Neurobiology of Aging 111 (2022) 14–23

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Depressive symptom profiles predict dementia onset and brain pathology in older persons. The AGES-Reykjavik study

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ARTICLE INFO

Article history:
Received 26 October 2020
Revised 6 September 2021
Accepted 7 September 2021
Available online 27 November 2021

Keywords:
late-life depression
dementia
Alzheimer's disease
hippocampus
white matter lesions

ABSTRACT

Late-life depression (LLD) increases risk for dementia and brain pathology, but possibly this is only true for one or more symptom profiles of LLD. In 4354 participants (76 ± 5 years; 58% female) from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, we identified five LLD symptom profiles, based on the Geriatric Depression Scale-15 (no LLD (57%); apathy (31%); apathy with emptiness (2%), mild LLD (8%) and severe LLD (2%)). Cox regression analyses showed that severe LLD, mild LLD and apathy increased risk of dementia up to 12 years, compared to no LLD. Additionally, hippocampal volume loss and white matter lesion increase, were assessed on 1.5 T MR images, at baseline and after 5 years follow-up. Only severe LLD showed increased WML volume over time, but not on hippocampal volume loss. WML increase over time mediated partially the relation between mild LLD and dementia but not for the other symptom profiles. It appears that hippocampal atrophy and LLD are independent predictors for dementia incidence, whereas for mild LLD the risk for dementia is partially mediated by WML changes.

1. Introduction

Dementia affects about 5%–8 % of the population aged 60 and over worldwide and is related to poorer quality of life, mortality and high societal costs (Fiest et al., 2016). As effective treatments are limited it is crucial to understand what the risk factors are to identify individuals at risk and potentially modify these risk factors so dementia could be prevented. One of such potentially modifiable is late-life depression (LLD) (Bellou et al., 2017), and psychological treatments have been shown to be effective in the treatment of LLD (Kiosses et al., 2011).

LLD is estimated to result in a two-fold increased risk for dementia and Alzheimer's disease (Cherbuin et al., 2015), however the nature of the relation between depression and dementia is not completely understood, as in some cases depression clearly precedes the onset of cognitive decline and dementia, whereas in other cases depression is comorbid to dementia (Byers and Yaffe, 2011; Cipriani et al., 2015; Zahodne et al., 2014).

The exact underlying mechanism between LLD and onset of dementia is unknown, but several mechanisms have been hypothesized. According to the vascular depression hypothesis, increased vascular lesions in white brain matter, results in depression and cognitive decline and possibly dementia (Alexopoulos et al., 1997; Almeida et al., 2017; Kirton et al., 2014; O'Shea et al., 2018). While the glucocorticoid cascade hypothesis states that depression is related to dysregulation of the hypothalamic-pituitary adrenal axis, resulting in chronic hypercortisolemia, which is related to cognitive decline and neurodegeneration (Lupien et al., 2005; McEwen and Magarinos, 1997). Whether LLD has a causal role in the onset of dementia or is merely a prodrome or early sign of dementia is however still undecided.

LLD can be defined as having an episode of major depressive disorder (MDD) or clinically relevant depressive symptoms at an older age (usually after the age of 60 years). However, people with LLD vary considerably in clinical presentation, prognosis, treatment response and neurobiology (Bell-McGinty et al., 2002; Diniz et al.,

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0197-4580/$ – see front matter © 2021 Published by Elsevier Inc.
https://doi.org/10.1016/j.neurobiolaging.2021.09.025

2016; Geerlings and Gerritsen, 2017; Joel et al., 2014). Because of this diversity attempts have been undertaken to examine more homogenous subtypes (Rush, 2007; Schotte et al., 1997). It could well be that only certain subtypes of LLD have an increased risk for dementia or that the underlying mechanisms between LLD and dementia differ per subtype of LLD.

Some previous studies applied data-driven approaches in older persons to identify subtypes based on depressive symptoms (Bogner et al., 2009; Hybels et al., 2009; Lee et al., 2012). These studies reported classes of older persons that differed by severity of depressive symptoms, but did not report classes that had qualitatively different symptom profiles. Bogner and colleagues (Bogner et al., 2009)included in their analysis also cognitive status as input for the latent classes and found that older persons with cognitive decline more frequently reported suicidal thoughts than older persons without cognitive decline. These findings suggest that depressed older persons with and without cognitive deficits may belong to different subtypes, as has also been previously suggested for LLD symptoms in relation to Parkinson's disease (Szymkowicz et al., 2018).

To get a better understanding of early signs of dementia it is also worthwhile to compare LLD depressive symptom profiles on levels of neuropathology. For instance, increased white matter hyperintensities (WMH) has previously been found in relation to LLD (Grool et al., 2013; Taylor et al., 2013) and also apathy (Grool et al., 2014). And in a meta-analysis we showed that in older persons late-onset depression is related to smaller hippocampal volume than early-onset depression (Geerlings and Gerritsen, 2017). Whether certain symptom profiles of LLD will show more or less hippocampal volume loss and increase in WMH over time is however unclear.

The aim of the current study is first to investigate whether we can identify symptom profiles of LLD that may have different risks for incident dementia. To identify symptoms profiles, we will use latent class analysis (LCA) on depressive symptoms, assessed with the Geriatric Depression Scale (GDS) (Stone et al., 2019) in a population of older persons. Second, we will examine which of the identified symptom profiles show increased risk for onset of dementia over 12 years of follow-up. And third we will investigate which of the identified symptom profiles show most hippocampal volume loss and increase in WMH over 5 years follow-up.

