Background and Purpose—Risk of death due to stroke in Japan is more than double the risk in the United States. It remains unknown why some ethnic groups are more prone to stroke than others. Our purpose was to compare the 20-year incidence of hospitalized stroke between Japanese-American men in the Honolulu Heart Program and white men in the Framingham Study.

Methods—This was a 20-year follow-up study beginning around 1965, a population-based study on the island of Oahu, Hawaii, and in Framingham, Mass. Participants were 7589 men in Honolulu and 1216 men in Framingham without prevalent coronary heart disease and stroke. Subjects were 45 to 68 years old when follow-up began. Main outcome measures were incident thromboembolic and hemorrhagic stroke.

Results—Framingham men had a 40% excess of thromboembolic stroke compared with Honolulu men after adjustment for age and other risk factors (62/1000 versus 45/1000, respectively, \(P < 0.001\)), whereas incidence of hemorrhagic stroke was nearly identical (14.8/1000). In both cohorts, each stroke type was consistently elevated in the presence of hypertension and cigarette smoking. Diabetes and body mass index increased the risk of thromboembolic stroke in both samples, and diabetes increased the risk of hemorrhagic events in Framingham. Alcohol intake and low total cholesterol were associated with hemorrhagic events in Honolulu but not in Framingham. Despite occasional differences in risk factor effects, none were significantly different between cohorts.

Conclusions—The incidence of thromboembolic stroke requiring hospitalization is markedly less in Honolulu than in Framingham. The difference in stroke incidence rates observed cannot be explained by the traditional risk factors. Further studies are needed to identify factors that protect Japanese-American men in Honolulu from stroke. (Stroke. 2002;33:230-237.)

Key Words: Asian-Americans ■ epidemiology ■ ethnic groups ■ risk factors ■ stroke ■ whites
these diverse samples. We hypothesize that any differences observed in incidence rates can be explained by different risk factor effects between the Japanese-American and white men enrolled in these 2 studies.

Methods

Study Samples
The Honolulu Heart Program began in 1965 as a follow-up study of 8006 Japanese-American men for the development of coronary heart disease and stroke. At the time of study enrollment, participants received a complete physical examination when they were 45 to 68 years old. The first medical director in the Honolulu Heart Program was recruited from the Framingham Study, and many procedures, collection instruments, and diagnostic criteria applied in Framingham were adopted in the Honolulu cohort.

The Framingham Study began in 1948 with a follow-up of 2336 men and 2873 women. The study participants in Framingham were white, resident in Framingham, Mass, and of similar age to the men enrolled in the Honolulu sample. As in Honolulu, participants received a complete physical examination at the time of study enrollment. In both cohorts, subjects also received repeat examinations during the course of follow-up. In addition, a comprehensive and comparable system of surveillance for morbidity and mortality due to stroke and other outcomes has been in place continuously since each study began. Examination and follow-up procedures for Honolulu and Framingham are described elsewhere.

Baseline Examinations
For each cohort, follow-up for thromboembolic and hemorrhagic stroke began at baseline examinations that were conducted around 1965. For Honolulu, this corresponded to the time of study enrollment. In Framingham, a cycle of repeat examinations was used that occurred at about this time. In Framingham, the selected examinations were given to 1647 surviving men of the original study sample. Among this group, 258 were excluded for falling outside the age range of the Honolulu sample (45 to 68 years). In both cohorts, men with prevalent coronary heart disease and stroke were excluded from follow-up.

Risk factors observed at the baseline examinations included age, hypertension, diabetes, total cholesterol levels, body mass index, cigarette smoking, and alcohol intake. A diagnosis of hypertension was made if a study participant was receiving antihypertensive medication or when systolic or diastolic blood pressures exceeded 160 and 95 mm Hg, respectively. A diagnosis of diabetes was based on a self-reported medical history or on the use of insulin or oral hypoglycemic therapy. Diabetes was also defined in Honolulu if a nonfasting serum glucose level was >12.5 mmol/L (225 mg/dL) after a 50-g glucose challenge, and in Framingham, it was defined if there was a history of nonfasting levels, from casual specimens, that were ≥8.3 mmol/L (150 mg/dL). Further details on risk factor definitions are provided elsewhere. The final samples available for follow-up included 7589 men from Honolulu and 1216 men from Framingham.

