Brain hyperintensity location determines outcome in the triad of impaired cognition, physical health and depressive symptoms

A cohort study in late life

Title: Brain hyperintensity location determines outcome in the triad of impaired cognition, physical health and depressive symptoms: A cohort study in late life

Author: Alison Murray Chris McNeil Sima Salarirad Ian Deary Louise Phillips Lawrence Whalley Roger Staff

PII: S0167-4943(15)30068-6
DOI: http://dx.doi.org/doi:10.1016/j.archger.2015.10.004
Reference: AGG 3233

To appear in: *Archives of Gerontology and Geriatrics*

Received date: 21-11-2014
Revised date: 30-7-2015
Accepted date: 14-10-2015

Please cite this article as: Murray, Alison, McNeil, Chris, Salarirad, Sima, Deary, Ian, Phillips, Louise, Whalley, Lawrence, Staff, Roger, Brain hyperintensity location determines outcome in the triad of impaired cognition, physical health and depressive symptoms: A cohort study in late life.Archives of Gerontology and Geriatrics http://dx.doi.org/10.1016/j.archger.2015.10.004

Brain hyperintensity location determines outcome in the triad of impaired cognition, physical health and depressive symptoms: A cohort study in late life

[a]Alison Murray: a.d.murray@abdn.ac.uk*

[a]Chris McNeil: c.mcneil@abdn.ac.uk.

[a]Sima Salarirad: s.salari@abdn.ac.uk.

[b]Ian Deary: iand@staffmail.ed.ac.uk

[a]Louise Phillips: louise.phillips@abdn.ac.uk

[a]Lawrence Whalley: l.j.whalley@abdn.ac.uk

[c]Roger Staff: r.staff@abdn.ac.uk.

[a]University of Aberdeen, Aberdeen, UK

[b]University of Edinburgh, Edinburgh, UK

[c]NHS Grampian, Aberdeen, UK

*Correspondence
Professor Alison D Murray
Aberdeen Biomedical Imaging Centre
Lilian Sutton Building
Foresterhill
Aberdeen AB25 2ZD

+44(0)1224 438362

UK

a.d.murray@abdn.ac.uk

Short Title: Brain hyperintensities and the triad of impairment in late-life

Abstract

Purpose of the study: Brain hyperintensities, detectable with MRI, increase with age. They are associated with a triad of impairment in cognitive ability, depression and physical health. Here we test the hypothesis that the association between hyperintensities and cognitive ability, physical health and depressive symptoms depends on lesion location.

Design and Methods: 244 members of the Aberdeen 1936 Birth Cohort were recruited to this study. 227 participants completed brain MRI and their hyperintensities were scored using Scheltens's scale. 205 had complete imaging, cognitive, physical health and depressive symptom score data. The relationships between hyperintensity location and depressive symptoms, cognitive ability and physical health were examined by correlation and structural equation analysis.

Results: We found that depressive symptoms correlated with hyperintensity burden in the grey matter ($r = 0.14$, $p = 0.04$) and infratentorial regions ($r = 0.17$, $p = 0.01$). Infratentorial hyperintensities correlated with reduced peak expiratory flow rate ($r = -0.255$, $p<0.001$) and impaired gait ($r = 0.13$, $p = 0.05$). No relationship was found between white matter and periventricular (supratentoral) hyperintensities and depressive symptoms. Hyperintensities in the supratentorial and infratentorial regions were associated with reduced cognitive performance. Using structural equation modelling we found that the association between hyperintensities and depressive symptoms was mediated by negative effects on physical health and cognitive ability.

Conclusions: Hyperintensities in deep brain structures are associated with depressive symptoms, mediated via impaired physical health and cognitive ability. Participants with higher cognitive ability and better physical health are at lower risk of depressive symptoms.

Abbreviations:

WMH: White matter hyperintensities; PVH: Periventricular hyperintensities; ABC36: Aberdeen 1936 Birth Cohort; GMH: Grey matter hyperintensities; ITH: infratentorial hyperintensities; SEM: Structural Equation Model; PCA: Principle Components Analysis.

Keywords: White matter hyperintensities; physical health; frailty; depression; cognition, cohort,

Introduction

We have demonstrated that magnetic resonance imaging-detected brain hyperintensities (Wardlaw et al., 2013) in the deep grey matter and infratentorial regions, attributed to cerebrovascular disease, are associated with increased depressive symptoms and have hypothesised that this is mediated by an effect on physical health (Murray et al., 2013). In cross-sectional and longitudinal reports from the Cardiovascular Health Study, hypertension is associated with a triad of impairments in mobility, mood and cognition (Hajjar et al., 2009), which in turn are associated with increased disability and mortality (Hajjar et al., 2011). This association is mediated by white matter hyperintensities (WMH) as evidence of microvascular injury. Elias et al. found, using path analysis in the Maine-Syracuse Longitudinal Study, that the negative relationship between systolic hypertension and physical ability is mediated by cognitive ability, but did not include brain imaging (Elias, Dore, Davey, Robbins, & Elias, 2010).

Despite recognised associations between WMH and impaired cognitive ability and physical health (Leaper et al., 2001), most previous studies have not specified location of brain hyperintensities on imaging (Guttmann et al., 1998). However, reports from the Leukoaraiosis and disability (LADIS) study identified WMH, rather than lacunar infarcts or periventricular hyperintensities (PVH), as significant predictors of depressive symptoms (Krishnan et al., 2006; O'Brien et al., 2006). A cross-sectional analysis from the Rotterdam study found the same association between WMH and depressive symptoms, but that this was not the case in a longitudinal analysis (Ikram et al., 2010). WMH, in turn, are associated with impaired cognitive ability. The LADIS study also found whole brain lesion burden to be associated with balance and gait disorders (Baezner et al., 2008). In a previous analysis of the 1921 Aberdeen Birth Cohort, we found brainstem hyperintensities were significantly associated with impaired gait speed and balance (Starr et al., 2003).

