Risk Profile and Prediction of Long-Term Ischemic Stroke Mortality

A 21-Year Follow-up in the Israeli Ischemic Heart Disease (IIHD) Project

David Tanne, MD; Shlomit Yaari, BSc; Uri Goldbourt, PhD

Background—Multinational comparisons demonstrate marked ethnic and regional variation in stroke mortality and risk-factor distribution. We assessed the role of ethnicity and estimated the cumulative effect of multiple risk factors on long-term ischemic stroke mortality.

Methods and Results—Civil servants and municipal employees in Israel (n=9734 men; age, ≥42 years), chosen by stratified sampling in 6 prespecified areas of birth (those born in Israel and those who were immigrants from 5 other regional-ethnic strata), were included in the Israeli Ischemic Heart Disease (IIHD) Project. Over a 21-year follow-up period, age-adjusted mortality rates per 10 000 person-years attributed to ischemic stroke (n=282; International Classification of Diseases [ICD]-9 codes 433 to 438) were higher among immigrants to Israel from northern Africa and the Mideast (17.1 to 19.0), than from 3 parts of Europe (11.3 to 12.4). Crude rates per 1000 subjects observed in those born in Asia or Africa (29.4 to 31.2) exceeded rates predicted by risk-factor profiles (21.4 to 24.9). Adjusted hazard ratios were 3.00 for age (per 10 years), 2.15 for left ventricular hypertrophy, 1.69 for systolic blood pressure (BP, per 20 mm Hg), 1.83 for diabetes mellitus, 1.83 for peripheral vascular disease, 1.79 for smoking (>20 cigarettes per day), 1.51 for coronary heart disease, 1.16 for percent cholesterol contained in the HDL fraction (%HDL, per 5% decrease), and 1.88 for diastolic BP (per 12 mm Hg; assessed in an alternative model). Accounting for regression dilution bias and assessed from repeat measurements, we found that hazard ratio estimates associated with diastolic BP, systolic BP, and percent HDL (per increments described) increased to 3.22, 2.23, and 1.23, respectively. Ischemic stroke mortality rates were 30-fold greater among subjects at the highest versus the lowest quintile of predicted probability according to risk-factor profiles (81.2 versus 2.6 per 1000 subjects).

Conclusions—Assessment of multiple risk factors provides useful quantitative prediction of long-term ischemic stroke mortality risk. Regional-ethnic variations are consistent with a hypothesis that other, undetermined inherent genetic or sociocultural factors act to increase ischemic stroke mortality rates in immigrants to Israel from the Mideast and northern Africa over that predicted by conventional risk factors. (Circulation. 1998;98:1365-1371.)

Key Words: cerebrovascular disorders • risk factors • epidemiology • mortality
Methods

Subjects

The participants of the IIHD Project were chosen by stratified sampling of civil servants and municipal employees in 1963 based on (1) men aged ≥40 years on inclusion, (2) place of work confined to the 3 largest urban areas in Israel (Tel-Aviv, Jerusalem, and Haifa), and (3) sampling fractions aimed at obtaining numbers of study subjects from 6 areas of birth (central Europe, eastern Europe, the Balkan countries, the Mideast, northern Africa, and Israel) proportional to the Israeli male population of this age. The sampling frame consisted of 24 330 eligible men, and the sampling ratios used were 1:4 for eastern Europe, 5:7 for central Europe, 5:6 for the Balkan countries, and 1:1 each for Israel, the Mideast, and northern Africa.

Participants underwent clinical and blood biochemical evaluations in 1963, 1965, and 1968. The response rate to the initial examination was 86.2%, and 98% of those living in 1965 were reexamined. There was no significant difference between the subjects examined and the nonresponders with respect to age, area of birth, or socioeconomic status. Further details of the study (population, sampling procedures, mortality, follow-up, and analysis) have been described elsewhere.11,12 The current report includes mortality follow-up over a 21-year period for the 9734 participants examined during the second round of examinations in 1965.

The underlying cause of death was documented on the basis of case-by-case determinations by a review panel until 1970 and by the use of the International Classification of Diseases (ICD)13 codes thereafter. Deaths from presumed ischemic stroke were based on ICD-9 codes 433 to 438. Our data do not permit separation of cardioembolic from noncardioembolic mechanisms.

