Title Sheet:

Relationship between baseline white matter changes and development of late life depressive symptoms: 3 year results from the LADIS study

Andrew Teodorczuk\textsuperscript{1*}, Michael J. Firbank\textsuperscript{1}, Leonardo Pantoni\textsuperscript{2}, Anna Poggesi\textsuperscript{2}, Timo Erkinjuntti\textsuperscript{3}, Anders Wallin\textsuperscript{4}, Lars-Olof Wahlund\textsuperscript{5}, Philip Scheltens\textsuperscript{6}, Gunhild Waldemar\textsuperscript{7}, Gabriele Schrotter\textsuperscript{8}, Jose M. Ferro\textsuperscript{9}, Hugues Chabriat\textsuperscript{10}, Hansjorg Bazner\textsuperscript{11}, Marieke Visser\textsuperscript{6}, Dominico Inzitari\textsuperscript{2}, and John T. O’Brien\textsuperscript{1}

1) Institute for Ageing and Health, Newcastle University, United Kingdom.
2) Department of Neurological and Psychiatric Sciences, University of Florence, Italy.
3) Memory Research Unit, Department of Neurology, University of Helsinki, Finland.
4) Institute of Clinical Neuroscience, Göteborg University, Sweden.
5) Karolinska University Hospital, Huddinge, Sweden.
6) Alzheimer Center/ Dept Neurology, VU University Hospital, Amsterdam, the Netherlands.
7) The Memory Disorders Research Group, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Denmark.
8) Department of Neurology, Medical University, Graz, Austria.
9) Serviço de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria, Lisboa, Portugal.
10) Department of Neurology, Hopital Lariboisiere, Paris, France.
11) Department of Neurology, University of Heidelberg, Universitätsklinikum Mannheim, Germany.

On behalf of the LADIS group
WHITE MATTER CHANGES AND DEPRESSIVE SYMPTOMS

* Address for correspondence: Andrew Teodorczuk, Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom. (Email: Andrew.Teodorczuk@ncl.ac.uk)

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5 Tables
ABSTRACT

Background: Growing evidence suggests that brain white matter changes and depressive symptoms are directly linked along the causal pathway. The authors investigated whether baseline severity of brain white matter changes predict longer term future depressive outcomes in a community sample of non-disabled older adults.

Method: In the Leukoaraiosis And Disability (LADIS) study, a longitudinal multicentre pan European study, 639 older subjects underwent baseline structural MRI and clinical assessments. Baseline severity of white matter changes was quantified volumetrically. Depressive outcomes were assessed in terms of depressive episodes and depressive symptoms, as measured by score on the Geriatric Depression Scale. Subjects were clinically reassessed annually for up to three years. Regression models were constructed to determine if severity of white matter changes at baseline predicted future depressive outcomes, after controlling for confounding factors.

Results: Baseline severity of white matter changes independently predicted depressive symptoms at both two (p<0.001) and three years (p=0.015). Similarly, white matter changes predicted incident depression (p=0.02). Over the study period the population became significantly more disabled (p<0.001). When the regression models were adjusted to account for the influence of the prospective variable transition to disability, baseline white matter changes severity no longer predicted depressive symptoms at three years (p=0.09) or incident depression (p=0.08).
Conclusions: Our results support the vascular depression hypothesis and strongly implicate white matter changes in the pathogenesis of late life depression. Furthermore the findings indicate that, over time, part of the relationship between white matter changes and depression may be mediated by a loss of functional activity. Management strategies should be directed at reducing disability as well as tighter control of vascular risk factors and symptomatically treating depression.
INTRODUCTION

It is generally assumed that brain white matter changes on MRI represent a surrogate marker for vascular damage and are involved in the pathogenesis of depression in older adults (Alexopoulos, 2006, Blazer and Hybels, 2005, Scheltens et al., 2003). Cross sectional studies have demonstrated a strong association between depressive symptoms and white matter changes, in particular frontal pathology (de Groot et al., 2000, Firbank et al., 2004, MacFall et al., 2001). Outcome studies have shown that white matter changes are associated with worsening clinical course, poorer treatment response and increased mortality (Baldwin et al., 2004, Levy et al., 2003, O’Brien et al., 1998). Finally, longitudinal studies suggest baseline severity of white matter changes may independently predict future depressive outcomes (Godin et al., 2008). Taken together these findings support the vascular depression hypothesis which proposes that frontostriatal dysfunction as a result of vascular damage predisposes, precipitates and perpetuates depressive symptoms in older adults (Krishnan et al., 1997).