2. Materials and methods

2.1. Study population

Participants were from the Age, Gene/ Environment Susceptibility (AGES)-Reykjavik Study, which is a continuation of the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association, and included men and women born in 1907 to 1935 living in the Reykjavik area. The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Icelandic Data Protection Authority, and by the Institutional Review Board for the National Institute on Aging, NIH. Written informed consent was obtained from all participants.

In 2002, 5,764 individuals randomly chosen from the survivors were examined for the AGES-Reykjavik Study. The study design and initial assessments of the cohort have been described elsewhere (Harris et al 2007). Examinations were completed within a 4- to 6-week time window, and included blood tests, blood pressure, ECG, anthropometry, physical and cognitive functioning and comprehensive questionnaires (first visit), brain MRI, CT and ultrasonography (second visit), and vision screening, hearing tests, and dementia assessment if indicated (third visit). Of the 5764 cohort members, 393 had a diagnosis of dementia and were excluded for this analysis. For the current study we only used the data of 4354 participants for whom we had complete data on brain volumes at baseline. Reasons for no MRI included contraindications, refusal, scheduling conflicts, home visit, and a small number did not have all of the sequences necessary for brain segmentation, or there were artifacts in the scan that precluded processing.

From 2007 to 2011 there was a follow-up examination of all surviving participants who agreed to participate (n = 3,316). Reasons for not attending the follow-up examination included: death (n = 1,039); refusal (n = 1,198); and lost to follow-up (could not be contacted by any means; n = 211). Of the 3,316 participants who attended the follow-up examination, 709 had missing MRI data and another 195 had missing data on depressive symptoms at baseline or at follow-up. Leading to follow-up sample of 2412 participants.

2.2. Depressive symptoms

The 15-item Geriatric Depression Scale (GDS-15) was used to assess depressive symptoms. The GDS-15 has been shown to be a reliable and valid questionnaire to assess depressive symptoms in an older population (Conradsson et al., 2013). The items have a no/yes answer option. Four out of the 15 items had to be transformed, as these were depicted positively (e.g., 'I feel happy'), whereas all other items were depicted negatively (e.g., 'I feel worthless'). In the GDS there are the following three apathy symptoms: 'I dropped many activities'; 'I prefer to stay home' and 'I am not full of energy'.

2.3.1. MRI protocol

All participants without contraindications were eligible for brain MRI scan on a study-dedicated 1.5-tesla Signa TwinSpeed system (General Electric Medical Systems, Waukesha, WI). The image protocol, described in detail elsewhere, included the following sequences: axial T1-weighted 3-dimensional spoiled gradient echo; a fluid-attenuated inversion recovery (FLAIR); a proton density/T2-weighted fast spin echo; and a T2*-weighted gradient echo–type echo planar sequence. All images were acquired to give full brain coverage, and slices were angled parallel to the anterior commissure–posterior commissure line.

2.3.2. Brain volumes, WMLs, and infarcts

Intracranial volume (ICV) and brain parenchyma compartments were segmented automatically with a previously described algorithm modified from the AGES-Reykjavik Study. The pipeline is based on a multispectral tissue segmentation method that estimated volumes for 4 tissue classes: gray and white matter regions, WMLs, and CSF. These 4 classes were summed to obtain total ICV. Calculation of regional tissue volumes was based on an anatomical atlas and a regional probabilistic atlas, created from a large sample of the AGES cohort (n = 314), which was warped nonlinearly to the T1-weighted images of each study participant. WMLs are considered present in the case of visible hyperintense signal on both T2-weighted and FLAIR images. White matter lesions (WMLs) were defined by trained radiographers who scored the location of subcortical WMLs in frontal, occipitoparietal, and temporal lobes using the Achten Scale (Achten et al., 2000), which provides a semiquantitative "volumetric" estimation for WML load by taking into account the lesion size and number. The size of the lesion is measured at the largest diameter and categorized into small ($\leq$3 mm), medium (4–10 mm), or large ($>$10 mm) lesions. Each size is given a weight to approximate volume, that number is multiplied by the number of lesions of the respective size, and they are all added together. For more details, please see Sigurdsson et al (Sigurdsson et al., 2012).

2.4. Assessment of dementia

Dementia ascertainment was a 3-step protocol, described previously (Harris et al 2007). In brief, all participants were screened using the Mini-Mental State Examination24 and the Digit Symbol Substitution Test. Those with positive screen results were administered a diagnostic battery of neuropsychological tests, and, among them, those with positive screen results were examined by a neurologist and a proxy interview was administered regarding medical history, social, cognitive, and daily functioning changes of the participant. A consensus diagnosis according to international guidelines was made by a panel that included a geriatrician, neurologist, neuropsychologist, and neuroradiologist. In addition to case identification at the baseline and follow-up exams, all participants that attended the baseline exam were tracked for dementia diagnosis through vital statistics and hospital records, and the nursing and home-based Resident Assessment Instrument (RAI), allowing for a more complete follow-up and less misclassification of cases as controls.

2.5. Other variables

Age, sex, education, physical activity, smoking, and alcohol intake (type and number of units per day) were assessed via questionnaires. Smoking history was categorized as current versus nonsmoker. Frequency of moderate or vigorous physical activity in the past 12 months was categorized into moderate/ high versus never/rarely/occasionally. Total alcohol intake (grams) was calculated as number of units times 14 g (1 unit). Systolic and diastolic blood pressure was measured with a standard mercury sphygmomanometer and the mean of 2 measurements was calculated. Hypertension was defined as self-report plus use of antihypertensive medications, or measured systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. Diabetes mellitus was defined as self-reported history of diabetes, use of blood glucose–lowering drugs, or fasting blood glucose level >7.0 mmol/L.

2.6. Statistical analysis

Multiple imputation (AregImpute in R version 2.13.1) was used to address missing values at baseline, with 10 iterations. Missing data was available for some of the lifestyle factors, but not for any of our outcome variables (e.g., dementia, brain measures). Dementia diagnosis at follow-up was not used for imputation.

