# White Matter Lesions and Temporal Lobe Atrophy Related to incidence of both Dementia and Major Depression in 70-year-olds followed over 10 years

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## Abstract

**Background:** A number of studies have suggested associations between dementia and depression in older adults. One reason could be that these disorders share structural correlates, such as white matter lesions (WMLs) and cortical atrophy. No study has examined whether these lesions precede both dementia and depression independently of each other in the general population.

**Methods:** We investigated whether WMLs and cortical atrophy on computed tomography (CT) predict dementia and depression in a population-based sample of 70-year-olds (*n*=380) followed over 10 years. Exclusion criteria were dementia, major depression, history of stroke and a Mini-Mental State Examination score below 26 at baseline in 2000-01. Dementia was diagnosed according to DSM-III-R and depression according to DSM-5. Primary outcomes included dementia and major depression at 10-year follow-up.

**Results:** Adjusted logistic regression models, including both WMLs and temporal lobe atrophy, showed that moderate-to-severe WMLs (OR 3.96, 95% CI 1.23-12.76) and temporal lobe atrophy (OR 2.93, 95% CI 1.13-7.60) predicted dementia during 10-year follow-up independently of major depression. Similarly, both moderate-to-severe WMLs (OR 3.84, 95% CI 1.25-11.76) and temporal lobe atrophy (OR 2.52, 95% CI 1.06-5.96) predicted depression even after controlling for incident dementia.

**Conclusion:** WMLs and temporal lobe atrophy preceded 10-year incidence of both dementia and depression in 70-year-olds. Shared structural correlates could explain the reported associations between dementia and depression. These brain changes may represent independent and complementary pathways to dementia and depression. Strategies to slow progression of vascular pathology and neurodegeneration could indirectly prevent both dementia and depression in older adults.

## Introduction

Dementia and depression are the two most common mental disorders in older adults and have a significant impact on quality of life [1]. A number of studies have suggested an association between these disorders. It has been hypothesized that depression in old age may be a prodromal state, [2] a risk factor [3] or a consequence of dementia [4]. However, the association could also be due to shared risk factors. Shared neuropathological substrates for these disorders include white matter lesions (WMLs) and cortical atrophy. WMLs, indicating small-vessel disease, and cortical atrophy, indicating neurodegeneration, are commonly seen on imaging of the aging brain [5]. In addition, cortical atrophy may also be an expression of small vessel disease [6]. Prospective population-based studies using magnetic resonance imaging (MRI) report that white matter changes increase the risk of subsequent dementia [7-9] and depression [10-12]. MRI studies have also shown that global cortical atrophy [13] and medial temporal lobe atrophy [14] predict conversion from mild cognitive impairment (MCI) to dementia. We have previously shown that WMLs and temporal lobe atrophy on computed tomography (CT) independently predict major depression in older adults who were followed for 5 years [15]. Few studies have examined whether WMLs and brain atrophy independently predict both dementia and major depression in older adults in the same population. One cross-sectional study reported that brain atrophy on MRI was related to cognitive impairment and WMLs to depressed mood, suggesting that depressed mood and cognitive function have different neuropathological correlates [16]. Longitudinal studies can give insight into pathomechanism that cross-sectional studies cannot provide. Furthermore, CT is the most commonly used brain imaging tool worldwide, and more studies are needed to examine the prognostic significance of brain atrophy and WMLs using this modality.

The aim of our study was to investigate the independent associations of WMLs and cortical atrophy in relation to development of dementia and depression in a population-based sample

of older adults who were followed for 10 years. With reference to our previous results on depression [15] we were primarily interested in atrophy of the temporal lobe.

## Methods

### Participants

The study is part of the Gerontological and Geriatric Population Studies (H70) [17] and the Prospective Population Study of Women (PPSW) [18] in Gothenburg, Sweden. The multidisciplinary H70 studies started in the 1970s with the aim to study health and health-related factors in 70-year-olds from Gothenburg, Sweden. PPSW started in 1968 with women born 1908, 1914, 1918, 1922 and 1930 who were followed up in1974, 1980, 1992 and 2000. All samples were systematically obtained, based on birth dates, from the Swedish Population Register, which covers names and addresses of all people living in Sweden. The studies included persons living in private households and in institutions. Data from each examination year are cross-sectional.