Information on death was derived from the Israeli Mortality Registry. For all hospital deaths until 1970, comparison of death certificates with the analyses of hospital records (including physician notes, autopsy reports, and death certificates) by a study panel revealed a >90% agreement. A comparison of our physicians’ analyses of a 25% random sample of hospital deaths versus death certificates showed an agreement of almost 100% for deaths due to cancer and 84% for deaths due to nonmalignant disease.

BP was measured in the right arm, with the subject in the recumbent position, ’30 to 45 minutes after arrival at the clinic and again 15 to 30 minutes later. Left ventricular hypertrophy (LVH) on ECG was diagnosed by R wave in lead aVF ≥2.0 mV or lead aVL ≥1.3 mV, S wave in V1 plus R wave in lead V5 or V6 ≥4.6 mV, or S wave in V2 plus R wave in lead V1 or V6 ≥4.6 mV.

TABLE 1. Age-Adjusted Ischemic Stroke Mortality Rates in 6 Regional-Ethnic Strata Defined by Area-of-Birth Immigration to Israel

<table>
<thead>
<tr>
<th>Area of Birth</th>
<th>Subjects, n</th>
<th>Person-Years of Follow-Up, n</th>
<th>No. of Ischemic Stroke Deaths</th>
<th>Age-Adjusted Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balkan countries</td>
<td>1688</td>
<td>34 184</td>
<td>43</td>
<td>11.3</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1337</td>
<td>27 541</td>
<td>32</td>
<td>11.6</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>1861</td>
<td>37 448</td>
<td>58</td>
<td>12.4</td>
</tr>
<tr>
<td>Israel</td>
<td>1377</td>
<td>27 718</td>
<td>44</td>
<td>15.9</td>
</tr>
<tr>
<td>Mideast</td>
<td>2291</td>
<td>48 100</td>
<td>71</td>
<td>17.1</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>1180</td>
<td>24 756</td>
<td>34</td>
<td>19.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9734</strong></td>
<td><strong>199 747</strong></td>
<td><strong>282</strong></td>
<td><strong>14.1</strong></td>
</tr>
</tbody>
</table>

*Rates for ischemic stroke mortality per 10 000 person-years of follow-up are directly age adjusted to the overall study-age distribution.

TABLE 2. Age-Adjusted Ischemic Stroke Mortality Rates by Baseline BP and ECG Evidence for LVH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects, n</th>
<th>Person-Years of Follow-Up, n</th>
<th>No. of Ischemic Stroke Deaths</th>
<th>Age-Adjusted Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>1273</td>
<td>27 647</td>
<td>12</td>
<td>5.4</td>
</tr>
<tr>
<td>120–130</td>
<td>1975</td>
<td>42 907</td>
<td>19</td>
<td>5.8</td>
</tr>
<tr>
<td>131–140</td>
<td>2160</td>
<td>45 764</td>
<td>39</td>
<td>9.2</td>
</tr>
<tr>
<td>141–151</td>
<td>2259</td>
<td>46 230</td>
<td>68</td>
<td>13.9</td>
</tr>
<tr>
<td>≥152</td>
<td>2048</td>
<td>36 811</td>
<td>144</td>
<td>31.0†</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;78</td>
<td>1948</td>
<td>42 003</td>
<td>26</td>
<td>7.3</td>
</tr>
<tr>
<td>78–80</td>
<td>2096</td>
<td>44 267</td>
<td>33</td>
<td>7.8</td>
</tr>
<tr>
<td>81–89</td>
<td>1619</td>
<td>33 905</td>
<td>31</td>
<td>9.4</td>
</tr>
<tr>
<td>90–95</td>
<td>2045</td>
<td>41 726</td>
<td>65</td>
<td>15.0</td>
</tr>
<tr>
<td>≥96</td>
<td>2000</td>
<td>37 314</td>
<td>127</td>
<td>30.7†</td>
</tr>
<tr>
<td><strong>LVH on ECG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9179</td>
<td>189 032</td>
<td>261</td>
<td>13.8</td>
</tr>
<tr>
<td>Yes</td>
<td>172</td>
<td>3136</td>
<td>11</td>
<td>35.0†</td>
</tr>
</tbody>
</table>

*Rates for ischemic stroke mortality per 10 000 person-years of follow-up are directly age adjusted to the overall study-age distribution.

