). In the general population, depressive symptoms have been shown to increase in the proximity of death, especially in the last years of life (Kozlov et al., 2020; Diegelmann et al., 2016; Schilling et al., 2018; Raab et al., 2018).

Risk factors for both depressive symptoms and cognitive disorders include lifestyle factors (such as smoking) and physical illnesses (such as hearing loss, cardiovascular disease, cerebrovascular disease, and traumatic brain injury among others) (Gold et al., 2020b; Kivipelto et al., 2018; Lawrence et al., 2019; Livingston et al., 2020; Santiago and Potashkin, 2021; Vyas and Okereke, 2020). Potentially modifiable risk factors are of relevance for prevention strategies. Though, the impact of risk factors on the course of depressive symptoms in dementia patients is not well understood.

The long-term courses (5 and 12 years) of neuropsychiatric symptoms (NPS) of the same patient sample comparing AD to DLB have been described previously (Vik-Mo et al., 2018; Vik-Mo et al., 2020). The depression domain of the neuropsychiatric inventory revealed no difference between the groups (Vik-Mo et al., 2018), but it assesses only mood-related items (Major et al., 2022). To our knowledge, no study has focused on a detailed assessment of the long-term course of depressive symptoms in DLB compared to AD. This is of great clinical importance as depressive symptoms are strongly associated with the patient's well-being, are known as accelerators of cognitive decline in dementia (Helvik et al., 2019; Rapp et al., 2011), and have great impact on functioning (Wu et al., 2021). Better knowledge of the course of depressive symptoms in neurodegenerative disease may facilitate assessment and treatment of patients. Treatment of depressive symptoms, especially by non-pharmacological interventions, can improve quality of life in people with dementia (Kishita et al., 2020).

The aims and hypotheses of this study were:

1) to evaluate the yearly assessments of depressive symptoms and specific domains in a cohort of patients with AD and DLB. We hypothesized that the burden of depressive symptoms would be higher in patients with DLB and that the differences between the groups remain over time.
2) to compare the depressive symptoms between AD and DLB patients from a time-to-death perspective. Comparing symptoms of patients who are the same proximity to death may yield different insight than comparing patients at the same time after inclusion in the study. We hypothesized that proximity to death would lead to increased levels of depressive symptoms.
3) to evaluate the effect of established risk factors of depression on the course of depressive symptoms. We hypothesized that these would be associated with increased depressive symptom load in both disorders.

2. Methods

2.1. Study participants

The dementia study of Western Norway (DemVest) is a longitudinal cohort study of patients with mild dementia who were assessed annually. Briefly, patients with mild dementia, defined as an MMSE score of at least 20 and a Clinical Dementia Rating scale score of at least one, were included. Exclusion criteria were absence of dementia, moderate or severe dementia, acute delirium, previous bipolar or psychotic spectrum disorder, terminal illness, or major somatic illness. More details of the DemVest study are provided elsewhere (Aarsland et al., 2008).

Dementia was diagnosed at the time of study inclusion according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition: DSM-IV) criteria based on structured interviews, clinical examination, standardized neuropsychological tests, and a neuropsychiatric assessment. Routine blood work, including the assessment of thyroid function and vitamin B12 status, was performed. Structural magnetic resonance imaging of the brain was used to rule out other causes of dementia such as tumors. The diagnosis of DLB was supported by dopamine transport imaging in a subgroup of patients with suspected DLB ($n = 41$). Neuropathological diagnosis after autopsy is available in 56 subjects of the DemVest cohort. Clinical diagnosis of DLB according 2005 consensus criteria had a sensivity of 73 % and specifity of 93 %. The sensitivity and specificity of a clinical diagnosis of AD were 81 % and 88 %, respectively (Skogseth et al., 2017). The final diagnosis, used for the current analysis, was determined through the consensus of a group of clinical specialists in neurology, psychiatry, and geriatric medicine, and neuropathological confirmation when available. From the original cohort of 223 patients, we included in this study 188 patients with completed MADRS assessment, a total of 111 participants with AD and 76 with DLB. We did not include patients with other cognitive disorders.

2.2. Assessment

Depressive symptoms: The Montgomery-Åsberg Depression Rating Scale (MADRS) was scored at baseline and annually. In this study, data from baseline and the first four consecutive yearly follow-ups were used.

A MADRS cut-off score of $\geq$14 showed acceptable sensitivity and specificity and is considered useful for assessing depression according to DSM-IV and ICD-10 criteria in elderly patients with and without dementia (Engedal et al., 2012; Leontjevas et al., 2009).

As the sum score may only reveal limited information on the individual symptom profile (Fried and Nesse, 2015), the analysis of previously defined MADRS item clusters (such as dysphoria, retardation, vegetative, and anhedonia subclusters) is used to dissect the depressive syndrome (Cao et al., 2019; Suzuki et al., 2005). MADRS item clusters were assessed as follows:

Dysphoria: items 2 (reported sadness), 9 (pessimistic thoughts), and 10 (suicidal thoughts).

Retardation: items 1 (apparent sadness), 6 (concentration difficulties), 7 (lassitude), 8 (inability to feel).

Vegetative: items 3 (inner tension), 4 (reduced sleep), 5 (reduced appetite).

Anhedonia: items 5 (reduced appetite), 7 (lassitude), 8 (inability to feel), 10 (suicidal thoughts).

Survival: Date of death was assessed regularly after inclusion through obtaining information from the Norwegian patient registry. To match the observation period for MADRS, we defined end of study with regard to survival as 1 year after the last observation of MADRS, i.e. 6.37 years.

Risk factors: At baseline subjects underwent a comprehensive evaluation and collection of data, as described in detail elsewhere (Aarsland et al., 2008). Subjects were classified as having or not having the following risk factors: Smoking habits (never/current/previous),

hearing loss, history of stroke, cardiac disease, head injury with loss of consciousness, other psychiatric disorder with treatment, presence of depressive symptoms at onset of cognitive decline, antidepressant treatment at baseline and presence of white matter hyperintensities (WMH).