The LADIS (Leukoaraiosis and Disability in the Elderly) study is a large multi centre pan-European three year longitudinal study of initially non-disabled elderly subjects which investigates the relationship between white matter changes and subsequent development of disability and depressive symptoms. We have previously reported on cross-sectional associations in the baseline sample (Firbank et al., 2005, O’Brien et al., 2006) and longitudinal results in a relatively non-disabled population at short term (one year) follow-up (Teodorczuk et al., 2007).
In this report we examine the role of white matter changes as an independent predictor of both depressive outcomes in the longer term (at two and three years). The main hypothesis was that severity of white matter changes at baseline would be significantly and independently associated with the development of depressive outcomes at both two and three year follow-up, even after adjusting for the contribution of potential confounders.
METHOD

Sample

639 subjects were recruited between July 2001 and January 2003 from the 11 European centres participating in the LADIS study (Amsterdam, Copenhagen, Florence, Graz, Göteborg, Helsinki, Huddinge, Lisboa, Mannheim, Newcastle upon Tyne and Paris). Most were recruited having presented to centres with mild cognitive disturbances (N=168), minor stroke (N=122), gait disturbances (N=28), psychiatric complaints (N=13) or other neurological disturbances (N=129). Further recruited subjects included those in whom white matter changes were incidentally found on structural neuroimaging taken in other clinical settings (N=107). Lastly, controls who were found to have white matter changes were recruited from other studies (N=72).

At entry subjects were included if they were: 1) aged between 65 and 84; 2) living in the community; 3) non-disabled as assessed by the Instrumental Activities of Daily Living (IADL) scale (no impairment at all or only one item compromised) (Lawton and Brody, 1969); 4) accompanied by an informant; and 5) found to have any degree of age-related white matter changes (ARWMC) on MRI scan, from mild to severe according to categorization into the three severity classes of a revised version of the Fazekas scale (Fazekas et al., 1987).

Subjects were excluded if they had either: 1) the presence of severe illnesses (e.g. cardiac, hepatic, renal failure, neoplastic or other relevant systemic disease) which would increase the likelihood of drop-out; 2) severe unrelated neurological diseases; 3) leukoencephalopathies revealed by brain imaging that turned out to be of
non-vascular origin (immunologic, demyelinating, metabolic, toxic or infectious); and 4) severe psychiatric disorders.

All procedures were explained to subjects who gave written consent to participate. Further details on design of the LADIS study have been previously reported (Pantoni et al., 2005).

**MRI acquisition**

Subjects had a baseline MRI scan at their respective centres. All centres used MRI systems with a field strength of 1.5T, apart from one centre which had a 0.5T system. A standard protocol was used (Pantoni et al., 2005). For the white matter rating, a FLAIR sequence was acquired with the following parameters: FOV 250 mm, 256x256 or 256x192 matrix, 5mm slice thickness, 0.5 mm slice gap, 19-28 slices, TE 100-140 ms, TR 6000-10000 ms, TI 2000-2500 ms, echoes per shot 7-24. Volumetric analysis was performed by a single rater in Amsterdam on a Sparc 5 workstation (SUN, Palo Alto, California) (van Straaten et al., 2006). No distinction was made between subcortical and periventricular white matter changes. Areas of white matter changes around infarcts and lacunes were disregarded.

Major steps in determining ARWMC by the operator were as follows: 1) lesions were marked using a “seed” and local thresholding was performed on each slice using home-developed software (Show Images, version 3.6.1 using a Canay-filter); 2) lesions were delineated and the total surface of the outlined area was calculated; and 3) total volume of ARWMC was established by multiplying with the interslice
distance. Further details of the quantification process are described elsewhere (Gouw et al., 2006).

**Assessment of depressive outcomes**

Depressive symptoms were assessed by the self-completed 15-item Geriatric Depression Scale (GDS). The GDS is a self-reported questionnaire specifically developed as a screening instrument for the presence of depressive symptoms in older populations (Yesavage, 1988). The maximum possible score is 15. Depressive symptoms were assessed at baseline as well as one, two and three years.

