Risk Factors for Stroke in Subjects With Normal Blood Pressure
A Prospective Cohort Study

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Background and Purpose—Although stroke is strongly associated with hypertension, some individuals with normal blood pressure (BP) experience a stroke. This prospective study explored risk factors for stroke in subjects with normal BP.

Methods—A total of 11,228 men and 17,174 women, 45 to 73 years old, were examined in a population-based cohort study. Normal BP was defined as BP <140/90 mm Hg and no treatment for hypertension. The incidence of stroke was followed over a mean period of 6 years.

Results—In the cohort, 10,938 (38%) had normal BP. Of them, 56 patients experienced a first-ever stroke (12% of all stroke). Compared with subjects without stroke during follow-up, these stroke subjects were older, had lower education, were often smokers and alcohol nondrinkers, and had a history of coronary heart disease (CHD), gastric ulcer, or renal calculus. Subjects with stroke had a higher body mass index (BMI) and a high-normal BP (130 to 139/85 to 89 mm Hg) more often. In a backward stepwise Cox-regression analysis, age (per 1 year; relative risk [RR], 1.12), current smoking (RR, 3.21), BMI (per SD; RR, 1.39), high-normal diastolic BP (RR, 2.35), history of CHD (RR, 4.92), and gastric ulcer (RR, 2.21) remained significantly associated with incidence of stroke.

Conclusion—In subjects with normal BP, there are a number of potentially modifiable risk factors associated with an increased incidence of stroke.

Key Words: blood pressure ■ risk factors ■ stroke

It is generally accepted that high blood pressure (BP) is the major risk factor for stroke. There is a continuous and linear relationship between BP and risk of stroke, which holds even in individuals with a normal BP. Yet, people are classified into those with hypertension and normal BP. The majority of literature is devoted to exploring the relationship between hypertension and stroke. Few researchers have studied this association in those who are normotensive. It is evidenced that apart from high BP, the pathological causes of stroke are manifold, including the formation of atheroma, embolism from the heart, intracranial small vessel disease, malformations of the vasculature in the brain, etc. In addition, biological, sociodemographic characteristics and lifestyle factors, such as aging, smoking, physical inactivity, alcohol consumption, and diabetes, are also considered risk factors for stroke. However, whether these risk factors are similarly related to stroke in normotensive subjects is unclear.

To our knowledge, a comprehensive risk factor analysis of the incidence of stroke in normotensive individuals has not been documented so far. Therefore, the purpose of this study is to explore the risk factors for incidence of first-ever stroke among individuals who have a normal BP.

Methods

Study Population
From 1991 to 1996, all men and women born between 1923 and 1950 and living in the Malmö area in the southern part of Sweden were recruited into the Malmö Diet and Cancer (MDC) study. Detailed information of the MDC study has been reported previously. The final cohort consisted of 28,449 subjects (11,226 men and 17,223 women) from the eligible population of 74,000 individuals. Participants were offered a health assessment program, including a self-administered questionnaire in combination with clinical examinations at a screening center. All participants were followed from the time of baseline examination until death, or until December 31, 1999. Those who had a history of stroke before the examination (according to self-report or hospital register) were excluded.

Stroke Registration
Records of patients with stroke were retrieved by the data linkage to the Stroke Register in Malmö (STROMA). Since 1989, all Malmö residents who have experienced stroke, whether hospitalized or nonhospitalized, have been registered in STROMA. Stroke cases that have moved out from Malmö were retrieved by data linkage with the National Hospital Discharge Register. Stroke was defined as rapidly developing clinical signs of local or global loss of cerebral function that lasted for >24 hours or led to...
death within 24 hours. Subtypes of stroke were coded according to the International Classification of Diseases (ICD), 9th Revision. Events were classified as cerebral infarction (ischemic; ICD 434), intracerebral hemorrhage (ICD 431), and subarachnoid hemorrhage (ICD 430). Patients with transient ischemic attacks were excluded. The subtype of stroke was verified by computed tomography (CT) scan, autopsy, or lumbar puncture. Stroke was classified as unspecified stroke (ICD 436) if CT or autopsy record was unavailable.

