Cerebrovascular Damage in Late-Life Depression Is Associated With Structural and Functional Abnormalities of Subcutaneous Small Arteries

Adam S. Greenstein, Raghupathy Paranthaman, Alistair Burns, Alan Jackson, Rayaz A. Malik, Robert C. Baldwin, Anthony M. Heagerty

Abstract—Late-life depression is increasingly viewed as a vascular illness because of patients exhibiting characteristic white matter brain lesions and in vivo large artery endothelial dysfunction. However, the “vascular depression” hypothesis pertains to the microvasculature, and this circulation has not been studied in this context. Our objective was to examine structure and function of small subcutaneous arteries in patients with late-life depression. Thus, 16 patients aged 71.8±4.0 years with late-life depression were compared with 15 control participants aged 72.1±5.9 years. There were similar cardiovascular profiles between the 2 groups. All of the participants underwent MRI brain scans and subcutaneous gluteal fat biopsy from which small arteries were isolated and studied using pressure myography. Cerebral microvascular damage in depressed patients was confirmed by assessment of basal ganglia Virchow-Robin space scores (depressed patients 3.9±1.7 versus controls; 2.5±1.6; P=0.01). Contractility to norepinephrine was equivalent in both groups, but relaxation of the small arteries to acetylcholine was significantly reduced in depressed patients (84.0±4.0% compared with control participants (96.0±1.4%; P=0.012). This difference in arterial relaxation was reduced but not entirely eliminated when NO synthase was inhibited. Depressed patients also exhibited hypertrophic wall growth with an increase in medial cross-sectional area (P=0.035, multiple ANOVA and wall thickness; P=0.04, multiple ANOVA). In conclusion, despite similar cardiovascular profiles, depressed patients with cerebral microvascular damage show abnormalities of subcutaneous small artery structure and function. (Hypertension. 2010;56:734-740.)

Key Words: ageing • endothelium • cerebrovascular disorders • remodeling • small artery

Depressive disorder in later life is common and associated with disability, increased healthcare use, and significant morbidity and mortality.1 Although the etiology of this disorder is heterogeneous,2 several lines of evidence support a link between vascular disease and late-life depression. Both stroke and myocardial infarction are linked with depression in a bidirectional manner, each contributing to the risk of occurrence of the other.4 In addition, lesions in brain white matter and basal ganglia (referred to here collectively as “WML”), visualized on MRI and known to be associated with ischemic damage,2 occur more often in depressed compared with nondepressed older people.4 This has led to the vascular depression hypothesis, which proposes distinct clinical5 and neuroradiological6 appearances in such patients. The presence of Virchow-Robin spaces (VRSs) in patients with depression7 lends further weight to this. These are perivascular spaces that, when abnormally dilated, are indicative of cerebral microangiopathy.8 They are seen as small linear structures with signal intensity equal to that of cerebrospinal fluid and have a distinctive anatomic distribution.9

A rapidly growing body of work has also demonstrated in vivo vascular changes in depressive disorder. Thus, endothelial dysfunction occurs in the large arteries of untreated patients10 and those taking antidepressant therapy.11 Compared with matched participants without depression there is also a greater prevalence12 and incidence13 of increased carotid intima-media thickness and an increase in aortic pulse wave velocity,14 even after adjustment for traditional risk factors. The studies to date, however, all pertain to large arteries, and, whereas endothelial dysfunction may be indicative of a proatherogenic state, this does not explain the development of microvascular pathology in the brain. We therefore designed a study to investigate small artery changes in late-life depression. Arteries studied were taken from

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A.S.G. and R.P. contributed equally to this publication.
The authors had full access to the data and take responsibility for its integrity. All of the authors have read and agree to the article as written.
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subcutaneous gluteal biopsies. Although clearly from a different circulatory bed than that implicated in the development of cerebral microvascular damage, structural changes in human cerebral small arteries in response to hypertension have been shown to be similar to those found taken from a subcutaneous gluteal biopsy.15

Methods

Subjects

After approval from the Local Research Ethical Committee, patients with depression were recruited from secondary care sites in greater Manchester. Control subjects were recruited from spouses or partners of depressed subjects or via an advert in community centers. All of the participants gave full informed consent. All of the procedures followed were in accordance with institutional guidelines and the guidelines from the Declaration of Helsinki.

