Hyperhomocyst(e)inemia and Risk of Ischemic Stroke Among Young Asian Adults

Nigel Choon-Kiat Tan, MRCP(UK); N. Venketasubramanian, MMed(IntMed); Seang-Mei Saw, PhD; Helen Tjoei-Lian Tjia, MMed(IntMed)

Background and Purpose—Hyperhomocyst(e)inemia is emerging as a possible risk factor for stroke, possibly because of accelerated atherosclerosis. There are no previous publications evaluating homocyst(e)ine in young Asian ischemic stroke patients. We conducted a case-control study examining homocyst(e)ine, vitamin B₁₂, and folate levels in young, first-ever Asian ischemic stroke patients.

Methods—We prospectively recruited 109 consecutive young (<50 years) first-ever hospitalized ischemic stroke patients and 88 age/gender-matched hospital-based controls during a period of 18 months. Prevalence of vascular risk factors was assessed; fasting homocyst(e)ine, vitamin B₁₂, and folate were assayed. Stroke mechanisms were subtyped using TOAST study criteria.

Results—Mean age was 43.8 (cases) and 43.1 (controls) years; 71.6% were male (cases and controls). Diabetes mellitus, hypertension, and hyperlipidemia were significantly more prevalent in cases. Mean fasting homocyst(e)ine levels were significantly higher in cases (13.7 μmol/L, 95% CI: 12.7 to 14.9) than controls (10.8 μmol/L, 95% CI: 9.9 to 11.8, P < 0.001). Mean vitamin B₁₂ levels were significantly lower in cases (299.5 pmol/L, 95% CI: 266.7 to 332.3) than controls (394.5 pmol/L, 95% CI: 357.9 to 431.0, P < 0.001). Folate levels were not significantly different. Mean homocyst(e)ine levels were significantly elevated in large-artery strokes (16.9 μmol/L, 95% CI: 14.5 to 19.7, P < 0.001) but not other stroke subtypes compared with controls. Compared with the lowest homocyst(e)ine quartile, the highest quartile was significantly associated with an adjusted odds ratio of 4.3 for ischemic stroke and 25.3 for large-artery stroke. Using a logistic regression model, the adjusted odds ratio was 5.17 (95% CI: 1.96 to 13.63, P = 0.001) for every 1 μmol/L increase in log homocyst(e)ine.

Conclusions—Hyperhomocyst(e)inemia is an independent risk factor for ischemic strokes in young Asian adults. The relationship between increasing homocyst(e)ine and stroke risk is strong, graded, and significant. The association with large-artery strokes suggests that hyperhomocyst(e)inemia may increase stroke risk via a proatherogenic effect. (Stroke. 2002;33:1956-1962.)

Key Words: ethnic groups ■ homocyst(e)ine ■ risk factors ■ stroke ■ young adults

Stroke remains a major cause of mortality and morbidity worldwide.¹ The burden of stroke arises largely from the elderly population. However, there remains a small but significant subset of younger patients with ischemic stroke, in whom conventional vascular risk factors play a smaller role. Unusual causes of stroke, such as arterial dissection or thrombophilia, are more common, although the final cause may remain undetermined in 21% to 31%.²,³

There is growing evidence that high homocyst(e)ine levels contribute to the pathogenesis of ischemic stroke.⁴ Homocyst(e)ine is believed to cause atherogenesis and thrombogenesis via endothelial damage, vascular smooth muscle proliferation, and coagulation abnormalities. High homocyst(e)ine levels are associated with increased risk of cardiovascular and cerebrovascular disease,⁵ although there are studies that show no increase in risk,⁶,⁷ and there is still debate as to the strength and validity of the association.⁸ This disparity may be partly explained by methodological differences between the different studies, such as use of fasting⁷,⁹ and nonfasting samples,³,⁶ differing timing of sampling post-stroke,³,⁷,⁹ and different subtypes of strokes studied.⁹

Prior studies of homocyst(e)ine and stroke involved whites and blacks; stroke among young Asians has not been well studied. There has been only 1 Asian series of young strokes, which did not specifically examine homocyst(e)ine.¹⁰ This gap in knowledge is of particular concern because ischemic stroke is projected to be a major cause of disability in developing countries in the year 2020.¹

The aim of our study was to examine whether there was an association between high homocyst(e)ine levels and ischemic...
stroke risk in young Asian patients. We also investigated homocyst(e)ine and stroke risk among different stroke subtypes.