2.3. Ethics

The Regional Committee for Medical and Health Research Ethics approved the study and a later notification detailing the use of biomarkers (REC number: 2010/633). The participants provided written consent after the study was explained in detail to them in the presence of a family member.

2.4. Statistical methods

All analyses were performed using Stata version 17. Descriptive statistics are presented as median (interquartile range) for continuous variables and as count (percentage, %) for categorical variables. The proportion of clinically relevant depression over time was assessed using logistic regression models, with robust estimation of standard errors allowing for the clustering of data. Time to death was illustrated using Kaplan-Meier plots.

The observed longitudinal development of depressive symptoms was illustrated in spaghetti plots. The longitudinal development was modelled using mixed models, with time, diagnosis group, and their interaction as fixed effects and with random intercepts and random slopes for time. Restricted cubic splines (3 knots) were used to allow for a nonlinear fixed effect of time. The impact of dropouts due to death was adjusted for using joint models with the effect of time on longitudinal depressive symptoms modelled parametrically with a linear and a quadratic component, and with a Weibull model for time to death, with risk depending on the current value of depressive symptoms. The diagnostic group was a covariate in both the longitudinal and survival submodels. Other covariates (risk factors) were entered similarly, and we present estimated differences with 95 % confidence interval and Wald *p*-value, and a *p*-value for the difference in longitudinal development assessed by the interactions between time (in linear and quadratic terms) and covariates. The interaction terms were tested simultaneously using likelihood ratio tests. For covariates where longitudinal developments were found to be different, the results are illustrated in prediction plots. For the risk factors, we present results for all patients, as well as those stratified by diagnosis group.

We used 'logit' with option 'vce(cluster)' for logistic regression, 'mixed' for mixed models, 'stjm' for joint modelling. Predicted proportions/means were estimated using 'margins' and plotted using 'marginsplot', apart from predictions from joint models which were plotted manually in R. The development of depressive symptoms in the years approaching death was assessed using 'stjmgraph'.

The interpretation of the longitudinal predictions from the joint model is the expected development if no one would die (Rizopoulos, 2012), whereas for the mixed model, where the dropout process is implicitly assumed independent of the longitudinal process (missing at random), the interpretation is unclear if this assumption is not correct.

3. Results

A total of 188 participants, of which 111 with AD and 76 with DLB, have been included in the analysis. Demographic and clinical information split by diagnostic group is available in Table 1. Both groups show similar baseline characteristics regarding age, years of education and body mass index. Distribution of risk factors show higher numbers of hearing loss, other previous psychiatric treatment and presence of depressive symptoms at onset of cognitive decline in patients with DLB. WMH were more frequent in AD patients.

Dropout of participants resulted mainly from death, with very few lost to follow-up or withdrawal. Patients with DLB had shorter survival than those with AD ($p < 0.001$, log-rank test). By the end of the study (6.37 years), 35 of 76 DLB (52 %) patients had died, compared with 27 of 111 AD (24 %) patients (see Supplementary Fig. S1).

Table 1
Characteristics of the study sample.

	ALL ($n = 187$)	AD ($n = 111$)	DLB ($n = 76$)
Centre			
Bergen	51 (27 %)	37 (33 %)	14 (18 %)
Haugesund	50 (27 %)	22 (20 %)	28 (37 %)
Stavanger	86 (46 %)	52 (47 %)	34 (45 %)
Males	72 (39 %)	32 (29 %)	40 (53 %)
Age (years)	77 (71, 81)	77 (71, 81)	77 (73, 81)
Education (years)	9 (7, 11)$^{n=183}$	9 (7, 11)	9 (7, 11)$^{n=72}$
BMI	24 (22, 27)$^{n=166}$	24 (21, 27)$^{n=102}$	24 (22, 28)$^{n=64}$
Smoking ($n = 176$)			
Never	92 (52 %)	57 (54 %)	35 (49 %)
Current	35 (20 %)	23 (22 %)	12 (17 %)
Previous	49 (28 %)	25 (24 %)	24 (34 %)
Hearing loss	54 (30 %)$^{n=181}$	25 (23 %)$^{n=110}$	29 (41 %)$^{n=71}$
Stroke	16 (9 %)$^{n=180}$	9 (8 %)$^{n=106}$	7 (9 %)$^{n=74}$
Cardiac disease	51 (28 %)$^{n=179}$	26 (25 %)$^{n=106}$	25 (34 %)$^{n=73}$
Head trauma	18 (10 %)$^{n=176}$	10 (10 %)$^{n=105}$	8 (11 %)$^{n=71}$
Other psychiatric disorder treatment	17 (10 %)$^{n=174}$	6 (6 %)$^{n=103}$	11 (15 %)$^{n=71}$
WMH	65 (35 %)	52 (47 %)	13 (17 %)
Depression at onset	54 (30 %)$^{n=179}$	28 (25 %)$^{n=110}$	26 (38 %)$^{n=69}$
Treatment for depression	60 (33 %)$^{n=181}$	35 (32 %)$^{n=109}$	25 (35 %)$^{n=72}$

Descriptive statistics are presented as median (interquartile range) for continuous variables and count (%) for categorical variables. The number of observed cases is indicated if less than the total number.
AD: Alzheimer's disease; DLB: dementia with Lewy bodies; BMI: body mass index; WMH: white matter hyperintensities.

3.1. MADRS sum scores and proportion of clinically depression

The spaghetti plots in Fig. 1 shows the individual trajectories of MADRS sum scores in both groups. It shows heterogeneous individual trajectories in both groups, with rather stable courses but also with marked changes between follow-ups. It visualizes a larger proportion of stably low MADRS scores in AD patients during early follow-ups.

