# Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes

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Keywords: ageing, depressive symptoms, white matter changes, dementia, cognitive decline

**Abstract**

Depressive symptoms have been associated with an increase risk of cognitive decline. Our aim was to evaluate the influence of depressive symptoms on cognition over time in independent older people, accounting for the severity of white matter changes (WMC).

The LADIS prospective multi-national European study evaluated the impact of WMC on the transition of independent older subjects into disability. Subjects were evaluated annually over a 3 year period with a comprehensive clinical protocol and a neuropsychological battery. Previous episodes of depression and current depressive symptoms were collected during each interview. If cognitive decline occurred it was classified as “cognitive decline not dementia” or dementia. MRI was performed at entry and at the end of the study. 639 subjects were included (74.1 ± 5 years old, 55% women, 9.6 ± 3.8 years of schooling).

Depressive symptoms at baseline but not previous depressive episodes were an independent predictor of cognitive impairment (dementia and cognitive impairment not dementia) during follow-up, independently of the effect of severity of WMC.

The LADIS Study is supported by the European Union within the Vth European Framework Program ‘Quality of life and management of living resources’ (1998–2002), contract No. QLRT-2000-00446.

Declaration of interest: All the co-authors read the manuscript and agree with the content.

## INTRODUCTION

Depressive symptoms have been associated with memory complaints[1] and worse cognitive performance in non demented older subjects[2,3], with worse performance in executive functions[2.4], attention and processing speed[4,5]. Moreover, cognitive impairment persists even after remission of late-life depression, and older individuals who were previously cognitively intact before depression are likely to be cognitively impaired in the remitted state of depression[6]. However, conflicting data exist concerning depressive symptoms and risk of cognitive decline and dementia[3,7,8,9,10]. A meta-analysis concluded that history of depression was a risk factor for Alzheimer disease (AD) rather than a prodromal phase[11], but a recent community-cohort study could not find evidence to support this hypothesis[12]. Some studies have found an increasing risk for AD[10,13], whereas others found that the risk was associated with vascular dementia but not with AD[14].

Few studies have investigated neuropsychological performance in depressed subjects taking into account cerebral white matter changes (WMC) and vascular risk factors. Two recent prospective studies failed to find vascular disease as a mediator to cognitive impairment and Alzheimer disease in depressive patients, although confirmed depressive symptoms as a risk factor for Alzheimer disease or mild cognitive impairment[15,16]. Others suggested that late onset depressed patients performed worse on neuropsychological testing and had more severe WMC[17,18,19,20]. Recently, WMC were found to be associated with increasing depressing symptoms[21], particularly deep WMC[22], and were found as predictor of depressive symptoms[23]. Due to these results we hypothesized that WMC could be a mediator between depressive symptoms and poorer neuropsychological performance in non demented older people. Our aim was to ascertain the influence of depressive symptoms on cognitive performance in a large sample of older subjects with WMC, to see if influence of depressive symptoms in cognition was lost when considering the effect of WMC severity, and to analyse this relationship over time.

## METHODS

The LADIS (Leukoaraiosis And DISability) study is a prospective multinational European project that studied the independent impact of WMC on the transition to functional disability in older people.. The rationale, methodology and baseline assessment are fully described elsewhere[24,25]. Investigators were trained and provided with a specifically developed handbook with guidelines for applying criteria and tools[24]. In short, inclusion criteria for the study were: i) 65 to 84 years of age; ii) presence of changes of ARWMC on MRI of any degree, according to the Fazekas et al.'s scale[26]; iii) no disability as determined by the Instrumental activity daily living scale (IADL) scale[27]. Patients were enrolled if they were independent in daily living activities, and they could have minor neurological, cognitive, mood or motor complaints, or incidental findings on cranial imaging caused by non-specific events, or otherwise volunteers, as detailed elsewhere[24]. All subjects were assessed with details concerning demographic, medical and neurological, functional, quality of life and motor status collected by trained medical personnel using a structured and comprehensive data questionnaire together with review of available records[24]. Depressive symptoms were assessed using the self rated 15-item Geriatric depression scale[28] and the observer rated Cornell scale for depression in dementia[29] for the severity of depressive symptoms, and DSM-IV criteria for major depressive episode[30]. We recorded history of previous depression and incident depressive episodes over the course of the follow-up.. History of previous depression was defined as a past depressive episode requiring treatment or hospital admission. If one or more previous depressive episodes had occurred, then age of depression onset, number of depressive episodes, treatment received, presence of any previous manic episodes and relation with stressful late event was collected. Incident depression (over the 3 year follow-up) was similarly defined as any depressive episode requiring treatment or hospital admission over the course of the study.