In 2000-01, all 70-year-olds born during 1930 in these studies were invited to a health examination. In total, there were 868 eligible individuals and 602 accepted to participate (response rate 69,0%). Of the 602, 579 participated in a psychiatric examination and were invited for a CT scan. Of these, 429 (74.1%) accepted to have a scan.

The 429 individuals who participated in the CT examination were less often women (70,0% versus 80.0%, $p$=0.006) compared to the 150 non-participants. There was no difference in the mortality rate or prevalence of psychiatric diagnoses (depression, dementia, stroke and any psychiatric diagnosis) between participants and non-participants.

Among the 429 who participated in CT, 49 individuals who had dementia, major depression, history of stroke or a score on the Mini-Mental State Examination (MMSE) [19] less than 26 at baseline were excluded from the present study, leaving 380 individuals. The participants

were invited for follow-ups after 5 and 10 years. The first follow-up was performed in 2005–2006. Among those surviving (n=367), 311 (response rate 84.7%) accepted a new psychiatric examination. A second follow-up was performed in 2009-2010. All subjects who had done a CT in 2000 were invited. Among those who had survived (n=330), 259 (response rate 78.5%) accepted a new psychiatric examination. In line with the Declaration of Helsinki, informed consent was obtained from all participants and/or their relatives, and the study was approved by the Ethics Committee for Medical Research at the University of Gothenburg.

**Neuropsychiatric Examinations and Interviews**

Semi-structured neuropsychiatric examinations were performed by trained psychiatric research nurses in 2000–2001, 2005–2006, and in 2009-2010. These examinations included ratings of the past month's psychiatric symptoms and signs according to Comprehensive Psychopathological Rating Scale (CPRS) [20], which is valid and reliable in older populations [21], Mini-International Neuropsychiatric Interview [22], self-reported history of depression, and assessment of current medications. Ratings of common symptoms and signs of dementia were also performed (e.g. assessments of memory, orientation, general knowledge, apraxia, visuospatial function, understanding proverbs, following commands, naming ability and language) as described in detail [23, 24]. Cognitive function was also measured with the MMSE [19].

The psychiatric nurses who performed the examinations were supervised and trained by geriatric psychiatrists. In training sessions, nurses and psychiatrists rated symptoms and signs among participants. Inter-rater reliability between geriatric psychiatrists and nurses was studied in 50 individuals who had dual rating by either psychiatric research nurses or psychiatrists. Kappa values for the presence versus absence of signs and symptoms necessary to diagnose depression were between 0.62 and 1.00 indicating "good" (reference range

kappa=0.61-0.80) or "excellent" (kappa=0.81-1.00) agreement. Inter-rater agreement for the symptoms and signs used to diagnose dementia was between 89.4% and 100.0% (kappa values between 0.74 and 1.00) [25].

**Measurements of Covariates**

At baseline, participants underwent a physical examination and blood tests. Body mass index (BMI) was calculated as $kg/m^2$. Systolic and diastolic blood pressure (SBP and DBP) was measured in the right arm in the seated position after 5 minutes rest using a mercury manometer. DBP was defined as Korotkoff phase 5. Hypertension was defined as SBP≥140 mm Hg and/or DBP≥90 mm Hg and/or taking antihypertensive medication. Blood samples were taken after overnight fasting. Plasma glucose and serum cholesterol concentrations were measured. The diagnosis of stroke was based on information from self-reports, close informants and the Swedish Hospital Discharge Register. Diagnoses of myocardial infarction, angina pectoris and claudicatio intermittens were based on self-report and key informant interviews. Diabetes mellitus was defined based on a physician's diagnosis, being on antidiabetic therapy or having two fasting venous or capillary whole blood glucose values ≥7.0 mmol/L.

**Diagnosis of Dementia and Depression**

Dementia was diagnosed by geriatric psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), third edition, revised [26], based on symptoms rated by the examiners during detailed neuropsychiatric examinations and close informant interviews, as described [24]. For all individuals, including those lost to follow-up, the diagnosis up to 2005 included information from the Swedish Hospital Discharge Registry. Diagnoses of major depression were made according to DSM-5 [27], as described previously [28]. The

DSM-5 uses the same symptom criteria as DSM-III-R [26], except that the use of the bereavement criterion in DSM-IV is not applied. Underlying organic factors, medical conditions, use of substances, schizophrenia/schizophreniform disorders or dementia were not considered as exclusion criteria in the diagnosis of major depression.