The proportion of patients scoring over a cut-off MADRS ≥14 was higher in DLB than in AD during the first 2 follow-ups (Supplementary Fig. S2). At follow-up 2, 30 % of DLB patients scored over the cut-off MADRS ≥14, compared to 14 % of AD patients. At follow-up 3 and 4 the proportion of patients with DLB scoring ≥14 decreased. The proportion remains lower in patients with AD during the first 3 follow-ups, showing an increase between follow-up 3 and 4.

Of the patients scoring MADRS ≥14, we assessed how many remitted (defined by MADRS <10) at a later follow-up. A total of 28 % of patients with AD and 26 % of patients with DLB remitted. Persistent depression (defined by MADRS ≥10 after an earlier score ≥ 14) showed 31 % of patients with AD and 41 % of patients with DLB. 31 % of AD and 30 % of DLB cases were not assessed again at later follow-ups after scoring MADRS ≥14.

In the mixed linear model, the predicted MADRS scores were higher for DLB than for AD at baseline (mean difference 2.2, 95 % CI 0.5 to 3.8; $p = 0.009$), but the changes over time were not statistically different between the diagnostic groups ($p = 0.48$). The predicted mean evolutions are plotted in Fig. 2a, which shows increasing variance at later time points, particularly in the DLB group, due to less patients remaining in the study. Findings were similar when accounting for dropout due to

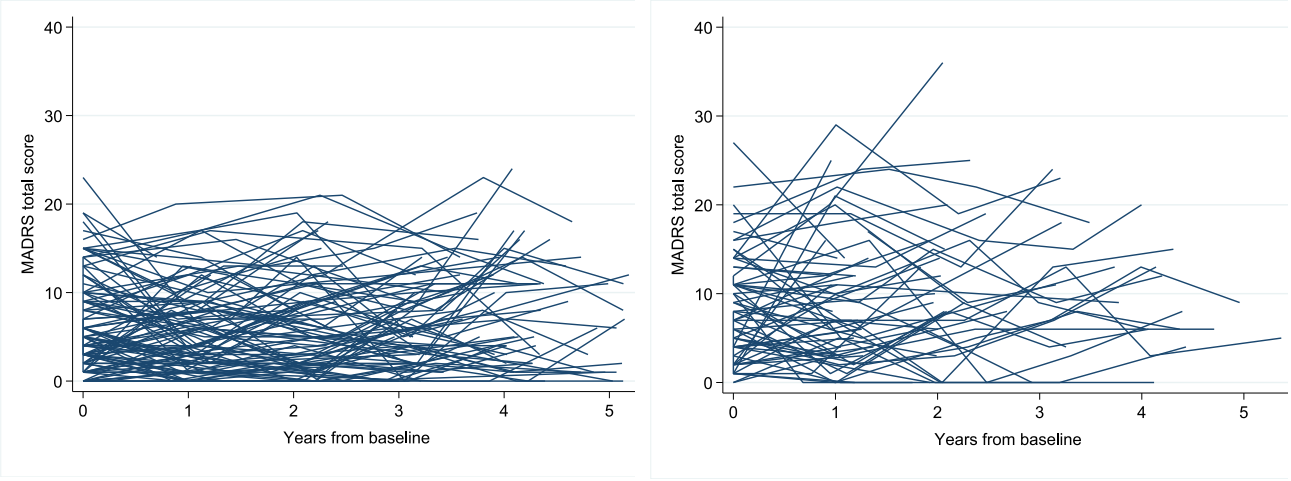

Fig. 1. Observed MADRS total score trajectories throughout up to 5.37 years of follow-up from diagnosis of a) Alzheimer's disease ($n = 108$) and b) dementia with Lewy bodies ($n = 70$) in the DemVest study. Patients with only one observation of MADRS were not included in the plots.

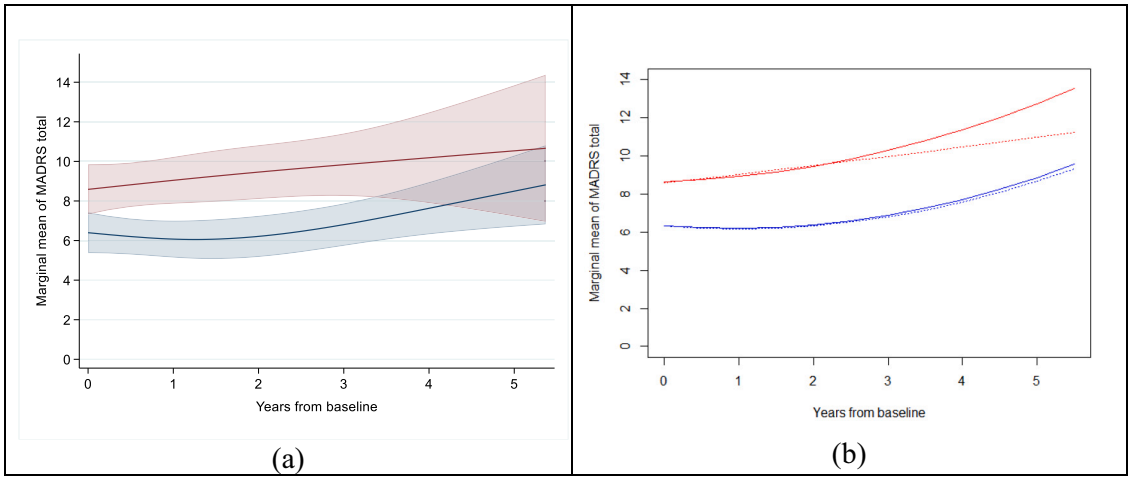

Fig. 2. Predicted mean levels of MADRS total throughout up to 5.37 years of follow-up from diagnosis for Alzheimer's disease ($n = 111$, blue) and dementia with Lewy bodies ($n = 76$, red) in the DemVest study. a) Longitudinal measures of MADRS modelled using a mixed linear model including fixed effect of time (modelled non-linearly using restricted cubic splines with 3 knots) and random intercepts and random effect of time. Shaded areas illustrate 95 % confidence bands. b) Allowing for non-random dropout using a joint model (solid) vs. the same mixed model as in plot (a) (dotted), however with fixed effect of time modelled using a quadratic polynomial. MADRS: Montgomery-Aasberg depression rating scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

death.