Detailed description of study variables is reported elsewhere[24]. The degree of WMC severity was rated on axial FLAIR sequences by central readers blind to clinical data using the 3 severity classes of a revised version of the Fazekas visual scale[26]. Medial temporal lobe atrophy was assessed on coronal T1 weighted sequences using the a widely used and well validated rating scale of medial temporal atrophy (MTA)[31].

**Neuropsychological assessment and cognitive criteria**

The LADIS neuropsychological battery has been described in detail elsewhere[25]. Neuropsychological evaluation was performed in all visits and included the MMSE[32] as global measure of cognitive function; the VADAS-Cog (ADAS plus delayed recall, symbol digit, digit span, mazes, digit cancellation and verbal fluency) as a comprehensive instrument to assess orientation, language, ideational and constructional praxis, immediate memory and delayed recall)[33]; Stroop[34] and Trail Making (TM) tests[35] as measures of executive function. Tests were grouped by cognitive domains, as follows: Executive function - Stroop, verbal fluency and Trail Making; Attention - digit cancellation and Symbol digit test; Speed and motor control - Trail A and time to complete Maze test; Memory - digit span, word recognition, word recall, delayed recall, Language - commands and naming (ADAS subtests). A compound measure for each domain was calculated using standard scores of individual tests. Global measures of three main domains were analysed: 1) memory = z scores (Immediate word recall + delayed recall + word recognition + digit span) / 4; 2) executive functions = z scores of ((Stroop3-2) + (TMB-TMA) + Symbol digit + verbal fluency) / 4; 3) speed and motor control = z scores (TMA + Mazes + Digit cancellation) / 3. Higher scores in VADAS and ADAS-Cog mean worse cognitive performance. Higher values in compound measures mean better performance.

Additionally, in the follow-up clinical visits patient cognitive status was classified by the clinician into the following groups: 1. demented; 2 cognitive impairment not demented; 3 no cognitive impairment. For this purpose, we used the following criteria and definitions: We considered two types of cognitive decline not dementia: 1. amnestic mild cognitive impairment (MCI), according to Petersen *et al,* (defined as memory complaint, preferably corroborated by an informant; impaired memory function for age and education, preserved general cognitive function, intact activities of daily living and no dementia)[36] and vascular cognitive impairment without dementia (VCIND) (defined as evidence of cognitive impairment and clinical consensus to identify significantly related vascular features; exclusion of dementia when impairments were not sufficiently severe to interfere with social or occupational functioning or when impairments

were more focal than the global requirement for a diagnosis of dementia)[37]. If dementia was present we considered the following criteria for subtypes, probable Alzheimer disease according to the NINCDS-ADRDA Work Group[38], probable vascular dementia according to NINDS-AIREN criteria[39], subtype of subcortical vascular dementia according to Erkinjuntti *et al*.[40], frontotemporal dementia according to McKhann *et al*.[41], and dementia with Lewy bodies[42]. The criteria for Alzheimer disease with vascular component was made when the investigator judgement considered that the clinical picture presented both aspects of Alzheimer disease and vascular dementia.

**Statistical analysis**

*Baseline assessment*

The influence of the severity of depressive symptoms on neuropsychological performance at baseline was analyzed through multiple linear regression analyses using the different neuropsychological scores as dependent variable. We considered, for the present study the following dependent variables: global measures of cognition (VADAS-Cog and MMSE) and main cognitive domains as described (memory, executive functions and speed/motor control). In the first model, we included the independent variables that were at baseline relevant for neuropsychological performance according to previous studies (age, educational level and WMC severity)[25,43]. In the second model, we added GDS total score at baseline. We postulated that if the effect of depressive symptoms on cognitive measures was mediated through WMC, then GDS should no longer be a significant predictor when taking into account WMC severity score. Scores of neuropsychological tests, compound measures and GDS were considered as continuous variables. Linear regression analyses were adjusted for gender, medial temporal lobe atrophy and history of previous depression.