**CT Scan Rating Methods**

The same CT scanner and scanning procedure were used for all scans. Ten millimetre continuous slices were obtained. No contrast enhancement was used. The scans were evaluated by a neurologist (MS) experienced in CT and MRI ratings of WMLs and other cerebral lesions. The neurologist was blind to all clinical data.

The Gothenburg scale was used to rate WMLs [29]. According to this scale, WMLs are defined as periventricular or subcortical areas of decreased attenuation below that expected for normal white matter. The changes were always diffusely distributed within the white matter. The scale gives a global measure of WMLs in the brain, and has been used in our epidemiological studies since 1986 [29]. It is a 0–3 point scale which takes into account the severity of the hypodensity of WMLs, including 0 (absence of any attenuation), 1 (mild attenuation), 2 (moderate attenuation), and 3 (severe attenuation).

A subjective scale with three grades (absent, mild or moderate and severe) was used to evaluate cortical atrophy. Location of atrophy was categorized as frontal, temporal, parietal or occipital regions, according to the anatomical subdivision [30], and severity was scored according to the extent of sulcal widening, as suggested by de Leon et al [31].

The intra-rater Kappa values for the CT assessment were between “fair” (kappa = 0.21-0.40) and “good” (kappa = 0.61-0.80) for both WMLs and atrophy [5]. Inter-observer agreement between the rater and a neuroradiologist was “fair” (kappa = 0.30) for WMLs, “moderate” for

temporal lobe atrophy (kappa = 0.43) and "fair" for the other cortical regions (kappa = 0.29–0.36).

**Statistical Analysis**

WMLs were dichotomized as none or mild versus moderate or severe lesions. Cortical atrophy was dichotomized as absence versus presence of atrophy in each brain region. Sex was a preselected covariate in all analyses. Additional covariates were only considered if they were related to the outcome variables ($p \leq 0.10$) and included baseline information on level of education (compulsory education versus higher education), myocardial infarction, angina pectoris, claudicatio intermittens, hypertension, diabetes mellitus, and levels of plasma glucose, serum cholesterol, BMI, SBP and DBP.

The statistical analyses were performed using logistic regression models in three steps: First, univariate logistic regression analyses were performed estimating the odds of dementia or major depression during follow-up in relation to WMLs or cortical atrophy at baseline. The primary outcomes were dementia and major depression in 2000-2010. Additional outcomes included dementia and major depression stratified by diagnosis in 2005 and 2010, respectively. Second, multivariate logistic regression analyses were performed including the covariates which were associated ($p \leq 0.10$) with the outcome in univariate models, adjusting for sex. Third, for the analyses on dementia, we also included major depression during 10-year follow-up as covariate. Similarly, for the analysis on depression, we included dementia during 10-year follow-up as additional covariate. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated.

We present the results for three models: Model I without adjustments, Model II including adjustments (i.e. sex and the covariates selected in step two, plus dementia or depression

during 10-year follow-up); and Model III including both WMLs and temporal lobe atrophy in the same regression model. Model III was only analyzed if Model II was significant.

Statistical analyses were performed using SPSS version 16.0. Results were considered statistically significant at a level of $p<0.05$.

## Results

Baseline characteristics are given in table 1. In total, 380 70-years-olds participated in the study. Among these, 25 were diagnosed with dementia and 26 with major depression during 10-year follow-up (three had both). Results are presented in table 2 for unadjusted (Model I) and adjusted (Model II and III) models.

70-year-olds with moderate to severe WMLs at baseline more often developed dementia at 10-year follow-up than those with no or mild WMLs (24.1% versus 5.1%; OR 4.59, 95% CI 1.48-14.23) (Model II). Those who had temporal atrophy more often developed dementia at follow-up compared to those with no atrophy in the temporal lobe (12.1% versus 4.2%; OR 3.29, 95% CI 1.29-8.39) (Model II). Similarly, both WMLs (24.0% versus 6.6%; OR 4.00, 95% CI 1.33-12.03) and temporal lobe atrophy (13.5% versus 5.6%; OR 2.58, 95% CI 1.11-5.99) predicted major depression during 10-year follow-up (Model II). Regression models including each of the other cortical areas showed that occipital lobe atrophy was associated with dementia at 10-year follow-up, adjusted for confounders (15.6% versus 5.7%; OR 5.04, 95% CI 1.47-17.26). No associations were found for parietal and frontal lobe atrophy.