For Aim 1, we used latent class analysis (LCA) with the Proc LCA procedure in SAS version 9 to identify symptom profiles of depression**.** To determine the number of classes, we used the Bayesian information criterion (BIC) and Akaike information criterion (AIC) with lower values indicating a better fitting model, entropy with higher values indicating a better fit, at least 1% of the cohort fitting into one class, and that adding another class adds clinical relevancy. We estimated 1–7 classes to assess best model fit. Participants were classified based on their most likely latent class membership for further analyses.

Additional exploratory analyses were conducted to describe the identified symptom profiles; these profiles were compared on lifestyle and vascular risk factors using analysis of variance for continuous variables and Chi-squared tests for categorical variables.

For Aim 2, we conducted Cox proportional hazard analysis to investigate the associations of the symptom profiles identified at Aim 1 with risk for dementia incidence during follow-up. Participants were followed from date of inclusion until diagnosis of dementia, death, loss to follow-up, or end of follow-up (October 2015), whichever came first. For those who died, the censoring date was date of death. Those who were lost to follow-up were assumed not to have dementia, and the censoring date was set halfway between date of inclusion and end of follow-up. The analyses were performed using proc Phreg in SAS 9.4 and were adjusted for age, sex, educational level, smoking, alcohol use, BMI, blood pressure and diabetes. To exclude possible reverse causation bias (Jack et al., 2013), we repeated these analyses after excluding the incident dementia cases that occurred during the first 5 years of follow-up.

For Aim 3, we used Repeated Measures of Analysis of Covariance to estimate the changes in hippocampal volume and WML over time, using the volumes measured at baseline and follow-up as dependent factor with two levels. The analyses were performed using proc Mixed in SAS 9.4 and were adjusted for age, sex, intracranial volume, educational level, smoking, alcohol use, BMI, blood pressure and diabetes.

For Aim 4 we added the brain measures to the Cox proportional hazard models to test whether the brain measures mediate the relation between the LLD symptom profiles and dementia onset. To test for significant mediation, we compared the coefficients from Aim 3 (LLD symptom profiles -> brain measures) to the coefficients from the combined Cox model (LLD symptom profiles -> dementia, adjusted for brain measures) using the Sobel test. The Sobel test is used to determine whether a variable carry (or mediates) the effect of an independent variable to the dependent variable—the outcome of interest. A significant test statistic offers evidence that an independent variable has an indirect effect (("Sobel Test - SAGE Research Methods," n.d.)).

Table 1
Sample characteristics at baseline

N	4354
Mean age (SD)	76 (5,4)
Sex, female N (%)	2548 (59)
Education, N (%)	
-primary	1438 (33)
-secondary	2079 (48)
-college	540 (12)
-university	297 (7)
Current smoking, n (%)	523 (12)
Mean alcohol, g/wk (range)	3 (0-40)
Hypertension, n (%)	3491 (80)
Mean systolic blood pressure, mm Hg (SD)	142 (20)
Mean diastolic blood pressure, mm Hg (SD)	74 (10)
Diabetes, N (%)	485 (11)
Antidepressant use, n (%)	610 (14)
Mean GDS-15 score (SD)	2 (3)

3. Results

The mean age of the study population at baseline was 76 years and 59% were female. Table 1 shows full descriptive of baseline characteristics of the study sample. During follow-up 843 persons developed dementia, 397 of whom had a diagnosis Alzheimer's disease.

3.1. Latent class analysis on GDS

The LCA rendered the best fitting result for 5 classes, see Table 2 for an overview of all Goodness of Fit statistics.

Fig. 1 shows the endorsement probabilities per class on the 15 GDS items and Table 3 gives an overview of each GDS item. As can be seen the five-class solution consisted of a class of participants with low LLD symptoms (49.5%), a class of participants scoring high on only apathy symptoms (36%), a class of participants scoring on apathy and emptiness (2%), a class of participants with mild LLD symptoms (10.5%) and a class of participants with severe

Table 2
Goodness of fit statistics for 2–7 class solutions

Number of Classes	Log likelihood	G2	AIC	BIC	ABIC	entropy
2	18493	3497	3559	3755	3656	0,84
3	18161	2831	2925	3223	3073	0,68
4	18038	2586	2712	3112	2911	0,68
5	17591	2412	2570	3071	2820	0,72
6	17908	2325	2515	3118	2816	0,71
7	17879	2268	2490	3193	2841	0,65