Here, we test the hypothesis that the association between brain hyperintensities and components of the triad of impaired cognitive ability, impaired physical health and depressive symptoms depends on lesion location. In addition, we hypothesise that hyperintensities in the deep grey matter and infratentorial regions are associated with depressive symptoms via an effect on impaired physical ability, rather than cognitive ability.

Methods

Study design and participants

The sample studied here is a sub-set of survivors of the Scottish Mental Survey of 1947, which examined the mental ability of almost all eligible Scottish schoolchildren born in 1936. We recruited 497 local survivors, aged approximately 64 years, into a longitudinal study of cognitive ageing and health; the 1936 Aberdeen Birth Cohort Study (ABC36), described more fully in Whalley et al. (Whalley et al., 2011). In 2004, 320 members of ABC36, selected at random, were invited to undergo brain MRI. 244 participants both agreed and were suitable for inclusion, aged approximately 68 years. Complete imaging data, suitable for inclusion were available for 227 of these participants. The structure of this study is summarised in Figure 1.This study received the approval of the Local Research Ethics Committee: The Grampian Research Ethics Committee, and informed, written consent was obtained from all participants.

Brain MRI acquisition and analysis

Brain MRI was carried out in 244 ABC36 participants on a 1.5T NVi system (General Electric, Milwaukee, Wi) between 2003 and 2005 using T2 axial (TR/TE 4900/81.4, slice thickness 5mm, space 1.2mm), fluid attenuation inversion recovery axial (FLAIR) (TR/TE 9002/1.33, TI 2200, slice thickness 5 mm, space 1.2 mm) and 3D T1 weighted spoiled gradient recalled acquisition (SPGR) (TR/TE 20/6ms, flip angle 35o, number of slices 124, effective slice thickness 1.6mm, matrix 256x192, in-plane resolution 1x1mm) sequences. Complete T2 and FLAIR MRI data were available in 243 and complete 3DT1 data in 233, the smaller number being due to movement during the relatively longer volumetric acquisition. T2 and FLAIR images were analysed using Scheltens's scale (Scheltens et al., 1993) which attributes scores based on hyperintensity size and number in the sub-cortical and deep white matter (WMH), periventricular white matter (PVH), deep grey matter (GMH) and infratentorial regions (ITH).

Cognitive assessment

A psychologist administered the following five neuropsychological tests: Raven's Progressive Matrices (RPM), a non-verbal reasoning measure of fluid intelligence; Auditory Verbal Learning Test (AVLT), a measure of immediate and delayed verbal memory; National Adult Reading Test (NART), a measure of reading and language ability, and a good measure of peak, or premorbid, intelligence; Uses of Common Objects (UCO) test, a measure of executive function or purposive action and Digit Symbol test (DS), a measure of processing

speed , attention and visual short-term memory. Cognitive scores measured at age 68, collected contemporaneously with brain MRI, were entered into the analyses.

Assessment of depressive symptoms

All participants completed the Hospital Anxiety and Depression Scale (HADS), a self-reported questionnaire of frequency of depressive and anxiety symptoms.(Zigmond & Snaith, 1983) As described previously (Murray et al., 2013) the mean of depression scores obtained at ages 64, 66 and 68 years were entered into the analyses. This reduces the effect of day-to-day variability in depression, and is a measure of long-term mood.

Assessment of physical health

Two measures were used to assess physical ability at age 68y; walk time (WT) and peak expiratory flow rate (PEFR). Walk time is the time in seconds taken to walk six metres, corrected for height. PEFR was measured using a spirometer and recorded as the best of three attempts in litres per minute. These measures reflect both physical fitness and motor control.

Statistical analysis

Bivariate (Pearson's) correlations were used to investigate relationships between variables using SPSS (IBM Corp. SPSS for Windows, Version 20.0. Armonk, NY:) Differences between correlation coefficients were analysed using the method of Steiger (Steiger, 1980). Structural equation models (SEM) were constructed to investigate the hypothesis that the negative influence of brain hyperintensities on outcome variables depends on their location. Specifically, we investigated whether the influence of hyperintensities in the deep grey matter (GMH) and infratentorial regions (ITH) on depressive symptom scores is direct or is mediated by poorer physical health and/or cognitive ability. Similarly, we investigated the influence of hyperintensities in the hemispheric white matter (WMH and PVH) on depressive symptom scores. Cognitive scores were all significantly and positively inter-correlated and principal components analysis (PCA) showed that 46% of the variance between scores is explained by a general cognitive factor '*g*', which was extracted as the first un-rotated principal component and used in subsequent analyses. To test the relationship of '*g'* to its parent variables, Pearson's correlations were performed and the following coefficients determined; RPM = 0.71, AVLT = 0.67, NART = 0.77, UCO = 0.58, DS = 0.66). PCA does not strictly extract 'factors' but this term finds general usage. Whereas extraction of '*g*' as a latent variable can be performed as part of structural equation modelling by inclusion of

different cognitive variables, with the number of variables and sample size presented here, a more parsimonious model is produced by extracting '*g*' before modelling. To test the hypothesis that a single cognitive score may be a better predictor of HADS than *'g'* we correlated each component of *'g'*, and *'g'* itself with HADS depression, and compared coefficients by the method of Steiger et al (1980). A physical health latent variable was extracted in a similar way, where 68% of variance between PEFR and time to walk 6 metres was explained by a 'PH' latent variable. SEMs were constructed using AMOS 18 (AMOS 18. AMOS for Windows, Version 18. Armonk, NY) and the goodness of fit was assessed according to the following criteria: chi-squared to degrees of freedom ratio close to 1, incremental fit index >0.95 and comparative fit index >0.95. In addition, the root mean square error of approximation was measured, where a value <0.05 indicates a good fit, and <0.08 an acceptable fit. For brevity in path diagrams, although anatomically incorrect, GMH and ITH are referred to as "deep brain (DB) hyperintensities" and WMH and PVH as "supratentorial (ST) hyperintensities".