†P<0.001.
TABLE 3. Cox Proportional Hazards Model for Ischemic Stroke Mortality Over a 21-Year Follow-Up Period Among 9734 Men in the IIHD Project*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change Increment</th>
<th>Adjusted HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 10 y</td>
<td>3.00</td>
<td>2.41–3.73</td>
<td></td>
</tr>
<tr>
<td>LVH on ECG</td>
<td>...</td>
<td>2.15</td>
<td>1.12–4.12</td>
</tr>
<tr>
<td>Systolic BP 20 mm Hg</td>
<td>...</td>
<td>1.69</td>
<td>1.55–1.84</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>...</td>
<td>1.86</td>
<td>1.20–2.89</td>
</tr>
<tr>
<td>PVD</td>
<td>...</td>
<td>1.83</td>
<td>1.06–3.14</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1–10 Cigarettes/d</td>
<td>1.57</td>
<td>1.08–2.27</td>
</tr>
<tr>
<td>CHD</td>
<td>...</td>
<td>1.51</td>
<td>0.96–2.36</td>
</tr>
<tr>
<td>% HDL</td>
<td>5% Relative decrease</td>
<td>1.16</td>
<td>1.01–1.33</td>
</tr>
<tr>
<td>Diastolic BP†</td>
<td>12 mm Hg</td>
<td>1.88</td>
<td>1.67–2.12</td>
</tr>
</tbody>
</table>

*See Methods for variables incorporated in model.
†Assessed in an alternative model incorporating the same variables except for use of diastolic instead of systolic BP.

History of myocardial infarction was corroborated by changes on ECG consistent with an old infarction or by search of the medical summaries and the ECG tracings at the time of the myocardial infarction with verification by 2 cardiologists. Definite angina was diagnosed by use of the World Health Organization (WHO) (Rose) chest pain questionnaire, in which typical presternal pain was caused by physical exertion and was relieved within 10 minutes by discontinuation of exertion or by intake of a vasodilating drug. History of peripheral vascular disease (PVD) was recorded on the basis of the presence of calf pain induced by walking that was relieved within 10 minutes by rest. History of diabetes mellitus and smoking status were recorded by subjects’ self-report during the medical history.

Blood samples were drawn with the subject in a nonfasting state and were kept refrigerated and shipped daily in ice-cooled containers to a central laboratory. There, total cholesterol, HDL cholesterol, uric acid, glucose, and hematocrit levels were determined.

Statistical Methods

Direct age-adjusted ischemic stroke mortality rates were calculated in person-years, taking into account the shifting age of the study population over the long follow-up period. Testing trend of increasing rates in tertiles or quintiles of risk factors was performed by use of the TREND utility. Multivariate analysis of ischemic stroke mortality was performed by use of the Cox proportional hazards model within the whole study cohort. The model incorporated age, area of birth (by introducing 5 indicator variables to account for the 6 regional-ethnic strata), diabetes mellitus, systolic BP, LVH on ECG, history of coronary heart disease (CHD) (myocardial infarction or angina), cigarette smoking status, PVD, body mass index, serum glucose, uric acid, percentage of serum cholesterol contained in the HDL fraction (%HDL), and hematocrit. In an alternative model, diastolic BP was included instead of systolic (because of the high intercorrelation between these 2 variables). Separate models were also performed within each area of birth. Adjusted hazard ratios (HR) and 95% CIs are presented.

To estimate the effect of area of birth, predicted ischemic stroke mortality rates were calculated by a logistic regression model for the 6 regional-ethnic strata, and rates were compared with the crude rates observed. To evaluate the extent to which classification of subjects by their risk factors discriminates between those destined to die of ischemic stroke and others, men were ranked according to probability calculated from a logistic regression model. Comparison of the predicted and observed rates of events yields an estimate of fit, whereas the gradient of increase in rates provides a measure of discrimination ability. Somers’ D, Goodman-Kruskal G, and the C statistic (area under the receiver operating curve) are presented as measures of rank correlation between the predicted and observed responses. The Hosmer-Lemeshow goodness-of-fit test was used to test the departure of observed from predicted number of events within quintiles of probability.

Regression dilution factors were estimated by dividing the difference in means between the highest and lowest quintiles in 1965 by the same difference in 1963, based on the 1965 measurements. Corrections for the RDB, associated with increments in the risk-factor variables, were made by multiplying the coefficients obtained from the Cox model by the corresponding regression dilution factors before exponentiation to obtain the estimated HR.