Follow-Up
Subjects were followed up after the baseline examinations for up to 20 years for incident thromboembolic and hemorrhagic hospitalized stroke. Transitory ischemic attacks were not considered outcomes. In Honolulu, cases of stroke were identified by a comprehensive surveillance system of discharge diagnoses at major medical facilities. Ascertainment of death was based primarily on obituary notices in island newspapers and by death certificate data that were filed with the State Department of Health. For all stroke diagnoses, medical records, death certificates, and autopsy reports were reviewed by a study neurologist according to standardized diagnostic criteria. In Honolulu, follow-up on vital statistics is virtually complete, and validity studies have indicated that nearly 100% of hospital discharge episodes have been identified.

Results
Table 1 provides the average age and age-adjusted risk factor levels that were observed in the Honolulu and Framingham cohorts at the baseline examinations. Although age ranges were the same in the 2 cohorts (45 to 68 years), Framingham men were on average 1.5 years older than men from Honolulu (55.8 versus 54.3, respectively, P<0.001). Among the other risk factors, only rates of hypertension were similar in Honolulu and Framingham (25.2% versus 23.1%, respectively). In contrast, the rate of diabetes in the Honolulu sample (17%) was 4 times greater than in Framingham (4.2%,

### Table 1: Average Age and Age-Adjusted Risk Factor Levels in the Sample of Men Enrolled in the Honolulu Heart Program and Framingham Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Honolulu (7589)</th>
<th>Framingham (1216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.3±5.6†</td>
<td>55.8±6.2§</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>25.2</td>
<td>23.1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>17.0</td>
<td>4.2§</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6±1.0 (218±38)‡</td>
<td>6.0±1.1 (231±42)§</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.8±3.1</td>
<td>26.3±3.5§</td>
</tr>
<tr>
<td>Cigarettes smoked/d, n</td>
<td>10.3±14.0</td>
<td>12.0±15.4</td>
</tr>
<tr>
<td>Alcohol intake, oz/mo</td>
<td>14.0±24.6</td>
<td>27.7±35.2§</td>
</tr>
</tbody>
</table>

*Sample size.†Mean±SD.‡Corresponding units in mg/dL.§Significant cohort difference (P<0.001).
the Honolulu sample (73.2/1000 versus 43.5/1000, respectively, \( P < 0.001 \)). Thromboembolic hospitalized events occurred in nearly 40% excess of thromboembolic hospitalized events in Honolulu compared with men in Framingham (62/1000 versus 45/1000, \( P < 0.001 \)).

In the 20-year course of follow-up, the slope of the relation between age and thromboembolic stroke was nearly identical between age and thromboembolic stroke that was left unexplained by the other risk factors. The Figure further describes the 20-year incidence of each hospitalized stroke type according to age. For thromboembolic stroke (top panel), incidence in Honolulu was significantly greater \( (P < 0.001) \) lower levels of total cholesterol (5.6 mmol/L [218 mg/dL]) than men in Framingham (6.0 mmol/L [231 mg/dL]). Men in Honolulu were also leaner. The average body mass index in Honolulu was 2.5 kg/m\(^2\) less than in Framingham (23.8 versus 26.3 kg/m\(^2\), \( P < 0.001 \)). Men in Honolulu smoked fewer cigarettes per day \( (P < 0.001) \) than Framingham men, and monthly alcohol intake in Honolulu was nearly half the amount consumed in Framingham (14.0 versus 27.7 oz/mo, respectively, \( P < 0.001 \)).

