Multivariate Prediction of Coronary Heart Disease in the Western Collaborative Group Study Compared to the Findings of the Framingham Study

RICHARD J. BRAND, PH. D., RAY H. ROSENMAN, M.D., ROBERT I. SHOLTZ, AND MEYER FRIEDMAN, M.D.

SUMMARY The Western Collaborative Group Study (WCGS) is a prospective epidemiological study of 3,154 initially well men, aged 39-59 years at intake in 1960-61, who were employed in ten participating companies in California. Clinical coronary heart disease (CHD) occurred in 257 men during a follow-up period of eight and one-half years. Coronary heart disease risk is predicted using the additive multiple logistic model with the risk factors: age, cholesterol, systolic blood pressure, hematocrit, ECG status, smoking at intake, and relative body weight. The predicted individual CHD risk levels, using the logistic results derived from the WCGS data, are highly correlated with predicted risk levels using a Framingham study (FS) equation for these same risk factors with 12-year follow-up. The observed number of CHD events in the WCGS is not significantly different from the expected number of events derived from the FS logistic equation, after correction for length of follow-up.

Multiple logistic analysis of the direct association between CHD incidence and behavior pattern gives an approximate relative risk of 1.9 (P = 0.0006) and 2.1 (P = 0.0015) for Type A compared to Type B men aged 39-49 and 50-59 years, respectively. It is estimated that removal of the excess risk associated with Type A behavior would correspond to a 31% (standard error = 6.6%) reduction of coronary heart disease incidence in the Western Collaborative Group Study population.

A FEATURE COMMON TO ALL PROSPECTIVE EPIDEMIOLOGICAL STUDIES of coronary heart disease (CHD) has been the absence of random choice in the selection of the study subjects from the over-all population to which it is desirable to generalize results. For example, even when a 100% survey of the community of Tecumseh was attempted, the 10% nonresponse rate, as well as the difficulty of proving that Tecumseh is representative of other communities, weakens the logical basis for wider application of the findings. Confidence in making generalizations based on the results must therefore accumulate through replication of such studies and from examination of the consistency of findings from one group to another.

A number of prospective studies have consistently shown biologically and statistically significant associations of traditional risk factors such as age, serum cholesterol, blood pressure, and cigarette smoking with the incidence of CHD. These and other factors have been studied in various combinations in an attempt to provide a composite assessment of CHD risk through use of multivariate analyses such as the multiple logistic risk model. However, little work has been reported which compares the results of different studies in the United States via these composite risk scores. In the present report the consistency of multivariate findings of the Western Collaborative Group Study (WCGS) and the Framingham Study (FS) is examined and factors which may introduce spurious differences in the multiple logistic results from one study to another are discussed.

A second common feature of the multivariate assessment of CHD risk has been the search for additional factors which have significant predictability that is not explained by association with other known CHD risk factors. In the present report the CHD predictability associated with the behavior pattern classification in the WCGS is assessed via the multiple logistic risk model in the context of a set of risk factors chosen for purposes of comparison with the FS results.

Methods and Material

The Western Collaborative Group Study (WCGS) is a prospective epidemiological study of 3,154 initially well men, aged 39-59 years at intake in 1960-61, who were employed in ten participating companies in California. Data collection was terminated with the annual follow-up examination in 1969, resulting in 8½ years of follow-up. Clinical CHD occurred in 257 men, giving a crude, average annual incidence rate of 9.6 per 1,000 subjects at risk. Detailed descriptions of the study population and methodology are provided in earlier reports and only those features which are particularly relevant to this report are again described.

The choice of a set of risk factors for assessing comparability of the WCGS and FS findings was based on two considerations. First it was desirable to include as many relevant risk factors as possible. Secondly, a set of risk factors that would provide data with follow-up length as close as possible to 8½ years was sought. The risk factors considered by Truett et al. for the FS provided the best choice for purposes of comparison, despite the longer follow-up (12 years) in the FS. The selected set of variables includes age, serum cholesterol, systolic blood pressure, cigarette smoking, relative body weight, ECG, and hematocrit. Other FS risk equations, which include blood sugar as a risk factor, could not be used for comparison purposes since this characteristic was not measured in the WCGS.

