Transient Ischemic Attack and Incident Depression

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Background and Purpose—Depression after stroke is common. Like stroke, transient ischemic attack (TIA) is a manifestation of long-term atherosclerotic damage to the brain. However, the risk of depression developing after a TIA is uncertain. We studied whether TIA increases the risk of incident late-life depression.

Methods—A cohort study of 5095 inhabitants of Rotterdam, the Netherlands, was performed between 1993 and 2005. Participants were aged 56 years or older and free of depression at baseline. TIA and depression were identified through regular standardized examinations and continuous monitoring of medical records. We estimated hazard ratios (HR) with time-varying Cox regression analyses, adjusting for sociodemographic and health-related factors.

Results—During follow-up, 407 depressive syndromes occurred, of which 103 met criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM) for depressive disorders. TIA was significantly associated with the risk of incident depressive syndromes (HR, 1.68; 95% CI, 1.12–2.51) and DSM-defined depressive disorders (HR, 2.42; 95% CI, 1.26–4.67). The risk of depressive syndromes increased with the number of TIA a person had experienced (HR, 1.45; 95% CI, 1.17–1.81), as did the risk of depressive disorders (HR, 1.63; 95% CI, 1.18–2.24). In persons without a history of depression at baseline, we found an almost 3-fold increased risk of DSM-defined depressive disorders (HR, 2.91; 95% CI, 0.96–8.81).

Conclusions—TIA was independently associated with an increased risk of incident depression. Our finding suggests that symptomatic cerebrovascular disease increases the vulnerability to late-life depression. (Stroke. 2011;42:1857-1861.)

Key Words: cohort study ■ depression ■ transient ischemic attack

In the first month after a stroke, up to 50% of patients develop depression, and the risk of depression remains high in the next year. Poststroke depression decreases the quality of life for patients and contributes to the burden of disease for primary caregivers. The vascular depression hypothesis posits that atherosclerotic brain damage, independent of functional disability associated with it, may predispose to late-life depression. Like stroke, transient ischemic attack (TIA) is common clinical manifestations of long-term atherosclerotic damage to the brain. Ischemic abnormalities on diffusion-weighted imaging can be found in 35% to 67% of patients in the acute phase after TIA, approximately half of which are located in the subcortex. Unlike stroke, TIA does not, per definition, give rise to permanent functional disabilities.

The possible risk of depression after a TIA has received far less attention than the risk conveyed by stroke. In 2 clinical studies, the prevalence of major depressive disorder in patients with carotid stenosis accompanied by TIA ranged between 28% and 40%. This finding was confirmed in 2 population-based but cross-sectional studies. To our knowledge, longitudinal studies are lacking. The aim of the present study was to assess whether TIA is associated with an increased risk of development of depression in a population of community-dwelling elderly persons.

Setting and Study Population

This study was embedded in the Rotterdam Study, a prospective study that started in 1989 among 7983 inhabitants of Ommoord, a district of Rotterdam, the Netherlands. Participants were 55 years of age or older. The study focuses on the occurrence and determinants of chronic diseases in the elderly. The Medical Ethics Committee of Erasmus Medical Center Rotterdam approved the study and written informed consent was obtained from all participants. Until 2004, 4 examination rounds took place, during which participants underwent an extensive interview and a physical examination.

During the second visit, the baseline of the current analysis, 5769 participants were screened for depressive symptoms. Participants completed either the validated Dutch version of the Center for Epidemiological Studies Depression Scale or the validated Dutch...

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version of the Hospital Anxiety and Depression Scale.\textsuperscript{15–16} Persons with a score of $\geq 16$ on the Center for Epidemiological Studies Depression Scale or $\geq 9$ on the Hospital Anxiety and Depression Scale were considered screen-positive. At baseline, we excluded 549 persons with depressive symptoms, 105 persons with dementia, 9 persons with bipolar disorder, 2 persons lost to follow-up directly after screening, and 9 persons with unknown TIA/stroke status. This resulted in a study population of 5095 persons free of depression at baseline.