Table 2 provides the overall 20-year incidence of thromboembolic and hemorrhagic hospitalized stroke in the sample of men enrolled in the Honolulu Heart Program and Framingham Study.

\[ \begin{array}{l|cc}
\text{Stroke Type} & \text{Honolulu} & \text{Framingham} \\
\hline
\text{Thromboembolic} & & \\
\text{Crude incidence} & 43.5 (330/7589) * & 73.2t (89/1216) \\
\text{Age-adjusted incidence} & 44.3 & 66.2 \text{‡} \\
\text{Risk factor–adjusted incidence} & 45.0 & 62.0 \text{‡} \\
\text{Hemorrhagic} & & \\
\text{Crude incidence} & 14.8 (112/7589) & 14.8 (18/1216) \\
\text{Age-adjusted incidence} & 14.9 & 13.8 \\
\text{Risk factor–adjusted incidence} & 14.6 & 14.2 \\
\end{array} \]

\*Number of events/sample size. 
†Adjusted for age, hypertension, diabetes, total cholesterol, body mass index, cigarettes smoked per day, and alcohol intake.
‡Significant cohort difference \( (P < 0.001) \).

Twenty-year incidence (rate/1000) of thromboembolic stroke (top) and hemorrhagic stroke (bottom) according to age in the sample of men enrolled in the Honolulu Heart Program and Framingham Study.

In Framingham, stroke incidence rose from 44.2/1000 in men 45 to 49 years old to 109/1000 in men \( \geq 60 \) \( (P < 0.001) \). For hemorrhagic stroke, the risk of hemorrhagic stroke increased consistently with age, from 10.2/1000 in men 45 to 49 years old to 22.6/1000 in those \( \geq 60 \) years old \( (P < 0.001) \). In Framingham, an effect of age on hemorrhagic stroke was less clear \( (P = 0.273) \), although the slope of the relation between age and hemorrhagic hospitalized events was similar to the slope in Honolulu.

Table 3 provides estimates of the relative risk of hospitalized thromboembolic stroke due to various risk factor differences in the sample of men in Honolulu and Framingham. Within each cohort, there was an \( \approx 2 \text{-fold} \) excess risk of hospitalized thromboembolic stroke in hypertensive men versus men without hypertension \( (P < 0.01) \). Effects of total cholesterol and alcohol intake were absent. An increase in body mass index on the order of 3 kg/m\(^2\) conferred a 10% to 30% excess in the risk of hospitalized stroke that was statistically significant and independent of other risk factors in each cohort \( (P < 0.05) \).

Whereas the above effects were similar between the cohorts, the effect of diabetes and cigarette smoking on the incidence of thromboembolic hospitalized stroke appeared to
differ between Honolulu and Framingham, although cohort differences in these effects were not statistically significant. In Honolulu, there was a 2-fold excess in the risk of thromboembolic stroke in the presence versus absence of diabetes ($P<0.001$). In Framingham, there was a >3-fold excess ($P<0.001$). For each 20 cigarettes smoked per day, the risk of hospitalized stroke increased in Framingham by 30% ($P<0.001$). Although the excess observed in Honolulu, the risk was increased by 70% ($P<0.001$). Smoking an additional 20 cigarettes per day in the presence versus absence of hypertension in each cohort ($P<0.001$) but not in Framingham, although a cohort difference in these effects was not statistically significant. In Honolulu, diabetes was not a risk factor for hemorrhagic events, whereas in Framingham, there was a 4- to 5-fold excess risk in the presence versus absence of diabetes, independent of the other risk factors ($P<0.05$).

**Discussion**

In terms of our original hypothesis, differences in rates of thromboembolic stroke and similarities in the incidence of hemorrhagic events could not be explained by different risk factor effects in Honolulu and Framingham. In light of the excess in stroke risk in Japanese men living in Japan and the contrasting stroke protection shown in Japanese-American men living in Honolulu, further studies are needed to identify factors that protect the men in Honolulu from stroke.