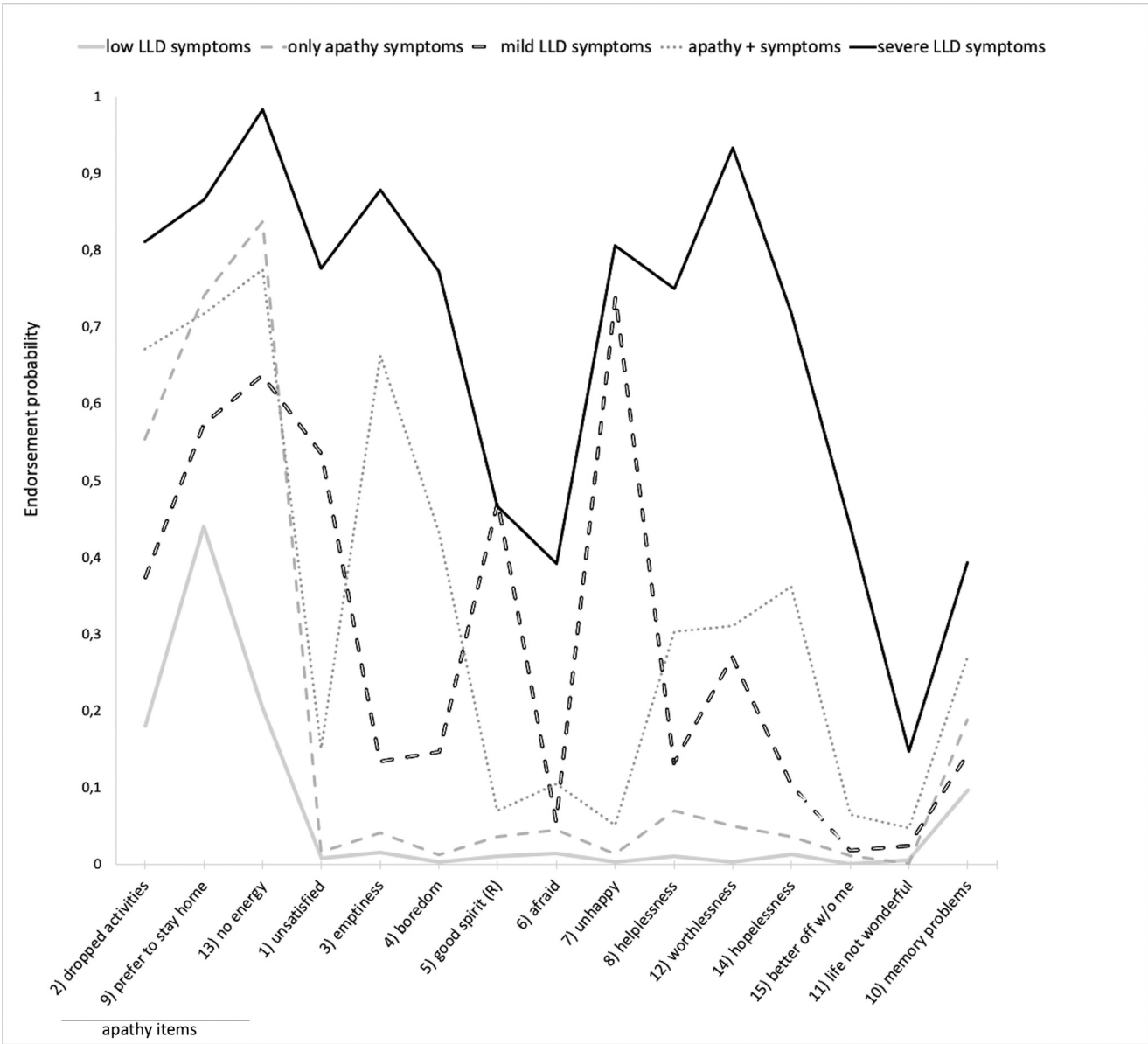

Fig. 1. Symptom endorsement probability for the five-class solution of the latent class analysis.
The y-axis depicts the chance a participant would score 'yes' on the separate items (=x-axis), for each of the defined LCA classes.

LLD symptoms (2%). These names for the symptom profiles were based on the endorsement probabilities (Fig. 1) and the averages on total GDS scores (Table 4).

As the Goodness of Fit statistics were highly similar for the 4, 5 and 6 class solutions we compared all these three solutions by examining the symptom profiles. In the 4-class solution the classes of mild LLD symptoms and the one apathy and emptiness were grouped together, whereas in the 6-class solution a 6th class was created out of the class with mild LLD symptoms, consisting of 1,5% of participants that score between severe LLD and mild LLD symptoms. Based on the goodness of fit statistics, where the optimal combination of Loglikelihood, G2, AIC, BIC and entropy seemed to be present for the 5-class solution and the observation that the 4 and 6 class solution did not provide more clinically useful solutions, we chose for the 5 class solution.

For full item description please see Table 3.

Table 3
GDS-15 items

1) I am not satisfied with life	9) I prefer to stay home[a]
2) I dropped many activities[a]	10) I have problems with memory
3) I feel my life is empty	11)It is wonderful to be alive (recoded)
4) I get bored often	12) I feel worthless
5) I am in good spirit (recoded)	13) I feel full of energy (recoded) [a]
6) I am afraid something bad may happen	14) My situation is hopeless
7) I feel happy (recoded)	15) I think most people are better off than me
8) I often feel helpless	

[a] : apathy items

Table 4
Exploratory comparison between LLD symptom profile on lifestyle and vascular risk

	No LLD	Only apathy	Apathy+	Mild LLD	Severe LLD	Statistics F-value /Chi$^{2;}$ *p*-value
N	2136	1508	72	383	86	
Mean age (SD)	75 (5)	77 (5)	77(5)	77 (5)	76 (6)	33.7; <0.001
Sex, female %	55%	62%	49%	65%	65%	35.1; <0.001
Education, %						
-college/ university	21%	19%	16%	12%	8%	8.5; <0.001
Current smoking, %	10%	14%	13%	14%	21%	19.9; 0.001
Mean alcohol (SD)	15 (33)	15 (34)	11 (22)	14 (29)	10 (26)	1.1; 0.38
Hypertension, %	78%	83%	75%	81%	83%	14.0; 0.007
Mean systolic blood pressure (SD)	132 (17)	131 (16)	138 (18)	140 (17)	129 (16)	1.7; 0.14
Mean diastolic blood pressure (SD)	81 (10)	83 (10)	86 (10)	82 (9)	82(10)	2.3; 0.06
Diabetes, %	11%	11%	10%	12%	15%	1.9; 0.75
Antidepressant use, %	10%	17%	26%	28%	75%	174.7; <0.001
Mean GDS-15 score (SD)	0.9 (0.8)	2.9 (0.9)	4.5 (1.5)	5.3 (1.5)	10.2 (1.9)	3696.1; <0.001
Total WML (ml)	16.2 (0.5)	18.3 (0.6)	14.5 (2.7)	19.7 (1.3)	18.6 (2.9)	3.27; 0.011
Total Hippocampal volume (ml)	5.7 (0.1)	5.7 (0.2)	5.7 (0.8)	5.7 (0.2)	5.6 (0.8)	1.26; 0.29

For endorsement probability per identified LLD symptom profile please see Fig. 1.