A logistic regression analysis including both WMLs and temporal lobe atrophy at baseline (Model III) showed that WMLs (OR 3.96, 95% CI 1.23-12.76) and temporal lobe atrophy (OR 2.93, 95% CI 1.13-7.60) independently predicted dementia at 10-year follow-up. A

similar analysis showed that WMLs (OR 3.84, 95% CI 1.25-11.76) and temporal lobe atrophy (OR 2.52, 95% CI 1.06-5.96) independently predicted depression at 10-year follow-up.

## Discussion

We found that both WMLs and temporal lobe atrophy were independently related to dementia and depression during 10-year follow-up in a population-based sample of 70-year-olds. These brain lesions have previously been associated with both dementia and depression, but associations have not been analyzed concurrently.

One previous cross-sectional clinical study examined WMLs and cortical atrophy on MRI in relation to both cognition and depressed mood in the same population [16]. The study included 20 individuals with Alzheimer's disease, 32 with cognitive impairment/dementia and 42 controls. Cognitive function was associated with gray matter atrophy while depressed mood was associated with frontal white matter lesions [16]. This study supports our finding of an association between cortical atrophy and dementia and the association between WMLs and depression. However, it does not support our finding of associations between WMLs and dementia or between cortical atrophy and depression. In contrast to our study, the study was cross-sectional, conducted in a clinical sample, examined cognitive and depressive symptoms rather than diagnoses, and used MRI to examine brain changes. These differences might explain our disparate results.

Depression and dementia often coexist in older adults [32], and depression has been suggested to increase the risk for dementia [2]. One reason for the frequent coexistence may be shared pathogenetic pathways [2, 32], e.g. related to WMLs and temporal lobe atrophy as found in the present study. In line with shared pathology, WMLs and cortical atrophy also have similar risk factors, such as age, hypertension and overweight. Alternatively, our

findings may reflect an increased vulnerability for psychiatric disorders in general in older adults who have WMLs or temporal lobe atrophy.

In contrast, our group has found that the level of ß-amyloid in cerebrospinal fluid (CSF) was increased in depression [33], and decreased in dementia [34, 35]. In addition, we have found a CSF biomarker profile related to depression in older adults which contrasts with the profile related to dementia [36]. These findings indicate non-shared pathology regarding neurochemical changes between dementia and depression. In the present study, we showed that the association between brain changes and dementia was independent from depression and vice versa.

We found that WMLs preceded both dementia and depression. These findings are in agreement with prospective population-based studies using MRI, which report that white matter changes precede dementia [7-9], and depressive symptoms [10-12], Also, cross-sectional studies report that the frequency of WMLs on CT are higher among demented than among non-demented [28] and that changes in the white matter detected by MRI are related to depression [37]. The association between WMLs on CT and depression is less clear. We have previously shown that WMLs predicted depression during 5-year follow-up [15]. This is in contrast to a cross-sectional study from our group where WMLs on CT were associated with dementia, but not with depression [28]. The present findings emphasize the importance of cerebrovascular disease in the pathogenesis of both dementia and depression in older adults.

We also found that temporal lobe atrophy preceded both dementia and depression. Our findings are in line with studies showing that the temporal lobe is one of the first regions to be affected by the degenerative process of Alzheimer's Disease (AD) [38], and that medial temporal lobe atrophy on MRI predicts dementia in patients with MCI [14]. In relation to depression, the findings confirm the results from our 5-year follow-up [15]. Furthermore, we now included subsequent dementia in the analyses on depression in 2005 and this did not

change the findings essentially. Previous cross-sectional hospital-based MRI studies report that temporal lobe atrophy is associated with concurrent major depression in older adults [39], while a cross-sectional CT study from our group did not show any relation between cortical atrophy and depression in older adults without dementia [40]. Further, we have previously shown that temporal lobe atrophy is related to decreased survival time in older adults [41]. Thus, degenerative processes in the temporal lobe, as measured with CT, may have severe consequences including dementia, depression and mortality.