Results

Descriptive statistics

Complete data, including brain MRI, mood, cognitive and physical ability were available for 204 participants. A comparison of participants with HADS depression scores greater than or equal to versus less than 6 is shown in Table 1 and indicates significantly lower '*g*', slower walk times and reduced PEFR in those with HADS depression scores >6. Total Scheltens's scores ranged from 0-47 (mean 16.5) and were highest in the frontal white matter. Most infratentorial hyperintensities were in the pons.

Correlations

Bivariate (Pearson's) correlations are shown in Table 2. There was a significant negative correlation between HADS-D scores and '*g*' (r= -.221, P<.001). The correlation between HADS-D and the following constituent components of '*g*' were calculated: UoO (r=.10, P=NS); RPM (r=-0.235, P<.001); DS (r=0.179, P<.01); AVLT (r=-.123, P<.05); NART(r=-.157, P<.05). These coefficient coefficients did not differ significantly and were not different to the correlation between HADS-D and '*g*'.

We found positive correlations between HADS-D and GMH (r=.138, P<.05), ITH (r=.169, P<.05) and walk time (r=.211, P<.05). In addition there were significant negative correlations between '*g*' and WMH (r= -.242, P<.001), PVH (r= -.206, P<.05) and ITH (r= -.177, P<.05). Walk time correlated significantly with PEFR (negatively) (r= -.416, P<.001) and with ITH (positively) (r= .211, P<.05). As expected, there were significant positive correlations between regional hyperintensity scores *(*r= .344 - .710, P<.001 for all). The correlation coefficients of "deep brain" hyperintensities (GMH+ITH) versus HADS-D differs significantly from the coefficient of "supratentorial" hyperintensities (WMH+PVH) versus HADS-D ($r_{db,}$=.183 vs r_{st}=.039, P<.05). This analysis was repeated for deep brain or supratentoral hyperintensities versus physical health ($r_{db,}$=-0.219 vs r_{st}=-0.024, P<0.01). No regional differential effect was seen for the correlation coefficients of '*g'* versus hyperintensity burden.

Structural equation modelling

Structural equation models are shown in Figures 2-4. Figure 2 demonstrates the direct effect of deep brain hyperintensities on depressive symptoms. Grey matter and infratentoral hyperintensity scores contribute to the latent lesion burden variable 'DB'. DB significantly contributes to mean HADS (standardised β = .24). Figure 3 includes the indirect effects of physical health and cognitive ability on means HADS score. Here DB contributes indirectly to increased depressive scores via its effects on physical health (standardised β = -.29) and cognitive function (standardised β = -.22). In this model it is revealed that there was no direct effect of the DB latent variable on depressive symptom scores. Figure 4 demonstrates that the latent variable ST derived from white matter and periventricular hyperintensity scores has no effect on physical health and no direct effect on depressive scores. The models shown in Figures 2-4 have good - excellent fit indices, with CMIN/DF 0.38 - 1.06, comparative fit indices 1.00 - 0.99 and RMSEA <.001 - .002.

Discussion

Main findings

Here we demonstrate, using correlation analysis and structural equation modelling in a healthy older sample, that the relationship between MRI detected hyperintensities and outcome varies according to lesion location. In particular, the negative relationship between

basal ganglia and brainstem hyperintensities and depressive symptoms is mediated by the negative effect of these deep brain lesions on physical health, and to a lesser extent, their negative effect on cognitive ability. The negative effect of subcortical and periventricular hyperintensities on depressive symptoms reported by other groups (Ikram et al., 2010; Wendell et al., 2010) was not found. However, the model did confirm the relationship of greater hyperintensity burden and lower cognitive ability, which may explain the observations of other groups that have not accounted for cognition in their analyses.

Brain hyperintensities and outcome variables

Associations between WMH and depressive symptoms are well documented.(Sheline et al., 2010) These results do not contradict the vascular depression hypothesis but indicate that the relationship between markers of cerebrovascular disease and depressive symptoms is indirect and is mediated by poorer cognitive and physical ability. These findings are consistent with previous reports of relationships between depression and MRI detected brain hyperintensities in the brainstem and cerebellum in a small sample (Agid, Levin, Gomori, Lerer, & Bonne, 2003) and adds new insights into the mechanism by which associations of medical co-morbidities with depressed mood may occur.(Millan-Calenti et al., 2011) A more recent systematic review also reports association of deep hyperintensities with depression (Wang, Leonards, Sterzer, & Ebinger, 2014). The association of GMH with cognitive ability and physical ability confirms a report of lacunes in the thalamus and putamen predicting poorer cognitive function, speed and motor control, independent of the effect of WMH.(Benisty et al., 2009) Functional disconnection of the basal ganglia and dorsolateral pre-frontal cortex is a proposed mechanism of the negative cognitive effect of bran hyperintensities (Mayda, Westphal, Carter, & DeCarli, 2011). The results suggest that brain hyperintensities mediate the relationship of hypertension on a triad of impaired cognition, mobility and mood (Hajjar et al., 2011) and add to this by illustrating that location of brain hyperintensities determines the outcome. In particular, we find that the association of deep brain hyperintensities with low mood is largely driven by their effect on poorer physical health, while subcortical and periventricular hyperintensities affect low mood indirectly via poorer cognitive ability only. We did not find any direct effect of WMH and PVH on physical health and these results conflict with findings in an older sample (Moscufo et al., 2011). These results do not preclude a common cause for both brain hyperintensities and outcome variables, in addition to the effect of hypertension.

Physical health and depressive symptoms

The association of late life depression and vascular co-morbidities is well recognised (Taylor, McQuoid, & Krishnan, 2004). It is not surprising that impaired physical ability in late life is associated with depressive symptoms. Poorer walking and balance abilities in older people will have inevitable negative effects on ability to undertake exercise and gain from the associated positive health benefits. Similarly, impaired physical ability will reduce confidence in undertaking group activities that involve social interaction and exercise, for example dancing or bowling, and the positive cognitive stimulation and contribution to cognitive reserve that comes from these (Eskes et al., 2010). Longitudinal study of the "Neurocognitive Outcomes of Depression" sample found the greatest risk of functional (physical) decline in those participants with both high WMH volumes on brain MRI and depression but did not analyse hyperintensity location (Hybels, Pieper, Payne, & Steffens, 2015).