A history of depression was recorded, along with the date of any incident depression. History of depression was defined as a past medical history for a depressive episode requiring treatment or hospital admission. Incident depression was defined as any depressive episode requiring treatment or hospital admission over the course of the study. Both history and incident depression were obtained through subject interview and evaluation of the case notes.

**Assessment of potential mediators or confounders**

All subjects had a comprehensive baseline demographic and clinical assessment administered by trained personnel. Information was collected on age, gender, education, occupational status, living conditions, previous medical conditions including stroke (as defined according to World Health Organisation (Hatano, 1976)) and hypertension (Chalmers et al., 1999), prescribed medication, lifestyle habits (alcohol and smoking) and vascular risk factors.
Further baseline assessments administered were as follows:

1. Functional status in terms of disability as measured by means of IADL. This is a scale developed to monitor function and independent living amongst older adults and measures a broad set of daily activities including shopping for personal items, preparing meals, performing housework and managing personal finances (Lawton and Brody, 1969).

2. Functional status in terms of the Disability Assessment for Dementia Scale (DAD). This is a 40 item questionnaire that includes basic items of living (Gelinas et al., 1999).

3. Mini mental state examination (MMSE) to assess cognition (Folstein et al., 1975).


Subjects were re-evaluated at one, two and three years. Transition to disability was defined as the change from none or one to at least two impaired IADL items. To increase reliability investigators were issued with a specifically designed handbook which contained guidelines for applying tools. A test of the interrater, intercenter reliability of IADL scoring showed good agreement in ratings of each scale item (K statistic ranging from 0.69 to 0.85) (Inzitari et al., 2007).

**Statistical analysis**

Data was collected in each centre and entered into a central electronic database on a specifically developed website (www.unifi.it/LADIS). In a community dwelling population it is normal for depression rating scales to be heavily skewed towards low
values. Hence, for analysis we divided our data into quintiles, using the same GDS range for each quintile as in our previous study (O'Brien et al., 2006). For the ARWMC volumes, a logarithmic transform was used to produce normally distributed data.

A two stage “step forward” regression analysis was used to determine the independent contribution of potential predictors of depressive outcomes. Initially, a univariate analysis was constructed to examine correlations between predictor variables and depressive symptoms at two and three years, the target variables. Baseline predictor variables included age, sex, baseline depressive symptoms (GDS), history of depression, educational level, smoking status, cognition (MMSE), history of stroke, hypertension and log ARWMC volume. As depressive symptoms (as measured by GDS) are on an ordinal (i.e. ordered, but not linear) scale, we used a Spearman rank order correlation coefficient (Rho) to determine the correlation.

Variables which correlated significantly were then entered in a stepwise forward method into a multivariate analysis to determine the independent contribution of each predictor variable. As well as an ordinal logistic regression model of predictors of quintile of depression scale score at two and three years, a further binary logistic regression was performed to compare predictors of incident depression over the study period.

In order to examine potential mechanisms by which white matter changes might depress mood, the prospective variable, transition to disability was included as an additional predictor variable in further models.
The significance level was set at $P<0.05$. 
RESULTS

Of the original 639 subjects, 501 subjects completed second year assessments and 440 subjects completed final assessments, representing an attrition rate of approximately 31% over the three years. Complete data were obtained from 399 subjects. Attrition resulted from subject dropout (N=73), missing data (N=124) and death (N=43). Baseline ARWMC, GDS and age were significantly higher in those without, as compared to those with, follow-up data (ARWMC: median 15.5 vs. 13.3 ml; p=0.043 Mann Whitney; GDS median 3 vs. 2; p <0.001, age 75.0 vs. 73.6 p 0.001).

Table 1 summarises the key characteristics of the subjects who completed all final year assessments.

Table 1

As expected for a community population the group GDS score remained stable over time. The mean GDS score was 2.86 at baseline and 2.96 at 3 year; paired t test found no significant change in GDS over the study (t = -0.8, P= 0.4). 85 subjects had at least one depressive episode during the study time period.