3.2. Development of depressive symptoms approaching death

Rescaling the assessment times relative to time of death or censoring, we see higher levels of MADRS in those who died than in those who survived (Fig. 3a). In the joint modelling analysis, we found a significant association between the longitudinal MADRS score and time to death ($p = 0.011$), indicating that a one-unit increase in MADRS is associated with 8 % higher risk of death (HR 1.08, 95 % CI 1.02–1.14). The association was similar in AD and DLB ($p = 0.76$) (Fig. 3b–c).

3.3. Symptom clusters of depressive symptoms

Prediction plots of dysphoria, retardation, vegetative, and anhedonia symptoms clusters are displayed in Fig. 4. Dysphoria did not show any marked changes over time. Levels were slightly higher in DLB, but tended to decrease at later follow-ups. Results from joint models showed a statistically significant difference at baseline (mean difference 0.2, 95 % CI 0.0 to 0.4; $p = 0.040$), non-significant change over time for AD ($p = 0.45$) and no difference in changes over time between AD and DLB ($p = 0.47$). Retardation levels were higher in DLB (mean difference at baseline 0.3, 95 % CI 0.1 to 0.5; $p = 0.015$) and markedly increased in both groups (test of effect of time in AD, $p < 0.001$; test of difference in evolution, $p = 0.30$). The vegetative subcluster levels were slightly higher in DLB (mean difference at baseline 0.2, 95 % CI 0.0 to 0.4; $p = 0.031$), with no changes over time in either group ($p = 0.64$ for AD; $p = 0.50$ for difference in mean trajectories). Finally, for anhedonia, scores were again higher in DLB (mean difference at baseline 0.2, 95 % CI 0.0 to 0.5; $p = 0.027$) and with increasing levels in both groups ($p = 0.005$ for AD; no significantly difference in mean development from baseline between the groups, $p = 0.39$).

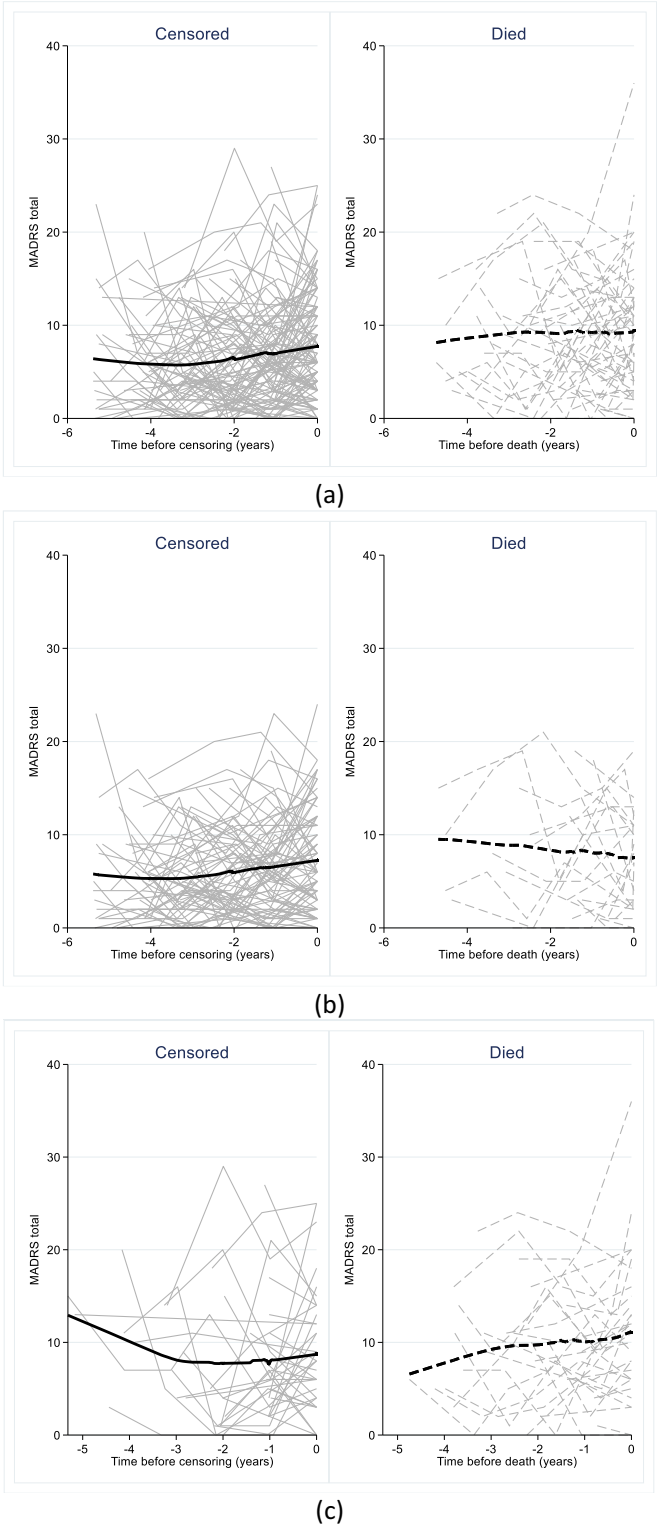

Fig. 3. Observed MADRS total scores in the time approaching censoring (left panels) and death (right panels) for a) the total sample ($n = 187$; 62 deaths), b) Alzheimer's disease ($n = 111$; 27 deaths) and c) dementia with Lewy bodies ($n = 76$; 35 deaths) in the DemVest study. MADRS: Montgomery-Aasberg depression rating scale.