Cognitive ability and depressive symptoms

The association of depressive symptoms and cognitive impairment in older people is common but it remains unclear whether depressive symptoms in late life are a prodromal symptom of cognitive decline and dementia (Brommelhoff et al., 2009). Depressive symptoms predict increased mortality regardless of cognitive impairment.(Lavretsky et al., 2010) In the Women's Health Initiative study Goveas et al (Goveas, Espeland, Woods, Wassertheil-Smoller, & Kotchen, 2011) found that clinically significant depression was associated with future cognitive impairment and dementia and subsequently, in the same sample, that depressive symptoms were associated with smaller frontal lobe volumes but not with hemispheric measures of cerebrovascular disease (Goveas et al., 2011). However, their method of measurement of white matter hyperintensities excluded the posterior fossa. The results presented here suggest brain hyperintensities may influence depressive symptoms through more than one route and that if the hyperintensities are in deep grey matter and infratentorial regions, they are also associated with poorer physical health.

Strengths and weaknesses

The strengths of this study are inclusion of well-characterised, non-demented, normal people, for whom brain MRI was available. Compared with 1936 Aberdeen Birth Cohort participants who did not undergo brain MRI, the current study sample were healthier and of higher cognitive ability. The findings here are thus both unlikely to underestimate relationships and

to be generalisable to the normal population. Weaknesses include use of the HADS depression score, which can be criticised as an insensitive measure, and use of a visual scoring method for brain MRI white matter hyperintensities. However, the Scheltens's scale is well validated, compares well with automated methods (Tiehuis et al., 2008) and, for this study in particular, it can be argued that use of an automated voxel-based method, (Grool, van der Graaf, Mali, Geerlings, & on behalf of the SMART Study Group, 2011) or of a global scale, would have excluded brainstem hyperintensities. A further weakness is that relationships illustrated here are derived from cross-sectional data and it is thus impossible to determine a causal link between intelligence or physical health and depressive symptoms. It is noteworthy, however that NART – an indication of maximum (premorbid) intelligence - is negatively associated with depressive symptom scores, providing evidence that a measure of maximum lifetime cognitive ability does influence depressive outcomes.

Conclusions and future work

This work confirms our first hypothesis; that the relationships between brain hyperintensities and components of the triad of impaired cognition, mobility and mood depend on lesion location. In addition, the association of hyperintensities in the deep grey matter and infratentorial regions with depressive symptoms demonstrated previously (Murray et al., 2013) is mediated largely by impaired physical health. Hyperintensities in these deep brain regions and supratentorial hyperintensities (WMH and PVH) both also have a negative effect on depressive symptoms mediated by reduced cognitive ability. Supratentorial (white matter and periventrivcular) hyperintensities only affect depressive symptoms indirectly via their relationship with cognitive ability. Future work should investigate the influence of lesion location on longitudinal change in these outcome variables, particularly on prediction of dementia and physical frailty and whether a common cause may influence brain imaging and outcome variables.

Acknowledgements

The authors would like to thank the participants of the Aberdeen 1936 Birth Cohort (ABC36). Image acquisition and image analysis for ABC36 were funded by the Alzheimer's Research Trust (now Alzheimer's Research UK). A.D.M., C.J.M., S.S., L.J.W., and R.T.S. have received grants from: Chief Scientist Office, Department of Health, Scottish Government; Biotechnology and Biological Sciences Research Council

Conflict of Interest

None of the authors have any financial, personal or potential conflict of interest with the material contained within this article.

Author Contribution

All authors drafted and revised the manuscript content. Murray and Staff developed the study concept and design. Whalley, Deary, Murray, Starr and Staff obtained funding. All authors analysed and interpreted data. McNeil and Staff performed the statistical analysis.

References

Agid, R., Levin, T., Gomori, J. M., Lerer, B., & Bonne, O. (2003). T2-weighted image hyperintensities in major depression: Focus on the basal ganglia. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 6*(3), 215-224. doi:10.1017/S146114570300347X

Baezner, H., Blahak, C., Poggesi, A., Pantoni, L., Inzitari, D., Chabriat, H., et al. (2008). Association of gait and balance disorders with age-related white matter changes: The LADIS study. *Neurology, 70*(12), 935-942. doi:10.1212/01.wnl.0000305959.46197.e6

Benisty, S., Gouw, A. A., Porcher, R., Madureira, S., Hernandez, K., Poggesi, A., et al. (2009). Location of lacunar infarcts correlates with cognition in a sample of non-disabled subjects with age-related white-matter changes: The LADIS study. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*(5), 478-483. doi:10.1136/jnnp.2008.160440

Brommelhoff, J. A., Gatz, M., Johansson, B., McArdle, J. J., Fratiglioni, L., & Pedersen, N. L. (2009). Depression as a risk factor or prodromal feature for dementia? Findings in a population-based sample of swedish twins. *Psychology and Aging, 24*(2), 373-384. doi:10.1037/a0015713

Elias, M. F., Dore, G. A., Davey, A., Robbins, M. A., & Elias, P. K. (2010). From blood pressure to physical disability: The role of cognition. *Hypertension, 55*(6), 1360-1365. doi:10.1161/HYPERTENSIONAHA.110.149823

Eskes, G. A., Longman, S., Brown, A. D., McMorris, C. A., Langdon, K. D., Hogan, D. B., & Poulin, M. (2010). Contribution of physical fitness, cerebrovascular reserve and cognitive stimulation to cognitive function in post-menopausal women. *Frontiers in Aging Neuroscience, 2*, 137. doi:10.3389/fnagi.2010.00137

Goveas, J. S., Espeland, M. A., Hogan, P., Dotson, V., Tarima, S., Coker, L. H., et al. (2011). Depressive symptoms, brain volumes and subclinical cerebrovascular disease in postmenopausal women: The women's health initiative MRI study. *Journal of Affective Disorders, 132*(1-2), 275-284. doi:10.1016/j.jad.2011.01.020

Goveas, J. S., Espeland, M. A., Woods, N. F., Wassertheil-Smoller, S., & Kotchen, J. M. (2011). Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: The women's health initiative memory study. *Journal of the American Geriatrics Society, 59*(1), 57-66. doi:10.1111/j.1532-5415.2010.03233.x; 10.1111/j.1532-5415.2010.03233.x

Grool, A. M., van der Graaf, Y., Mali, W. P., Geerlings, M. I., & on behalf of the SMART Study Group. (2011). Location of cerebrovascular and degenerative changes, depressive symptoms and cognitive functioning in later life: The SMART-medea study. *Journal of Neurology, Neurosurgery, and Psychiatry, 82*(10), 1093-1100. doi:10.1136/jnnp.2010.232413

Guttmann, C. R., Jolesz, F. A., Kikinis, R., Killiany, R. J., Moss, M. B., Sandor, T., & Albert, M. S. (1998). White matter changes with normal aging. *Neurology, 50*(4), 972-978.