Materials and Methods

Cases
The National Neuroscience Institute and Tan Tock Seng Hospital medical complex is one of the largest secondary-care subsidized public hospitals in Singapore. Consecutive Asian patients aged between 20 and 50 years presenting between October 1999 and April 2001 with a first-ever ischemic stroke were invited to participate in our study if they presented within 48 hours of onset. Stroke was defined as a clinical syndrome with rapidly developing symptoms and signs of focal neurological deficits that lasted for >24 hours. Ischemic stroke was defined as a stroke with either a normal CT brain or evidence of an neuroanatomically appropriate infarct on CT or MRI brain done within 1 week of onset. Hemorrhagic strokes and venous infarcts were excluded.

Every case was evaluated using a standard protocol, including CT brain within 24 hours of admission, duplex ultrasound of extracranial vessels, and echocardiography. An MRI of the brain with MR angiography and diffusion-weighted imaging was performed at the discretion of the clinician.

Strokes were classified using the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria into large-artery, cardioembolic, small-artery/lacunar strokes, strokes of other etiology and strokes of undetermined etiology. Classification was based on clinical, imaging, and laboratory information; it was performed blinded to homocyst(e)ine levels.

Controls
Controls were consecutive age and gender group–matched Asian patients admitted for acute conditions other than ischemic strokes to the same hospital. These included both medical and surgical patients with varied conditions such as pneumonia, fractures, appendicitis, and migraine.

Risk Factor Assessment
Baseline demographic data and history of conventional vascular risk factors (diabetes mellitus, hypertension, hyperlipidemia, and smoking status) were obtained for all patients. Patients were considered to have diabetes mellitus if they had a past history of diabetes mellitus or if they were found to fulfill World Health Organization criteria for diagnosis of diabetes mellitus. Patients were considered hypertensive if they had a past history of hypertension. Subjects were considered to have hyperlipidemia if they had a past history of hyperlipidemia or if their fasting serum total cholesterol was more than 5.2 mmol/L. Patients were considered current smokers if they were currently smoking at presentation or had stopped within the past 2 months. Ex-smokers were those who had stopped more than 2 months before presentation, and patients were considered nonsmokers if they had never smoked previously.

Exclusion Criteria for Cases and Controls
Patients with known ischemic heart disease, previous ischemic strokes, peripheral vascular disease, hypothyroidism, epilepsy, and renal impairment were excluded. Pregnant patients and those taking drugs that might affect homocyst(e)ine, vitamin B12, or folate metabolism were also excluded.

This study was approved by an institutional review board. Informed consent was obtained from all participants.

Laboratory Analysis
Within 5 days of stroke onset, an overnight fasting sample of blood was obtained for analysis in all patients. All samples were taken and processed using a standard protocol. Fasting blood was chilled on ice immediately after being taken. Serum was separated within 4 hours by centrifugation at 5000 rpm at 4°C for 5 minutes and then stored at −80°C until analysis. Total serum homocyst(e)ine was measured using reversed-phase high-performance liquid chromatography with fluorescent detection after precolumn derivatization (Bio-Rad Laboratories). Vitamin B12 and folate were measured using a microparticle enzyme assay (Abbott Laboratories).

Statistical Analysis
Baseline differences in proportions between cases and controls were tested using the χ² test for categorical data, and differences in means were compared using the t test for continuous data. Because serum homocyst(e)ine was positively skewed, natural logarithmic transformation was used and results were expressed as geometric means. Results were considered significant if P<0.05.