3.4. Risk factor analysis

We analyzed the impact of different established risk factors on the levels and course of depressive symptoms over time in general and for AD and DLB separately (see Table 2).

Previous smoking and hearing loss at baseline were associated with higher MADRS scores during follow-up in the total sample.

In AD, current smoking status, hearing loss, depressive symptoms during the onset of cognitive impairment, and antidepressant treatment at inclusion were significantly associated with more severe depressive symptoms. For head trauma, we found statistically significant difference in changes over time in MADRS total score ($p = 0.006$). Fig. 5a showing an approximately linear, slight increase over time for those without head trauma, and an initial decrease followed by a more steep increase for those with head trauma.

In DLB only cardiac disease was significantly associated with depression ($p = 0.038$; see Fig. 5b).

Finally, we found a statistically significant association between presence of WMH and fewer depressive symptoms. Patients with WMH had stable, low depressive symptoms, while those without experienced increased depressive symptoms over time (see Fig. 5c).

We conducted a sensitivity analysis on a subgroup of participants who did not have WMH at baseline ($n = 112$; AD 59, DLB 63) and found in AD without WMH a marked increase in MADRS levels after the one-year follow-up. Increases in the retardation and anhedonia subclusters were again the main drivers of the increase in mean MADRS levels, with no significant differences between the diagnostic groups. Furthermore, the proportion of patients with clinically significant depression was >20 % at FU 2 and 3 (see Fig. S4). In our investigation of the baseline risk factors' association with depressive symptoms over a five-year follow-up period, hearing loss ($p = 0.003$) and current smoking ($p = 0.027$) were significantly associated with increased depression levels in AD. Rescaling the assessment times relative to time of death or censoring, in the joint modelling analysis, we did not find a significant association between the longitudinal MADRS score and time to death ($p = 0.16$).

Sensitivity analysis of patients who did not display depressive symptoms at the onset of cognitive decline and were not on antidepressant medication at baseline ($n = 95$; AD 65, DLB 30). AD and DLB showed similar distinctions in this subgroup when compared to the entire sample, although AD patients generally had lower levels of depressive symptoms. Only a small number of AD patients showed MADRS scores indicative of clinically significant depression, in contrast to DLB (refer to Fig. S5). Our analysis of the depressive symptom subclusters demonstrated a comparable longitudinal pattern to the entire sample, with the most pronounced change being an increase in retardation levels in both AD and DLB. When the assessment times were rescaled relative to the time of death or censoring, our subsample analysis indicated no significant association between the longitudinal MADRS score and time to death in the joint modelling analysis ($p = 0.75$), contrasting with the entire sample analysis. In our investigation of the baseline risk factors' association with depressive symptoms over a five-year follow-up period, we identified a significant relationship between hearing loss and depressive symptoms in all patients within the subgroup ($p = 0.014$). Moreover, this relationship reached statistical significance also in the DLB patients of the subgroup ($p < 0.001$). However, we did not observe a significant association with WMH in the subsample ($p = 0.4$), despite it being significant in the entire sample.

4. Discussion

In one of the few longitudinal studies of depression in DLB, we found that patients with DLB had higher baselines MADRS scores and showed a continuous increase, while an increase occurred later in patients with AD. The increase was mainly in the retardation and anhedonia symptom clusters, whereas dysphoria scores remained stable. The mood related items of the dysphoria cluster (reported sadness, pessimistic thoughts, and suicidal thoughts) represent more specific depressive symptoms, while items in the retardation and anhedonia cluster might be in a higher degree also affected by dementia- or aging related disease processes. It is possible that the higher levels of anhedonia and retardation