Hajjar, I., Quach, L., Yang, F., Chaves, P. H., Newman, A. B., Mukamal, K., et al. (2011). Hypertension, white matter hyperintensities, and concurrent impairments in mobility,

cognition, and mood: The cardiovascular health study. *Circulation, 123*(8), 858-865. doi:10.1161/CIRCULATIONAHA.110.978114

Hajjar, I., Yang, F., Sorond, F., Jones, R. N., Milberg, W., Cupples, L. A., & Lipsitz, L. A. (2009). A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: Relationship to blood pressure and other cardiovascular risks. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 64*(9), 994-1001. doi:10.1093/gerona/glp075

Hybels, C. F., Pieper, C. F., Payne, M. E., & Steffens, D. C. (2015). Late-life depression modifies the association between cerebral white matter hyperintensities and functional decline among older adults. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry,* doi:S1064-7481(15)00113-X [pii]

Ikram, M. A., Luijendijk, H. J., Vernooij, M. W., Hofman, A., Niessen, W. J., van der Lugt, A., et al. (2010). Vascular brain disease and depression in the elderly. *Epidemiology (Cambridge, Mass.), 21*(1), 78-81. doi:10.1097/EDE.0b013e3181c1fa0d

Krishnan, M. S., O'Brien, J. T., Firbank, M. J., Pantoni, L., Carlucci, G., Erkinjuntti, T., et al. (2006). Relationship between periventricular and deep white matter lesions and depressive symptoms in older people. the LADIS study. *International Journal of Geriatric Psychiatry, 21*(10), 983-989. doi:10.1002/gps.1596

Lavretsky, H., Zheng, L., Weiner, M. W., Mungas, D., Reed, B., Kramer, J. H., et al. (2010). Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *The American Journal of Psychiatry, 167*(5), 589-597. doi:10.1176/appi.ajp.2009.09020280

Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., Crawford, J. R., & Whalley, L. J. (2001). Neuropsychologic correlates of brain white matter lesions depicted on MR images: 1921 aberdeen birth cohort. *Radiology, 221*(1), 51-55.

Mayda, A. B., Westphal, A., Carter, C. S., & DeCarli, C. (2011). Late life cognitive control deficits are accentuated by white matter disease burden. *Brain : A Journal of Neurology, 134*(Pt 6), 1673-1683. doi:10.1093/brain/awr065

Millan-Calenti, J. C., Maseda, A., Rochette, S., Vazquez, G. A., Sanchez, A., & Lorenzo, T. (2011). Mental and psychological conditions, medical comorbidity and functional limitation: Differential associations in older adults with cognitive impairment, depressive symptoms and co-existence of both. *International Journal of Geriatric Psychiatry, 26*(10), 1071-1079. doi:10.1002/gps.2646; 10.1002/gps.2646

Moscufo, N., Guttmann, C. R., Meier, D., Csapo, I., Hildenbrand, P. G., Healy, B. C., et al. (2011). Brain regional lesion burden and impaired mobility in the elderly. *Neurobiology of Aging, 32*(4), 646-654. doi:10.1016/j.neurobiolaging.2009.04.010

Murray, A. D., Staff, R. T., McNeil, C. J., Salarirad, S., Phillips, L. H., Starr, J., et al. (2013). Depressive symptoms in late life and cerebrovascular disease: The importance of intelligence and lesion location. *Depression and Anxiety, 30*(1), 77-84. doi:10.1002/da.22022; 10.1002/da.22022

O'Brien, J. T., Firbank, M. J., Krishnan, M. S., van Straaten, E. C., van der Flier, W. M., Petrovic, K., et al. (2006). White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: The LADIS study. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 14*(10), 834-841. doi:10.1097/01.JGP.0000214558.63358.94

Scheltens, P., Barkhof, F., Leys, D., Pruvo, J. P., Nauta, J. J., Vermersch, P., et al. (1993). A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *Journal of the Neurological Sciences, 114*(1), 7-12.

Sheline, Y. I., Pieper, C. F., Barch, D. M., Welsh-Bohmer, K., McKinstry, R. C., MacFall, J. R., et al. (2010). Support for the vascular depression hypothesis in late-life depression: Results of a 2-site, prospective, antidepressant treatment trial. *Archives of General Psychiatry, 67*(3), 277-285. doi:10.1001/archgenpsychiatry.2009.204

Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., & Whalley, L. J. (2003). Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. *Journal of Neurology, Neurosurgery & Psychiatry, 74*(1), 94-98.

Steiger, J. H. (1980). Tests for comparing elements of a correlation matrix. *Psychological Bulletin, 87*, 245-251.