**Baseline Characteristics**
The screening examination included a self-reported questionnaire as well as clinical examinations.

**Sociodemographic Characteristics**
Marital status was classified into 2 groups (ie, unmarried [single, divorced, or widowed] or married [cohabiting]). Educational level was divided into low (≤8 years), moderate (9 to 12 years), and high (college/university) levels. Occupational status was categorized into 2 groups on the basis of the Swedish socioeconomic classification.13 Functional status in normotensive subjects with and without stroke was adjusted for age.

**Lifestyle Factors**
Subjects were categorized into smokers and nonsmokers. Duration of smoking and daily cigarette consumption were assessed for smokers. Information on the total alcohol consumption was converted into 4-category variables. Subjects who reported zero consumption of alcohol were categorized as no alcohol intake. Levels of alcohol intake in consumers were defined according to an assumption of biological risk.14 Category ranges for men and women, respectively, were as follows: <20 g and <15 g alcohol daily (low), 20 to 40 g and 15 to 30 g daily (medium), and >40 g and >30 g daily (high). Physical activities during leisure time were revealed through 18 questions covering a range of activities in the 4 seasons.16 The number of minutes per week for each activity was multiplied by an intensity coefficient, and an overall leisure time physical activity score was created. Scores were divided into 4 quartiles and subsequently categorized as low (quartile 1), moderate (quartile 2 to 3), and high (quartile 4) levels.

**History of Chronic Disease and Family History of Cardiovascular Disease**
Information about historical records of stroke and coronary heart disease (CHDs; myocardial infarction or angina pectoris) was obtained in the questionnaire. Questions also covered other diseases and their treatment, such as diabetes mellitus, hypertension, asthma, cancer, struma, renal calculus, rheumatoid arthritis, gastric ulcer, and inflammatory colitis. Investigations also incorporated the family history of stroke or myocardial infarction.

**Clinical Examination**
By using a mercury sphygmomanometer, BP was measured once in the right arm after 5 minutes rest at the screening center. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or treatment for hypertension.15 Among the subjects who had a normal BP, 4 subgroups were established: normal (<130 mm Hg) and high-normal systolic BP (130 to 139 mm Hg) groups, and normal (<85 mm Hg) and high-normal diastolic BP (85 to 89 mm Hg) groups.16 Body weight, height, and waist and hip circumferences were measured, and the calculation of body mass index (BMI) and waist-to-hip ratio were calculated. BMI was classified into normal weight (<25.0), overweight (25.0 to 29.9), and obesity (≥30.0).

**Statistical Analysis**
Logistic regression model was used to compare baseline characteristics in normotensive subjects with and without stroke with adjustments for age.

To explore the association between baseline risk factors and incidence of stroke, Cox-regression analysis was performed in 2 steps. First, all variables showing a significant relation to stroke in the initial analysis was run into the model. Secondly, a backward stepwise Cox-regression model was run. Variables with P values >0.10 were removed from the stepwise model. All comparisons were 2-sided, and a 5% level of significance was used. Statistical analyses were conducted by SPSS software (version 11.5).

**Results**
Of 28 449 participants, 514 were excluded because records of BP were missing (n=47) or had a history of stroke (n=467).

The mean duration of follow-up was 5.7±1.6 years, and 466 patients had experienced first-ever stroke during follow-up. The incidence per 100 000 person years was 294 (95% CI, 267 to 321).

**Stroke in Subjects With Normal BP**
Thirty-eight percent of the cohort (n=10 983) had a normal BP (<140/90 mm Hg; no treatment for hypertension). Of those normotensives, 56 patients (90 of 100 000 person years; 95% CI, 68 to 117) experienced a first-ever stroke. Of them, 37 patients (66.1%) were classified as cerebral infarction (ischemic), 7 intracerebral hemorrhage (12.5%), and 5 subarachnoid hemorrhage (8.9%). The remaining 7 patients (12.5%) were unspecified for subtype of stroke.