Cognition declined over the three years. The mean MMSE score was 27.85 (sd 2.2) at baseline and 27.11 (sd 3.5) at 3 year; paired t test found a significant change over the study (t = 4.9, P<0.001).
Over the study period the population became more disabled (table 2). Repeated measure ANOVA showed a significant difference over the three years ($F=22; p<0.001$). 68 subjects were classed as having made a transition to disability at two years and 95 at three years.

Table 2

Table 3 shows the results of the stepforward analysis of predictors of two year GDS. On univariate analysis log ARWMC volume, baseline GDS, cognition (MMSE) and years of education significantly correlated with depressive symptoms at two years. When these variables were entered into the multiple regression model, only baseline log ARWMC volume and baseline GDS remained predictive of depressive symptoms.

Table 3

Table 4 shows the results of the stepforward analysis of predictors of three year GDS. Again, only baseline GDS and log ARWMC volume significantly and independently predicted quintile GDS at three years in the multivariate analysis. Sex, years of education and MMSE were no longer significant.

Table 4
A binary regression model was undertaken to investigate the relationship between white matter changes and incident depression (Table 5). In the regression model, including all the significant correlators from the univariate analysis, only log ARWMC volume and history of depression independently predicted depressive episodes over the three years.

Table 5

In order to examine the influence of disability, further regression models were constructed including in the analysis the prospective variable, transition to disability. Baseline white matter changes severity continued to significantly and independently predict two year depressive symptoms in the new model (OR= 1.49 (CI: 1.24 –1.8) p<0.001). However, severity of white matter changes no longer independently predicted 3 year GDS (OR = 1.17 ( 0.97-1.4); p = 0.09) or incident depression over the study period (OR = 1.27 (0.97-1.65); p=0.08). Transition to disability predicted both 3 year GDS (OR=2.11 (1.31-3.39); p=0.002) and 3 year incident depression (OR=2.16 (1.17-4) p=0.012) but failed to predict GDS at 2 years (OR = 1.3 (0.76-2.225) p=0.3).
DISCUSSION

The main result of this pan European study is that baseline severity of white matter changes in a non-disabled community population, independently and significantly predicts depressive episodes as well as depressive symptoms at both two and three years. Though MMSE and years of education are correlated with GDS in the univariate analysis, they do not predict depressive scores in the logistic regression models. As expected, baseline GDS score significantly predicted future depressive symptoms.

These results not only build on our previous finding that baseline severity of white matter changes predicts one year depressive symptoms (Teodorczuk et al., 2007), but also demonstrate that such pathology is predictive of the clinically more meaningful depressive episodes. In the shorter study we were unable to demonstrate such an effect, potentially because of the relatively small number of depressive episodes over the one year period.

On further analysis, when the prospective variable transition to disability is included in the regression model, severity of white matter changes continues to significantly predict GDS at two but not three years. Furthermore, in the new analysis white matter changes severity at baseline no longer predicts incident depression. These findings demonstrate that the independent effect of white matter changes on mood weakens with time as the community population becomes more disabled. One possible explanation of our findings would be that, in the more disabled three year population, transition to disability is also a driver of depressive outcomes and so mediates the effect of the other significant covariates from the univariate analysis. Another
explanation would be that disability and depression are both so strongly associated with white matter changes that it is difficult to determine causality using regression techniques.

Other community studies have investigated the longitudinal relationship between white matter changes and late life depression. Recently, the 3C Dijon study found that severity of white matter changes independently predicts future risk of incident depression, however the influence of transition to disability was not specifically examined (Godin et al., 2008). In line with our results the large Cardiovascular Health study found that, after controlling for functional impairment, total severity of white matter changes no longer independently predicts future depressive symptoms (Steffens et al., 2002). Lastly the PROSPER study found no longitudinal associations over three years between white matter changes and depressive outcomes in an age and sex adjusted logistic regression model (Versluis et al., 2006). However there were low levels of depressive symptoms in the PROSPER population which, together with low ARWMC volume of subjects, may have led to negative results.