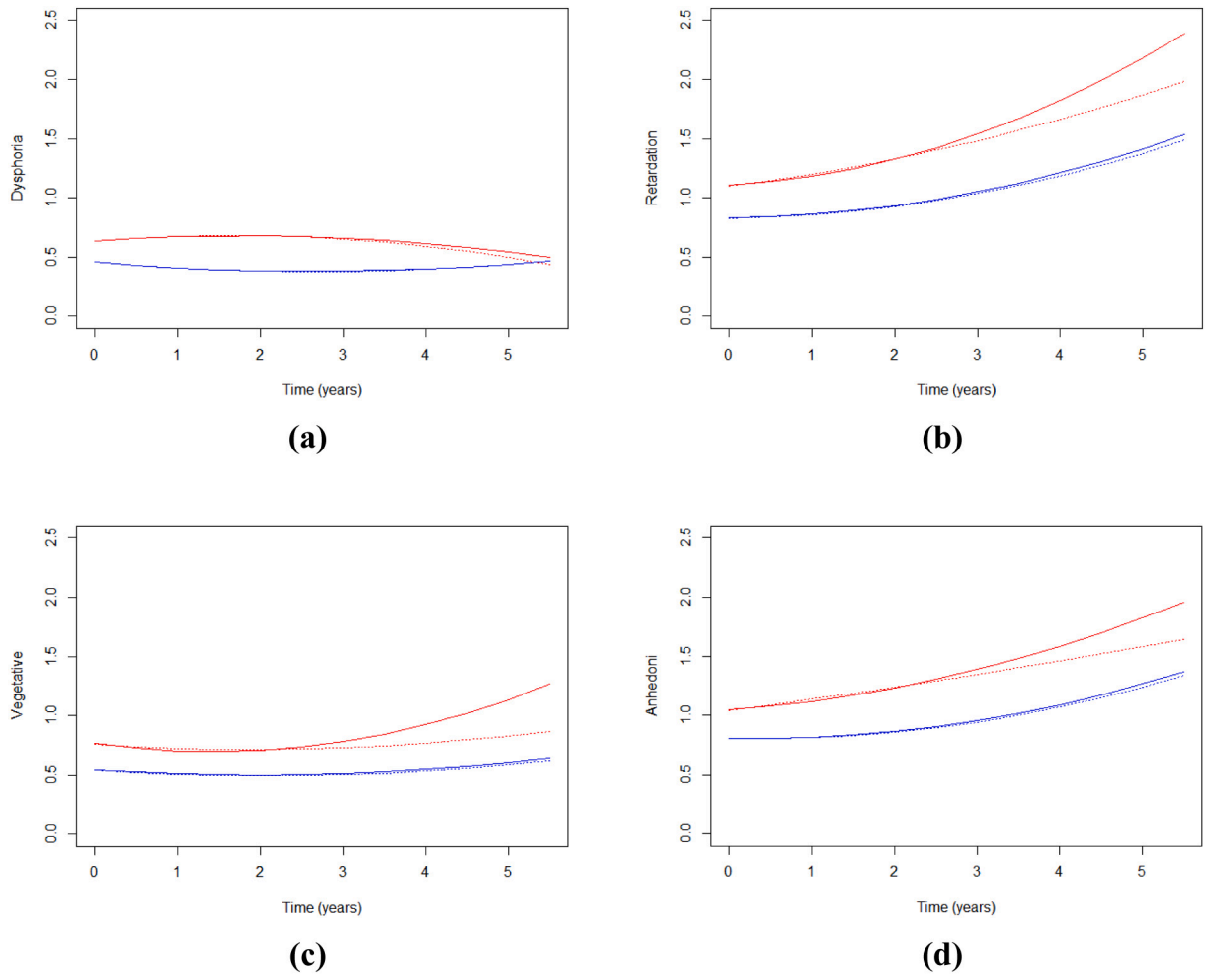

Fig. 4. Predicted mean levels of a) dysphoria, b) retardation, c) vegetative and d) anhedonia subdomains of MADRS throughout five years of follow-up from diagnosis of Alzheimer's disease (n = 111, blue) and Dementia with Lewy bodies (n = 76, red) in the DemVest study. Solid lines: Results from joint models of repeated measures of depressive symptoms and time to death. The longitudinal submodel is a mixed linear model including fixed effect of time (modelled non-linearly using a quadratic polynomial) and random intercepts and random effect of time. Dotted lines: Corresponding results from the same mixed linear models when not adjusting for non-random dropout due to death. MADRS: Montgomery-Aasberg depression rating scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in DLB compared to AD may be partially accounted for by the non-cognitive symptoms associated with DLB, such as parkinsonism (bradykinesia) and involvement of the peripheral autonomic nervous system. This underlines the importance of the analysis of individual symptoms and their causal associations, as sum-scores can obfuscate important insights (Fried and Nesse, 2015).

Very few studies have explored the symptom clusters, but an earlier study also reported that pervasive anhedonia showed the highest ORs for the diagnosis of DLB compared with AD (Chiu et al., 2017).

As we reported earlier in the same cohort, after 1 year, the proportion of patients with persistent depression was higher in the DLB/PDD group (45.5 %) than in the AD group (28 %) (Fritze et al., 2011a). Though, we didn't include patients with Parkinson's disease dementia in this analysis. Other studies have reported a decrease in depression over time in AD (Borza et al., 2015; Helvik et al., 2019). During the first 3 years, we found lower proportions of patients scoring MADRS ≥14 in AD compared to DLB, but less difference at later follow-ups. Also means of total MADRS scores were closer in both groups at later follow-ups indicating a delayed increase in mean depressive symptoms in AD compared to DLB.

Of the AD patients who had no depressive symptoms at the onset of cognitive decline and were not using antidepressants at baseline only a small proportion had clinically significant depressive symptoms at later follow-up, whereas in DLB the proportion was high also in this specific subgroup.

As DLB is a more devastating disorder with faster progression, increasing symptom burden, and earlier death than AD (Mueller et al., 2017) we analyzed depressive symptoms backward from the point of death. Patients with DLB showed increasing depressive symptoms in proximity to death, but this was not the case for patients with AD.

Depressive symptoms show a significant relationship with established risk factors for depression such as previous smoking and hearing loss in AD, but not in DLB. Cardiac disease was the only factor associated with the severity of depressive symptoms in DLB. Though, in the subgroup of patients not depressed at onset of cognitive decline and not using antidepressants at baseline, association between hearing loss and depressive symptoms became significant also in DLB, strengthening the association between hearing loss and depressive symptoms.

We were surprised by the finding that WMH were significantly associated with fewer depressive symptoms in patients with AD. In addition, AD patients without WMH showed a marked increase in depressive symptoms after the one-year follow-up. This contradicts earlier findings that a greater white matter hyperintensity burden is associated with depression, which is also reflected by the high prevalence of depression in vascular dementia of 30 % (Kuring et al., 2018). In this study, we did not specify the severity or localization of the WMH.

Table 2
Associations between baseline risk factors and depressive symptoms (MADRS total) in dementia throughout five years of follow-up from diagnosis.