*Longitudinal assessment*

The influence of previous depressive episodes and of depressive symptoms severity on the cognitive status over time was assessed using the Cox proportional hazards model. As dependent variable, we considered the results of last cognitive evaluation of each patient as described in the methods section: any cognitive decline (dementia and cognitive impairment not dementia) versus no cognitive decline in the last observation. We considered previous depression

and GDS score as independent variables. We divided the range of GDS scores into quintiles, and performed analysis on these quintiles, following the methodology of Firbank et al of the LADIS group[21]. We adjusted analysis for age, gender, education, WMC and medial temporal lobe atrophy (MTA). Age and educational level were considered continuous variables. Presence of previous depression, GDS quintiles, gender, MTA and WMC severity were considered categorical variables. We repeated the Cox proportional hazards model controlling also for cognitive global measures at baseline: (MMSE and VADAS-Cog at baseline). Data were analysed using SPSS 16.0 software.

**RESULTS**:

639 subjects were included (74.1 ± 5 years old, 55% women, 9.6 ±3.8 years of schooling). Characteristics of study sample at baseline are presented in table 1.

**Table 1. Sample characteristics at baseline**

| | |
|---|---|
| 15-item GDS score (mean ± sd) | 3.16 ± 2.9 |
| 15-item GDS>5: number subjects (%) | 121 (19%) |
| Current major depressive episode: number subjects (%) | 40 (6%) |
| Previous depression: number subjects (%) | 176 (27.5%) |
| Age onset depression (mean ± sd) | 55 ± 18 years old |
| **ARWMC severity** | |
| Mild: number subjects (%) | 284 (44%) |
| Moderate: number subjects (%) | 197 (31%) |
| Severe: number subjects (%) | 158 (25%) |

89% (568), 78.4% (501), and 75% (480) of the subjects from the initial sample were followed-up at months 12, 24 and 36 respectively. At the end of follow-up it was possible to ascertain vital status or IADL in 633 patients (99.1% of initial sample). Fifty-one patients missed complete cognitive evaluation in any follow-up clinical visit, therefore for those 51 patients no cognitive diagnosis was

attributed. Considering the cognitive diagnosis ascertained in the last clinical visit, dementia was diagnosed in 90 patients during the study, and 147 patients had cognitive impairment not dementia at the last clinical evaluation.

**Relations between cognitive evaluation and GDS score at baseline**

Previous history of depression was weakly correlated with GDS total score at baseline (Spearman's rho .27, $p<0.01$). Using multiple linear regression analysis we found that depressive symptoms (measured by the GDS score) at baseline predicted poorer performance in global measures of cognition (MMSE and VADAS-COG), cognitive compound measures of executive functions, speed and motor control and memory, independently of other potential confounders (table 2). Previous history of depression was not a significant factor on the performance in cognitive measures at baseline except for speed and motor control, but this association disappeared when GDS score at baseline was taking into account (table 2).WMC severity predicted independently worse performance in the MMSE and compound measures of executive functions and speed and motor control, but not in ADAS-cog and compound measure of memory (table 2).