When comparing all symptom profiles on lifestyle and vascular risk factors (Table 4) the class with severe LLD symptoms was significantly older, more often female, less often highly educated, more often current smoker and more often had hypertension, compared to the other classes. The low LLD symptoms class and apathy + emptiness class consisted of most men and had less often hypertension compared to the other classes. No differences were found for hippocampal volume, but at baseline volume of WML was largest for those with only apathy symptoms, mild LLD symptoms and severe LLD symptoms.

3.2. LLD symptom profiles and risk for dementia

In total there were 843 new incident dementia cases over on average 9 years of follow-up (with max of 12 years) of which 387 cases fulfilled the criteria for Alzheimer's disease. The Cox proportional hazard model, adjusted for age, gender, educational level, lifestyle and vascular risk factors showed that compared to participants with low LLD symptoms (reference group) the participants with only apathy symptoms (HR = 1.35; 95% CI: 1.16–1.57; $p <$ 0.001), mild LLD (HR = 1.63; 95% CI: 1.22–2.18; $p = 0.001$) and severe LLD symptoms (HR = 1.81; 95% CI: 1.15–2.83; p=0.01) had significantly increased risk for all cause dementia incidence over follow-up of 9 years. Whereas the group with apathy + emptiness had a borderline significant decreased risk for dementia (HR = 0.58; 95%CI: 0.32–1.05; $p = 0.07$) (Fig. 2 and Table 5).

A similar Cox proportional hazard model with Alzheimer's disease as outcome showed only a significant increased risk for the largest class with only apathy symptoms: HR = 1.26; 95% CI: 1.01–1.56; $p = 0.04$.

We excluded the first five years of incident cases to control for possible reversive causation bias, these results showed largely similar findings (see table S1 and Figure S1 in supplementary material).

Additionally, to underline that the symptom profiles identified by LCA are more than just increase in symptom severity we re-ran the Cox proportional hazard with 5 groups based on the number of GDS symptoms (0–1; 2–4; 5–7; 8–10; 10+). The two most severe LLD groups were not significantly related to incident dementia, whereas the two lower severity groups (scores 2–4 and scoring 5–7) were associated with increased risk for dementia (see table S2 in supplementary material). Here the incidence of dementia per group were 33% in the lowest GDS symptom class, and respectively 10%, 37%, 40% and 21% in the subsequent classes with increased severity of GDS symptoms.

3.3. LLD symptom profiles and brain volumes

Repeated measures ANOVA on hippocampal and WML volumes at baseline and follow-up showed that on between subject level there were significant effects of the LLD symptom profiles on both WML ($F_{(4,2421)} = 3.73$; $p = 0.005$) and hippocampal volume (($F_{(4,2421)} = 2.68$; $p = 0.03$). On within-subject level the LLD symptom profiles had an additional significant effect on changes in white matter lesion volume over time ($F_{(4,2241)} = 2,78$; $p = 0.025$), but not for changes in hippocampal volume over time ($F_{(4,2421)} =$ 1,692; $p = 0.14$).

See Fig. 3A (WML) and 3B (hippocampal volume) for illustration of main effect (between subjects) and effect of LLD symptom profiles over time (within-subjects).

Post-hoc analyses on WML showed that compared to the group with low LLD symptoms those with only apathy symp-

