Trajectory of Functional Decline Before and After Ischemic Stroke
The Northern Manhattan Study

Mandip S. Dhamoon, MD, MPH; Yeseon P. Moon, MS; Myunghee C. Paik, PhD; Ralph L. Sacco, MD, MS; Mitchell S.V. Elkind, MD, MS

Background and Purpose—Previous research in our cohort showed a delayed decline in functional status after first ischemic stroke. We compared the long-term trajectory of functional status before and after ischemic stroke.

Methods—The Northern Manhattan Study contains a prospective, population-based study of stroke-free individuals age ≥40 years, followed for a median of 11 years. The Barthel index (BI), a commonly used measure of activities of daily living, was assessed annually. Generalized estimating equations were used to assess functional decline over time before stroke and beginning 6 months after stroke. Follow-up was censored at the time of recurrent stroke.

Results—Among 3298 participants, 210 participants had an ischemic stroke during follow-up and had poststroke BI assessed. Mean age (±SD) was 77±9 years, 38% were men, 52% were Hispanic, 37% had diabetes, and 31% had coronary artery disease. There was no difference in rate of functional decline over time before and after stroke (P=0.51), with a decline of 0.96 BI points per year before stroke (P<0.0001) and 1.24 BI points after stroke (P=0.001). However, when stratified by insurance status, among those with Medicaid or no insurance, in a fully adjusted model, there was a difference in slope before and after stroke (P=0.04), with a decline of 0.58 BI points per year before stroke (P=0.02) and 1.94 BI points after stroke (P=0.001).

Conclusions—In this large, prospective, population-based study with long-term follow-up, there was a significantly steeper decline in functional status after ischemic stroke compared with before stroke among those with Medicaid or no insurance, after adjusting for confounders. (Stroke. 2012;43:2180-2184.)

Key Words: epidemiology ▪ disability ▪ rehabilitation

The commonly held view is that stroke is a discrete event and that, following the 3-to-6-month recovery period after stroke, functional status would remain constant over time, or at best improve with rehabilitation, if no recurrent events occurred.¹ However, stroke is caused by conditions, such as hypertension, diabetes, and hyperlipidemia, that may have an ongoing and cumulative effect on vessel dysfunction and may cause subclinical infarcts that can reduce functional status over the long-term. Although the short-term effects of stroke on disability are well-described,²⁻⁹ the long-term course of functional status before and after stroke is less clear. Our previous research has shown that there was a steady linear decline in functional status over 5 years after stroke among those with Medicaid or no insurance.¹⁰ This decline occurred even when recurrent clinical stroke and myocardial infarction were censored, and in models adjusted for demographic variables, stroke severity, and vascular risk factors. An important unresolved question was whether the decline was caused by the stroke (or mechanisms triggered by the stroke) or was simply a result of aging and independent of any clinical stroke. To our knowledge, no previous study has compared the slope of functional status over time before and after ischemic stroke.

Our hypothesis was that the decline in functional status after recovery from stroke is steeper than it is before stroke, even in the absence of recurrent clinical strokes. Our objectives were to compare the annual decline in functional status, measured by the Barthel index (BI), a commonly used measure of activities of daily living, before and beginning 6 months after first ischemic stroke, adjusting for potential confounders. The modeling techniques proposed here to assess for a change in slope before and after vascular events have not been employed to examine this question. Also, we employed repeated measures of functional outcomes, which are rarely collected in healthy individuals, but were collected in the Northern Manhattan Study.
Methods
The Northern Manhattan Study is a prospective, population-based cohort of 3298 subjects, designed to describe the prevalence of vascular risk factors and incidence of vascular outcomes in a community-based sample of a racially and ethnically diverse population. The study was approved by the Institutional Review Boards of Columbia University and the University of Miami, and informed consent was obtained from all participants.

Cohort Selection
The cohort was recruited between 1993 and 2001 as described elsewhere.11 Subjects were enrolled if they: were age ≥40 years, lived in a predefined geographic area of northern Manhattan for at least 3 months in a household with a telephone, and did not have a history of stroke. Subjects were contacted by random digit dialing of both published and unpublished telephone numbers. The telephone response rate was 91% (9% refused to be screened), and 87% of eligible subjects indicated willingness to participate. The enrollment response rate was 75%, resulting in an overall response rate of 68%.