Comparable methods for measuring age, relative body weight, systolic blood pressure, and smoking were employed in the two studies. Reported cigarette smoking was categorized as a four-level variable with values 0, 1, 2, and 3 corresponding to no smoking, less than a pack, exactly a
pack and more than one pack a day, respectively. Relative body weight was calculated using internally derived median weight for height as was done for the FS.

Hemoglobin was not measured in the WCGS but the hematocrit was determined at the second yearly follow-up exam. In order to apply the FS logistic equation to the WCGS data, the logistic coefficient for hemoglobin (dg/100 ml) was scaled for use with hematocrit (%) as the predictor through the relationship, B (hematocrit) = B (hemoglobin) \times (Av. hemoglobin/Av. hematocrit). The data from FS exam No. 4, when both hemoglobin and hematocrit were measured for the same subjects, were used to provide the ratio of the averages needed for scaling. For men aged 39–49, the factor was 3.1477 (dg per 100 ml)/% and for men aged 50–62, the factor was 3.1223 (dg per 100 ml)/%.

Intake serum cholesterol was determined by the Abell-Kendall method in the WCGS and by that of Sperry in the FS. During the first FS follow-up exam, the Abell-Kendall method was used and resulted in only small changes in mean cholesterol levels compared to earlier levels obtained from the same subjects using the Sperry method.

The risk prediction is accomplished in both studies via the multiple logistic model in which CHD risk (R) is represented by the equation,

\[
R = 1/(1 + e^{-(b_0 + b_1X_1 + \cdots + b_kX_k)})
\]

where \(b_0, b_1, \ldots, b_k\) are \(k+1\) logistic coefficients estimated from data consisting of CHD status at a specified time and measured levels for \(k\) risk factors, \(X_1, X_2, \ldots, X_k\), for each subject. Alternatively, the logistic model can be expressed in the linearized form

\[
\ln (R/(1-R)) = b_0 + B_1X_1 + \cdots + B_kX_k
\]

where the quantity \(\ln (R/(1-R))\) is called a logit of \(R\) and is the transformation from which this model derives its name.

The coefficients in the multiple logistic risk model were estimated from WCGS data by the method of maximum likelihood. Discriminant analysis was used to provide initial values, followed by Gauss-Newton iteration. This approach was found to be more efficient computationally than the equivalent Walker-Duncan method of iteration for obtaining the maximum likelihood estimates. The estimated logistic coefficients divided by their estimated standard errors obtained from asymptotic maximum likelihood theory provided test statistics with approximately "standard" normal distributions for assessing the statistical significance of each estimated coefficient. Maximum likelihood estimated logistic risk equations for the chosen set of predictors were obtained for the FS data from the report by Halperin et al.

In the WCGS the diagnosis of manifest or clinical CHD was defined to include three categories. One was a history of classical angina pectoris without apparent myocardial infarction, which was manifested during follow-up by 51 subjects. The second was designated symptomatic myocardial infarction (MI) verified by hospital and physicians' records confirming MI by ECG and diagnostic serum enzyme changes. During follow-up this category was comprised of 135 subjects, including 104 who survived and 31 who died in connection with their initial CHD event. The diagnosis of acute MI in 104 surviving subjects was based upon the occurrence of a symptomatic CHD event accompanied by definitive electrocardiographic and serum enzyme changes. Postmortem examination was performed in 24 of the 31 deceased subjects and demonstrated the presence of acute coronary thrombosis and/or acute MI in 23 instances and severe, diffuse coronary atherosclerosis in one subject who was found dead in bed. No other anatomic or toxicological findings were noted to controvert inclusion of this subject as sudden coronary death. The diagnosis of acute MI was confirmed by antemortem hospital findings in four of the seven deceased subjects who did not undergo autopsy examination. Three other deceased subjects who did not undergo autopsy were included because of sudden death. One subject died suddenly while driving his car and the other two subjects dropped dead suddenly. None of the three had exhibited any other acute or chronic illness that might controvert including them as sudden coronary death. The third category, termed unrecognized MI, occurred during follow-up in 71 subjects whose serial electrocardiograms during annual resurvey were adjudged by the independent electrocardiographer and medical referee to show definite evidence of the occurrence of MI that, however, was either "silent" or clinically unrecognized.