Results

Over a 21-year follow-up, a total of 3276 (33.7%) deaths were recorded among the 9734 participants. Deaths attributed to ischemic stroke (282 cases) accounted for 8.6% of the total mortality.

Predictors of Ischemic Stroke Mortality: Age-Adjusted Analysis

Ischemic stroke mortality rates varied 1.7-fold between highest and lowest according to area of birth (Table 1). Immigrants to Israel from Asia and Africa had higher age-adjusted rates (17.1 to 19.0 per 10,000 person-years) than counterparts born in the 3 parts of Europe (11.3 to 12.4).

A strong association was demonstrated between systolic and diastolic BP and between presence of LVH on ECG and ischemic stroke mortality (Table 2). Age-adjusted rates rose almost 6-fold from the lowest to the highest quintile for systolic BP (5.4 to 31.0, respectively) and >4-fold for...
diastolic BP (7.3 to 30.7). Subjects with LVH on ECG exhibited a 2.5-fold increased risk of fatal ischemic stroke compared with those without (35.0 versus 13.8, \( P < 0.001 \)).

Age-adjusted rates were more than doubled among subjects with either history of angina (29.7 versus 14.4), diabetes mellitus (30.8 versus 13.6), or PVD (31.3 versus 13.6) versus those without (\( P < 0.01 \) for each). Rates increased from 12.2 among nonsmokers to 18.6, 14.1, and 18.7 among men smoking 1 to 10, 11 to 20, and \( > 20 \) cigarettes per day on entry, respectively (\( P = 0.01 \)). Serum glucose levels were positively associated in a dose-response manner with fatal ischemic stroke rates. Age-adjusted rates increased from 11.3 to 13.5 and 19.0 for increasing serum glucose tertiles (\( P < 0.001 \)). A positive trend existed among nondiabetic subjects also, with rates rising from 11.0 to 12.2 and 14.8 for increasing tertiles (\( P = 0.009 \)). Trends for increasing rates of ischemic stroke mortality were found with decreasing tertiles of %HDL and increasing tertiles of uric acid and hematocrit, but they fell short of a conventional type I error probability.

**Predictors of Ischemic Stroke Mortality: Multivariate Analysis**

Age, the strongest independent predictor of ischemic stroke mortality, was associated with tripling of risk per 10-year
<table>
<thead>
<tr>
<th>Variable</th>
<th>Change Increment</th>
<th>Adjusted HR</th>
<th>HR Corrected for RDB</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic BP</td>
<td>12 mm Hg</td>
<td>1.88</td>
<td>3.22</td>
<td>2.58–4.02</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>20 mm Hg</td>
<td>1.69</td>
<td>2.23</td>
<td>1.95–2.55</td>
</tr>
<tr>
<td>%HDL</td>
<td>5% Relative decrease</td>
<td>1.16</td>
<td>1.23</td>
<td>1.02–1.49</td>
</tr>
</tbody>
</table>

Increment (Table 3). LVH on ECG was independently associated with more than doubling of risk. An increase of \( \approx 1 \) SD in systolic BP (20 mm Hg) was associated with a 1.69-fold greater risk, whereas a corresponding change in diastolic BP (12 mm Hg), assessed in an alternative model, conferred a 1.88-fold greater risk. Diabetes mellitus, history of PVD, and CHD on entry were each associated with excess risk of >50%, and cigarette smoking (>20 cigarettes per day) was associated with excess of approximately 80%. A 5% relative decrease in the %HDL was associated with 16% excess risk of fatal ischemic stroke. Compared with subjects born in northern Africa, the adjusted HR associated with the other regional-ethnic strata were as follows: the Mideast 0.94 (95% CI, 0.58 to 1.52), Israel 0.76 (95% CI, 0.45 to 1.29), eastern Europe 0.63 (95% CI, 0.39 to 1.04), central Europe 0.62 (95% CI, 0.35 to 1.09), and the Balkan countries 0.56 (95% CI, 0.33 to 0.94).

Separate Cox proportional hazards models performed for each regional-ethnic group (data not shown) demonstrated interarea associations between most risk factors and fatal ischemic stroke that resemble the associations obtained in the entire study cohort. However, overall lower HRs were noted in subjects born in Asia or Africa versus those born in Europe for diabetes mellitus (1.4 to 1.7 versus 1.8 to 4.5), PVD (0.6 to 0.7 versus 1.4 to 4.7), and smoking >20 cigarettes per day (0.6 to 1.4 versus 1.9 to 2.5).

