Cerebral haemodynamics and depression in the elderly

H Tiemeier, S L Bakker, A Hofman, P J Koudstaal, M M B Breteler

Background: Evidence from epidemiological and neuroimaging studies suggests that cerebrovascular disease is associated with depressive disorders in the elderly, but the extent to which it contributes to the pathogenesis of late life depression is unclear.

Objective: To investigate the relation between cerebral haemodynamics and depression in a population based study, using transcranial Doppler ultrasonography.

Methods: Cerebral blood flow velocity and CO₂ induced vasomotor reactivity in the middle cerebral artery were measured in 2093 men and women who participated in the Rotterdam study. All subjects were screened for depressive symptoms using the Center of Epidemiological Studies Depression scale, and those with a score of 16 or over had a psychiatric work up. In a semistructured interview, diagnoses of depressive disorders according to the DSM-IV and subthreshold depressive disorder were established. Analyses of covariance controlled for age, sex, stroke, cognitive score, and cardiovascular risk factors were used to compare means of haemodynamic variables.

Results: Subjects with depressive symptoms had reduced blood flow velocities (mean difference, −2.9 cm/s; 95% confidence interval [CI], −5.0 to −0.8; p = 0.008) and lower vasomotor reactivity (mean difference −0.5%/kPa; 95% CI, −1.0 to −0.05; p = 0.03). Blood flow velocity was reduced most in subjects suffering from a DSM-IV depressive disorder (mean difference, −4.9 cm/s; 95% CI, −8.5 to −1.4; p = 0.006). The overall reduction in vasomotor reactivity was accounted for by subjects with subthreshold depressive disorder.

Conclusions: Depression in late life is associated with cerebral haemodynamic changes that can be assessed by transcranial Doppler ultrasonography. The observed reduction in cerebral blood flow velocity could be a result of reduced demand in more seriously depressed cases with a DSM-IV disorder, whereas reduced CO₂ induced cerebral vasomotor reactivity is a possible causal factor for subthreshold depressive disorder.

The Rotterdam study provided an opportunity to examine the relation between cerebral haemodynamics and depression in a population based sample of older adults. We conducted this study to evaluate whether cerebrovascular impairment, as measured by transcranial Doppler, is related to depression. Our a priori hypothesis was that subjects with depressive disorders have a reduced flow velocity and reduced vasomotor reactivity.

METHODS
Subjects

The investigation was conducted as part of the Rotterdam study, a population based cohort study ongoing since 1990, in which all inhabitants aged 55 and over in a suburb of Rotterdam were invited to participate. In the third survey we added assessments of depressive symptoms and cerebral haemodynamics to the protocol. Measurements were conducted between 1997 and 1999. Screening for depressive symptoms was carried out during the home interview part of the survey, in which 4730 subjects participated.

In 3101 consecutive participants we attempted to perform transcranial Doppler ultrasonography as part of the standard clinical investigation at the research centre. No transcranial Doppler measurements were carried out in the remainder (n = 1629), owing to the unavailability of a technician. In 990 subjects (32%), transcranial Doppler was undertaken but no results were obtained. In most cases this was because of window failure on both sides (n = 771) or because of restlessness or discomfort prevented the study being done (n = 36). In 183 participants haemodynamic measurements could not be carried out for other reasons, such as ambiguous flow direction or lack of time. Subjects in whom no transcranial
Doppler data were obtained were older (p < 0.001) and more likely to be female (p < 0.001). The prevalence of psychiatric symptoms in the analytical sample was found to be lower than in the study population as a whole (5.3% vs. 7.8%). A further 18 subjects were excluded because they did not have complete screening for depression. The final study sample consisted of 2093 participants in whom adequate depression and haemodynamic indices were obtained.

The Rotterdam Study was approved by the medical ethics committee of Erasmus University Medical School. After complete description of the study to the subjects, written informed consent was obtained.