**Table 2. Associations between cognitive evaluation and GDS score at baseline**

| | MMSE | VADAS | MEMORY | EXECUTIVE | SPEED |
|---|---|---|---|---|---|
| Model 1 | $R^2$ = .16* | $R^2$=.33* | $R^2$ = .17* | $R^2$ = .31* | $R^2$ = .25* |
| Age (years) | n.s. | .15 ŧ * | n.s. | -.15 ŧ * | -.14 ŧ * |
| Gender | n.s. | n.s. | n.s. | n.s. | n.s. |
| Educational level (years) | .31 ŧ * | -.39 ŧ * | .28 ŧ * | .39 ŧ * | .34 ŧ * |
| WMC severity | -.11 ŧ * | .14 ŧ * | n.s. | -.16 ŧ * | -.17 ŧ * |
| MTA | -.15 ŧ * | -.24 ŧ * | -.24 ŧ * | -.20 ŧ * | -.13 ŧ * |
| Previous depression | n.s. | n.s. | n.s. | n.s. | -.12 ŧ * |
| | | | | | |
| Model 2 | $R^2$ change = .006* | $R^2$ change = .021* | $R^2$ change = .009* | $R^2$ change = .039* | $R^2$ change = .034* |
| Age (years) | n.s. | .15 | n.s. | -.15 | -.14 ŧ * |
| Gender | n.s. | n.s. | n.s. | n.s. | n.s. |
| Educational level (years) | .29 ŧ* | -.36 ŧ * | .26 ŧ * | .35 ŧ * | .30 ŧ * |
| WMC severity | -.10 ŧ * | .13 ŧ * | n.s. | -.14 ŧ * | -.16 ŧ * |
| MTA | -.14 ŧ * | -.24 ŧ * | -.40ŧ * | -.20 ŧ * | -.12 ŧ * |
| Previous depression | n.s. | n.s. | n.s. | n.s. | n.s. |
| GDS score | -.08 ŧ * | -.16 ŧ * | -.10 ŧ * | -.22 ŧ * | -.20 ŧ * |

Legend: GDS: Geriatric depression scale; MMSE: Mini-Mental State Examination; WMC = white matter changes; MTA = medial temporal atrophy

Values are Beta ŧ; * p< 0.05; n.s.: not significant

**Longitudinal impact of depressive symptoms and previous depression in cognition**

Using Cox regression analysis we found that GDS score at baseline was an independent predictor of cognitive impairment (dementia and cognitive impairment not dementia) in the follow-up (table 3), independently of the effect of severity of WMC. Severe WMC remained predictor of cognitive decline. Previous depression was not predictor of cognitive impairment.

**Table 3. Cox regression analysis, dependent variable: cognitive decline (combined dementia and cognitive impairment not dementia).**

| | β | HR | *P* | 95.0% CI | |
|---|---|---|---|---|---|
| Age | .03 | 1.0 | .048 | 1.00 | 1.06 |
| Gender | -.27 | .77 | .061 | .58 | 1.01 |
| Educational level | -.05 | .96 | .013 | .92 | .99 |
| WMC severity | | | .048 | | |
| WMC severity (moderate vs. mild) | .32 | 1.4 | .064 | .98 | 1.9 |
| WMC severity (severe vs. mild) | .41 | 1.5 | .020 | 1.06 | 2.12 |
| MTA | | | .022 | | |
| MTA (1 vs. 0) | .01 | 1.0 | .968 | .68 | 1.49 |
| MTA (2 vs. 0) | .37 | 1.45 | .092 | .94 | 2.23 |
| MTA (3 vs. 0) | .66 | 1.9 | .018 | 1.1 | 3.3 |
| MTA (4 vs. 0) | .92 | 2.4 | .095 | .8 | 7.2 |
| Previous depression | .18 | 1.2 | .257 | .88 | 1.6 |
| GDS score | | | .004 | | |
| GDS (quintile 1 vs 0) | .31 | 1.4 | .293 | .76 | 2.4 |
| GDS (quintile 2 vs 0) | .83 | 2.1 | .002 | 1.2 | 3.7 |
| GDS (quintile 3 vs 0) | .77 | 2.3 | .006 | 1.4 | 3.9 |
| GDS (quintile 4 vs 0) | .86 | 2.4 | .002 | 1.4 | 3.99 |

Legend: GDS: Geriatric depression scale; WMC = white matter changes; MTA = medial temporal atrophy

Controlling for global cognitive measures at baseline, the predictive effect of GDS score was unchanged (table 4).