Crude rates of ischemic stroke mortality observed among subjects immigrating from Asia or Africa (29.4 to 31.2 per 1000 subjects) exceeded the rates predicted on the basis of the individual risk-factor profiles (21.4 to 24.9). Conversely, the observed rates among immigrants from Europe were below predicted levels (Table 4). There are important age differences between subjects from the different areas of birth, and thus the area-of-birth order in the observed crude rates is not fully maintained in the age-adjusted analysis.

Crude rates were >30-fold greater among subjects at the highest quintile of probability compared with the lowest quintile, on the basis of individual risk-factor profiles (81.2 versus 2.6 per 1000 subjects), as shown in Table 5. Nearly 60% of events were observed among subjects in the highest quintile of probability. The rank correlations between the observed and predicted responses assessed by Somers’ D (0.55), Goodman-Kruskal G (0.56), and the C statistic (0.77) are consistent with a satisfactory agreement between predicted and observed rates. The Hosmer-Lemeshow goodness-of-fit test \( (P=0.28) \) does not point to a meaningful departure of the model from the observed data.

To illustrate the incremental significance of risk factors for fatal ischemic stroke, we have calculated risk as a function of the number of risk factors identified at baseline separately for subjects with systolic BP \( \geq 160 \) mm Hg or diastolic BP \( \geq 105 \) mm Hg versus counterparts with lower baseline BP measurements (Figure 1). Crude rates were 3-fold greater among subjects with higher BP than among counterparts with lower baseline BP and increased with an increasing number of additional risk factors (rate range per 1000 subjects, 42 to 91 for men with higher BP versus 12 to 41 for men with lower BP, for 0, 1, or \( \geq 2 \) additional risk factors).

### Regression Dilution Factor
Regression dilution factors estimated from repeated measurements on 2 rounds of examination were highest for diastolic BP (1.85) and systolic BP (1.53) and \(<1.5\) for %HDL, serum glucose, and uric acid. Age-adjusted ischemic stroke mortality rates by quintiles of baseline BP measurements versus by quintiles of an estimation of an individual’s average BP (usual BP) are depicted in Figure 2. Both diastolic and systolic BP measurements displayed a curvilinear relationship with ischemic stroke mortality with an increase in rates that occurred predominantly above the second quintile. Estimated HR after correction for the corresponding RDB increased for diastolic BP from 1.88 to 3.22, for systolic BP from 1.69 to 2.23, and for %HDL from 1.16 to 1.23 (Table 6).

### Discussion
The 21-year follow-up of almost 10 000 participants included in the IIHD Project cohort provided nearly 200 000 person-years of follow-up of a working male population in Israel of marked ethnic, cultural, and occupational diversity, representing immigrants from >20 countries on 3 continents.

### Area of Birth
Stroke mortality is known to vary markedly among regions and ethnic groups.\(^2\)\(^{–}\)\(^2\)\(^0\) Data, however, are derived mainly from multinational comparisons and are limited from areas such as the Mideast and northern Africa. Subjects born in Asia or Africa exhibited higher age-adjusted ischemic stroke mortality rates than those born in Europe, as shown also in a population-based study from northern Israel.\(^19\) The trends in risks of ischemic stroke mortality observed among areas of birth after adjustment are consistent with a role for attributes specific to areas of birth beyond the conventional stroke risk factors. Although subjects born in Europe exhibited lower ischemic mortality rates than predicted by their risk-factor profile, those born in Asia or Africa exhibited higher rates than predicted. Opposite trends were found for CHD in the same cohort,\(^2\)\(^1\) suggesting possible effects of additional factors involved in predilection to end-organ damage.

The relative contribution of genetic, environmental, and behavioral factors to the differences observed is still unclear. Genetic factors may affect predisposition and distribution of atherosclerosis and cardiovascular disease.\(^2\)\(^1\)\(^–\)\(^2\)\(^2\) In an autopsy study comparing cerebral atherosclerosis in Israeli Jewish subjects of European and Asian or African origin, no differences have been identified in the severity of atherosclerosis in arteries of the circle of Willis, but correlations between severity of cerebral and coronary atherosclerosis were weaker among those born in Asia or Africa.\(^2\)\(^3\) Higher stroke mortality rates were reported among Jewish subjects in Israel than in...
Montreal, suggesting additional behavioral or environmental effects.\textsuperscript{24} Ethnic variation in ischemic stroke mortality in our cohort is consistent with a hypothesis that other, undetermined inherent genetic or sociocultural differences act to increase the incidence and/or case fatality from ischemic stroke in immigrants from Africa and Asia over that predicted from their profiles of conventional risk factors.