Methods for the assessment of the dichotomous behavior pattern by a structured psychological interview in the WCGS have been described elsewhere. Type A behavior is characterized by enhanced aggressiveness and competitive drive, preoccupation with deadlines, and chronic impatience and sense of time urgency, in contrast with the more relaxed and less hurried Type B behavior pattern. This characteristic was not assessed in the FS.

As in the multiple logistic analysis of the FS data, subjects who were lost to follow-up without occurrence of new CHD were considered as noncases. For the WCGS subjects 92.5% of the total possible person-years of follow-up were completed. Comparable published results for men aged 40–62 years in the FS could not be located, although it would appear that follow-up completeness was similar in the two studies. Corresponding completion rates for Type A and Type B subjects were similar — 91.3% and 93.7% respectively — so longer exposure to CHD risk among Type B subjects could produce, at most, a slight attenuation in the estimated association between behavior pattern and CHD incidence.

In the WCGS population, intake serum cholesterol measurements were missing on 12 subjects. Hematocrit measurements were missing on 579 subjects who were absent from follow-up at the second annual resurvey examination when hematocrit was determined. These subjects were retained in the analysis by using grand means of the respective measurements to fill in for missing values. Although the properties of this method for handling missing values have not been thoroughly studied, this approach has strong intuitive appeal. With this method no appreciable bias would be anticipated in the estimation of logistic coefficients including the one for hematocrit. However, some exaggeration of the statistical significance of the estimated logistic coefficient for hematocrit should occur. This distortion was believed acceptable in order to take advantage of the information available for the other more important risk factors.

Results

Comparable of WCGS and FS Findings

A summary of results obtained when the multiple logistic risk equation is fitted to the WCGS data is shown in table 1
for men grouped by intake ages 39-49 and 50-59, along with corresponding results obtained from the FS.*

In view of the structural constraints introduced into data analysis by assumption of the multiple logistic model, the goodness of fit of the model to the WCGS data must be assessed. In the absence of well-established criteria for assessing statistical significance of departures from this model, we used methods which have become traditional in epidemiological literature. Observed and estimated expected numbers of CHD cases are compared after grouping sub-

Table 1. Multiple Logistic Risk Equations Fitted by Maximum Likelihood Estimation to 12-year Coronary Heart Disease Incidence in Framingham and 8.5-year Incidence in the WCGS

<table>
<thead>
<tr>
<th>WCGS (Men 39-49 yr)</th>
<th>CHD Observed (OBS) and Expected (EXP) Numbers of CHD Cases by Decile of Estimated Risk (Behavior Pattern Excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>FS (Men 40-49 yr)</td>
<td>Log Coeff</td>
</tr>
<tr>
<td>WCGS (Men 39-49 yr)</td>
<td>Log Coeff</td>
</tr>
<tr>
<td>FS (Men 50-62 yr)</td>
<td>Log Coeff</td>
</tr>
</tbody>
</table>

*Including Behavior Pattern as a risk factor.

Abbreviations: FS = Framingham Study; WCGS = Western Collaborative Group Study; Chol = serum cholesterol; R BW = relative body weight; SBP = systolic blood pressure; Hct = hematocrit; Cig = cigarette; Beh Pattern = Behavior pattern; Log coeff = logistic coefficient; SE = standard error; P = significance probability.