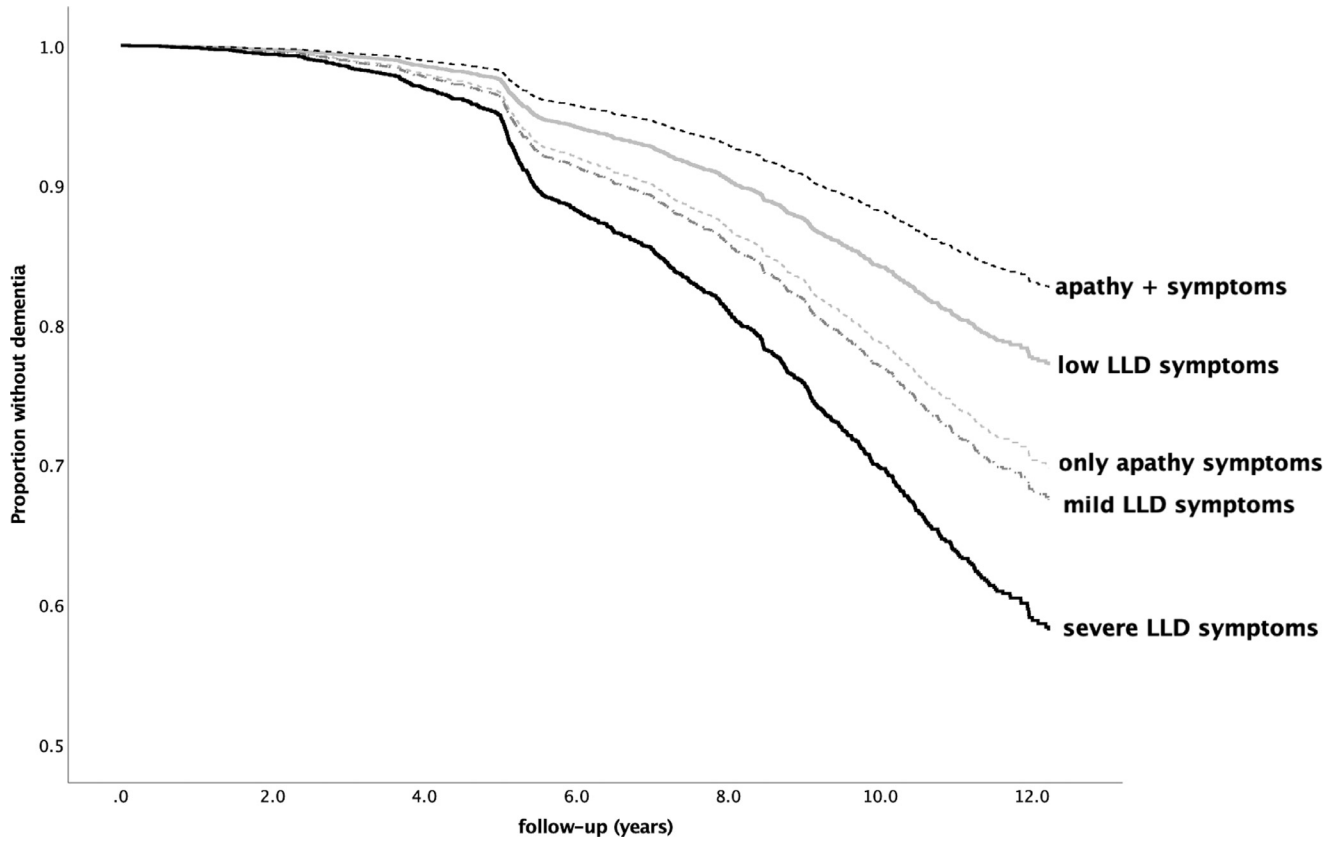

Fig. 2. All cause dementia incidence per LLD symptom profile.
Adjusted for age, sex, educational level, lifestyle and vascular risk factors.

Table 5
Hazard Ratios per LLD symptom profile for all cause dementia and Alzheimer's disease

symptom profiles	All cause dementia				Alzheimer's disease			
		HR	95% CI	*p*-value	cases	HR	95% CI	*p*-value
No LLD (N = 2136)	340	1 (REF)			179	1 (REF)		
Only apathy (N = 1508)	341	1.35	1.16 – 1.57	0	153	1.26	1.01 – 1.56	0.04
Apathy+ (N = 72)	11	0.58	0.32 – 1.01	0.07	4	0.5	0.19 – 1.35	0.17
Mild LLD (N = 383)	92	1.63	1.22 – 2.18	0.005	38	1.4	0.88 – 2.22	0.16
Severe LLD (N = 86)	22	1.86	1.15 – 2.83	0.007	7	1.35	0.61 – 2.96	0.46

Adjusted for age, sex, educational level, lifestyle and vascular risk factors.

toms (mean difference = 0.96 ml; 95%CI: 0.25–1.67; $p = 0.008$), mild LLD symptoms (mean difference = 1.14 ml; 95%CI: 0.04–1.81; $p = 0.048$) and severe LLD symptoms (mean difference = 2.21 ml; 95%CI: 0.11–4.98; $p = 0.046$) had significantly more WML volume at baseline and follow-up. As the within-subject analyses showed a significant effect over time of LLD symptom profiles, we also looked at post-hoc changes in WML over time. The low LLD symptoms group showed a percentage increase over time of 35%, while the only apathy group showed increase of 37%, the apathy + group showed increase of 34 %, the mild LLD group an increase of 35 % and the severe LLD group showed an increase of 42 %. And it was only this latter effect of severe LLD versus no LLD that reached significance ($p = 0.03$).

3.4. Mediation analyses LLD symptom profiles, brain and dementia risk

By adding hippocampal volume loss and WML increase over time as independent variables to the Cox proportional hazard models we tested whether changes in these brain measures could explain part of the relation between LLD symptom profiles and dementia risk. As seen in Table 6, when hippocampal volume loss in ml was added to the model, the hazard ratios for LLD symptom profiles did not decrease in strength, suggesting that hippocampal volume loss and symptom profiles are independent predictors for dementia onset. When WML increase was added to the model, the HR for mild LLD decreased with 9 % and a Sobel test showed that this difference was significant (Z-score = 1.96; *p*-value = 0.05), suggesting that WML increase partially mediates the relation between mild LLD and risk for dementia, but not for the other LLD symptom profiles (All Z-scores <1.5; $p > 0.05$).

4. Discussion

In this large population-based cohort of older persons without dementia we first showed that based on the GDS-15 it is possible to identify 5 different symptom profiles and second, that