Baseline Assessment
All participants underwent a thorough baseline examination, including comprehensive medical history, physical examination, review of medical records, and fasting blood samples. Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Race/ethnicity was based on self-identification modeled after the US census. Smoking was defined as either nonsmoker or smoker (within the last year). Hypertension, coded as present or absent, was defined as a systolic blood pressure recording ≥140 mm Hg or a diastolic blood pressure recording ≥90 mm Hg (based on the average of 2 blood pressure measurements) or the patient’s self-report of a history of hypertension or antihypertensive use. Diabetes mellitus was defined by self-report, fasting blood glucose level ≥126 mg/dL, or insulin/oral hypoglycemic drug use. Fasting total cholesterol was obtained using a Hitachi 705 automated spectrophotometer (Boehringer Mannheim). Hypercholesterolemia was defined as a patient’s self-report of hypercholesterolemia, use of lipid-lowering therapy, or a fasting total cholesterol level >240 mg/dL. Moderate alcohol use was classified as 1 drink/month to 2 drinks/day. Physical activity was assessed using a questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics, and was classified as any or none, as previously described.12

Prospective Follow-Up
Subjects were followed up annually by telephone. Only 2 subjects were completely lost to follow-up after their baseline examination, and the average annual contact rate was 99%. The telephone interview assessed any change in vital status, neurological symptoms and events, hospitalizations, and functional status via the BI. Previous research has demonstrated the reliability of phone assessments of functional status using the BI.13 For this analysis, the BI was analyzed as a continuous variable to increase power to describe the course of change over time.14

A positive screen for any potential neurological event was followed-up by an in-person assessment to determine whether a stroke had occurred. We prospectively screened all admissions and discharges to detect hospitalizations and outcomes that may not have been captured by telephone interview. Nearly 70% of vascular events led to hospitalizations at Columbia University Medical Center. Hospital records were reviewed to classify all outcomes as previously reported.11 Stroke diagnostic evaluation included computerized tomography and/or magnetic resonance imaging of the brain, and a consensus of stroke neurologists assessed stroke subtype using modified Stroke Data Bank criteria and all available information, as described in a previous publication.14 Only individuals who had a first ischemic stroke during follow-up were included in this analysis.

Statistical Analysis
Statistical analyses were conducted using SAS Version 9.1.3 (SAS Institute). For descriptive purposes, means were calculated for continuous variables and proportions for categorical variables. The goal of the primary analysis was to determine whether functional status over time is different before and after ischemic stroke. Because of correlations among repeated measures of outcomes in the same individual, generalized estimating equations were used with an identity link function. Any BI assessments occurring within the 6 months after stroke were ignored, given that the course of recovery during this period is well-documented,16,17 and our interest was the long-term course of functional status after this initial period of recovery. Follow-up was censored at the time of recurrent stroke. The time variable was realigned, setting time of stroke as 0, with negative values reflecting years before stroke. The primary question was whether the time trend changed before versus after stroke. To conduct hypothesis testing, we set the model as follows:

\[ Y = \text{intercept} + \beta_1 \times \text{FU} + \beta_2 \times \text{FU} \times \text{poststroke} + \beta_3 \times \text{poststroke} \times \sum \beta \times \text{covariates}, \]

where FU indicates time of follow-up assessment since stroke, poststroke = 0 if the time of follow-up is before the stroke, and poststroke = 1 if follow-up is after the stroke. Note that \( \beta_1 \) represents annual change in BI before stroke and \( \beta_2 \) represents the additional annual change in BI after stroke. The above model gives a broken

Figure. Conceptual depiction of the course of functional status before and after stroke among those with Medicaid or no insurance.
Table 1. Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Demographics</th>
<th>210 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>77.2 (9.0)</td>
</tr>
<tr>
<td><strong>Men, (%)</strong></td>
<td>80 (38.1)</td>
</tr>
<tr>
<td><strong>Non-Hispanic white (%)</strong></td>
<td>44 (21.0)</td>
</tr>
<tr>
<td><strong>Non-Hispanic black (%)</strong></td>
<td>55 (26.2)</td>
</tr>
<tr>
<td><strong>Hispanic (%)</strong></td>
<td>109 (51.9)</td>
</tr>
<tr>
<td><strong>Other race (%)</strong></td>
<td>2 (1.0)</td>
</tr>
<tr>
<td><strong>Received at least high school education (%)</strong></td>
<td>86 (41.0)</td>
</tr>
<tr>
<td><strong>Married (%)</strong></td>
<td>60 (28.6)</td>
</tr>
<tr>
<td><strong>Risk Factors (%)</strong></td>
<td>64 (30.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>210 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIabetes mellitus (%)</strong></td>
<td>78 (37.1)</td>
</tr>
<tr>
<td><strong>Any physical activity (%)</strong></td>
<td>121 (57.6)</td>
</tr>
<tr>
<td><strong>Moderate alcohol use (%)</strong></td>
<td>58 (27.6)</td>
</tr>
<tr>
<td><strong>History of coronary artery disease (%)</strong></td>
<td>64 (30.5)</td>
</tr>
</tbody>
</table>

*As defined in text.

line as in the Figure at the time of stroke and the change in BI at the time of stroke equals $\beta_2$. When $\beta_2$ is 0, pre- and poststroke slopes are the same and our hypothesis is $\beta_2=0$.