Table 2. WCGS Observed (OBS) and Expected (EXP) Numbers of CHD Cases by Decile of Estimated Risk (Behavior Pattern Excluded)

<table>
<thead>
<tr>
<th>Decile of risk</th>
<th>Men 39-49 yr</th>
<th>Men 50-59 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OBS</td>
<td>EXP</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>45.6</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>24.6</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>18.2</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>14.4</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>11.5</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>9.3</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>7.6</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4.7</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Total | 145 | 145.0| 112 | 112.0|

Correlation coefficient (OBS vs EXP) | 0.974 | 0.826|

Regression coefficient (OBS on EXP) | 1.04 | 0.893|

Total at risk | 2249 | 905|

Comparison of risk predictions is accomplished by applying both the FS risk equation and the internally derived WCGS risk equation (excluding behavior pattern) to each member of the WCGS population. These results are summarized in the form of scatter diagrams for men both in the younger (fig. 1) and older (fig. 2) age decades. The good relative agreement between the WCGS and FS estimated

jackets by decile of estimated risk. In addition, coefficients of correlation between observed and expected CHD cases and the regression coefficients of observed on expected CHD cases are provided for subjects in the two age decades. The correlation coefficients and the regression coefficients both should be unity except for sampling variation, under the hypothesis that CHD risk follows the logistic model. The departures of these measures from unity give a general measure of the lack of fit, but without knowing the sampling distributions there is no way to determine what size departure would lead to rejection of the model.

In table 2 the observed and estimated expected numbers of CHD cases in the risk decile groups are compared for subjects in the two age decades in the WCGS population using the WCGS logistic risk equation with only the FS variables included as risk factors. The goodness of fit is assessed in table 3 for the WCGS logistic equation including the behavior pattern as a risk factor. Observed vs. expected results are again compared by age decade for all subjects as well as separately for Types A and B subjects. In general, the agreement between observed and expected events is comparable with that found in the FS analysis.* In the absence of any obvious inadequacy of the model it can be provisionally accepted as a basis for further examination of the implications of these findings.

Comparison of risk predictions is accomplished by applying both the FS risk equation and the internally derived WCGS risk equation (excluding behavior pattern) to each member of the WCGS population. These results are summarized in the form of scatter diagrams for men both in the younger (fig. 1) and older (fig. 2) age decades. The good relative agreement between the WCGS and FS estimated
CHD risk scores is summarized by product moment correlation coefficients of 0.82 and 0.89 for men in the younger and older decades respectively.

Any lack of agreement between the CHD risks estimated from the WCGS and FS equations is a reflection of the accumulated sampling variability associated with all of the estimated coefficients in both logistic risk equations, in addition to any real difference in the underlying CHD risk process in the two populations. For each age decade, the observed differences in the estimated logistic coefficients, along with their standard errors and corresponding single comparison significance probabilities, are summarized in Table 4. None of the observed differences in logistic coefficients are statistically significant at the 0.05 level. Thus there is no solid evidence to indicate in these two populations that any of the risk factors considered have different predictive strengths as assessed via a multiple logistic model.

Another way of assessing the comparability of the WCGS and FS findings is based on absolute risk levels as reflected in total CHD events. When the FS equations in Table 1 are applied to the WCGS subjects, 198.9 and 144.3 new CHD cases are expected in the younger and older age decades, respectively. By comparison, 145 and 112 new CHD cases were observed in these two groups. A number of factors could contribute to the sizable differences in absolute risk levels. An obvious difference between the two studies is the length of follow-up. The FS equation predicts 12 year CHD incidence while the WCGS equation predicts 8.5 year CHD incidence. In the absence of any adjustment, the FS equation would be expected to overestimate the number of new CHD cases.