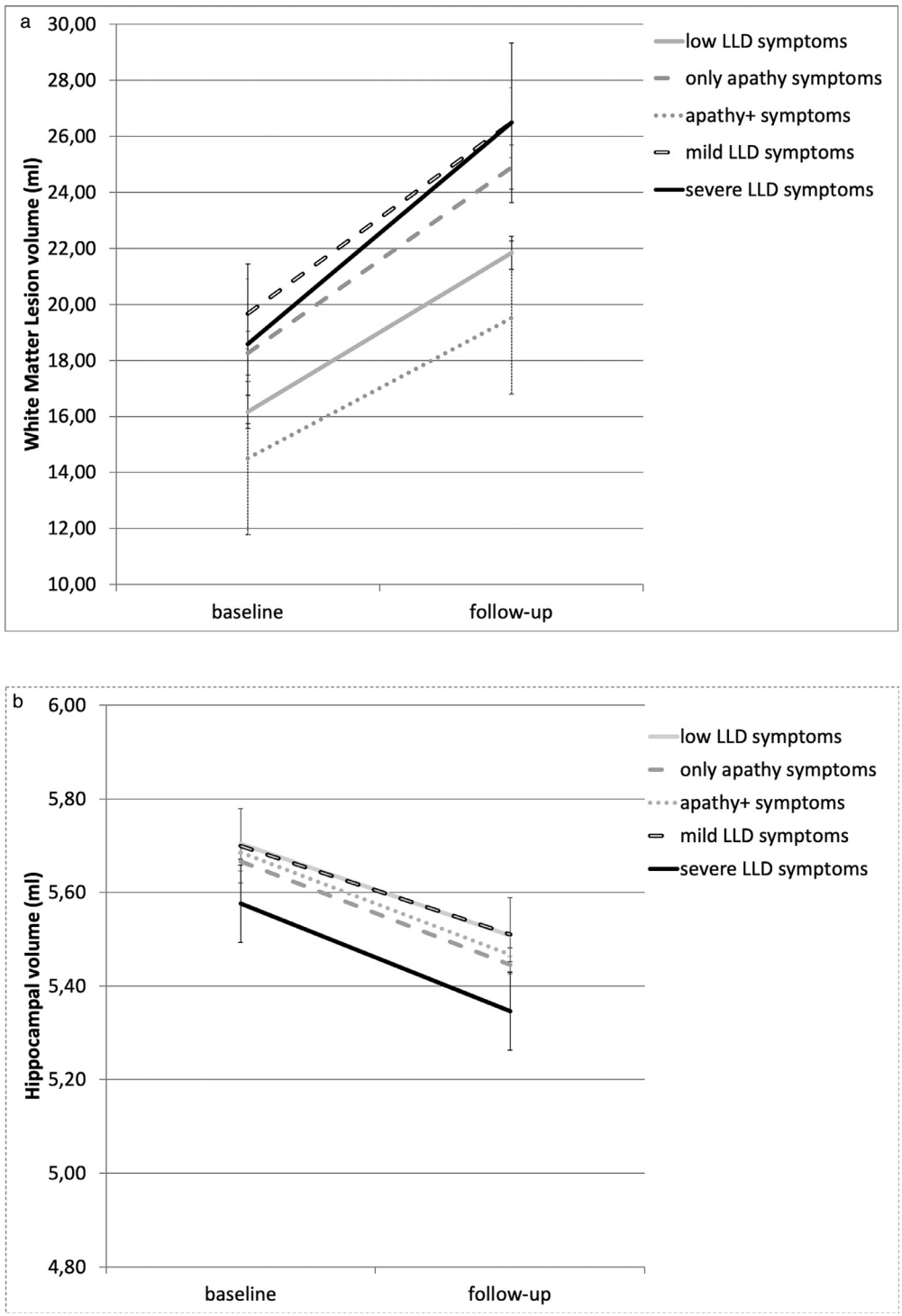

Fig. 3. Relation between LLD symptom profiles and changes in white matter lesion volume (A) and hippocampal volume (B) over time. Adjusted for age, sex, educational level, ICV, lifestyle and vascular risk factors.

the symptom profiles with apathy only; mild LLD and severe LLD symptoms had increased risk for incident dementia over 9 years of follow-up. Moreover, we found that these same three symptom profiles showed significantly more white matter lesions (WML) compared to the low LLD symptoms profile, and that the severe LLD symptom profile showed more increase in WML over time. For hippocampal volume we observed significant lower volumes for the symptom profile with only apathy symptoms and the profile with severe LLD symptoms compared to the low LLD symptom profile, but there was no significant effect in decrease of hippocampal volume over time. Only for the mild LLD symptom profile we found that WML volume increase over time mediated partially the relation between depressive symptoms and dementia onset. In contrast, it appeared that hippocampal volume loss over time was an independent predictor from depressive symptoms for dementia onset.

Preceding studies on subgroups of LLD also observed an increased dementia risk in persons with apathy (Moretti et al., 2002;

Table 6
Cox proportional hazard model for all-cause dementia predicted by LLD symptom profiles and brain measures

	Cases	HR	95% CI	*p*-value
Low LLD symptoms N = 2136)	340	1 (REF)		
Only apathy symptoms (N = 1508)	341	1.54	1.132–1.96	0.000
Apathy+ symptoms (N = 72)	11	0.61	0.23–1.65	0.331
Mild LLD symptoms (N = 383)	92	1.75	1.07–2.85	0.026
Severe LLD symptoms (N = 86)	22	2.21	0.99–4.80	0.06
Hippocampal volume loss in ml		15.64	11.71–20.89	0.000
Low LLD symptoms (N = 2136)	340	1 (REF)		
Only apathy symptoms (N = 1508)	341	1.40	1.11–1.78	0.005
Apathy+ symptoms (N = 72)	11	0.64	0.24–1.73	0.381
Mild LLD symptoms (N = 383)	92	1.48	0.91–2.42	0.114
Severe LLD symptoms (N = 86)	22	2.05	0.96–4.44	0.09
WML increase in ml		1.04	1.03–1.05	0.000

Adjusted for age, sex, educational level, ICV, lifestyle and vascular risk factors.

Ruthirakuhan et al., 2019; van Dalen et al., 2018). Unlike these preceding studies we did not use a predefined set of criteria for LLD or apathy, but used a data-driven approach, namely latent class analysis (LCA).

A review on studies using LCA in depression showed that most of the LCA studies describe severity classes, from no symptoms to many symptoms (Ulbricht et al., 2018). This is also true for the few studies performed in older persons with depression symptoms (Lee et al. 2012; Hybels et al. 2009; Bogner et al. 2009). Our results suggest that not only the severity of symptoms matter, but also the content of symptoms, as we saw that not all symptoms were equally distributed and associated with dementia risk. For instance, compared to the other symptom profiles, only the severe LLD symptom profile participants scored high on feeling helpless and worthless and this group had the highest incidence of dementia. Similarly, we also saw that not all participants who report apathy symptoms showed increased incidence of dementia, as was previously suggested (van Dalen et al., 2018).