Depression assessment
Depressive disorders were assessed using a two step procedure. First, participants completed the Dutch version of the original Center for Epidemiology Studies Depression scale (CES-D) during the home interview. The CES-D is a 20 item self reported measure of symptoms experienced in the past week, scored on a scale of 0 to 3 points. The validity of the CES-D has been well established. We used a score of 16 as a cut off point, as this has been found to have a high sensitivity (95.6%) and high specificity (85.6%) of 16 and above on the CES-D represents clinically significant depression, as defined in the appendix of DSM-IV.

The PSE-10 scores. The diagnostic categories include minor depression, as defined by the DSM-IV criteria, with an algorithm based on the PSE-10 scores. The diagnostic categories include minor depression, as defined in the appendix of DSM-IV.

Of the 2093 subjects included in the analyses, 116 (5.5%) were screen positive for depression as measured by the CES-D. A psychiatric work up was performed in 111 of these participants (95.6%). Four subjects refused to participate in this evaluation, and one screen positive subject could not be reached. A depressive disorder as defined by the DSM-IV criteria was established in 42 cases. The remaining subjects were either classified as having anxiety disorders or other psychiatric disease (n = 8) or did not meet criteria for an axis I psychiatric disorder (n = 61, subthreshold depressive disorder).

To define late onset depression we used the data from the baseline interview with a physician. All subjects in the present analysis responded to the questions about psychiatric history. Participants who reported a history of depression before the age of 60 were considered to be suffering from early onset depression.

Transcranial Doppler assessment
Transcranial Doppler ultrasonography was done using a Multi-Dop X-4 instrument (DWL, Sipplingen, Germany), and the cerebral blood flow velocity (cm/s) was measured in the middle cerebral artery on both sides if possible. End diastolic, peak systolic, and mean cerebral blood flow velocity were recorded automatically.

CO2-induced cerebral vasomotor reactivity measurements were done as follows. The cerebral blood flow velocity was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fitted over mouth and nose, until a steady expiratory end tidal CO2 was obtained. Next, participants inhaled a mixture of 5% carbon dioxide in 95% oxygen for two minutes. Cerebral vasomotor reactivity was defined as the percentage increase in cerebral blood flow velocity occurring during inspiration of 5% CO2, divided by the absolute increase in end tidal CO2 in the same period (%kPa). End tidal pCO2, (kPa) was recorded continuously with a CO2 analyser (Multiinx, Datascop, Hoevelaken, Netherlands). End respiratory CO2 was assumed to reflect arterial CO2. TCD-8 DWL special software (VMR-CO2) was used. All transcranial Doppler data were stored on hard disc for off-line analysis. The mean of the right and left haemodynamic variables was used for analyses if both middle cerebral arteries could be insonated adequately. A one sided haemodynamic variable was used if there was unilateral window failure.

Measurements of other covariates
The following were considered to be possible confounding variables: age, sex, education, cognitive function (measured by the mini mental state examination (MMSE)), antihypertensive treatment, and antidepressant treatment. Education was measured on an ordinal scale and later dichotomised into low and high. Information on current antidepressant or anti-hypertensive drug treatment was obtained during the home interview. The following cardiovascular risk factors were assessed: stroke, smoking, systolic and diastolic blood pressure, diabetes mellitus, and total cholesterol. A history of stroke was obtained from all subjects through direct questioning and computerised linkage with general practitioner medical records. The history was considered positive when confirmed by a physician. Cigarette smoking was analysed in categories of current and former smoker. Sitting blood pressure was measured twice on the right arm with a random zero sphygmomanometer. Diabetes mellitus was defined as the use of insulin or oral blood glucose lowering drugs, or serum glucose concentrations of more than 11.0 mmol/l. Fasting blood samples were taken and serum total cholesterol was measured using an automated enzymatic procedure. The ankle to brachial index was used as an indicator of peripheral atherosclerosis. We assessed the ratio of the systolic blood pressure measured at the tibial artery to that measured at the right arm. Subjects with an ankle to brachial index of less than 0.9 were considered to suffer from peripheral arterial disease.

Statistical analysis
The associations between haemodynamic variables and depressive disorders were addressed in three ways.