Previous reports from the LADIS study that severity of white matter changes predicts disability provide an interesting insight into the potential mechanisms which lead to depression (Inzitari et al., 2007). It is already known that a mutually reinforcing reciprocal relationship exists between disability and depressive symptoms in late life (Ormel et al., 2002); disability not only predicts depression but is also a consequence of depression. Taken together with our findings it is conceivable that white matter changes, in part, leads to a worsening in functional ability and an amplification loop may then be set up in the more disabled population, as the transition to disability leads
to depressive symptoms which in turn worsens functional ability. Thus, in the more disabled third year population, the relative influence of a potential indirect pathway mediated by disability may become greater and the independent contribution of white matter changes on depressive outcomes declines.

Clinically, the value of this study lies in developing our understanding of the evolution of depression and the further implications concerning potential treatment strategies. Importantly, our results suggest a need for tighter control of vascular risk factors; firstly because of the strong independent effect of white matter changes on depressive outcomes and secondly, because white matter pathology is an independent predictor of disability (Inzitari et al., 2007). Furthermore, as a consequence of putative indirect mechanisms, whereby vascular damage may depress mood, rehabilitation based strategies targeted at improving functional abilities may prove beneficial in the prevention and treatment of late life depressive illnesses.

The strengths of the study are the large, multicentre, pan European design and the size of the population, together with its relatively heterogeneous composition, all of which increase the generalisability of the findings. Further strengths include measurement of all scans by a single operator and the use of a volumetric scale which is less operator dependent and less susceptible to ceiling effects (van Straaten et al., 2006).

The limitations are firstly, attrition over the three years makes it possible that the data may reflect methodological problems rather than a real effect. However our attrition rate is not uncommon for studies of this magnitude. Furthermore, the fact that those who were lost to follow up had a greater degree of white matter changes and
depressive symptoms make any effect seen in subsequent analyses more impressive. Secondly, GDS gives an indication of depressive symptoms over the past week, thus it may not capture the phenomenon under investigation. However, we used two depressive outcomes and found the results to be complimentary, suggesting we are observing a real effect. Thirdly, arguably some of the symptoms measured on GDS may actually represent a dysexecutive syndrome. Although this may be possible, it is becoming increasingly clear that, in older adults, depression is as much a cognitive disorder as a mood disorder and thus such overlapping symptomatology will always occur (Steffens and Potter, 2008). Lastly, we may have underestimated the number of cases of depression over the study as a result of our definition of incident depression, “a depressive episode requiring treatment or hospital admission”. However this limitation makes a type II error more likely and the fact that we demonstrate significant results over three years suggests validity of the study has not been compromised.

Future research should be directed at determining the influence of progression in white matter changes on future depressive outcomes. In addition the findings from other longitudinal studies using complementary neuroimaging techniques, such as diffusion tensor imaging, should be linked, in order to develop an integrated perspective of the complex pathways that lead to depressive illnesses in later life (Kumar and Ajilore, 2008).
Acknowledgement

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Disclosures

Dr Andrew Teodorczuk reports no competing interests
Dr Michael J. Firbank reports no competing interests
Dr Leonardo Pantoni reports no competing interests
Dr Anna Poggesi reports no competing interests
Professor Timo Erkinjuntti reports no competing interests
Professor Anders Wallin has been on the advisory board and received speaker honoraria from GSK, Janssen-Cilag, Lundbeck, Novartis, Pfizer.
Professor Lars-Olof Wahlund reports no competing interests
Professor Philip Scheltens reports no competing interests
Professor Gunhild Waldemar has received consultancy honoraria from Pfizer and Lundbeck.
Dr Gabriele Schrotter reports no competing interests
Professor José M. Ferro reports no competing interests
Dr Hugues Chabrier reports no competing interests
Professor Hansjörg Bäzner reports no competing interests
Dr Marieke Visser reports no competing interests
Professor Domenico Inzitari reports no competing interests
Professor John T. O’Brien reports no competing interests
REFERENCES

*Biological Psychiatry* **60**, 1304-5.


patients with severe cerebral age-related white matter changes: the LADIS study.


APPENDIX. List of participating centres and personnel.