Taylor, W. D., McQuoid, D. R., & Krishnan, K. R. R. (2004). Medical comorbidity in late-life depression. *International Journal of Geriatric Psychiatry, 19*(10), 935-943. doi:10.1002/gps.1186

Tiehuis, A. M., Vincken, K. L., Mali, W. P., Kappelle, L. J., Anbeek, P., Algra, A., & Biessels, G. J. (2008). Automated and visual scoring methods of cerebral white matter hyperintensities: Relation with age and cognitive function. *Cerebrovascular Diseases (Basel, Switzerland), 25*(1-2), 59-66. doi:10.1159/000111500

Wang, L., Leonards, C. O., Sterzer, P., & Ebinger, M. (2014). White matter lesions and depression: A systematic review and meta-analysis. *Journal of Psychiatric Research, 56*, 56-64. doi:10.1016/j.jpsychires.2014.05.005 [doi]

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet.Neurology, 12*(8), 822-838. doi:10.1016/S1474-4422(13)70124-8 [doi]

Wendell, C. R., Hosey, M. M., Lefkowitz, D. M., Katzel, L. I., Siegel, E. L., Rosenberger, W. F., & Waldstein, S. R. (2010). Depressive symptoms are associated with subclinical cerebrovascular disease among healthy older women, not men. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 18*(10), 940-947. doi:10.1097/JGP.0b013e3181d57a2b

Whalley, L. J., Murray, A. D., Staff, R. T., Starr, J. M., Deary, I. J., Fox, H. C., et al. (2011). How the 1932 and 1947 mental surveys of aberdeen schoolchildren provide a framework to explore the childhood origins of late onset disease and disability. *Maturitas, 69*(4), 365-372. doi:10.1016/j.maturitas.2011.05.010

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361-370.

Figures

Figure 1. Study Design

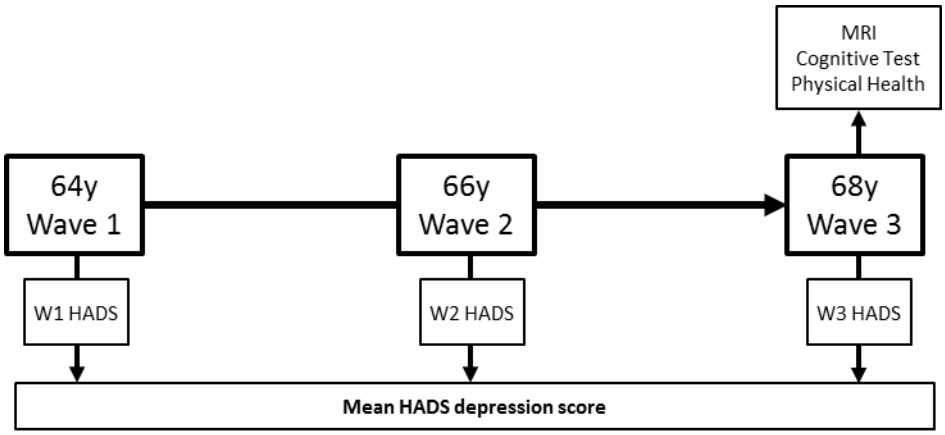

Figure 2. Path diagram of structural equation models of the influence of deep brain (DB) hyperintensities on depressive symptoms (mean HADS-D). GMH = grey matter hyperintensities, ITH = infratentorial hyperintensities. Standardised regression weights in bold are statistically significant (P<0.05). e3, e4 and e6 are variable error terms within the model.

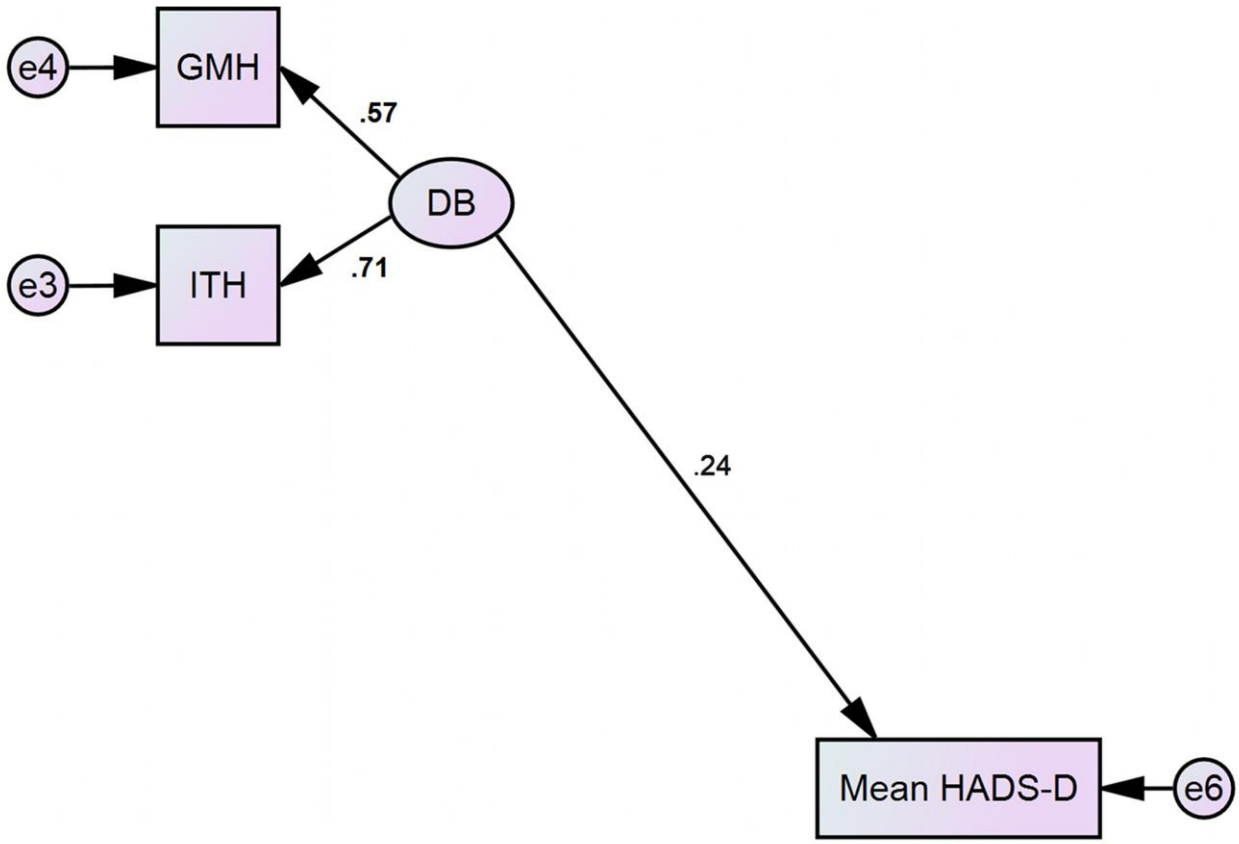

Figure 3. Path diagram of structural equation models of the influence of deep brain (DB) hyperintensities on depressive symptoms (mean HADS-D) with physical health and cognition as mediating factors. g = general intelligence factor, PH = physical health, Standardised regression weights in bold are statistically significant (P<0.05). e3, e4, e5, e6 and e7 are variable error terms within the model.