First, analysis of covariance (ANCOVA) was used to calculate means of the screen positive subjects and the reference group, adjusted for age and sex. Haemodynamic indices were entered as continuous variables. In addition, we controlled these analyses for education, antihypertensive and antidepressant drug treatment, cognitive function, and cardiovascular risk factors. We also performed an ANCOVA to evaluate possible differences between subjects with depressive disorders and subjects with subclinical depressive symptoms. Subjects without a psychiatric work up and those with other psychiatric disorders were excluded from subgroup analyses. Analyses were run both excluding and adjusting for subjects with a history of stroke (n = 7 in the screen positive group, including two subjects with depressive disorder) or taking antidepressant drugs.

Second, logistic regression analysis was used to calculate the odds ratios for the association between haemodynamic variables and the presence of depressive disorders. We assessed tertiles of haemodynamic variables to allow for a non-linear relation. Because of the relatively small number of cases we did not use more categories. In this model we included only the variables associated with haemodynamic indices to avoid an overfitted model.

Third, we used stratified analyses to study possible effect modification by peripheral arterial disease and a history of depression.
RESULTS
Table 1 compares the demographic characteristics and confounding variables of the 116 participants who were screen positive and the 1977 participants who were screen negative for depression. Age, sex, education, a history of major depression before age 60, previous stroke, and cognitive function were all associated with current depressive symptoms. However, the cardiovascular risk factors smoking, diabetes, systolic and diastolic blood pressure, antidepressant and antihypertensive drug treatment, total cholesterol, and diabetes mellitus were not related to depressive symptoms.

Subjects with depressive symptoms as determined by the CES-D had a lower mean cerebral blood flow velocity (age and sex adjusted mean difference, 2.9 cm/s; 95% confidence interval (CI), −5.0 to −0.8; p = 0.007) and reduced vasomotor reactivity (age and sex adjusted mean difference, −0.7 %/kPa; 95% CI, −1.2 to −0.2; p = 0.008). Table 2 shows the relation between cerebral haemodynamic variables and depressive symptoms, with additional adjustment for education, history of stroke, antidepressant and antihypertensive drug treatment, cognitive function, and cardiovascular risk factors.

In a further analysis, screen positive subjects were classified according to the severity of the depressive symptoms (table 3). Subjects with subthreshold depressive disorder and DSM-IV depressive disorders were included as distinct groups. The results showed a consistent pattern for end diastolic, mean, and peak systolic blood flow velocity. Blood flow velocity of subjects with depressive disorders was significantly lower than in the reference group. The mean values of subjects with a subthreshold depressive disorder lay in between. A different pattern was observed for vasomotor reactivity. Subjects with

---

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of participants with and without depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-depressed (n=1977)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.1 [6.5]</td>
</tr>
<tr>
<td>Male</td>
<td>54.1%</td>
</tr>
<tr>
<td>Primary education only</td>
<td>42%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.3%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6%</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>16%</td>
</tr>
<tr>
<td>Former smoker</td>
<td>56%</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.9 [1.8]</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>143 [18]</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75 [11]</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.8 [1.0]</td>
</tr>
<tr>
<td>Antidepressant drug treatment</td>
<td>1.7%</td>
</tr>
<tr>
<td>Antihypertensive drug treatment</td>
<td>35%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>17%</td>
</tr>
<tr>
<td>Major depression before age 60</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Values are unadjusted mean (SD) or percentages
*p<0.05; **p<0.001, adjusted for age and sex were appropriate.

MMSE, mini mental state examination.

---

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Association between cerebral haemodynamic variables and depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-depressed (n=1977)</td>
</tr>
<tr>
<td>Blood flow velocity (cm/s)</td>
<td>Mean</td>
</tr>
<tr>
<td>End diastolic</td>
<td>32.5</td>
</tr>
<tr>
<td>Mean</td>
<td>50.5</td>
</tr>
<tr>
<td>Peak systolic</td>
<td>86.5</td>
</tr>
<tr>
<td>Vasomotor reactivity (%/kPa)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Analysis of covariance with haemodynamic data entered as continuous variables and adjusted for age, education, cognitive function, smoking, systolic and diastolic blood pressure, antidepressant and antihypertensive drug treatment, total cholesterol, diabetes mellitus, and history of stroke.