**Helsinki, Finland** (Memory Research Unit, Department of Clinical Neurosciences, Helsinki University): Timo Erkinjuntti, MD, PhD, Tarja Pohjasvaara, MD, PhD, Pia Pihanen, MD, Raija Ylikoski, PhD, Hanna Jokinen, LPsych, Meija-Marjut Somerkoski, MPSych, Riitta Mäntylä, MD, PhD, Oili Salonen, MD, PhD; **Graz, Austria** (Department of Neurology and MRI Institute, Medical University Graz): Franz Fazekas, MD, Reinhold Schmidt, MD, Stefan Ropele, PhD, Brigitte Rous, MD, Katja Petrovic, MagPsychol, Ulrike Garmehi, Alexandra Seewann, MD; Gabriele Schrotter, MD **Lisboa, Portugal** (Serviço de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria): José M. Ferro, MD, PhD, Ana Verdelho, MD, Sofia Madureira, PsyD; **Amsterdam, The Netherlands** (Department of Radiology and Neurology, VU Medical Center): Philip Scheltens, MD, PhD, Ilse van Straaten, MD, Frederik Barkhof, MD, PhD, Alida Gouw, MSc, Wiesje van der Flier, PhD; **Goteborg, Sweden** (Institute of Clinical Neuroscience, Goteborg University): Anders Wallin, MD, PhD, Michael Jonsson, MD, Karin Lind, MD, Arto Nordlund, PsyD, Sindre Rolstad, PsyD, Ingela Isblad, RN; **Huddinge, Sweden** (Karolinska Institute, Neurotec Department, sektion of Clinical Geriatrics): Lars-Olof Wahlund, MD, PhD, Milita Crisby, MD, PhD, Anna Pettersson, physiotherapist, Kaarina Amberla, PsyD; **Paris, France** (Department of Neurology, Hopital Lariboisiere): Hugues Chabriat, MD, PhD, Karen Hernandez, psychologist, Annie Kurtz, psychologist, Dominique Hervé, MD; **Mannheim, Germany** (Department of Neurology, University of Heidelberg, Klinikum Mannheim): Michael Hennerici, MD, Christian Blahak, MD, Hansjorg Baezner, MD, Martin Wiarda, PsyD, Susanne Seip, RN; **Copenhagen, Denmark** (The Memory Disorders Research Group, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Denmark): Gunhild Waldemar, MD,
WHITE MATTER CHANGES AND DEPRESSIVE SYMPTOMS

DMSc, Egill Rostrup, MD, MSc; Charlotte Ryberg, MSc, Tim Dyrby MSc, Olaf B. Paulson, MD, DMSc; **Newcastle-upon-Tyne, UK** (Institute for Ageing and Health, University of Newcastle): John O'Brien, DM, Sanjeet Pakrasi, MD, Andrew Teodorczuk, MRCPsych, Mani Krishnan MRCPsych, Michael Firbank, PhD, Philip English, DCR.

The Coordinating centre is in **Florence, Italy** (Department of Neurological and Psychiatric Sciences, University of Florence): Domenico Inzitari, MD (Study Coordinator); Luciano Bartolini, PhD, Anna Maria Basile, MD, PhD, Eliana Magnani, MD, Monica Martini, MD, Mario Mascalchi, MD, PhD, Marco Moretti, MD, Leonardo Pantoni, MD, PhD, Anna Poggesi, MD, Giovanni Pracucci, MD, Emilia Salvadori, PhD, Michela Simoni, MD.

The **LADIS Steering Committee** is formed by Domenico Inzitari, MD (study coordinator), Timo Erkinjuntti, MD, PhD, Philip Scheltens, MD, PhD, Marieke Visser, MD, PhD, and Peter Langhorne, MD, BSc, PhD, FRCP who replaced in this role Kjell Asplund, MD, PhD beginning with 2005.
Table 1. Characteristics for the study group who completed all final year assessments.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>399</td>
</tr>
<tr>
<td>Age at inclusion</td>
<td>73.6 (5)</td>
</tr>
<tr>
<td>Sex F:M</td>
<td>217:182</td>
</tr>
<tr>
<td>GDS at inclusion: median (range)</td>
<td>2 (0-14)</td>
</tr>
<tr>
<td>Incident depression: Number (%)</td>
<td>85 (21 %)</td>
</tr>
<tr>
<td>Transition to disability over 3 years: Number (%)</td>
<td>95 (24%)</td>
</tr>
<tr>
<td>History of depression: Number (%)</td>
<td>105 (26 %)</td>
</tr>
<tr>
<td>History of hypertension: Number (%)</td>
<td>279 (70 %)</td>
</tr>
<tr>
<td>History of stroke: Number (%)</td>
<td>110 (28 %)</td>
</tr>
<tr>
<td>Years of education</td>
<td>10 (4)</td>
</tr>
<tr>
<td>MMSE at inclusion</td>
<td>27.8 (2.2)</td>
</tr>
<tr>
<td>DAD at inclusion</td>
<td>98.4 (6.4)</td>
</tr>
<tr>
<td>ARWMC volume in ml: median (range)</td>
<td>13.3 (1 – 156)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise specified.
Data obtained in subjects at baseline.