	ALL				AD				DLB			
	# obs/pat/death	β (95 % CI)	p^1	p^2	# obs/pat/death	β (95 % CI)	p^1	p^2	# obs/pat/death	β (95 % CI)	p^1	p^2
Sex	632/187/62	−0.6 (−2.1, 0.9)	0.43	0.25	418/111/27	−1.3 (−3.0, 0.5)	0.16	0.22	214/76/35	1.5 (−1.0, 4.0)	0.23	0.55
Age (years)	632/187/62	−0.0 (−0.1, 0.1)	0.41	0.56	418/111/27	−0.1 (−0.2, 0.0)	0.23	0.76	214/76/35	−0.0 (−0.2, 0.1)	0.64	0.73
Education (years)	624/183/60	−0.0 (−0.3, 0.2)	0.79	0.93	418/111/27	0.0 (−0.2, 0.3)	0.84	0.88	206/72/33	−0.1 (−0.6, 0.4)	0.63	0.69
BMI	572/166/50	−0.1 (−0.3, 0.0)	0.13	0.48	387/102/24	−0.1 (−0.3, 0.1)	0.18	0.59	185/64/26	−0.2 (−0.5, 0.1)	0.16	0.74
Smoking	598/176/56				400/105/24				198/71/32			
Current		1.6 (−0.3, 3.5)	0.10	0.81		2.6 (0.6, 4.6)	**0.011**	0.11		NA		
Previous		2.0 (0.2, 3.7)	**0.026**			0.8 (−1.2, 2.8)	0.44			NA		
Hearing loss	632/187/62	2.4 (0.8, 4.0)	**0.003**	0.13	418/111/27	2.3 (0.4, 4.2)	**0.017**	0.18	214/76/35	1.5 (−1.0, 4.1)	0.24	0.90
Stroke	612/180/59	−0.1 (−2.7, 2.4)	0.92	0.12	404/106/25	−0.6 (−3.5, 2.3)	0.71	0.42	208/74/34	−0.0 (−4.3, 4.2)	0.99	0.13
Cardiac disease	606/179/59	0.7 (−0.9, 2.4)	0.38	0.39	403/106/26	−0.1 (−2.0, 1.8)	0.94	0.44	203/73/33	*3.2 (0.2, 6.2)*	***0.035***	**0.038**
Head trauma	598/176/57	1.2 (−1.3, 3.7)	0.34	0.39	401/105/25	*3.1 (−0.3, 6.5)*	*0.071*	**0.006**	197/71/32	1.3 (−2.8, 5.5)	0.53	0.59
Other psychiatric disorder treatment	585/174/57	0.2 (−2.2, 2.7)	0.85	0.92	390/103/26	1.9 (−1.6, 5.4)	0.28	0.48	195/71/31	−1.8 (−5.3, 1.7)	0.31	0.71
WMH	632/187/62	*−1.8 (−3.5, −0.1)*	***0.043***	**0.019**	418/111/27	*−1.1 (−3.0, 0.8)*	*0.27*	**0.003**	214/76/35	−2.0 (−5.2, 1.3)	0.23	0.59
Depression at onset	616/179/59	2.4 (0.9, 4.0)	**0.002**	0.32	415/110/27	3.0 (1.3, 4.7)	**0.001**	0.076	201/69/32	0.6 (−2.1, 3.4)	0.65	0.49
Treatment for depression	612/181/59	2.4 (0.9, 3.9)	**0.001**	0.64	411/109/27	3.0 (1.3, 4.6)	**<0.001**	0.33	201/72/32	1.2 (−1.4, 3.9)	0.36	0.77

Results from the longitudinal submodels of joint models for repeated assessments of depressive symptoms and time to death. The presented estimates (β) are the mean difference between the trajectories of depressive symptoms, which is significantly different from zero if $p^1 < 0.05$. Statistically significant values are shown in bold ($p < 0.05$). Each baseline variable was assessed separately. p^2 signifies the *p*-value from a test of difference in changes over time (i.e. interaction between time variables and baseline variable). If p^2 non-significant, the presented results are from models without interaction term (i.e. assuming parallel developments), if $p^2 < 0.05$ the results are for differences at baseline (and shown in italic), and further illustrated in Fig. 5a–d.
MADRS: Montgomery-Aasberg depression rating scale; AD: Alzheimer's disease; DLB: dementia with Lewy bodies; # obs/pat/death: number of observations/patients/deaths included in each analysis; CI: confidence interval; BMI: body mass index; WMH: white matter hyperintensities; NA: not available due to non-convergence.

Associations between volumes of total and frontal deep WMH and depressive symptoms have been investigated in individuals of the same patient sample earlier (Soennesyn et al., 2012) showing that in particular frontal deep WMH were positively correlated with baseline severity of depressive symptoms, and seemed to be associated with persistent and incident depression at the year follow-up (Soennesyn et al., 2012). A meta-analysis reported that the impact of WMH on depressive symptoms is dependent on the localization and volume (Wang et al., 2014). Our results suggest that while WMH are a risk for depression and dementia, other factors, i.e. neurodegenerative changes, are more important than cerebrovascular disease for the course of depression.

Depression in the elderly and in the context of neurodegenerative diseases is a heterogeneous clinical syndrome, and the causal mechanisms contributing to these symptoms are varied and complex (Linnemann and Lang, 2020). Furthermore, it is likely that the relative contributions of the different factors vary over time. Not only neurodegenerative processes but also predisposing (e.g., personality styles), psychological (e.g., coping styles), and social factors (e.g., isolation) are of relevance. One might argue that living with a relatively rapidly progressing disease with frequent troublesome neuropsychiatric (e.g., hallucinations, sleep disorders, anxiety (Hynninen et al., 2012)), medical, and social consequences could contribute to higher allostatic load explaining more severe depressive symptoms in DLB than in AD (Bentley et al., 2021; Kobrosly et al., 2014). More research is needed to understand how different factors impact the course of depressive symptoms over time.

A major limitation of this study is the lack of a normal aging group as a comparison group and thus we cannot exclude the effect of aging itself on depressive symptoms. Other limitations include that yearly assessment of depressive symptoms might be too infrequent as interim changes can be missed. Although MADRS is considered a consistent tools for detecting depression in AD independently of the severity of dementia (Müller-Thomsen et al., 2005) the reliability of their subjective depressive feelings may decline as cognitive decline or loss of language becomes too severe. It is also described that a decline in cognitive functioning may be associated with decreases in patient–informant congruence and increases in rates of patients denying depressive symptoms when informants endorsed observing features of the same (Gold et al., 2020a). It is well known that combined AD and DLB neuropathology is common, especially at later disease stages (Gibson et al., 2023). Though, this might explain the approximation of depressive symptom severity between both groups. Finally, even though the DemVest study is one of the largest longitudinal studies including people with DLB, the sample sizes might still be too small, especially in DLB due to higher mortality rates, to detect associations between risk factors and depressive symptoms.