Our results show that WMLs and temporal lobe atrophy predict dementia and depression independent from each other. It may be that there is one neurodegenerative and one vascular pathway to both dementia and depression in older adults. Similar suggestions regarding geriatric depression has been proposed by others [42]. Also, two separate studies found that WMLs increase the risk for dementia independently from brain atrophy [9] and medial temporal lobe atrophy predict dementia independently from WMLs [14]. A cross-sectional study of patients with Alzheimer's disease found that white matter hyperintensities were not associated with medial temporal lobe atrophy [43]. Further, in individuals with small vessel disease, brain atrophy and WMLs were independently related to cognitive decline [44]. Taken together, our study gives support for one neurodegenerative and one vascular pathway to both dementia and depression. Our study is the first to show these pathways in a population-based sample of older adults where dementia and depression were studied concurrently in the same population.

Our findings suggest that changes in the brain precede the onset of dementia and depression in older adults. However, for depression, the temporal aspect is complex. First, depression has been found to increase the risk for cerebrovascular disease [45]. Secondly, depression is an episodic disorder and those who had depression during follow-up could have had previous

episodes of depression which may have increased the risk for cerebrovascular disease. Unfortunately, we had no reliable information on previous depression. Another complex aspect is the temporal sequence between the vascular and degenerative processes involved in dementia and depression in older adults. It has been suggested that vascular pathology precedes cortical atrophy, at least in AD [46]. If so, treating the vascular factors may indirectly reduce the risk of atrophy and thereby prevent dementia and depression.

The strengths of the study include the population-based sample, the high response rates, the long follow-up and the comprehensive examinations performed by experienced psychiatric research nurses. However, some methodological issues and limitations must be addressed. First, some of the subgroups were rather small and results should be interpreted cautiously. Second, attrition is an issue that must be considered in follow-up studies. To reduce the influence of attrition, we used the Swedish Hospital Discharge Register to obtain data on dementia for individuals lost to follow-up in 2005-2006. Third, CT is less sensitive than MRI in detecting WMLs and is more severely affected by bone hardening artifacts, which is particularly severe in the region of the medial temporal lobe [47]. However, CT is better in delineating clinically relevant WMLs [48], is comparable to MRI in detecting brain atrophy [44] and is the worldwide most used imaging technique. In addition, there is insufficient evidence to suggest that MRI is superior to CT in identifying cerebrovascular changes related to dementia [49]. Also, CT may be more suitable than MRI for older adults, as it is less sensitive to motion artefacts and has a shorter examination time. Despite that visual rating of WMLs and cortical atrophy on CT is a rather crude method, we identified associations with both dementia and depression. Fourth, all scans were rated by a single person which may increase the risk for systematic error. Fifth, we did not analyse dementia subtype in this study, due to the small number of persons when dividing by subtypes.

## Conclusion

In this population-based study, we found that WMLs and temporal lobe atrophy were related to 10-year incidence of both dementia and depression in 70-year-olds. These results suggest that cerebrovascular changes and neurodegeneration are vulnerability markers for the two most common mental disorders in older adults. Individuals with these brain imaging changes should be followed closely by the health care system as they are at increased risk of adverse outcomes. Strategies to slow progression of vascular pathology and neurodegeneration may indirectly prevent dementia and depression.

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**Table 1**
Baseline characteristics of the 70-year-olds and those who were diagnosed with dementia or major depression at follow-up