### Assessment of Incident Depression

Assessment of depression has been described in detail before.\textsuperscript{17} Information on incident depression that occurred during follow-up was obtained from psychiatric examinations, self-reported histories of depression, and medical records. The psychiatric examination during examination rounds consisted of a screening with the Center for Epidemiological Studies Depression Scale. Subsequently, a trained clinician conducted a semistructured interview (Schedules for Clinical Assessment in Neuropsychiatry) in the screen-positive participants to obtain DSM-IV–defined diagnoses.\textsuperscript{18} The self-reported history of depression, solicited during examination rounds, included standardized questions to ascertain whether and when participants had experienced a depressive episode and, if so, whether they had been treated. Trained research assistants scrutinized the general practitioners’ medical records and copied the information about a potential depression. Two research physicians independently assessed this information according to a predefined protocol and discussed discordant assessments. Based on these sources, we categorized depressions as: (1) depressive disorders, ie, DSM-IV–defined major depressive disorder or dysthymia as diagnosed by a psychiatrist or another mental health professional; (2) “other depressive syndromes,” ie, depression recorded by a general practitioner, self-reported depression for which the participant consulted a health professional, or DSM-IV–defined minor depression; or (3) “clinically relevant depressive symptoms” if at least 1 clinically relevant core symptom of major depression had been reported.

We defined the date-of-onset as the day of the first report of symptoms according to one of the sources described or the first prescription date of an antidepressant drug, whichever occurred first.

### Assessment of TIA and Stroke

Assessment procedures for TIA and stroke have been described elsewhere in detail.\textsuperscript{19} Prevalent and incident TIA were ascertained by a research physician who screened all participants by asking for transient neurological symptoms during examination rounds. In addition, research physicians reviewed the information from the medical files and, if available, brain imaging results from hospital records. An experienced neurologist verified all diagnoses. Follow-up for all events was completed until October 1, 2005, for 96% of potential person-years.

To ascertain a TIA, focal symptoms had to have started suddenly and had to have stopped within seconds to a maximum of 24 hours.\textsuperscript{9} A stroke was diagnosed if a patient had typical symptoms that lasted $>24$ hours. Focal brain symptoms included hemiparesis, hemihypesthesia, dysphasia, dysarthria, amaurosis fugax, hemianopia, hemiataxia, diplopia, or vertigo. The date-of-onset of an incident attack was determined with the information from the sources described. History of TIA at baseline was positive if a TIA had occurred before baseline interview. Participants who had a history of stroke at baseline or an incident stroke after baseline could not be identified with a TIA after the stroke.

### Covariables

The following baseline covariables were considered potential confounders:\textsuperscript{20} age, sex, socioeconomic status, disability in activities of daily living, history of depression, smoking, and hypertension. In addition, diabetes mellitus, history of cardiovascular disease, atrial fibrillation, and current use of antihypertensive medication were included as time-varying covariables.

Socioeconomic status was determined in terms of the combination of highest education attained and net income. Disability in activities of daily living was assessed with the Modified Stanford Health Assessment Questionnaire.\textsuperscript{21} Self-reported smoking use was categorized as none, former, and current. The average of 2 blood pressure measurements in sitting position was used for our analysis. The criteria for diabetes mellitus were fasting plasma glucose level of $\geq 7.0$ mmol/L, nonfasting glucose, or an oral glucose tolerance test result of $\geq 11.1$ mmol/L, or treatment with an antidiabetic medication or diet. History of cardiovascular disease encompassed angina pectoris and claudicatio intermittens, both established with the Rose questionnaire, as well as a history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and peripheral artery bypass graft, as verified in the medical files. Information on current use of antihypertensive medication was obtained from an online pharmaceutical database.

### Data Analysis

To study the effect of TIA on the risk of incident depression, we estimated hazard ratios (HR) with Cox proportional hazards analyses. We performed the analyses with 3 increasingly stringently defined outcomes: depressive syndromes and depressive symptoms (categories 1, 2, and 3), depressive syndromes (categories 1 and 2), and depressive disorders (category 1). The exposure of having had a TIA or stroke compared to no cerebrovascular event was entered in the model as a time-varying variable. The models were adjusted for all confounders described. We thus obtained risk estimates for the effect of TIA on the risk of depression, not through stroke. To further ascertain the temporal relationship between TIA and subsequent depression, we repeated this model in persons without a history of depression at baseline. Finally, we fitted a model in which the number of TIA was entered as a time-varying exposure variable, again adjusted for intermediate stroke and all covariables.