Other studies that investigated LLD symptoms in relation to brain pathology found that higher depressive symptoms in older participants were related to reduced hippocampal volume(Donovan et al., 2015; O'Shea et al., 2018; Szymkowicz et al., 2019) and increased WML lesion volume (Kirton et al., 2014; Lavretsky et al., 2008), similarly others showed that higher levels of apathy were related to increased WML volumes(Oudega et al., 2020; Tay et al., 2019). In line with preceding studies showing that depression is related to smaller hippocampal volumes (Geerlings and Gerritsen, 2017; Videbech and Ravnkilde, 2004) we found that the symptom profile with severe LLD showed the smallest hippocampal volume both at baseline and follow-up. Whereas most of these studies had a cross-sectional design the few longitudinal studies that have been conducted show that higher depressive symptoms are related to faster rate of increase of WML(Kirton et al., 2014) and some also showed that depressive symptoms were related to hippocampal atrophy over time (Lebedeva et al., 2018) or that higher depressive symptoms were related to more hippocampal volume loss in women but not men(Elbejjani et al., 2015). So far, no study compared separate apathy and LLD symptom profiles on brain pathology.

Contrary to what we expected, no differential changes in hippocampal volume over time among the symptom profiles was observed. It appeared that hippocampal volume loss was not part of the mechanism that can explain the relation between LLD and dementia incidence. The observation that the severe LLD symptom profile showed significant increase of WML over time suggests that particularly this subtype is at risk for vascular brain pathology. As such, our results fit better in the vascular depression hypothesis for dementia (Alexopoulos et al., 1997; Almeida et al., 2017; Kirton et al., 2014; O'Shea et al., 2018), than with the glucocorticoid cascade hypothesis (Lupien et al., 2005; McEwen and Magarinos, 1997). It has frequently been suggested that LLD is a risk factor for dementia onset, because LLD is also related to hippocampal atrophy and increase in WML (Geerlings et al., 2008; Vu and Aizenstein, 2013). Possibly, we did not find mediation effects for hippocampal volume loss, because the dementia follow-up was longer than the follow-up for brain measures. At baseline we excluded dementia cases, to ensure that we would only investigate the relation between depressive symptoms at baseline and incident dementia at follow-up. However, it could well be that there is some underreporting of depressive symptoms due to already ongoing cognitive deterioration, which could lead to having less insight in their mood. Paradoxically that would mean that those with poorer cognitive function report the fewest depressive symptoms, whereas in our sample we saw that participants who fulfilled the criteria for mild cognitive impairment reported more depressive symptoms than those who did not fulfill the criteria for MCI. Future studies are therefore needed to further unravel the relation between LLD, brain and dementia. Recently is was suggested that WML and hippocampal atrophy synergistically affect cognitive decline (van Leijsen et al., 2019), whether this synergy also plays a role in explaining the relation between LLD and dementia onset is however not known.

It would be particularly interesting to understand the exact timing of events, so far LLD and vascular brain pathology are not part of the hypothetical model for AD pathology yet (Jack et al., 2013), our results at least suggest that LLD, WML and hippocampal atrophy are largely independent risk factors for dementia onset.

With respect to the latent class analyses, unexpectedly we also found a small proportion of participants that fulfilled the criteria for apathy, but also scored on the symptoms emptiness and boredom. This small group with apathy, emptiness and boredom, (N = 72) was more often male and had less often hypertension and showed when compared to participants with only apathy symptoms a lower risk for incident dementia. This suggests that there are people who do not show the increased risk for dementia when they report apathy symptoms as has been previously found (Van Dalen 2018). A possible explanation may be that participants in this specific symptom profile reported these symptoms of apathy, emptiness and boredom due to external factors, such as being lonely and having no fun activities to do, whereas they possibly would have liked to be more active. Which is much different from true apathy, which reflects more internalized symptoms, where people feel like they do not want to be involved in any activity. As this group was rather small but showed a decreased risk for incident dementia and lower WML volumes replication of our latent classes is required.

When comparing the five identified symptom profiles on lifestyle and vascular risk factors it became apparent that the severe LLD group scored most unfavorable on every factor and that the no LLD group scored most favorable. Because all analyses were adjusted for lifestyle and vascular risk factors, we assume that the estimated hazard ratios for dementia onset cannot be explained by these differences in vascular risk.

In conclusion, our study shows that by using LCA we identified several symptom profiles of LLD with a short screening instrument for depressive symptomology – some of which not previously identified - and that these symptom profiles are related to risk of dementia and differential patterns of WML volume increase over time. Limited evidence was found for a mediation between LLD and dementia onset by changes in hippocampal and WML volumes, suggesting that LLD leads to dementia via different mechanisms.

Author contributions

Lotte Gerritsen, Sigurdur Sigurdsson, Palmi V. Jonsson, Vilmundur Gudnason, MD, Lenore J. Launer, Mirjam I. Geerlings, LG, MIG, LJL conducted analyses and wrote the primary version of the manuscript. LJL, SS, PvJ VG played substantial roles in collecting the data and commenting on written manuscripts. By submitting this manuscript, we verify that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Acknowledgements

The AGES Reykjavik study was funded by the Icelandic Heart Association, National Institute of Aging contracts (N01-AG-12100 and HHSN271201200022C) and Althingi the Icelandic Parliament. This work was supported by Alzheimer Nederland (grant number WE.03-2017-06)

Disclosure statement

The authors have no conflicts of interest to declare.

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