Inclusion Criteria for Patients and Control Subjects

Patients were included if they were aged >60 years at the time of assessment, on stable medication, and satisfied criteria for past or present history of depressive episode, moderate or severe, psychotic or nonpsychotic (World Health Organization, International Classification of Diseases, 10th Revision). Patients with history of stroke, space-occupying lesion, neurodegenerative disorders including Parkinson disease, dementia, previous head injury with loss of consciousness, history of another psychiatric disorder other than depression, atrial fibrillation, or severe valvular heart disease were excluded. Patients who had undergone electroconvulsive treatment within 3 months of initial recruitment were also excluded. Control participants had no previous history of psychiatric disturbance.

All of the studies were performed at the Manchester Wellcome Trust Clinical Research Facility. Age, sex, civil status, smoking status, alcohol intake, medical history (including cardiovascular disease), and current medication were recorded for each subject. In addition, waist circumference, weight, and height were measured, and fasting blood was taken for estimation of glycaemia and lipids. Psychiatric measures included International Classification of Diseases, 10th Revision, symptom checklist for depressive episode; Montgomery Åsberg Depression Rating Scale for severity16 and the Mini-Mental Status Examination.17 Blood pressure was measured sitting, after 15 minutes of rest, by a semiautomatic machine (Omron 705 CP, White Medical) with the mean of 3 readings recorded.

Neuroimaging Evaluation

This was conducted using a 1.5T Phillips Gyroscan scanner (Phillips Medical Systems), and the imaging protocol used was the axial fluid-attenuated inversion recovery, T1-weighted inversion recovery, and T2-weighted fluid-attenuated inversion recovery sequence. Slices were 3.0 mm thick with no interslice gap.

All of the ratings were done by an experienced neuroradiologist (A.J.) who was blind to patient group. The assessment of white matter lesion load was performed on matched T1-weighted inversion recovery and T2-weighted fluid-attenuated inversion recovery images using a scoring system based on the modified Scheltens scale, which has 4 subscales: cortical deep white matter (0 to 24); periventricular hyperintensities (0 to 6), basal ganglia changes (0 to 24), and infratentorial changes (0 to 24). Heavily T1-weighted inversion recovery and T2-weighted fluid-attenuated inversion recovery im-
ages were used to score the presence of visible VRSs using a locally developed scoring scheme, which reflects their distribution and number.18 VRS numbers were scored as follows: centrum semiovale and in the external and extreme capsules were scored as 0=none, 1=<5 in either hemisphere, and 2=>5 in either hemisphere; mesencephalon was scored as 0=absent and 1=present; and basal ganglia were scored as 0=only in the substantia innomina and <5 on either side, 1=only in the substantia innomina and >5 dilated VRS on either side, 2=>0<5 in lentiform nucleus on either side, 3=5 to 10 in lentiform or >0<5 in caudate nucleus on either side, 4=>10 in lentiform nucleus and <=5 in caudate nucleus on either side, and 5=>10 in lentiform nucleus and >5 in caudate nucleus on either side. These findings are also reported (in more detail) in a parallel article.19

Gluteal Fat Biopsy and Small Artery Pharmacological and Structural Studies

The technique of gluteal fat biopsy and subsequent isolation and study of subcutaneous arteries have been outlined in previous publications20 and are expanded on in the online Data Supplement, which accompanies this article (please see http://hyper.ahajournals.org).