In contrast to the >2-fold excess in the risk of death due to stroke in Japan relative to the United States, the incidence of thromboembolic stroke was significantly less in the Japanese men in the Honolulu Heart Program than the white men in the Framingham Study. No differences were observed in the incidence of hemorrhagic events between the 2 samples. The proportion of hemorrhagic events of all strokes was greater in Honolulu than in Framingham (25% versus 17%), however, which is consistent with higher rates of hemorrhagic stroke in Japanese populations.

Although it is not clear that the observed difference in risk factor profiles between Honolulu and Framingham gave one cohort a risk advantage over the other, adjustment for these factors failed to appreciably diminish the large difference in the risk of thromboembolic stroke ($P<0.001$). Although the Honolulu sample was younger, had lower levels of total cholesterol and hospitalized hemorrhagic stroke in Framingham. Differences observed between the 2 populations in the effects of any of the risk factors (Table 4) were not statistically significant.

As with thromboembolic events, the effect of diabetes on hemorrhagic stroke appeared to be stronger in Framingham than Honolulu, although a cohort difference in these effects

**TABLE 3. Age- and Risk Factor-Adjusted Relative Risk of Thromboembolic Stroke in the Sample of Men Enrolled in the Honolulu Heart Program and Framingham Study According to Various Risk Factor Differences**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor Difference</th>
<th>Honolulu</th>
<th>Framingham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Present vs absent</td>
<td>2.3‡</td>
<td>2.1‡</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present vs absent</td>
<td>2.1‡</td>
<td>3.6‡</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>1.0 (40)§</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>3</td>
<td>1.2‡</td>
<td>1.3‡</td>
</tr>
<tr>
<td>Cigarettes smoked/d</td>
<td>20</td>
<td>1.7‡</td>
<td>1.3‡</td>
</tr>
<tr>
<td>Alcohol intake, oz/month</td>
<td>20</td>
<td>1.1‡</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*For continuous risk factors, estimated relative risks compare the risk of stroke in men with a high vs low risk factor level where risk factors differ by the amount specified.
†Adjusted for all other risk factors.
‡95% confidence interval.
§Corresponding units in mg/dL.
Significant risk factor effect: | $P<0.05$ | | $P<0.01$ | $P<0.001$.

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There were no differences in the proportion of hemorrhagic events between the 2 samples. The proportion of hemorrhagic events of all strokes was greater in Honolulu than in Framingham, although a cohort difference in these effects was not statistically significant. In Honolulu, diabetes was not a risk factor for hemorrhagic events, whereas in Framingham, there was a 4- to 5-fold excess risk in the presence versus absence of diabetes, independent of the other risk factors ($P<0.05$).
TABLE 4. Age- and Risk Factor–Adjusted Relative Risk of Hemorrhagic Stroke in the Sample of Men Enrolled in the Honolulu Heart Program and Framingham Study According to Various Risk Factor Differences

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor Difference</th>
<th>Honolulu Adjusted</th>
<th>Framingham Adjusted</th>
<th>Honolulu Risk Factor–Adjusted†</th>
<th>Framingham Risk Factor–Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Present vs absent</td>
<td>3.1#</td>
<td>3.5#</td>
<td>3.3#</td>
<td>3.4¶</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present vs absent</td>
<td>1.4</td>
<td>4.9¶</td>
<td>1.3</td>
<td>4.5¶</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>1.0 (40)§</td>
<td>0.7#</td>
<td>1.0</td>
<td>0.7#</td>
<td>1.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>3</td>
<td>1.1</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Cigarettes smoked/d</td>
<td>20</td>
<td>1.7#</td>
<td>1.7¶</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Alcohol intake, oz/mo</td>
<td>20</td>
<td>1.3#</td>
<td>1.1</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*For continuous risk factors, estimated relative risks compare the risk of stroke in men with a high versus low risk factor level where risk factors differ by the amount specified.
†Adjusted for all other risk factors.
§95% confidence interval.
Corresponding units in mg/dL.
Significant risk factor effect: †P<0.05, ‡P<0.01, #P<0.001.