ANOVA was used to compare mean homocyst(e)ine levels between different TOAST stroke subtypes, after correction for confounders. Posthoc pairwise comparison was done with Bonferroni’s adjustment for multiple comparisons. Multivariate logistic regression models were constructed with stroke as the major outcome variable and homocyst(e)ine as the main covariate, adjusting for confounding factors. Interaction terms (homocyst(e)ine and diabetes mellitus, homocyst(e)ine and hypertension, homocyst(e)ine and hyperlipidemia, vitamin B12 and diabetes mellitus, vitamin B12 and hypertension, vitamin B12 and hyperlipidemia) were evaluated for interaction in the logistic regression model and found to be not statistically significant. SPSS version 10.0 was used for all statistical analyses.

Results
One hundred ninety-seven patients participated in this study, comprising 109 cases and 88 controls. The 109 cases represented 3.1% of approximately 3500 ischemic stroke patients of all ages admitted during the study period.

Cases Versus Controls
The baseline characteristics of cases and controls are summarized in Table 1. There were no statistically significant differences in age or gender ratios. The mean age was 43.8 years in cases, and 43.1 years in controls (P=0.423). The percentage of males was 71.6% in both cases and controls (P=1.0). Racial composition for cases (n=109) was 82 Chinese (75.2%), 9 Indians (8.3%), 15 Malays (13.8%), and 3 of other races (2.8%). Racial composition for controls (n=88) was 50 Chinese (56.8%), 16 Indians (18.2%), 15 Malays (17.0%), and 7 of other races (8.0%); the difference was statistically significant (P=0.027).

The prevalence of conventional vascular risk factors such as diabetes mellitus, hypertension, and hyperlipidemia were significantly higher in cases compared with controls. There was no significant difference in smoking status between cases and controls.

Mean levels of fasting serum homocyst(e)ine were significantly higher in cases (13.7 μmol/L, 95% CI: 12.7 to 14.9) compared with controls (10.8 μmol/L, 95% CI: 9.9 to 11.8, P<0.001). Mean vitamin B12 levels were significantly lower in cases (299.5 pmol/L, 95% CI: 266.7 to 323.3) compared with controls (394.5 pmol/L, 95% CI: 357.9 to 431.0, P<0.001). There was no significant difference in folate levels between cases and controls.

Stroke Subtypes
The 109 cases were classified using TOAST criteria (Table 2). The most frequent type of stroke was small-artery/lacunar stroke (n=48), followed by large-artery stroke (n=30).
Strokes from other etiologies or of undetermined etiology were less frequent (n=18), whereas cardioembolic strokes were least frequent (n=13). There was no significant difference in proportion of smokers/ex-smokers between the stroke subtypes and controls (large-artery 36.7%, cardioembolic 38.5%, small-artery/lacunar 43.8%, other/undetermined etiology 50%, controls 44.3%, P=0.90).

There was a significant difference in mean homocyst(e)ine levels between the different stroke subtypes before and after adjustment for age, gender, and vitamin B12 levels (ANOVA, P=0.001). Strikingly, the subgroup with large-artery strokes had the highest mean homocyst(e)ine levels of all the subgroups. Posthoc analysis showed mean homocyst(e)ine levels were significantly higher in large-artery strokes (16.9 \mu mol/L, 95% CI: 14.5 to 19.7) compared with controls (10.8 \mu mol/L, 95% CI: 9.9 to 11.8, P<0.001). Homocyst(e)ine levels were also significantly higher in large-artery strokes compared with small-artery/lacunar strokes (12.5 \mu mol/L, 95% CI: 11.1 to 14.1, P=0.024). These differences remained significant after adjustment for age, gender, and vitamin B12 levels. This difference was unlikely to be a result of a difference in smoking status because there were fewer smokers in the large-artery group (36.7%) compared with controls (44.3%) or small-artery/lacunar strokes (43.8%). No other stroke subtypes showed significantly different homocyst(e)ine levels compared with controls.