In all analyses, each participant contributed person-years from baseline date until follow-up ended, which was when depression, dementia, death, or loss to follow-up occurred, or at the end of study period on October 1, 2005. Two-sided $P<0.05$ was considered statistically significant. For all statistical analyses, we used SPSS for Windows version 13.0.

### Table 1. Baseline Characteristics of Study Population (n=5095)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>70.0 (8.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2939 (57.7)</td>
</tr>
<tr>
<td>Education, primary school only, n (%)</td>
<td>934 (18.3)</td>
</tr>
<tr>
<td>Income in €, median (range)</td>
<td>2690 (750–7000)</td>
</tr>
<tr>
<td>Disability, mean (range)</td>
<td>1.3 (1.0–4.0)</td>
</tr>
<tr>
<td>History of depression, n (%)</td>
<td>1641 (32.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>2598 (51.0)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>868 (17.0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1140 (22.4)</td>
</tr>
<tr>
<td>Body mass index, mean (range)</td>
<td>26.5 (14.7–48.0)</td>
</tr>
<tr>
<td>Total cholesterol, mean (range)</td>
<td>6.6 (2.2–18.0)</td>
</tr>
<tr>
<td>HDL cholesterol, mean (range)</td>
<td>1.4 (0.4–6.3)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>537 (10.5)</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>1006 (19.7)</td>
</tr>
<tr>
<td>Chronic heart failure, n (%)</td>
<td>206 (4.0)</td>
</tr>
<tr>
<td>Use of antihypertensive medications, n (%)</td>
<td>1558 (30.6)</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; SD, standard deviation.
Results

Table 1 presents the baseline characteristics of the study population. The mean age was 70 years, with a range of 56 to 101 years, and 58% of the participants were female. The most prevalent cardiovascular risk factor was history of smoking, with 51% former smokers and 17% current smokers. At baseline, 1641 participants had a history of depression. One or more TIA were diagnosed in 86 participants before baseline and in 239 persons during follow-up.

In our study population, a total of 736 incidents of depression occurred during 42 090 person-years. Of these episodes, 407 were depressive syndromes, including 103 DSM-defined depressive disorders. In the 325 persons with a TIA, 27 persons developed depression, and 13 of these 27 persons had no history of depression. The mean time between the (first) TIA and a depressive syndrome was 3.8 years (SD, 2.8; median, 3.8; range, 0.0–11), counting cases of TIA present at baseline from that time onward. The Figure shows the Kaplan-Meier survival curves. After 12 years of follow-up, twice as many participants with a TIA developed a depressive syndrome.

Table 2 shows the risk of incident depression associated with TIA. TIA was more strongly associated with depression the more stringently depression was defined: the risk of depressive symptoms and syndromes combined was 1.30 (95% CI, 0.94–1.80), the risk of depressive syndromes was 1.68 (95% CI, 1.12–2.51), and the risk of depressive disorders was 2.42 (95% CI, 1.26–4.67). Like TIA, stroke was also related to depressive syndromes (HR, 1.52; 95% CI, 1.01–2.27) and to depressive disorders (HR, 3.35; 95% CI, 1.82–6.18; not shown in Table 2). The HRs showed the same pattern in the subsample of persons without a history of depression at baseline.

Finally, we assessed the risk of incident depression related to the number of TIAs. Of 325 persons with a TIA at or after baseline, 233 had had 1 attack, 62 had 2 attacks, 19 had 3 attacks, 9 had 4 attacks, and 2 had 5 attacks. A higher number of TIAs were associated with more depressive symptoms and syndromes (HR, 1.23; 95% CI, 1.01–1.50), depressive syndromes (HR, 1.45; 95% CI, 1.17–1.81), or depressive disorders (HR, 1.63; 95% CI, 1.18–2.24).