cholesterol, had lower body mass index, smoked fewer cigarettes per day, and consumed less alcohol, diabetes in Honolulu was 4 times more prevalent than in Framingham. Although part of the excess of diabetes in Honolulu is likely to be genuine, its measurement for cohort comparisons is not especially precise. Because of the potential for recall bias, ethnic differences in how diabetes is perceived and the way medical care is used, and the use of different cut points to define diabetes from casual serum specimens in Framingham and postchallenge responses in Honolulu, a comparable definition of diabetes was difficult to construct. It is not clear whether the differences in the classification of diabetes in the 2 cohorts could have contributed to the associations observed. Previous studies, however, have shown that Asians living in the United States have at least 2 to 3 times higher rates of diabetes than whites, despite the relatively low body mass index commonly observed in Asians. This is consistent with our findings reflecting significantly higher rates of diabetes in the Japanese-American population.

It may be that the effects of diabetes on stroke are more similar than the data in this report might suggest. Here, the smaller prevalence of diabetes in Framingham might include cases of diabetes that are more severe than in the Honolulu sample, whereas the higher prevalence in Honolulu might reflect a more heterogeneous set of mild and moderate metabolic disorders. Such a possibility could explain the weaker association that diabetes has with stroke in Honolulu versus Framingham, particularly for hemorrhagic events. This is the first finding from Framingham that suggests that diabetes promotes hemorrhagic stroke, whereas in Honolulu, only a relation with thromboembolic events has been described. In Honolulu, there is also a positive relation between serum glucose levels and an increased risk of thromboembolic events that further suggests that the association between diabetes and stroke in Honolulu is real. Diabetes is a potent risk factor for stroke in Framingham as well. The issue here is not that a comparison of the effect of diabetes on the risk of stroke between the 2 cohorts has meaning, but rather that diabetes is a consistent risk factor for stroke whether the sample is from Honolulu or Framingham.

Discounting the findings related to diabetes, the lower rate of thromboembolic stroke in Honolulu might simply be a reflection of the Honolulu men having a healthier cardiovascular risk profile. Although this is consistent with environmental influences having an important role in promoting stroke between the 2 cohorts, the possibility for a difference in genetic predisposition needs further study. Indeed, after risk factor adjustment, a large cohort effect on the risk of thromboembolic stroke persists.

Within each cohort, the importance of cardiovascular risk factor profiles in promoting stroke seems clear. Whether from Honolulu or Framingham, thromboembolic and hemorrhagic stroke risks were consistently elevated in the presence of hypertension and cigarette smoking. Although cigarette smoking has been associated with each stroke subtype in a previous report from Honolulu, this is the first report to further confirm an association between smoking and hemorrhagic events in Framingham.

The effects of total cholesterol and alcohol intake on the risk of thromboembolic stroke were also similar between the cohorts. Although there was a weak positive association in Honolulu, previous reports have shown that the relation is
In summary, despite significant cohort differences, risk factor effects on thromboembolic and hemorrhagic stroke do not differ appreciably between Honolulu and Framingham. The possibility exists that unknown genetic influences could offer some level of stroke protection in Honolulu that is not available in Framingham. In light of the excess in stroke risk in Japanese men living in Japan and the contrasting stroke protection in Japanese men living in Honolulu, a stronger role of unknown environmental risk factors on stroke resistance in the Honolulu sample seems likely. Whether all strokes were of the same origin or causation in the 2 cohorts is not clear.