**Age and Clinical Determinants**

The major risk factors identified in our cohort (older age, high BP, history of diabetes mellitus, PVD, CHD, and cigarette smoking) are in agreement with a large body of evidence.\textsuperscript{3–8,25–27} The risk of ischemic stroke mortality increased directly with elevations in BP, whether systolic or diastolic, with rates increasing steeply from above the second quintile. Corrections for the RDB gave more reliable estimates of risk with a more than tripling of the second quintile. Risk increased substantially with the highest quintile of probability in our cohort exhibited a 40-fold greater risk of ischemic stroke mortality than those at the lowest quintile. Risk increased substantially with the number of risk factors present. It is notable that variables, readily determined on routine examination, have such a predictive power on ischemic stroke mortality rates measure over \textgreek{>20} years, irrespective of interventions and treatment during follow-up. Stroke prevention strategies are gradually improving. Quantitative estimates of the magnitude of increased risk for ischemic stroke mortality in the presence of multiple risk factors may help both patient and physician to more fully appreciate the need for measures to limit risk factors and for aggressive risk-factor management.

**Blood Lipids**

There are conflicting data regarding the association between serum lipid levels and ischemic strokes. Recent reports, however, show that treatment of dyslipidemia reduces the risk of stroke and total mortality.\textsuperscript{30} In our cohort, HDL cholesterol levels were inversely associated with fatal ischemic strokes, and total cholesterol positively was associated. Low HDL cholesterol emerged, adjusting for multiple risk factors, as an independent predictor of ischemic stroke mortality.\textsuperscript{31}

**Multiple Risk Factors**

Risk factors interact to increase the probability of stroke in subjects with multiple risk factors. Analyses of data from the Framingham study have described a general cerebrovascular risk profile that can be used to identify 10% of the population that will have at least one third of the strokes.\textsuperscript{27} Subjects at the highest quintile of probability in our cohort exhibited a \textgreek{>30}-fold greater risk of ischemic stroke mortality than those at the lowest quintile. Risk increased substantially with the number of risk factors present. It is notable that variables, readily determined on routine examination, have such a predictive power on ischemic stroke mortality rates measure over \textgreek{>20} years, irrespective of interventions and treatment during follow-up. Stroke prevention strategies are gradually improving. Quantitative estimates of the magnitude of increased risk for ischemic stroke mortality in the presence of multiple risk factors may help both patient and physician to more fully appreciate the need for measures to limit risk factors and for aggressive risk-factor management.

**Limitations**

Long-term mortality data were obtained from death certificates, known for their potential inaccuracies. A validation study suggested that deaths from stroke could be grouped fairly into hemorrhagic and ischemic strokes by death certificate diagnosis.\textsuperscript{32} In our study design, we do not have data regarding interventions and treatment during long-term follow-up. These limitations represent analytical shortcomings that may lead to underestimation of true risks identified in the present analysis. Finally, risks associated with prior stroke, congestive heart failure, or atrial fibrillation, all extremely rare on inclusion in our working male population, as well as risk profiles applicable for women, could not be assessed in this study.

In summary, our data facilitate the estimation of risk for long-term ischemic stroke mortality in an immigrant working male population of marked ethnic and cultural background in Israel and provide a quantitative determination of risk based on multiple risk factors. Ethnic variations observed in ischemic stroke mortality are consistent with a hypothesis that other, undetermined inherent genetic or sociocultural differences act to increase ischemic stroke mortality rates in immigrants to Israel from Asia and Africa over that predicted from their profile of risk factors. Further studies assessing genetic, environmental, and behavioral factors on stroke risk among different populations are warranted.

**Acknowledgments**

Data collection, analysis, baseline, and 2 incidence examinations (1963, 1965, and 1968) were part of a collaborative study by the National Institute of Health, the Ministry of Health, Israel; and the Hadassah medical organization, supported by PL 480 counterpart funds, research agreement No. 375106. The Israeli Academy of Sciences, Fund for Basic Research, supported the mortality follow-up from 1970 to 1978.

**References**


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Circulation. 1998;98:1365-1371
doi: 10.1161/01.CIR.98.14.1365

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