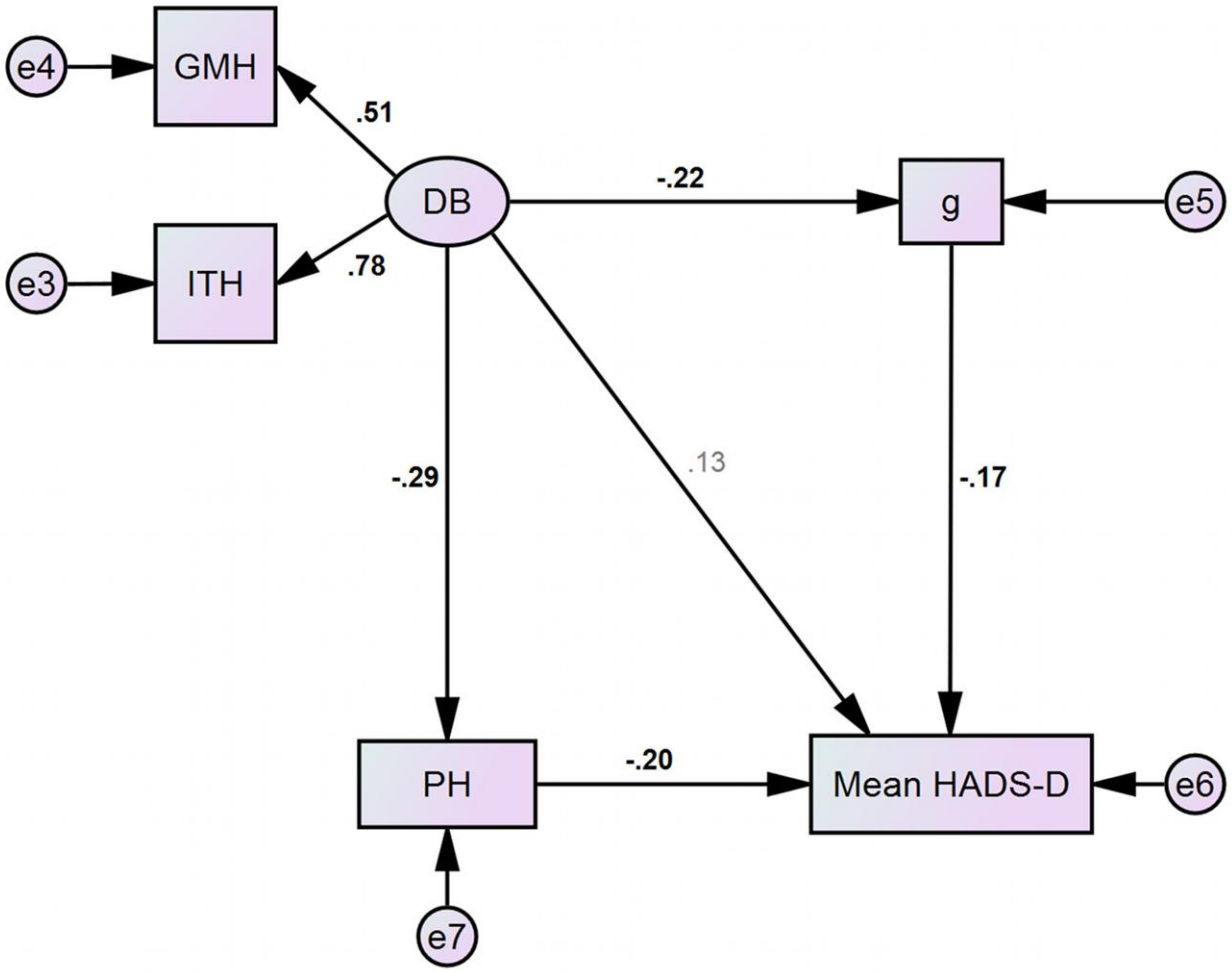

Figure 4. Path diagram of structural equation models of the influence of supratentorial (ST) hyperintensities on depressive symptoms (mean HADS-D) with physical health and cognition as mediating factors. g = general intelligence factor, PH = physical health, WMH = white matter hyperintensities, PVH = periventricular hyperintensities, Standardised regression weights in bold are statistically significant (P<0.05). e3, e4, e5, e6 and e7 are variable error terms within the model.