Statistical Analysis

Statistical analysis was performed using SPSS for Windows. Data are expressed as the mean±SEM. Statistical comparisons were made using the Student unpaired t test or, for multiple readings across a range of intraluminal pressures or a cumulative dose response, a multiple ANOVA. P<0.05 was considered significant. Simple linear univariate analysis was performed using the statsdirect program to assess the potential influence of confounding variables (age; smoking; civic status; alcohol intake; cholesterol subfractions; systolic and diastolic blood pressures; fasting glucose; history of diabetes mellitus, hypertension, or ischemic heart disease; and treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor 1 blockers, or calcium channel blockers) on endothelial function and wall structure (wall thickness and cross-sectional area).

Results

The baseline characteristics of the study participants are presented in the online Data Supplement. There were no significant differences between the 2 groups apart from Montgomery Åsberg Depression Rating scale score, which was higher in the depressed group, and a greater degree of married participants in the control group. Blood pressure tended to be higher in the control group, which also had a lesser degree of statin use, but neither difference was significant. Three patients (18%) in the depressed group had a history of ischemic heart disease compared with 2 control participants (13%). None of the participants had a history of stroke. Fourteen (88%) of the participants in the depressed group were on antidepressants. Of these, 8 participants were on selective serotonin reuptake inhibitors alone or in combination with tricyclics (2 subjects). Four participants were on noradrenergic and specific serotonergic antidepressants, and 2 were taking selective noradrenaline reuptake inhibitors. One participant was prescribed lithium, and 4 participants were taking anxiolytic/hypnotic drugs.

Neuroimaging

VRs in the basal ganglia and the subinsular region were significantly higher in the depressed group (Table) compared with controls. There were no statistically significant differences in the regional Scheltens scores.

Subcutaneous Small Artery Function

There were no differences in contractility to norepinephrine when patients with depression were compared with control participants (Figure 1 and in the online Data Supplement). Endothelial function, assessed by measuring the ability of acetylcholine to dilate a preconstricted vessel, was significantly reduced in depressed patients (P=0.028 for multiple ANOVA comparing multiple points of 2 cumulative dose responses between depressed patients and control partici-


papillary muscle mass. Final resting diameter after $10^{-5} \text{ M}$ acetylcholine also differed significantly between the groups (depressed patients: $84.0\pm 4.0\%$ versus control participants $96.0\pm 1.4\%$; $P=0.012$). Seven patients with depression and 12 control participants underwent assessment of endothelial function after $N^\text{G}$-monomethyl-L-arginine (L-NMMA; inhibitor of NO synthase) incubation. There was a small reduction in relaxation after this protocol in both groups, but arteries from depressed patients still exhibited less relaxation than the controls ($P=0.015$, multiple ANOVA). A difference in final resting diameter after maximal acetylcholine dilation after incubation with L-NMMA was also seen (depressed patients: $67\pm 9\%$ versus control participants: $83\pm 3\%$; $P=0.17$), but this was not significant.

Vasodilatory responses to acetylcholine within groups were also compared before and after incubation with L-NMMA (Figure S1 in the online Data Supplement). In the control group there was a significant difference in final resting diameter after $10^{-5} \text{ M}$ acetylcholine (before L-NMMA incubation: $96.0\pm 1.5\%$ versus after L-NMMA incubation: $83.0\pm 3.0\%$; $P=0.01$). This difference was not significant when the cumulative dose-response curves were compared using a multiple ANOVA ($P=0.08$). In the depressed patients there was a reduction in final resting diameter to $10^{-5} \text{ M}$ acetylcholine after L-NMMA incubation, but this was not significant (before L-NMMA incubation: $85\pm 3\%$ versus after L-NMMA incubation: $67\pm 9\%$; $P=0.14$). At lower doses of acetylcholine the cumulative dose responses appeared to approximate, and overall the difference between the curves using a multiple ANOVA in this group was not significant ($P=0.06$).