| Characteristic | Baseline sample 2000-2001 (*n*=380)[a] *n* (%) or mean (SD) | Dementia 10-year follow-up (*n*=25) *n* (%) or mean (SD) | Dementia 2005 (*n*=12) *n* (%) or mean (SD) | Dementia 2010 (*n*=19) *n* (%) or mean (SD) | Major depression 10-year follow-up (*n*=26)[b] *n* (%) or mean (SD) | Major depression 2005 (*n*=15)[c] *n* (%) or mean (SD) | Major depression 2010 (*n*=12) *n* (%) or mean (SD) |
|---|---|---|---|---|---|---|---|
| Women | 216 (56.8) | 16 (64) | 9 (75.0) | 12 (63.2) | 20 (76.9) | 12 (80.0) | 3 (75.0) |
| Education (compulsory school) | 153 (40.7) | 9 (36.9) | 4 (33.3) | 6 (31.6) | 7 (28.0) | 3 (21.4) | 4 (33.3) |
| BMI (kg/m$^2$) | 27.1 (4.2) | 26.3 (4.0) | 25.8 (4.7) | 25.7 (3.5) | 27.5 (3.7) | 28.2 (4.1) | 27.2 (3.8) |
| Myocardial infarction | 26 (6.8) | 5 (20.0) | 1 (8.3) | 4 (21.1) | 2 (7.7) | 0 | 2 (16.7) |
| Angina pectoris | 120 (31.6) | 11 (44.0) | 3 (25.0) | 9 (47.4) | 14 (53.8) | 8 (53.3) | 7 (58.3) |
| Diabetes | 57 (15.0) | 7 (28.0) | 4 (33.3) | 4 (21.1) | 3 (11.5) | 3 (20.0) | 0 |
| Plasma glucose (mmol/l) | 5.9 (1.8) | 6.9 (4.2) | 6.1 (2.3) | 6.8 (4.6) | 5.7 (1.7) | 6.0 (2.1) | 5.3 (0.8) |
| Serum cholesterol (mmol/l) | 5.9 (1.1) | 6.3 (1.1) | 6.4 (1.0) | 6.3 (1.2) | 5.7 (1.0) | 5.6 (1.1) | 5.8 (1.0) |
| Antidepressant treatment | 24 (6.3) | 5 (20.0) | 2 (16.7) | 5 (26.3) | 8 (30.8) | 6 (40.0) | 2 (16.7) |
| Cardiovascular drugs[d] | 96 (25.3) | 6 (36.0) | 3 (25.0) | 7 (36.8) | 6 (23.1) | 6 (40.0) | 0 |
| WMLs (moderate-to-severe) | 29 (7.6) | 7 (28.0) | 4 (33.3) | 5 (26.3) | 6 (23.1) | 5 (33.3) | 1 (8.3) |
| Temporal lobe atrophy | 116 (30.5) | 14 (56.0) | 8 (66.7) | 11 (57.9) | 13 (50.0) | 9 (60.0) | 4 (33.3) |

Key: BMI, body mass index; WMLs, white matter lesions.
[a]Owing to missing values, the group sizes of the following measures were reduced: education (n=376), BMI (n=377), plasma glucose (n=375), and serum cholesterol (n=378).
[b]Owing to missing values, the group size of education was reduced (n=25).
[c]Owing to missing values, the group size of education was reduced (n=14).
[d]Antihypertensives, anticoagulants, cholesterol- and triglyceride-lowering, and antidiabetics.

**Table 2**
White matter lesions and temporal lobe atrophy at baseline in relation to dementia and major depression after 5 and 10 years in 70-year-olds (continues on next page).