Values are unadjusted means and adjusted differences, using pairwise comparison with non-depressed reference group.

CI, confidence interval; CES-D, Center for Epidemiology Studies depression scale.

---

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Association between cerebral haemodynamic variables and depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-depressed (n=1929)</td>
</tr>
<tr>
<td>Blood flow velocity (cm/s)</td>
<td>Mean</td>
</tr>
<tr>
<td>End diastolic</td>
<td>32.5</td>
</tr>
<tr>
<td>Mean</td>
<td>50.5</td>
</tr>
<tr>
<td>Peak systolic</td>
<td>86.5</td>
</tr>
<tr>
<td>Vasomotor reactivity (%/kPa)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Analysis of covariance with haemodynamic data entered as continuous variables and adjusted for age, sex, education, cognitive function, smoking, systolic and diastolic blood pressure, antidepressant and antihypertensive drug treatment, total cholesterol, and diabetes mellitus. Subjects with stroke were excluded.

Values represent unadjusted means and adjusted differences (95% confidence interval), using pairwise comparison with a non-depressed reference group, same covariates.
subthreshold depressive disorder had a lower vasomotor reactivity than non-depressed reference subjects, whereas there was no clear cut difference between subjects with depressive disorders and the reference group. Very similar estimates were observed if we excluded subjects with a history of stroke or those taking antidepressant drugs, rather than adjusting for those variables.

Table 4 shows the odds ratios for depressive symptoms per tertile of haemodynamic variables adjusted for age, sex, and cognitive function. The particular contributions of subjects with subthreshold depressive disorder and subjects with DSM-IV depressive disorders are also presented in the table. It can be seen that more subjects with depressive disorders were found in the lowest tertile of blood flow velocity. For vasomotor reactivity, the middle and the lower tertiles were associated with an increased risk of subthreshold depressive disorder.

The observed relations between depressive status and cerebral haemodynamic variables were not altered after we controlled for a history of major depression before age 60 and peripheral arterial disease. There were more subjects with peripheral arterial disease in the group with subthreshold depressive disorder (28.8%) and the group with depressive disorders (25.0%) than in the reference group (16.5%). However, the relation between blood flow velocity or vasomotor reactivity and depression was neither explained by nor modified by peripheral arterial disease (data not shown).

**DISCUSSION**

This study shows that haemodynamic changes as assessed by transcranial Doppler ultrasonography are associated with depressive symptoms. Both cerebral blood flow velocity and vasomotor reactivity were found to be lower in subjects with depressive symptoms, after the effects of age, sex, education, history of stroke, cognitive function, and cardiovascular risk factors were controlled for. These results support the view that cerebrovascular impairment may be a cause of depressive symptoms in the elderly. To our knowledge this study is the first to report results of transcranial Doppler ultrasound measurements and depression. Most studies using transcranial Doppler ultrasonography in psychiatric settings have looked at dementia or panic disorders.

The strength of the present large population based study is the psychiatric work up in subjects who were screen positive on the CES-D. A previous study in an elderly Dutch population reported high sensitivity using the same cut off point, and misclassification of disease is thus unlikely to have influenced our results. Furthermore, we were able to determine in which group depressive symptoms were caused by depressive disorders. The prevalence of depressive symptoms in the Rotterdam study (7.8%) falls within the range reported in a recent review of community prevalence of depressive symptoms in the elderly and is comparable with the prevalence of 9.0% reported in the USA.

The term “vascular depression” was introduced by Alexopoulos. He postulated that geriatric depression encompasses a high percentage of patients with cerebrovascular disease. While there are few clinical differences between early and late onset depression, the hypothesis has been supported by studies showing that persons with late onset depression have more neuroradiological abnormalities than non-depressed individuals. This finding could only partially be replicated in a population based study. Steffens et al reported hyperintensities in the basal ganglia, but other white matter lesions were not related to depressive symptoms as measured by a shortened version of the CES-D.