CRediT authorship contribution statement

Conception and design of study: BR, ID, DA.
Acquisition of data: DA.
Analysis and/or interpretation of data: ID, BR, DA.
Drafting the manuscript: BR.
Revising the manuscript critically for important intellectual content:

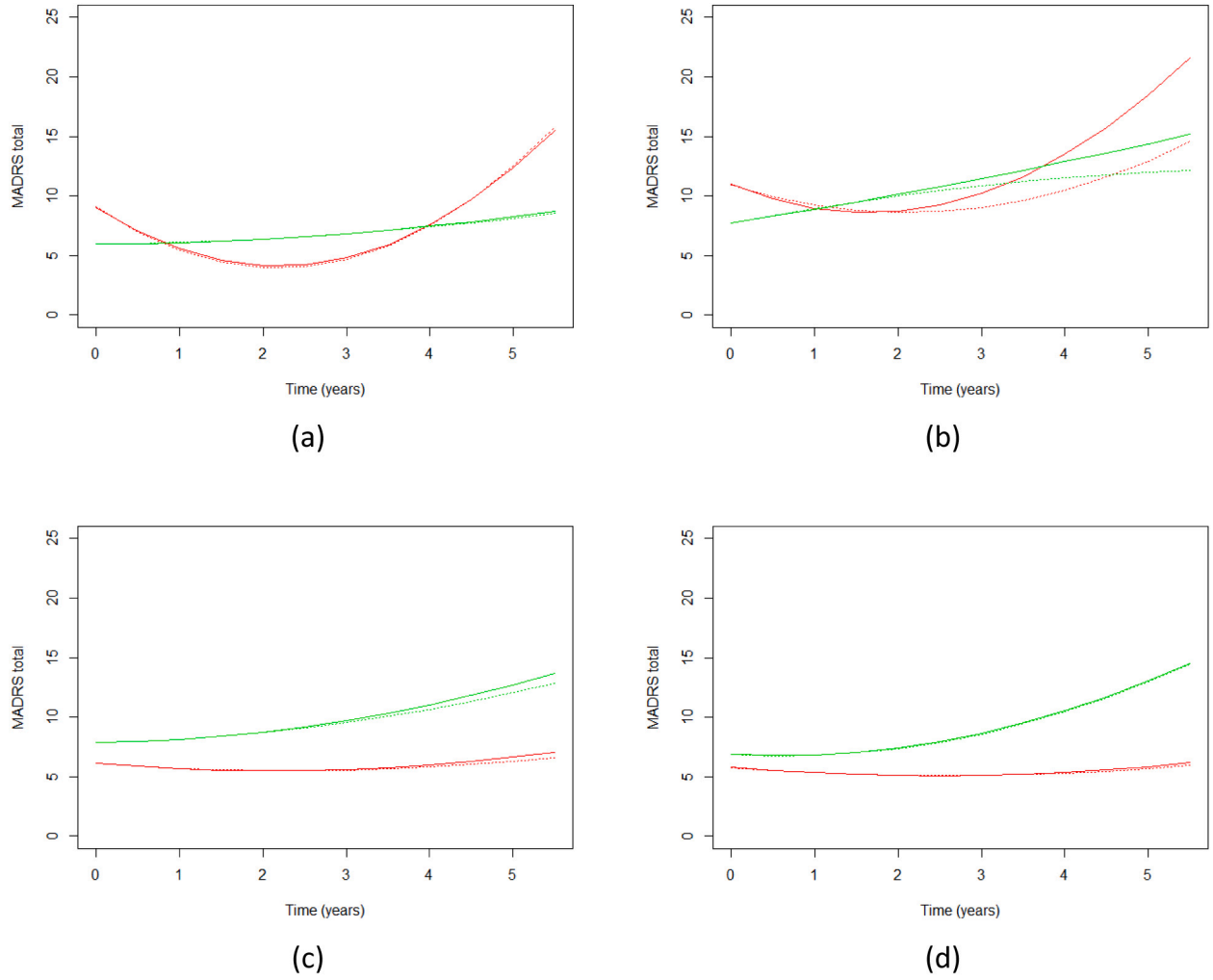

Fig. 5. Predicted mean MADRS total score over time for patients with (red) and without (green) the baseline risk factor. a) head trauma, AD patients ($n = 105$; 10 with head trauma); b) cardiac disease, DLB patients ($n = 73$; 25 with cardiac disease); c) WMH, all patients ($n = 187$; 65 with WMH); d) WMH, AD patients ($n = 111$; 52 with WMH). Solid lines: Results from joint models of repeated measures of MADRS and time to death. The longitudinal submodel is a mixed linear model including fixed effect of time (modelled non-linearly using a quadratic polynomial) and random intercepts and random effect of time. Dotted lines: Corresponding results from the same mixed linear models when not adjusting for non-random dropout due to death. See further details in Table 2. MADRS: Montgomery-Aasberg depression rating scale; WMH: white matter hyperintensities; AD: Alzheimer's disease; DLB: dementia with Lewy bodies. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Conflict of interest

DA has received research support or honorariums from Astra-Zeneca, H Lundbeck, Novartis Pharmaceuticals, Sanofi, Evonik, Roche Diagnostics, and GE Health; and served as paid consultant for H Lundbeck, Eisai, Heptares, Mentis Cura, Eli Lilly, Cognetivity, Enterin, Acadia, Sygnature, Biogen, Cognetivity, EIP Pharma, and Acadia.

The remaining authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.04.076.

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