In model building, we sequentially added groups of confounder variables defined by epidemiological relevance. The first model included no covariates, and successive models included demographic variables, vascular risk factors, and social variables. We present separate models by insurance status given that our previous study showed a significant interaction between time of follow-up assessment and insurance status after first ischemic stroke and decline of functional status over time only among those with Medicaid or no insurance. Model diagnostics, including residual plots and goodness of fit measures, were used to evaluate the final model, including linearity of the time trends. We chose the first-order autoregressive working correlation structure and compared the quasi-likelihood information criterion (QIC) obtained with this model with one using the unstructured working correlation structure.

Results

Among all 3298 participants, 235 participants had a first ischemic stroke during a median of 11 years of follow-up, 210 participants of which were included in this analysis after excluding 51 participants who died within 6 months after stroke. These 210 participants, who provide the basis for these analyses, were followed for an average of 5.6 years before stroke and 4.9 years after stroke; there were a total of 1694 prestroke BI assessments and 1390 poststroke assessments among them. Baseline characteristics of the study population are described in Table 1.

Table 2 describes an unadjusted model of the time trend of BI before and after stroke. There was no difference in functional decline over time before and after stroke ($P=0.6$), with a decline of 0.84 BI points per year before stroke ($P<0.0001$) and 1.11 points after stroke ($P=0.006$). Stroke was associated with an immediate mean drop of 17.47 points on the BI scale ($P<0.0001$). When we adjusted for confounders, results were similar: there was no difference in functional decline over time before and after stroke ($P=0.51$), with a decline of 0.96 BI points per year before stroke ($P<0.0001$) and 1.24 points after stroke ($P=0.001$).

We created separate adjusted models examining the functional time trend before and after stroke, 1 model for those with Medicare or private insurance, and 1 model for those with Medicaid or no insurance (Table 3). Among those with Medicaid or no insurance, in a fully adjusted model, there was a difference in slope before and after stroke ($P=0.04$), with a decline of 0.58 BI points per year before stroke and 1.94 BI points after stroke (Figure). However, among those with Medicare or private insurance, in a fully adjusted model, there was no difference in slope before and after stroke ($P=0.3$). By plotting the residuals against time and lowest curves, we found no evidence for nonlinearity of the curves in these models.

Discussion

In this large, prospective, population-based study with long-term follow-up, there was a significantly steeper decline in functional status after recovery from ischemic stroke compared with before stroke among those with Medicaid or no insurance, after adjusting for confounders. Specifically, the decline was more than 3 times as steep after stroke (1.94 BI points per year) compared with that before stroke (0.58 BI points per year). No other study has modeled the trajectory of functional status before and after stroke using analysis of repeated measures of function while adjusting for confounders. Given that recurrent strokes were censored in this analysis, it is likely that some aspect of the first stroke, or the effect of clinically silent infarcts, causes the decline, and not only aging. Furthermore, the trajectory of functional decline was linear and not stepwise, suggesting that the decline may be caused by ongoing effects of chronic exposures rather than by episodic drops in function from discrete events. We found

Table 2. Unadjusted and Adjusted Models Examining the Time Trend of Functional Status Before and After Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in BI Score</th>
<th>Standard Error</th>
<th>$P$ Value</th>
<th>Change in BI Score</th>
<th>Standard Error</th>
<th>$P$ Value</th>
<th>Change in BI Score</th>
<th>Standard Error</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual change before stroke</td>
<td>-0.84</td>
<td>0.15</td>
<td>&lt;0.0001</td>
<td>-1.00</td>
<td>0.17</td>
<td>&lt;0.0001</td>
<td>-0.96</td>
<td>0.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Additional annual change after stroke</td>
<td>-0.27</td>
<td>0.45</td>
<td>0.6</td>
<td>-0.23</td>
<td>0.43</td>
<td>0.6</td>
<td>-0.28</td>
<td>0.42</td>
<td>0.5</td>
</tr>
<tr>
<td>Change in BI score at time of stroke</td>
<td>-17.47</td>
<td>2.25</td>
<td>&lt;0.0001</td>
<td>-17.34</td>
<td>2.30</td>
<td>&lt;0.0001</td>
<td>-17.37</td>
<td>2.30</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BI indicates Barthel index.

*Including age, sex, race/ethnicity, level of education, and insurance status, as defined in text.