Different mechanisms for altered cerebral blood flow velocity as measured by transcranial Doppler have been postulated. Reduced blood flow may reflect altered cerebral metabolism, an intrinsic property of the vascular smooth muscle, or a neuronal dysfunction of sympathetic nerve fibres. Metabolic autoregulation is probably of key importance and explains the increased flow velocity during cognitive activity. Reduced vasomotor reactivity is a well recognised symptom of depressive disorder, a reduction of blood flow velocity might be an epiphenomenon of depression. The decreased blood flow velocity in our study could reflect the diminished demand in depressive states and does not necessarily support the vascular hypothesis.

Vasomotor reactivity, on the other hand, is probably a good indicator of microangiopathy. A reduced vasomotor reactivity indicates that the cerebral arterioles are unable to dilate in order to compensate for increased demand. In patients with stroke or transient ischaemic attacks reduced vasomotor reactivity has often been reported. In a subset of 73 patients with MRI scans who participated in this study, we previously observed that vasomotor reactivity was related to deep subcortical and periventricular white matter lesions. However, in the present study we did not confirm our hypothesis.
that reduced vasomotor reactivity is associated with depressive disorders. The observed impairment of vasomotor reactivity in subjects with depressive symptoms was accounted for by cases with subthreshold depressive disorder. If this is not a chance finding, it suggests that cerebral microangiopathy may be less important in the more severely diseased and more often cause subthreshold depressive disorder. Interestingly, a recent neuropathological necropsy study also found no evidence of microvascular disease either locally or generally in the brain of depressed patients.41

Limitations
Some limitations of the study must be discussed. This was a cross-sectional study and it cannot show whether the observed association with cerebrovascular changes precipitates or results from the depressive symptoms. Furthermore, we should consider whether selection influenced the outcome of the study. In the first place, transcranial Doppler measurements were not performed in all subjects participating in the third survey of the Rotterdam study; however, this omission was entirely random so it did not introduce bias. Second, transcranial Doppler measurements were unsuccessful in nearly one third of the subjects, and participants in whom transcranial Doppler measurements were unsuccessful were on average older and more often female. This was expected, as temporal bone acoustic thickness increases with age and in postmenopausal women,42 and this adversely affects the transmission of ultrasound. Hyperostosis, which is predominantly found in women, is also thought to preclude transcranial Doppler measurements.43 As old age and female sex are positively associated with depressive symptoms, persons with mood disorders were underrepresented in our study. This selection may have impeded the detection of modest associations. However, we think it unlikely that the observed relations between cerebral haemodynamic variables and depressive symptoms were a result of selection. There is no indication that haemodynamic changes differ in women or very old depressed subjects.

Conclusions
We have shown that depressive symptoms are associated with changes in both blood flow velocity and vasomotor reactivity. Our finding of reduced vasomotor reactivity suggests that vascular pathology may be a causal factor in subjects with subthreshold depressive disorder but not in DSM-IV depressive disorders. Furthermore, our data indicate that reduced cerebral blood flow velocity could be caused by reduced demand in depressed subjects and does not necessarily reflect microangiopathy.

ACKNOWLEDGEMENTS
The Rotterdam Study is supported in part by the NESTOR programme for geriatric research in the Netherlands (Ministry of Health and Ministry of Education), the Municipality of Rotterdam, the Netherlands Heart Foundation, and the Netherlands Organisation for Scientific Research (NWO). MMBB is a fellow of the Royal Netherlands Academy of Arts and Sciences.

Authors' affiliations
H Tiemeier, A Hofman, M M B Breteler, Department of Epidemiology & Biostatistics, Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands
S L M Bakker, P J Koudstaal, Department of Neurology, Erasmus Medical Centre Rotterdam

REFERENCES

Want full access but don't have a subscription?

Pay per access

For just US$25 you can have instant access to the whole website for 30 days. During this time you will be able to access the full text for all issues (including supplements) available. You will also be able to download and print any relevant pdf files for personal use, and take advantage of all the special features Journal of Neurology, Neurosurgery, and Psychiatry online has to offer.

www.jnnp.com