Incidence of stroke in subjects with high-normal systolic BP (130 to 139 mm Hg) and normal systolic BP (<130 mm Hg) was 160 (95% CI, 91 to 259) and 76 (95% CI, 54 to 104) per 100 000 person years, respectively.

Among subjects who had normal BP, stroke patients were older and had a lower level of education than subjects without stroke. Nearly half of the stroke patients were current smokers and had smoked for ≥30 years but had a low consumption of alcohol (Table 1).

In addition, 55% of the patients were either overweight or obese, which was higher than in the nonstroke subjects. High-normal systolic BP (130 to 139 mm Hg) and high-normal diastolic BP (80 to 84 mm Hg) were significantly higher in stroke patients than in controls. Furthermore, incidence of stroke was highly associated with a previous coronary heart event and concurrent diseases, such as diabetes, gastric ulcer, and renal calculus (Table 2).

**Multivariable Analysis**
In the backward stepwise Cox-regression model, 5 variables remained significantly associated with stroke (Table 3). The risk of stroke was significantly associated with age (relative risk [RR], 1.12), current smoking (RR, 3.21), BMI (RR, 1.39), high-normal diastolic BP (85 to 89 mm Hg; RR, 2.35), family history of coronary heart event (RR, 4.92), and gastric ulcer (RR, 2.21).

**Discussion**
The relationship between elevated BP and an increased incidence of stroke has been established in many prospective studies.1-3 Hypertension is generally regarded as the most important risk factor for stroke in the general population. However, some individuals experience a stroke even if their BP is within the normal range.1,5 To our knowledge, this is
the first prospective study to estimate the comprehensive risk factors for stroke in normotensive subjects. Besides increasing age and a high-normal diastolic BP, the present results showed that smoking, obesity, history of CHD, and gastric ulcer were associated with stroke in this group.

The multivariate analysis identified traditional risk factors (age, high-normal diastolic BP, smoking, obesity, and history of CHD) and a new risk factor for stroke (gastric ulcer). Smoking had a comparatively high prevalence (49%) and high RR (RR, 3.21; 95% CI, 1.82 to 5.66). Besides age, smoking was the risk factor that accounted for most strokes in the population of normotensive subjects. In terms of population-attributable risk, it can be estimated that ≈39% of incident strokes were attributed to smoking among normotensive subjects.

However, there was a strong association between obesity and stroke. Previous studies of overweight/obesity and stroke are limited, and the results have not been fully consistent.19,20 The reason for this association is not completely understood. BMI is associated with a low-grade inflammation,21 which is associated with an increased incidence of stroke.22 BMI and low-grade inflammation are associated with dyslipidemia, diabetes, and hypertension. The greatly increased risk for obese subjects could be related to risk factors (dyslipidemia and inflammation) that were unavailable in this study, or to obesity, per se. Alternatively, it is possible that obese subjects more often developed hypertension during the 6-year follow-up period. Nevertheless, the present results show that obesity is an important risk marker for stroke even in the absence of high BP.

### Table 1. Sociodemographic Characteristics and Lifestyle Factors in the Normotensive Individuals With or Without First-Ever Stroke During a Mean Follow-Up of 6 Years