Mean vitamin B12 levels were significantly different between stroke subtypes before and after adjustment for age and gender (P=0.002). The subgroup with large-artery strokes had the lowest mean vitamin B12 levels of all the subgroups. Vitamin B12 levels were significantly lower in large-artery strokes (265.6 pmol/L, 95% CI: 203.0 to 328.2, P=0.006).

### TABLE 1. Baseline Demographics, Conventional Vascular Risk Factors, Fasting Serum Homocyst(e)ine, Vitamin B12, and Folate Levels in Cases and Controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Crude Odds Ratio</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (SD)</td>
<td>43.8 (5.87)</td>
<td>43.1 (6.60)</td>
<td>...</td>
<td>...</td>
<td>0.423</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78 (71.6)</td>
<td>63 (71.6)</td>
<td>...</td>
<td>...</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>31 (28.4)</td>
<td>25 (28.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78 (71.6)</td>
<td>80 (90.9)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (28.4)</td>
<td>8 (9.1)</td>
<td>3.97</td>
<td>1.72–9.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46 (42.2)</td>
<td>69 (78.4)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (57.8)</td>
<td>19 (21.6)</td>
<td>4.97</td>
<td>2.64–9.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (19.3)</td>
<td>49 (55.7)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88 (80.7)</td>
<td>39 (44.3)</td>
<td>5.63</td>
<td>2.79–9.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>63 (57.8)</td>
<td>49 (55.7)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex- or current smoker</td>
<td>46 (42.2)</td>
<td>39 (44.3)</td>
<td>0.92</td>
<td>0.52–1.61</td>
<td>0.774</td>
</tr>
<tr>
<td>Homocyst(e)ine (\mu mol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>12.7</td>
<td>11.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td>(5.0–74.1)</td>
<td>(2.7–29.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean†</td>
<td>13.7</td>
<td>10.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12.7–14.9)</td>
<td>(9.9–11.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 (pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>281.0</td>
<td>320.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td>(44.0–647.0)</td>
<td>(107.0–1325.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>299.5</td>
<td>394.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(266.7–332.3)</td>
<td>(357.9–431.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate (nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>16</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td>(8–38)</td>
<td>(6–28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>17.9</td>
<td>16.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(16.7–19.1)</td>
<td>(15.5–18.2)</td>
<td></td>
<td>0.248</td>
<td></td>
</tr>
</tbody>
</table>

*χ² test for categorical variables, unpaired t test for continuous variables.
†Homocyst(e)ine levels expressed as geometric means.
and also in small-artery/lacunar strokes (303.3 pmol/L, 95% CI: 253.8 to 352.8, \( P = 0.039 \)) compared with controls (394.5 pmol/L, 95% CI: 357.9 to 431.0). These differences remained significant after adjustment for age and gender. There was no significant difference in folate levels between stroke subtypes.

### Risk of Ischemic Stroke

Fasting homocyst(e)ine showed a strong, graded, and independent relationship to risk of ischemic stroke (Figure 1). The highest quartile of homocyst(e)ine was associated with a crude odds ratio (OR) of 3.4 (95% CI: 1.5 to 7.8) compared with the lowest quartile. After adjustment for age, sex, vascular risk factors, and vitamin B\(_{12}\), the adjusted OR was 4.3 (95% CI: 1.5 to 12.6).

Fasting homocyst(e)ine was also a strong risk factor for large-artery stroke (Figure 2). Compared with the lowest quartile, the highest quartile was associated with a crude OR of 11.4 (95% CI: 2.9 to 45.7). After adjustment for age, sex, vascular risk factors, and vitamin B\(_{12}\), the adjusted OR was 25.3 (95% CI: 3.2 to 196.9).

Logistic regression was performed with ischemic stroke as the dependent variable with continuous variables (homocyst(e)ine and vitamin B\(_{12}\)) and categorical variables (diabetes mellitus, hypertension, and hyperlipidemia) as independent variables.