†Including demographic variables, as well as alcohol use, physical activity, diabetes, marital status, and coronary artery disease.
there to be functional decline among those with Medicaid or no insurance, possibly reflecting poorer access to healthcare,\textsuperscript{18,19} poorer management of risk factors,\textsuperscript{19–21} or other effects of lower socioeconomic status.\textsuperscript{22,23} The effect of insurance status was similar to that seen in previous research on functional status and quality of life in the Northern Manhattan Study\textsuperscript{10,24}; additional research may clarify mechanisms of this effect.

There are several biological mechanisms through which ischemic stroke may cause delayed functional decline. The ischemic penumbra undergoes delayed neuronal death through apoptosis and necrosis that can take place over days to weeks after the stroke\textsuperscript{25}; this may cause delayed functional decline by delayed extension of infarcted tissue. Longer-term decline may be caused by other factors. For example, a single ischemic stroke may cause changes in inflammatory profiles\textsuperscript{26} that may have an ongoing deleterious effects on brain structure and function. In animal models, stroke sets in motion an endogenous inflammatory cascade that contributes to ongoing brain damage beyond the effect of ischemia alone.\textsuperscript{27} Changes in inflammatory profiles resulting from ischemic stroke may have a delayed and longstanding effect that may persist years after stroke.\textsuperscript{28} Such changes may cause subclinical, insidious decline in brain function that compromises functional status. Alternatively, static functional impairment after stroke may lead to progressive cardiovascular impairment and reduced fitness, which adversely affect performance in activities of daily living.\textsuperscript{29} Additional research may clarify the mechanisms of decline seen in this study.

Clinically silent infarcts may also account for the decline in function seen after stroke in this study. Silent infarcts are at least 5 times as prevalent as clinical strokes,\textsuperscript{30,31} share the same risk factors as clinical strokes,\textsuperscript{31,32} accumulate over time in the absence of clinical strokes,\textsuperscript{33} and are associated with stroke and cognitive impairment.\textsuperscript{34,35} Asymptomatic brain magnetic resonance imaging abnormalities, including white matter hyperintensities and infarcts, have been associated with functional impairment cross-sectionally,\textsuperscript{36} at 3 months,\textsuperscript{37} and over 4 years of follow-up.\textsuperscript{38}

Advantages of this study include its population-based design and random sampling techniques, which allow for good generalizability to the urban, multiethnic source population. Furthermore, the Northern Manhattan Study follows a large sample of individuals with little loss to follow-up, and its repeated measures of a well-validated functional scale are a unique strength that allows detailed modeling of the trajectory of functional status over time. Also, the identification and classification of vascular events, such as stroke, is thorough and validated, which allows one to answer focused questions about the effects of first ischemic stroke.

Limitations of this study include the lack of data on outpatient longer-term rehabilitation, ie, physical or occupational therapy received after stroke, which may have an impact on outcomes. Another limitation is that covariates, including medical risk factors, demographic information, and insurance status, are assessed at entry into the study and not at the time of stroke. Hence, it is the association of these factors at study entry with long-term outcomes that is being assessed. The advantage of this is that the timing of data collection is appropriate to the study question, which focuses on baseline predictors of long-term outcome. Furthermore, the status of most of the covariates is unlikely to change over time, especially demographic characteristics and some medical and social risk factors. The advantage of the modeling strategy is that it allows one to assess whether the slope of decline is different before and after an event. However, the model assumes that the effect of baseline factors is the same before and after stroke, which may not be the case. Finally, the decline in functional status applies to older stroke patients, as seen in this cohort, but these findings cannot be directly applied to younger patients, and more research is needed on long-term functional outcomes in younger stroke survivors.

### Conclusion

In summary, we have found epidemiological evidence of a long-term and linear decline in functional status after stroke, at least among those with limited resources, which is more than 3 times as steep as is the decline before stroke. This decline was seen even in the absence of recurrent clinical strokes. Considering these findings, it is possible that stroke may be not only a discrete event, but also an ongoing, chronic condition with effects on function. In terms of functional status, strokes may be considered as events that occur on a continuum of functional decline. Additional research is needed to clarify the cause of this decline and to identify the elements of ischemic stroke that would result in such a long-term decline, even in the absence of recurrent events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in BI Score</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual change before stroke</td>
<td>-1.16</td>
<td>0.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Additional annual change after stroke</td>
<td>0.51</td>
<td>0.52</td>
<td>0.3</td>
</tr>
<tr>
<td>Change in BI score at time of stroke</td>
<td>-18.64</td>
<td>3.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BI indicates Barthel index.

*Adjusted for age, sex, race/ethnicity, level of education, alcohol use, physical activity, diabetes, marital status, and coronary artery disease, as defined in text.
Acknowledgments
M.S.V.E. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References
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