| Variables                          | Without Stroke (n = 10,812) | With Stroke (n = 56) | P Value*
|-----------------------------------|-----------------------------|---------------------|---------
| **Age**                           |                             |                     |         |
| Mean:±SD                          | 55.0±6.7                    | 60.4±6.3            | <0.001  |
| 50 y (%)                          | 33.2                        | 10.7                | reference |
| 51 to 60 y (%)                    | 40.9                        | 25.0                | 0.002†  |
| ≥61 y (%)                         | 25.9                        | 64.3                | <0.001† |
| **Male (%)**                      |                             |                     | 0.21    |
| Married                           | 64.6                        | 63.9                |         |
| Unmarried                         | 35.4                        | 36.1                | 0.62    |
| **Education level (%)**          |                             |                     |         |
| Low (<≤8 years)                   | 33.5                        | 65.5                | reference |
| Moderate (9–12 y)                 | 36.8                        | 20.0                | 0.03†  |
| High (college/university)         | 29.7                        | 14.5                | 0.01†  |
| **Occupation condition (%)**      |                             |                     |         |
| Manual work                       | 62.9                        | 69.8                |         |
| Nonmanual work                    | 37.1                        | 30.2                | 0.63    |
| **Smoking status**                |                             |                     |         |
| Current smoking (%)               | 26.9                        | 49.1                | <0.001  |
| Years of smoking (mean:±SD)      | 23±13                       | 29±15               | <0.01   |
| Amount of cigarettes/daily (mean:±SD) | 14±8                | 15±7                | 1.0     |
| **Leisure time physical activity (%)** |                     |                     |         |
| Low                               | 23.9                        | 31.5                | reference |
| Moderate                          | 51.4                        | 46.3                | 0.22†  |
| High                              | 24.8                        | 22.2                | 0.23†  |
| **Alcohol consumption**           |                             |                     |         |
| Alcohol intake (gram/daily; mean:±SD)†  | 0.91±0.49                 | 0.82±0.61           | 0.09    |
| Alcohol intake in men/women (%)   |                             |                     |         |
| No                                | 15.2/15.1                   | 23.6/25.5           | reference |
| Low (<≤20 g/15 g/day)             | 68.0/57.9                   | 67.3/56.4           | 0.23/0.27† |
| Medium (20–40 g/15–30 g/day)      | 13.9/20.0                   | 5.5/14.5            | 0.08/0.23† |
| High (>≥40 g/30 g/day)            | 3.0/6.8                     | 3.0/3.6             | 0.82/1.0† |

*P value was adjusted for age (excepting the variable of age itself).
†P values for comparisons with reference category.
‡Mean values were log-transformed because of skewed distributions.
Blood pressure (mm Hg) were presented.

Diabetes mellitus is a classic risk factor for stroke. In our analysis, the prevalence of diabetes was significantly higher in stroke patients, but the relationship became nonsignificant in the multivariable analysis. Whether the absence of a significant relationship could be explained by lack of statistical power or if diabetes is associated mainly with stroke in hypertensive subjects remains to be explored.

Physical inactivity is another risk factor for stroke. Previous studies of physical activity suggest that the protective effects are greater for hypertensive than normotensive subjects. However, lack of statistical power is another possible explanation for the nonsignificant findings.

Gastric ulcer was significantly associated with incidence of stroke in this study. However, the diagnosis of disease was based on self-reported data, lacking laboratory records. Therefore, we can only speculate about the causal relations with stroke. Infection with the microorganism Helicobacter pylori is a major cause of gastric ulcer. H pylori infection has been associated with CHD and may be important for development of atherosclerosis. The relationship between gastric ulcer and incidence of stroke remains to be clarified. Because gastric ulcer is a potentially treatable condition, this relationship could have important clinical implications.

Change of exposure during the follow-up period is an inherent problem in prospective cohort studies. The risk factors in this study were assessed only once. We do not know whether some subjects developed hypertension during the follow-up. However, the follow-up in the present study was rather short, ≈6 years, and it can be assumed that relatively few subjects developed high BP. The diagnosis of hypertension should ideally be assessed by several BP measurements on several different occasions. In this study, BP was measured only once. If BP had been measured repeatedly for subjects who initially had high BP, the number with hypertension would be lower and, hence, the normotensive group larger. However, the present sample would still be classified as normotensive.

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Atrial fibrillation (AF) is an important risk factor for stroke. However, the information on AF is difficult to acquire from a population-based cohort, and the validity of self-reported AF is probably low because most older people are unaware of occurrence and type of cardiac arrhythmia. The absence of data on blood lipids, glucose, and inflammatory markers is another limitation of the study.

**Conclusion**

In this population-based study of subjects with normal BP, a number of potentially modifiable risk factors were associated with an increased incidence of stroke.

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**References**

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