The results are summarized in Table 3. Fasting homocyst(e)ine was seen to be an important independent risk factor, with an adjusted OR of 5.17 (95% CI: 1.96 to 13.63) for every 1 pmol/L increase in log homocyst(e)ine. Hyperlipidemia was the most important independent risk factor of the conventional vascular risk factors. Vitamin B\(_{12}\) was a protective factor, resulting in an adjusted OR of 0.997 (95% CI: 0.995 to 0.999) for every 1 pmol/L increase in vitamin B\(_{12}\).

### Discussion

Homocyst(e)ine is postulated to cause ischemic stroke via various mechanisms. It may promote atherogenesis by damaging the vascular matrix, increasing oxidative injury to arterial endothelium, and enhancing proliferation of vascular smooth muscle. High levels of homocyst(e)ine have been associated with extracranial carotid disease. It may also be prothrombotic and impair vasomotor regulation. Homocyst(e)ine is thus a biologically plausible factor in the pathogenesis of ischemic stroke, in particular large-artery strokes.

This is the first study to examine homocyst(e)ine and vitamin levels in young Asian patients with ischemic stroke. Our results show that there is a independent association between elevated homocyst(e)ine levels and ischemic stroke in young Asian adults. We have demonstrated a strong and graded relationship between increasing homocyst(e)ine and ischemic stroke risk. In addition, there is an association between increasing homocyst(e)ine and risk of large-artery strokes that is strong, graded, and significant.
Results from previous studies have been conflicting, ranging from no association or weak associations \(^6,7\) to moderate to strong associations \(^3,9,15,16\) between homocyst(e)ine and stroke risk. This might be because of methodological differences. Nonfasting homocyst(e)ine was sampled for some studies \(^3,6,15\), whereas fasting specimens were used for other studies \(^7,9,16\), which is the recommended method. \(^17\) Two studies sampled homocyst(e)ine during widely varying times in the post-stroke convalescent period; \(^3,7\) prior evidence has shown that convalescent homocyst(e)ine levels are higher than in samples taken in the acute phase of stroke. \(^18,19\)

Only 1 study \(^9\) has evaluated the relationship between homocyst(e)ine and stroke subtype. This resulted in ischemic strokes of varying etiologies (large-artery, cardioembolic, lacunar) being included in the final analysis of all other studies. Notably, 22.5% of a Swedish series of young strokes were a result of arterial dissection alone. \(^7\) The underlying cause of a cardioembolic stroke is different from that of a large-artery stroke or a lacunar stroke. Being atherogenic, homocyst(e)ine may play a role in large-artery strokes only and not in cardioembolic strokes.

Strengths of our study compared with prior studies included (1) use of fasting specimens, (2) narrow and uniform time window of 5 days post-stroke for blood sampling, (3) a standard protocol for stroke evaluation and classification, and (4) masked stroke classification using validated TOAST criteria. \(^20\)

We selected age- and gender-matched hospital controls for comparison. Control patients were from the same hospital as the cases, came from the same neighboring region, and had similar socioeconomic status and the same referral base. Although there was a difference in racial composition between cases and controls, a Singapore study has shown no significant difference in homocyst(e)ine levels between the different racial groups. \(^21\) In our cohort, we also found no significant difference in homocyst(e)ine levels between the different races, thus this is unlikely to bias our study appreciably.

Homocyst(e)ine may be increased in ill hospitalized patients irrespective of illness type, \(^22\) perhaps because of tissue damage. Critics \(^8\) cite this as a possible reason why prior studies comparing ill stroke patients with healthy population controls \(^3,7,9\) found an association with stroke and homocyst(e)ine. Our study used hospital controls, therefore any difference in homocyst(e)ine arising from using hospital controls would tend to reduce the difference between cases and controls and thus bias our results toward the null. Our finding therefore of a difference despite hospital controls