Differences in stroke subclassifications could also provide better insight into both mechanisms and pathophysiology and perhaps account for the varying incidence of thromboembolic strokes. It is unlikely, however, that even a more refined diagnostic classification system could explain the 40% excess of thromboembolic stroke in Framingham versus Honolulu.

Acknowledgments

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References

There have been multiple studies documenting ethnic and racial differences in stroke incidence as well as the predisposing risk factors of stroke. Rodriguez and collaborators add to this literature; they report that Caucasian men in the Framingham study had a 40% increased risk of thromboembolic stroke compared with Japanese-American men in the Japanese Heart program. This difference in thromboembolic stroke incidence was maintained after adjusting for the presence of traditional clinical risk factors such as hypertension, diabetes, body mass index, and alcohol intake. Given that the investigators focused on 7 traditional clinical factors and no social environmental index, and alcohol intake. Given that the investigators focused on 7 traditional clinical factors and no social environmental factors, it is not surprising that the racial/ethnic differences in thromboembolic stroke could not be fully explained.

There are possible unknown genetic influences that may explain these differences in stroke incidence. However, a more likely explanation for the stroke protection among Japanese men in the Honolulu Heart program compared with Caucasians in the Framingham Heart study compared with Japanese living in Japan1 is attributed to unknown social environmental factors. This difference in risk of stroke within the same racial group provides the opportunity to explicate the role social environmental factors may have on stroke incidence.

It is necessary to examine the effects of individuals’ social environment to understand racial/ethnic differences in stroke incidence and risk factors. The social environment is comprised of several different factors including intrapersonal factors (eg, depression, diet, body mass index, stress, social economic status), interpersonal factors (eg, social isolation or social support), institutional factors (eg, access to care), and community factors (eg, cultural norms). It will be imperative for future studies to examine not only the specific impact each factor has on stroke incidence but also how they interact to influence stroke risk factors and subsequent development of stroke.

Public health programs and national guidelines for stroke prevention continue to focus on the identification of risk factors in the general population without addressing the specific needs of racial/ethnic groups. The ability to provide targeted information and effective public health interventions to different racial/ethnic groups is dependent on studies capable of identifying salient risk factors for each particular group.

Epidemiology, in general, has been successful at documenting associations between exposure to risk factors and disease. However, determining the causal mechanisms among these associations is required to further advance stroke research. It is imperative for the next generation of research to continue to identify other potential stroke risk factors, the magnitude of these associations, and the processes and reasons for racial and ethnic differences in stroke incidence.

Effective educational and interventional stroke programs should take into account differences in magnitude and prevalence of stroke risk factors in different racial/ethnic groups. Stroke prevention guidelines must account for and convey these differences to health care professionals. The failure to use information that describes risk factors in different racial/ethnic groups when creating prevention programs may be responsible for the continued failure to achieve the goals of reducing stroke incidence.
Much has been accomplished to relieve the burden of stroke on the American people, with declines in stroke mortality since the 1960s. The mortality gap, however, between certain population subgroups, defined by race/ethnicity, socioeconomic status, and geography, continues to increase. Parallel to these trends is evidence that a number of deleterious risk behaviors have either stopped improving or worsened, which forecasts difficulty in achieving further declines in stroke incidence. We possess a wealth of knowledge about cause, diagnosis, and prevention of stroke incidence but have only limited effectiveness in applying and implementing that knowledge. The next generation of research, needed to attain the Year 2010 health objectives of reducing stroke rates, will require us to understand the process and reasons for these racial/ethnic differences in stroke risk. This will require identifying and focusing on additional risk factors, improved methodologies that can incorporate qualitative analyses and multi-level data, better dissemination of information about specific racial/ethnic risk factors, and improved guidelines for stroke.

References
Risk of Hospitalized Stroke in Men Enrolled in the Honolulu Heart Program and the Framingham Study: A Comparison of Incidence and Risk Factor Effects

Stroke. 2002;33:230-236
doi: 10.1161/hs0102.101081

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/33/1/230