**Table 4. A and B. Cox regression analysis controlling for cognitive measures at baseline. Dependent variable: cognitive decline (combined dementia and cognitive impairment not dementia).**

A. Controlling for VADAS-Cog

| | β | HR | *P* | 95.0% CI | |
|---|---|---|---|---|---|
| GDS score | | | .029 | | |
| GDS (quintile 1 vs 0) | .15 | 1.16 | .621 | .64 | 2.10 |
| GDS (quintile 2 vs 0) | .71 | 2.03 | .007 | 1.21 | 3.40 |
| GDS (quintile 3 vs 0) | .56 | 1.75 | .050 | 1.00 | 3.05 |
| GDS (quintile 4 vs 0) | .53 | 1.70 | .072 | .95 | 3.04 |
| VADAS-Cog | .03 | 1.03 | .000 | 1.02 | 1.05 |

VADAS-Cog (ADAS plus delayed recall, symbol digit, digit span, mazes, digit cancellation and verbal fluency)

B Controlling for MMSE

| | β | HR | *P* | 95.0% CI | |
|---|---|---|---|---|---|
| GDS score | | | .011 | | |
| GDS (quintile 1 vs 0) | .31 | 1.36 | .302 | .76 | 2.43 |
| GDS (quintile 2 vs 0) | .77 | 2.17 | .003 | 1.3 | 3.62 |
| GDS (quintile 3 vs 0) | .72 | 2.05 | .010 | 1.17 | 3.54 |
| GDS (quintile 4 vs 0) | .80 | 2.24 | .005 | 1.27 | 3.92 |
| MMSE at baseline | -.09 | .917 | .001 | .87 | .97 |

MMSE: Mini-Mental State Examination

## Discussion

Our study showed that, in older subjects with white matter changes living with full autonomy, depressive symptoms were associated with worse cognitive performance (in global cognitive measures, executive functions and speed) at baseline and were predictors of further cognitive decline over a 3 year follow-up period, independently of the severity of white matter changes.

The strengths of the study include a large sample size of rigorously assessed older people, the prospective nature of the study and our ability to carefully control for other variables implicated in cognition (age, education, medial

temporal atrophy). We also controlled results for global cognitive performance at baseline. Our study has some limitations, namely related with the sample selection. We designed the study to investigate subjects with white matter changes, so we must be cautious in the generalization of the results since we did not include subjects without any though the majority of older people do develop some degree of WMC.

One of the controversial aspects in the associations between depressive symptoms and cognitive performance in cross-sectional analysis is that we can always hypothesized that depressive symptoms interfere with the cognitive tasks performance, but has no further impact on cognition[1,2,4,5]. Several attempts were made to explain worse cognitive performance in co morbid depression: depression could be a result of awareness of cognitive difficulties, or on the opposite way, could be the early manifestation of incipient cognitive impairment[3,7,8,10,11]. In the Rotterdam study history of depression, particularly of early onset, but not presence of depressive symptoms was associated with an increased risk for Alzheimer disease[9]. In the Italian Study on Aging depressive symptoms at baseline predicted change over time of global cognitive decline[44], similarly to the 3C study[14]. In these studies white matter changes were not taken into account. Several studies attempted to identify the cognitive domain and mechanism of those deficits: executive functions were proposed as a mediator for impaired verbal memory deficit[4], and others proposed processing speed as a mediator for the different cognitive domains[5]. In line with this, in our study previous depression was not associated with evolution for cognitive decline, but was associated with worse performance at baseline for speed and motor control.

Biological explanations have been proposed to explain association between depressive symptoms and cognitive decline, including the hyperactivity of the hypothalamic–pituitary–adrenal axis with enhanced adrenal responsiveness to ACTH and glucocorticoid negative feedback with subsequent hypercortisolemia[45], and also the glucose intolerance, reduced heart rate, platelet reactivity, the presence of inflammatory proteins secondary to depression[46]. It has also been pointed out that patients with depression can adapt an unhealthy lifestyle as well as poor medication adherence[47]. In

consequence, late-onset depression could represent an expression of vascular damage due to frontostriatal disconnection. Some detailed pathological studies have supported this view[48] though a recent community based study conducted with neuropathological examination, late-life depression was not associated with cerebrovascular or Alzheimer pathology[49]. Few reports approached the evolution of subjects with subjects with depressive symptoms taking into account white matter changes[50]. We found that WMC and depressive symptoms predict dementia in older subjects. It is possible that depressive symptoms and WMC have an additive or synergistic effect for the future development of dementia, and our results shed important new light on the relation between depressive symptoms, vascular pathology and cognitive impairment.

We thank Dr. Ana Catarina Oliveira Santos for the technical advice in statistical approach.

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