Small Artery Structure and Distensibility

Small artery structure from subcutaneous fat was compared in 16 patients with depression and 14 control participants (Figure 2 and online Data Supplement). Compared with arteries from control participants, those from patients with depression showed a significant increase in wall thickness ($P=0.04$, multiple ANOVA across pressure range 3 to 180 mm Hg; at 100 mm Hg of intraluminal pressure, control group wall thickness: $24\pm 1.4 \mu \text{m}$ versus depressed group wall thickness: $27\pm 1.5 \mu \text{m}$; $P=0.07$) and medial cross-sectional area ($P=0.035$, multiple ANOVA across pressure range 3 to 180 mm Hg; at 100 mm Hg of intraluminal pressure, control group wall cross-sectional area: $10184\pm 1029 \mu \text{m}^2$ versus depressed group wall cross-sectional area: $13295\pm 1108 \mu \text{m}^2$; $P=0.05$). There were no significant differences in lumen diameter, wall:lumen ratio, or small artery distensibility.

Univariate Analysis

One-by-one univariate analysis was performed to evaluate the contribution of each variable that may be considered to have been a confounding factor in the differences seen in endothelial function and wall structure (eg, history of ischemic heart disease, smoking history, and age). With regard to wall thickness, there were no significant correlations between the potential confounding factors (including separation into depressed or nondepressed groups). Pertaining to endothelial function, separation into depressed or nondepressed groups was the only factor with a significant correlation coefficient ($r=0.58$; $P<0.001$). There were a number of variables that were significantly associated with wall cross-sectional area, including diastolic blood pressure ($r=-0.45$; $P=0.02$), triglycerides ($r=-0.41$; $P=0.03$), and fasting plasma glucose ($r=0.4$; $P=0.04$). The correlation of group membership (depressed or nondepressed) with wall cross-sectional area was $r=0.34$ with a significance of $P=0.06$.

Discussion

This case-control study has demonstrated that patients with late-life depression have impaired small subcutaneous fat arterial function and abnormal wall structure compared with control subjects. The findings cannot be explained by differences in traditional risk factors such as type 2 diabetes mellitus, ischemic heart disease, high-density lipoprotein cholesterol, triglycerides, or blood glucose. Blood pressure was higher in control participants, but this was not significant, and, indeed, the structural pattern of wall growth traditionally associated with hypertension was observed in depressed patients. Treatment with angiotensin-converting enzyme inhibitors or calcium channel blockers, which are known to influence small artery endothelial function or wall remodeling, was similar between the 2 groups of patients studied. Depressed patients were more likely to be taking statins, which can improve small artery endothelial function, but despite this, relaxation to acetylcholine was impaired compared with control participants.
The vascular findings are consistent with previous research highlighting impaired vascular function in late-life depressive disorder, although ours is the first study to examine structure and function in small arteries. In type 2 diabetes mellitus, small artery endothelial dysfunction is caused by downregulation of NO synthase. Thus, in this study, a reduction in NO bioavailability appeared to largely, but not exclusively, account for the observed endothelial dysfunction, and this may reflect additional alterations to endothelium-derived hyperpolarizing factor release or the cyclooxygenase pathway.

We also report significant structural alterations to the small arteries in depression. The changes are characterized by hypertrophic growth of the small artery wall, more commonly seen in patients with type 2 diabetes mellitus. Thus, in depressed patients, despite arterial remodeling, there was preservation of the lumen with an increase in wall thickness and wall cross-sectional area. This finding may be particularly relevant, because hypertrophy of the small artery wall is one of the most sensitive prognostic indicators for subsequent incidence of cardiovascular events.

There are a number of explanations for our small artery findings. The nature of the gluteal fat biopsy does not allow a large number of participants to be studied, and, thus, the findings may be unique to this cohort. However, our findings of endothelial dysfunction concur with previous studies, which have identified late-life depression as a risk factor for this defect. The structural changes to the small arteries may reflect an additional abnormality of small artery autoregulation, because hypertrophic remodeling has been found previously in tandem with damage to autoregulatory capacity. In patients with type 2 diabetes mellitus, a dual process of loss of autoregulation and hypertrophic remodeling has been proposed as a contributory factor in the development of target organ damage. Clearly, the small arteries studied were from a different circulation from those that may be involved in the pathogenesis of vascular depression, which are presumably small penetrating pial arteries. As such, the findings are associative, but it should be noted that the structural and functional changes that occur in human subcutaneous small arteries in response to hypertension and diabetes mellitus are mirrored in mesenteric, coronary, and cerebral arteries.