### TABLE 3. Risk Factors for Ischemic Stroke Modeled With Logistic Regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Crude Odds Ratio</th>
<th>95% CI</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocyst(e)ine</td>
<td>4.28</td>
<td>1.93–9.47</td>
<td>5.17*</td>
<td>1.96–13.63</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.97</td>
<td>1.72–9.18</td>
<td>3.16</td>
<td>1.15–8.68</td>
<td>0.026</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.97</td>
<td>2.64–9.38</td>
<td>2.84</td>
<td>1.34–6.03</td>
<td>0.007</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.63</td>
<td>2.79–9.94</td>
<td>5.42</td>
<td>2.51–11.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitamin B(_12)</td>
<td>0.997</td>
<td>0.995–0.999</td>
<td>0.997†</td>
<td>0.995–0.999</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*For every 1 \(\mu\)mol/L increase in log homocyst(e)ine.
†For every 1 pmol/L increase in vitamin B\(_12\).
lends strength to the epidemiological association between hyperhomocyst(e)inemia and stroke.

Our study found significantly higher mean homocyst(e)ine levels in stroke cases compared with controls. This is similar to previous studies.\textsuperscript{3,9,15,16} We have also found that homocyst(e)ine levels are significantly higher in large-artery strokes but not other stroke subtypes. This is a relatively new finding. This association has only been found in another recent Australian study\textsuperscript{9}—stroke subtyping was not done for all earlier studies. Given that high homocyst(e)ine levels are associated with carotid atherosclerosis,\textsuperscript{13,14} our findings are consistent with previous studies.\textsuperscript{3,9,15,16} We have also found that homocyst(e)ine levels in stroke cases compared with controls. This is similar to the Australian study,\textsuperscript{9} except that the odds ratios are higher in our study. Both studies show an association of homocyst(e)ine with large-artery strokes. Interestingly, despite ethnic differences, the proportion of patients with large-artery strokes in our study (27.5\%) is very similar to the Australian study (28.7\%).

Large-artery strokes can be a result of intracranial or extracranial atherosclerosis. There is a racial difference in the patterns. Our case population included Chinese and Indians. Chinese stroke patients tend to have predominantly intracranial arterial stenosis,\textsuperscript{23,24} whereas Indians have both intra- and extracranial stenosis.\textsuperscript{23,25} Whites tend to have more extracranial atherosclerosis than Chinese.\textsuperscript{23} In our study, 77\% (23/30) of those with large-artery strokes had intracranial atherosclerosis. The other 7 cases all had internal carotid artery stenosis: 3 had proximal stenosis of 80\% to 99\%, 3 had distal stenosis, and 1 had total occlusion.

Putting together the evidence associating homocyst(e)ine and large-artery strokes from our Asian study and the Australian study,\textsuperscript{9} we suggest that regardless of race or site of atherosclerosis (intra- or extracranial), homocyst(e)ine may increase large-artery stroke risk. In Asians, however, it seems to do so via intra- rather than extracranial atherosclerosis, unlike whites. This may represent genetic factors in susceptibility to atherogenesis resulting from hyperhomocyst(e)inemia and is an area for future study.

Notably, though the Australian study found a smaller association between small-artery/lacunar strokes and homocyst(e)ine,\textsuperscript{9} this association was not present in our study. Lacunar infarcts may be attributed to atherosclerosis of small arteries and lipohyalinosis. This absence of association in our study may suggest that lipohyalinosis may be a more important factor than atherosclerosis among young Asian patients with lacunar infarcts.