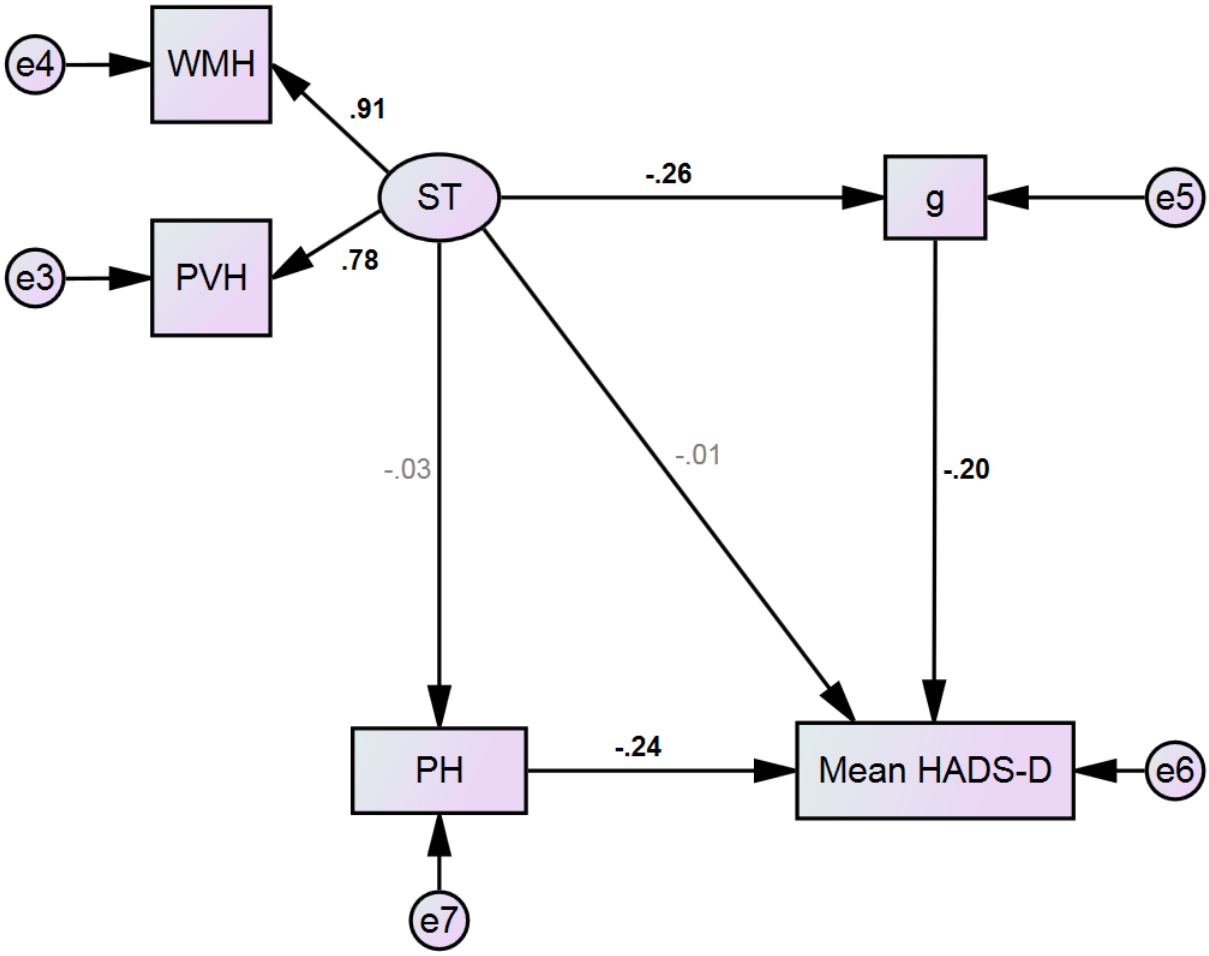

Table 1. Participant characteristics according to level of depressive symptoms

	All participants, n=206-227	Not depressed (HADS≤6), n=194-213	Borderline/case, (HADS >6), n=12-14
***g* (as IQ), mean ± SD**	100.0 ± 15.0	100.6 ± 14.7	89.5 ± 17.3*
PEFR (l/min), mean ± SD	354 ± 120	360 ± 121	265 ± 71**
6m walk time (s), mean ± SD	4.45 ± 0.89	4.37 ± 0.83	5.62 ± 0.98***
TS, mean ± SD	16.5 ± 10	16.3 ± 9.6	18.8 ± 14.6
WMH, mean ± SD	7.93 ± 5.3	7.93 ± 5.24	7.93 ± 6.44
PVH, mean ± SD	4.57 ± 2	4.62 ± 1.92	3.93 ± 2.89
GMH, mean ± SD	2.46 ± 2.66	2.37 ± 2.57	3.79 ± 3.66$^{\#}$
ITH, mean ± SD	1.48 ± 2.38	1.38 ± 2.25	3.14 ± 3.61**

Physical health parameters of walk time and peak expiratory flow rate (PEFR) were corrected for participants' height. g as IQ = general intelligence factor quotient, TS= whole brain hyperintensity (Sheltens') score; WMH = white matter hyperintensities, PVH = periventricular hyperintensities, GMH = grey matter hyperintensities, ITH = infratentorial hyperintensities. Variables of not depressed versus borderline/caseness were compared by t-test. (*=$P\leq0.05$, **=$P\leq0.01$, ***=$P\leq0.001$, $^{\#}$=$P\leq0.1$).

Table 2. Correlations between hyperintensities, physical health, cognition and depressive symptoms

		Walk Time	PEFR	TS	WMH	PVH	GMH	ITH	HADS
g	R (P-value) 	-.065 (.356) 205	.121 (.085) 204	-.238 (.001) 206	-.242 (<.001) 206	-.206 (.003) 206	-.101 (.150) 206	-.177 (.011) 206	-.222 (.001) 205
Walk time	R (P-value) 		-.416 (<.001) 221	.030 (.656) 223	-.021 (.751) 223	-.031 (.645) 223	.064 (.345) 223	.130 (.053) 223	.216 (.002) 222
PEFR	R (P-value) 			-.149 (.025) 224	-.056 (.400) 224	-.082 (.224) 224	-.157 (.018) 224	-.255 (<.001) 224	-.223 (.001) 223
TS	R (P-value) 								.107 (.118) 226
WMH	R (P-value) 					.710 (<.001) 227	.500 (<.001) 227	.484 (<.001) 227	.054 (.467) 226
PVH	R (P-value) 						.473 (<.001) 227	.344 (<.001) 227	.011 (.929) 226
GMH	R (P-value) 							.402 (<.001) 227	.136 (.037) 226
ITH	R (P-value) 								.169 (.011) 226

PEFR = peak expiratory flow rate (l/min) normalised for height. Walk Time (corrected for height). TS = Total Scheltens's score, WMH = white matter hyperintensities, PVH = perinventricular hyperintensities, GMH = grey matter hyperintensities, ITH = infratentorial hyperintensities. Correlations between Total Scheltens's score and its constituent regional Scheltens's scores are not shown (n=204-227 for all variables).