In this study, the Scheltens measure of WMLs did not differentiate depressed subjects from controls. This is at odds with the majority of studies in this area, but our findings are not unprecedented and are in keeping with a general trend to analyze white matter damage using automated functions or VRS scores. Excessive VRSs in the basal ganglia are associated with treatment resistance in late-onset depression, vascular dementia, and asymptomatic subjects at risk of stroke, and in these studies the amount of dilated VRSs predicted diagnosis (depression or stroke) better than WML scores.

This study has a number of limitations. The small numbers of participants limits the interpretative value of the findings with respect to the WML, VRS, and the small artery data. There is absence of reliable data regarding duration of symptoms, and this also limits discussion of potential interactions between WML and chronicity of depression. We also acknowledge that confounding by unmeasured variables could play a role. For example, nutrition might be different.
In depressed people and adversely affect microvascular function. There was an inverse correlation between wall cross-sectional area and both diastolic blood pressure and triglycerides. Triglyceride levels were lower in the depressed group and, although this may be because of greater statin use, neither difference (triglyceride level or use of statin) was statistically significant. As such, it is difficult to interpret these observations, and there are no published studies on the effect of triglycerides and small artery structure. There was also a positive correlation between wall cross-sectional area and fasting glucose, which was equivalent between the 2 groups. Overall, the cross-sectional nature of the study limits understanding of causal relationships, and treatment with antidepressants is a potential confounder. However, although an initial study with paroxetine suggested that this drug may cause reduction in NO bioavailability, subsequent studies have shown that the selective serotonin reuptake inhibitors most commonly used in this study improve vascular endothelial function. Thus, both paroxetine and citalopram increase plasma NO metabolic end products in control participants and in patients with depression. In addition, sertraline improves brachial artery flow-mediated dilation in depressed patients with coronary artery disease.

Despite these limitations, this study has demonstrated altered vascular function and structure in subcutaneous small arteries from patients with late-life depression. Our findings are in agreement with an emerging consensus that depression in later life is associated with vascular abnormalities, not explained by traditional cardiovascular risk factors. Impaired subcutaneous small artery endothelial function and abnormal wall growth were seen in tandem with dilated VRSs in the basal ganglia, which are markers of cerebral microangiopathy. Thus, this study provides a tentative physiological basis for the findings that vasoprotective drugs can improve the prognosis of late-life depression and, if replicated, could lead to a dual approach to treatment based on both depression management and vasoprotective agents. Endothelial dysfunction can be reversed by treatment with statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. Perhaps even more pertinently, angiotensin-converting enzyme inhibitors, angiotensin II receptor 1 blockers, and calcium channel blocking drugs are also able to
reverse hypertrophic remodeling in type 2 diabetes mellitus, a similar small artery phenotype to that which we have found in the depressed patients. Beyond the implications for the development of therapies to lessen the burden of vascular disease in depression, this work also establishes a basis for additional mechanistic and functional studies into the effects of depression on the microcirculation.

Perspectives
Late-life depression is increasingly viewed as a vascular illness because of patients exhibiting characteristic microvascular white matter brain lesions and in vivo large artery endothelial dysfunction. We undertook the first small artery study in this patient population and used MRI to demonstrate the presence of microvascular lesions in the brain. Although risk factors associated with small artery damage were comparable between the groups studied, depressed patients showed both abnormal growth of the subcutaneous gluteal small artery wall and endothelial dysfunction. The functional damage was not entirely explained by damage to NO bioavailability, which is usually responsible for vascular dysfunction, suggesting additional pathogenic mechanisms. The arteries studied were from a different circulation than that involved in the disease process, which are presumably penetrating pial arteries. However, previous studies of the subcutaneous gluteal small artery have shown that this microcirculation undergoes similar adaptive processes to disease compared with those in arteries from cardiac, cerebral, and mesenteric circulatory beds. As such, our findings are therefore in support of a generalized microvascular pathology in late-life depression.