Discussion

In this population-based cohort, we found that with potential confounders having been taken into account, TIA was significantly associated with depressive syndromes and depressive disorders. The risk increased with the number of TIAs a person had experienced. To the best of our knowledge, the association between TIA and depression has not been studied prospectively before.

After stroke, between 10% and 50% of patients developed depression in the first month, and 1 year later the risk is still higher than 30%.

Table 2. Transient Ischemic Attacks and Risk of Incident Depression Using Cox Proportional Hazard Models

<table>
<thead>
<tr>
<th></th>
<th>Depressive Syndromes and Symptoms (n=736)</th>
<th>Depressive Syndromes Only (n=407)</th>
<th>Depressive Disorders Only (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Complete study population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=5095)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA (n=325)</td>
<td>1.30 (0.94–1.80)</td>
<td>0.12</td>
<td>1.68 (1.12–2.51)</td>
</tr>
<tr>
<td>Persons without history of depression (n=3454)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA (n=196)</td>
<td>1.38 (0.85–2.24)</td>
<td>0.19</td>
<td>1.99 (1.11–3.56)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; TIA, transient ischemic attack.

*Adjusted for age, sex, socioeconomic status, activities of daily living, history of depression, smoking, hypertension, diabetes, history of cardiovascular disease, heart failure, and use of antihypertensive medications.

†Adjusted for age, sex, socioeconomic status, activities of daily living, smoking, hypertension, diabetes, history of cardiovascular disease, heart failure, and use of antihypertensive medications.
myocardial infarction and heart failure explained the association between TIA and depression, but the risk estimates barely changed.23

Although the mean time between TIA and depression was 3.8 years, we found that time to depression in persons with TIA was significantly shorter than time to depression in persons without a TIA. The HR was 1.68 (95% CI, 1.12–2.51) for depressive syndromes and 2.42 (95% CI, 1.26–4.67) for depressive disorders. Furthermore, the survival curves show that the strength of the association between TIA and depression did not change over time. Therefore, the somewhat long time-lapse between TIA and depression may reflect that post-TIA depression is typically a consequence of vascular changes rather than a reactive response to an acute event. Possibly, depression after TIA occurs mainly in patients with white matter abnormalities.7–8

In the majority of published prospective studies, however, MRI-visualized cerebrovascular disease has not been associated with incident depression,24–28 nor has any measure of extracerebral atherosclerosis.29 This suggests that symptomatic cerebrovascular disease, more than generalized atherosclerosis per se, predisposes to late-life depression. Alternatively, carotid stenosis, a common cause of TIA, has been associated with depression in several clinical studies,10,11,30 and a significant reduction of depressive symptoms was found in patients who underwent carotid artery stent placement.30 Studies are needed based on MRI data that verify TIA diagnosis, ischemic pathophysiology, and location, as well as presence of comorbid vascular brain disease.6 At the same time, the clinical relevance of an independent risk factor for depression may be higher if it can be assessed without imaging or laboratory tests.

The strengths of our study were the large population-based cohort and long follow-up period. Detailed information on the occurrence of TIA was collected with systematic repeated interviews and continuous monitoring of medical files. Each potential TIA was classified according to a stringent protocol by multiple raters. Participants were also monitored continuously for incident depression and interviews were conducted by clinicians who used DSM-IV criteria to diagnose depression. Even so, we might have missed some reactive depressions that occurred soon after a TIA, because this type of depression tends to be comparatively short-lived. We adjusted for a considerable number of sociodemographic and health-related confounders. Nevertheless, although our findings are consistent, the relatively small number of post-TIA depressions calls for replication of our findings in other population-based cohorts.

Conclusions
We found that TIA is associated with incident depression, as is stroke. Symptomatic cerebrovascular disease, irrespective of the duration of initial symptoms and loss of function, appears to predict new-onset depression over an extended period of time. The high risk for post-TIA depression justifies greater attention for this long-term and frequently debilitating psychiatric outcome.

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Disclosures
None.

References


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