| | | | | | |
|---|---|---|---|---|---|
| | | **Dementia 10-year follow-up (total n=380, dementia n=25)** | | | |
| | | ***n*/N (%)[a]** | | **OR (95% CI)** | |
| | **No/mild WMLs** | **Moderate/severe WMLs** | **Model I (unadjusted)** | **Model II (adjusted)[b]** | **Model III[g]** |
| **WMLs** | 18/351 (5.1) | 7/29 (24.1) | 5.89 (2.22-15.59)[h] | 4.59 (1.48-14.23)[h] | 3.96 (1.23-12.76)[h] |
| | **No atrophy** | **Atrophy** | | | |
| **Temporal lobe atrophy** | 11/264 (4.2) | 14/116 (12.1) | 3.16 (1.39-7.19)[h] | 3.29 (1.29-8.39)[h] | 2.93 (1.13-7.60)[h] |
| | | **Dementia 2005 (total n=380, dementia n=12)** | | | |
| | | ***n*/N (%)[a]** | | **OR (95% CI)** | |
| | **No/mild WMLs** | **Moderate/severe WMLs** | **Model I (unadjusted)** | **Model II (adjusted)[c]** | **Model III[g]** |
| **WMLs** | 8/351 (2.3) | 4/29 (13.8) | 6.86 (1.93-24.36)[h] | 5.61 (1.27-24.74)[h] | 5.04 (1.12-22.64)[h] |
| | **No atrophy** | **Atrophy** | | | |
| **Temporal lobe atrophy** | 4/264 (1.5) | 8/116 (6.9) | 4.82 (1.42-16.33)[h] | 3.82 (1.03-14.24)[h] | 3.60 (0.94-13.73) |
| | | **Dementia 2010 (total n=259, dementia n=19)** | | | |
| | | ***n*/N (%)[a]** | | **OR (95% CI)** | |
| | **No/mild WMLs** | **Moderate/severe WMLs** | **Model I (unadjusted)** | **Model II (adjusted)[d]** | **Model III[g]** |
| **WMLs** | 14/241 (5.8) | 5/18 (27.8) | 6.24 (1.95-19.98)[h] | 5.39 (1.53-19.07)[h] | 5.19 (1.38-19.46)[h] |
| | **No atrophy** | **Atrophy** | | | |
| **Temporal lobe atrophy** | 8/188 (4.3) | 11/71 (15.5) | 4.13 (1.59-10.74)[h] | 3.85 (1.41-10.50)[h] | 3.71 (1.33-10.36)[h] |
| | | **Major depression 10-year follow-up (total n=330, depression n=26)** | | | |
| | | ***n*/N (%)[a]** | | **OR (95% CI)** | |
| | **No/mild WMLs** | **Moderate/severe WMLs** | **Model I (unadjusted)** | **Model II (adjusted)[e]** | **Model III[g]** |
| **WMLs** | 20/305 (6.6) | 6/25 (24.0) | 4.50 (1.62-12.53)[h] | 4.00 (1.33-12.03)[h] | 3.84 (1.25-11.76)[h] |
| | **No atrophy** | **Atrophy** | | | |
| **Temporal lobe atrophy** | 13/234 (5.6) | 13/96 (13.5) | 2.66 (1.19-5.98)[h] | 2.58 (1.11-5.99)[h] | 2.52 (1.06-5.96)[h] |

| | Major depression 2005 (total n=311, depression n=15) | | | | |
|---|---|---|---|---|---|
| | ***n*/N (%)[a]** | | **OR (95% CI)** | | |
| | **No/mild WMLs** | **Moderate/severe WMLs** | **Model I (unadjusted)** | **Model II (adjusted)[f]** | **Model III[g]** |
| **WMLs** | 10/286 (3.5) | 5/25 (20.0) | 6.90 (2.15-22.13)[h] | 6.11 (1.74-21.45)[h] | 6.02 (1.63-22.23)[h] |
| | **No atrophy** | **Atrophy** | | | |
| **Temporal lobe atrophy** | 6/221 (2.7) | 9/90 (10.0) | 3.98 (1.37-11.54)[h] | 3.90 (1.30-11.66)[h] | 3.88 (1.24-12.15)[h] |

| | Major depression 2010 (total n=259, depression n=12) | | | | |
|---|---|---|---|---|---|
| | ***n*/N (%)[a]** | | **OR (95% CI)** | | |
| | **No/mild WMLs** | **Moderate/severe WMLs** | **Model I (unadjusted)** | **Model II (adjusted)** | **Model III[g]** |
| **WMLs** | 11/241 (4.6) | 1/18 (5.6) | 1.23 (0.15-10.10) | - | - |
| | **No atrophy** | **Atrophy** | | | |
| **Temporal lobe atrophy** | 8/188 (4.3) | 4/71 (5.6) | 1.34 (0.39-4.61) | - | - |

Key: CI, confidence interval; OR, odds ratio; WMLs, white matter lesions.

[a]*n*/N (within each group of temporal lobe atrophy or WMLs) = (participants with dementia/depression during follow-up)/(total number of participants).
[b]Adjusted for sex, diabetes, myocardial infarction, plasma glucose, serum cholesterol, and major depression. Covariates that were significant in the adjusted model included myocardial infarction and serum cholesterol.

[c]Adjusted for sex, diabetes, and major depression. None of the covariates were significant.

[d]Adjusted for sex , myocardial infarction, plasma glucose, and major depression. Myocardial infarction was significant in the adjusted model.

[e]Adjusted for sex, angina, and dementia. Covariates that were significant included in the adjusted model gender and angina.

[f]Adjusted for sex, angina, and dementia. None of the covariates were significant.

[g]WMLs and temporal lobe atrophy in the same regression analysis. Adjusted for the same factors as in Model II.

[h]$p<0.05$, logistic regression model.