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Disclosures
None.

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19. Paranthaman R, Greenstein et al Small Artery Structure and Function in Depression 739


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Cerebrovascular damage in late-life depression is associated with structural and functional abnormalities of subcutaneous small arteries

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**Methods:**

**Gluteal fat biopsy:**

A single subcutaneous gluteal fat biopsy was obtained from each subject by using 3 to 5 ml of 2% lignocaine, allowing tissue (2x1.5x1.5cm) to be harvested and placed immediately in ice-cold physiological saline solution (PSS). Small arteries 100 to 150μm in diameter were dissected from the tissue and carefully cleaned under a dissecting microscope. Isolated vessels were then transferred to an arteriographic bath chamber (Living systems Instrumentation) and cannulated as described previously. The chamber was placed on the stage of an inverted microscope and superfused with PSS, gassed with 5% CO2/95% air (pH 7.4 to 7.45) at 37°C, at a superfusion rate of 20mL/min. PSS composition was (mM) 139NaCl, 4.7KCl, 25NaHCO3, 1.17KH2PO4, 1.17MgSO4, 0.026EDTA, 1.6CaCl2 and 5.5glucose. Lumen diameter was recorded with the use of a Video Dimension Analyser (Living Systems Instrumentations) connected to a chart recorder. Vessels were connected to a pressure servo system (Living Systems Instrumentation) and pressurised to 60mmHg; any vessel with a leak was discarded. Vessels were allowed to equilibrate to 37°C for 1 hour and then challenged with 60mM KPSS until a steady vasoconstriction was attained.

**Pressure myography: Pharmacological assessment**

After viability assessment with KPSS, each vessel was stimulated as follows: (1) Cumulative addition of norepinephrine (Sigma-Aldrich), 10^-9, 3x10^-9, 10^-8, 3x10^-8, 10^-7, 3x10^-7, 10^-6, 3x10^-6, 10^-5M with 3 to 5 minutes incubation per concentration. (2) Endothelial function was assessed via the cumulative response to Acetylcholine (Ach) (Sigma-Aldrich) achieved by adding serial concentrations (M) 10^-9, 3 x10^-9, 10^-8, 3x10^-8, 10^-7, 3x10^-7, 10^-6, 3x10^-6, 10^-5 to a preconstricted vessel with 10^-5 norepinephrine. (3) After 1 hour of incubation with 5x10^-5M L-NG-monomethyl-arginine (L-NMMA) (Sigma-Aldrich), an inhibitor of nitric oxide synthase, the response to Ach was repeated as in (2).

**Pressure myography: Passive structure assessment**

Passive structure was determined for each vessel after completion of the functional studies. The vessel was superfused for 20 minutes with Ca-free PSS containing 2mmol/l ethylene glycol-bis (-amino ethyl ether)-N,N,N',N'-tetraacetic acid to ensure the vessels were devoid of active tone. To determine the structural and mechanical properties of the arteries, the intraluminal pressure was reduced to 3mmHg to determine the unstressed diameter and then increased in steps to 20, 40, 60, 80, 100, 120, 140, 160 and 180mmHg.

**Calculations**

The wall/lumen ratio was calculated as WT/D x 100, where WT is wall thickness and D is lumen diameter. Wall cross sectional area (CSA) was calculated as: CSA=π(D + 2WT /2)^2 - π(D/2)^2.