GDS, Geriatric Depression Scale; MMSE, Mini Mental State Exam; ARWMC, age related white matter changes; DAD, Disability Assessment in Dementia Scale.
Table 2 Disability in Dementia scores over the study period

<table>
<thead>
<tr>
<th>Year</th>
<th>DAD score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>98.4 (6.4)</td>
</tr>
<tr>
<td>1</td>
<td>97.7 (7.3)</td>
</tr>
<tr>
<td>2</td>
<td>96.5 (11.1)</td>
</tr>
<tr>
<td>3</td>
<td>93.9 (16.3)</td>
</tr>
</tbody>
</table>

Data are mean (SD)

DAD, Disability Assessment in Dementia Scale

Data obtained in 383 subjects.
Table 3 *Step forward regression analysis of predictors of quintile of GDS at 2 years (N=399)*

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rho</td>
<td>P Value</td>
</tr>
<tr>
<td>Baseline log ARWMC volume</td>
<td>0.27</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Baseline GDS Quintile</td>
<td>0.64</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>-0.16</td>
<td>0.002*</td>
</tr>
<tr>
<td>Years of education</td>
<td>-0.20</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Age in years at inclusion</td>
<td>0.07</td>
<td>0.15</td>
</tr>
<tr>
<td>Smoking (never vs. current/past)</td>
<td>-0.05</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline history of hypertension</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>Baseline history of Stroke</td>
<td>0.05</td>
<td>0.3</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.07</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data obtained in 399 subjects.

GDS, Geriatric Depression Scale; MMSE, Mini Mental State Exam; ARWMC, age related white matter changes.

*p<0.05
Table 4. *Stepforward regression analysis of predictors of quintile GDS at 3 years (N=399)*

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<tbody>
<tr>
<td></td>
<td>Rho</td>
<td>P Value</td>
</tr>
<tr>
<td>Baseline log ARWMC volume</td>
<td>0.16</td>
<td>0.001*</td>
</tr>
<tr>
<td>Baseline GDS Quintile</td>
<td>0.58</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Years of education</td>
<td>-0.1</td>
<td>0.023*</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>-0.1</td>
<td>0.048*</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.12</td>
<td>0.013 *</td>
</tr>
<tr>
<td>Smoking (never vs. current/past)</td>
<td>-0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline history of hypertension</td>
<td>0.01</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline history of stroke</td>
<td>0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>Age in years at inclusion</td>
<td>0.09</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data obtained in 399 subjects.

GDS, Geriatric Depression Scale; MMSE, Mini Mental State Exam; ARWMC, age related white matter changes.

*p<0.05
### Table 5 – Stepforward regression analysis of predictors of incident depression over 3 years

\( (n=399) \)

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Binary Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rho</td>
<td>P Value</td>
</tr>
<tr>
<td>Baseline log ARWMC volume</td>
<td>0.099</td>
<td>0.047 *</td>
</tr>
<tr>
<td>Baseline history of depression</td>
<td>0.342</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>-0.098</td>
<td>0.051</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.096</td>
<td>0.057</td>
</tr>
<tr>
<td>Years of education</td>
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</tr>
<tr>
<td>Smoking (never vs. current/past)</td>
<td>-0.035</td>
<td>0.5</td>
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<tr>
<td>Baseline history of hypertension</td>
<td>-0.021</td>
<td>0.7</td>
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<tr>
<td>Baseline history of stroke</td>
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<td>0.3</td>
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<tr>
<td>Age in years at inclusion</td>
<td>0.035</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Data obtained in 399 subjects.

GDS, Geriatric Depression Scale; MMSE, Mini Mental State Exam; ARWMC, age related white matter changes.

*p<0.05