Vitamin status in young patients with ischemic stroke has not been well studied. Vitamin B\textsubscript{12} and folate are negatively correlated with homocyst(e)ine.\textsuperscript{4,5} Our study found significantly lower vitamin B\textsubscript{12} levels in cases compared with controls but no significant difference in serum folate. Vitamin B\textsubscript{12} levels were also significantly lower in large-artery and lacunar strokes compared with controls. A Swedish study of young adults with ischemic stroke found no significant difference in serum folate, whereas vitamin B\textsubscript{12} was slightly but nonsignificantly lower in cases.\textsuperscript{7} Unlike studies with older patients in which folate levels were lower in cases,\textsuperscript{9} the Swedish results and ours may suggest that in young ischemic stroke patients, low vitamin B\textsubscript{12}, rather than folate, may be associated. This may be related to folate, but not vitamin B\textsubscript{12}, supplementation in the diet. However, the small sample size of both studies makes this association provisional, requiring further examination in future studies. Supplementation of vitamin B\textsubscript{12} and folate is known to reduce homocyst(e)ine levels.\textsuperscript{5} Although our results seem to suggest that low vitamin B\textsubscript{12} levels may increase stroke risk, the small deleterious effect must be interpreted with caution. Ongoing trials will determine if vitamin supplementation can reduce homocyst(e)ine levels and therefore stroke risk.\textsuperscript{26,27}

There has only been 1 other study of young Asian adults younger than 50 years with ischemic stroke; it is interesting to compare our results with this Thai series.\textsuperscript{10} In our series, young strokes constituted only 3.1\% of all ischemic strokes admitted, lower than the 16\% quoted in the Thai series\textsuperscript{10} and slightly lower than figures from developed countries.\textsuperscript{10,28} It seems that the proportion of young ischemic stroke patients has decreased in the 8 years between both Asian studies, perhaps because of improved health care.

Ischemic stroke patterns also seem to be changing in young Asian strokes. In this Thai series of 56 patients, 16 (28.5\%) were cardioembolic strokes. Of these 16 patients, 13 (23\%) were caused by rheumatic heart disease.\textsuperscript{10} In contrast, only 13 (12\%) of our 109 cases were cardioembolic, and only 2 (1.8\%) were caused by rheumatic heart disease. The prevalence of strokes caused by rheumatic heart disease has decreased, perhaps implying that rheumatic heart disease has become less common with improving healthcare in Asia or that diagnosis and treatment is made earlier. The threat of ischemic stroke in Asia in the future may not come from rheumatic heart disease but from newer risk factors like homocyst(e)ine.

Potential limitations of our study are those present in all case-control studies. Although cases were selected consecutively, confounding can never be fully eliminated. Our cohort was also relatively small (197 patients total). A study design using equal numbers of hospital- and population-based controls might have reduced selection bias resulting from using only 1 source of controls. Methylene tetrahydrofolate reductase genotype was not assessed in our study. Although this has been shown to affect homocyst(e)ine levels, 1 study has shown no significant association with risk of ischemic stroke or any stroke subtype.\textsuperscript{8} These results await confirmation from other studies. Physical activity and lifestyle factors were also not assessed in our study because the evidence for association between these factors and homocyst(e)ine has been mixed; a Singapore study has showed no association after adjustment for folate.\textsuperscript{29}

In conclusion, our study suggests that in young Asian adults with ischemic stroke, elevated fasting homocyst(e)ine is an important independent risk factor. Of the different stroke...
subtypes, only large-artery strokes were associated with elevated homocyst(e)ine levels. We have also shown a strong, graded relationship between increasing homocyst(e)ine levels and ischemic stroke risk, in particular risk of large-artery strokes. We conclude therefore that fasting homocyst(e)ine levels should be assessed in young Asian patients with first-ever ischemic strokes, especially those with large-artery strokes.

Acknowledgments
This study was supported by grants from the National Neuroscience Institute of Singapore Pte Ltd. The authors would like to thank the following for their valuable assistance: Professor Simon Shorvon, A/Prof Lee Wei Ling, Dr Yee Woon Chee, Dr Yeo Chin Pin, Ms Tan Hui Lang, Dr Jennifer Teo, and Dr Kuldeep Kaur.

References
Hyperhomocyst(e)inemia and Risk of Ischemic Stroke Among Young Asian Adults
Nigel Choon-Kiat Tan, N. Venketasubramanian, Seang-Mei Saw and Helen Tjoei-Lian Tjia

Stroke. 2002;33:1956-1962
doi: 10.1161/01.STR.0000021899.08659.C8
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/33/8/1956

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/