Stress (σ) = P x D / 2WT, where P is pressure and 1mmHg = 1334dyn/cm².
Strain ($\varepsilon$) = ($D - D_0$) / $D_0$, where $D_0$ is the lumen diameter at 3mmHg.
Table S1: Characteristics of study sample (t test for parametric data and Mann-Whitney test for non-parametric data and Chi-squared tests for categorical data). Data are mean (Standard deviation) unless specified
* Montgomery Asberg Depression Rating Scale
†: Mini-Mental State Examination
‡: Number of smokers per group
§: Pack-years of smoking are for those who had ever smoked
|| CCB: Calcium channel blocker, ACE: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin II receptor I blocking agent.
<table>
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<tr>
<th>Demographic variable</th>
<th>Depressed (n=16)</th>
<th>Controls (n=15)</th>
<th>P value</th>
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<tr>
<td>Age, yrs</td>
<td>71.8 ± 4</td>
<td>72.1 ± 5.9</td>
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<td>Women, n(%)</td>
<td>12(75)</td>
<td>9(60)</td>
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<td>Married, n(%)</td>
<td>2(12.5)</td>
<td>11(73.3)</td>
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<td>MADRS * Score</td>
<td>14.8 ± 11.1</td>
<td>2.5 ± 1.7</td>
<td>&lt;0.001</td>
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<td>MMSE† Score</td>
<td>28.9 ± 1</td>
<td>29.2 ± 1.1</td>
<td>0.35</td>
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<td>Alcohol units/week</td>
<td>5.3 ± 12.6</td>
<td>8.1 ± 9.8</td>
<td>0.48</td>
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<td>Smoking status‡, n(%)</td>
<td>4(16)</td>
<td>2(9.5)</td>
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<td>Smoking pack years §</td>
<td>25.9 ± 27.8</td>
<td>17 ± 23</td>
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<td>Taking statin, n(%)</td>
<td>10(62.5)</td>
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<td>Hypertension, n(%)</td>
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<td>2(12.5)</td>
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<td>History of Ischaemic Heart Disease, n(%)</td>
<td>3 (18)</td>
<td>2(15)</td>
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<td>Body mass index (kg/m²)</td>
<td>28.9 ± 4.6</td>
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<td>Waist circumference (cm)</td>
<td>97.9 ± 13.3</td>
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<td>Systolic Blood Pressure (mm Hg)</td>
<td>139 ± 14.7</td>
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<td>Diastolic Blood Pressure (mm Hg)</td>
<td>75.1 ± 12.1</td>
<td>76.7 ± 9.4</td>
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<td>Total cholesterol (mg/dL)</td>
<td>181 ± 34</td>
<td>174 ± 27</td>
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<td>High Density Lipoprotein (mg/dL)</td>
<td>61 ± 27</td>
<td>54 ± 11</td>
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<td>Triglycerides (mg/dL)</td>
<td>132 ± 45</td>
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<td>Glucose (mg/dL)</td>
<td>104 ± 31</td>
<td>107 ± 27</td>
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<td>Treatment with ACE,ARB or CCB† (%)</td>
<td>6(37.5)</td>
<td>8(53.3)</td>
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</table>

Table S1
Figure S1: A, Cumulative dose responses of pre-constricted arteries to increasing doses of Acetylcholine in control subjects before incubation with LNMMA (☐, n=15) and after incubation with LNMMA (■, n=12) (p = 0.08, multiple ANOVA). B Cumulative dose responses of pre-constricted arteries to increasing doses of Acetylcholine in depressed patients before incubation with LNMA (◊, n = 16) and after incubation with LNMMA (♦, n = 7) (p = 0.06, multiple ANOVA).
Figure S2: A: Strain-pressure relations in small arteries from control subjects (□, n=14) and patients with depression (♦, n=16).  
B: Wall stress vs intraluminal pressure in small arteries from control subjects (□) and patients with depression (♦).  
C: Stress-strain relations in small arteries from control subjects (□) and patients with depression (♦).
(♦). All points are shown ± standard error bars. There is no statistical significance between the groups.