### Table 3. WCGS Observed and Expected Numbers of CHD Cases by Decile of Estimated Risk (Including Behavior Pattern)

<table>
<thead>
<tr>
<th>Decile of risk</th>
<th>Total subjects</th>
<th>Behavior pattern</th>
<th>Total subjects</th>
<th>Behavior pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OBS</td>
<td>EXP</td>
<td>OBS</td>
<td>EXP</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>47.5</td>
<td>27</td>
<td>28.0</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>25.6</td>
<td>15</td>
<td>15.9</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>18.2</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>14.0</td>
<td>13</td>
<td>9.7</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>11.3</td>
<td>7</td>
<td>7.8</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>9.0</td>
<td>3</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>7.1</td>
<td>7</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5.5</td>
<td>7</td>
<td>4.3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4.1</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2.6</td>
<td>2</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>95</td>
<td>95.0</td>
</tr>
<tr>
<td>Correlation coefficient (OBS vs EXP)</td>
<td>0.978</td>
<td>0.962</td>
<td>0.970</td>
<td>0.826</td>
</tr>
<tr>
<td>Regression coefficient OBS on EXP)</td>
<td>1.01</td>
<td>0.920</td>
<td>1.21</td>
<td>0.893</td>
</tr>
<tr>
<td>Total at risk</td>
<td>2249</td>
<td>1067</td>
<td>1182</td>
<td>905</td>
</tr>
</tbody>
</table>

### Figure 1 Scatter diagram of estimated CHD risks for WCGS subjects using FS and WCGS logistic risk equations (ages 39–49 yr). Solid dots indicate CHD cases and open circles, noncases.

### Figure 2 Scatter diagram of estimated CHD risks for WCGS subjects using FS and WCGS logistic risk equations (ages 50–59 yr). Solid dots indicate CHD cases and open circles, noncases.
events for subjects in the WCGS. Also, chance variation is present both in the process leading to observed new CHD events among WCGS subjects and also in estimating the FS equation used to compute the expected CHD events in the WCGS groups.

Length of follow-up and, to some extent, chance can be examined as possible sources of discrepancy between observed and expected CHD events. The pattern of occurrence of new CHD events in the WCGS shows approximately equal numbers of new events in yearly follow-up intervals. This pattern would be consistent with increasing yearly incidence rates occurring among decreasing numbers still at risk for initial CHD events. The use of this pattern as a provisional basis for adjusting for length of follow-up leads to a linear correction factor (8.5/12), after which the adjusted expected CHD events are 140.9 and 102.2, respectively, which are close to the 145 and 112 new CHD cases observed in the two age decades of the WCGS subjects.

It is necessary to assess whether or not the differences between observed and adjusted, expected CHD cases can be explained by chance. Although both the observed and the expected cases are subject to chance variation, published results from the FS do not provide sufficient detail for assessing the role of chance in determining the number of expected cases. The effect of chance on the number of observed cases can be assessed by considering the CHD outcomes of WCGS subjects as independent but not identical dichotomous trials with probability of CHD for each individual computed by the FS risk equation corrected for length of follow-up. The differences between observed and adjusted, expected cases, divided by standard errors of the differences, gave approximately normally distributed test statistics which were 0.37 ($P = 0.71$) and 1.1 ($P = 0.27$) in the younger and older groups, respectively. Thus, although this is only a partial consideration of the role of chance, after adjustment for length of follow-up, there is no indication of statistically significant differences in the absolute risk levels in the two studies.

**Table 4. Observed Difference in Logistic Coefficients in the WCGS and FS**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men 39-49 yr</th>
<th>Men 50-59 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference of log coeff (WCGS - FS)</td>
<td>SE</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0312</td>
<td>0.0521</td>
</tr>
<tr>
<td>Chol</td>
<td>0.0051</td>
<td>0.0031</td>
</tr>
<tr>
<td>SBP</td>
<td>0.0091</td>
<td>0.0083</td>
</tr>
<tr>
<td>R BW</td>
<td>-0.0144</td>
<td>0.0127</td>
</tr>
<tr>
<td>Hot</td>
<td>0.0379</td>
<td>0.0452</td>
</tr>
<tr>
<td>Cig smoking</td>
<td>-0.1581</td>
<td>0.1248</td>
</tr>
<tr>
<td>ECG</td>
<td>-1.1094</td>
<td>0.5682</td>
</tr>
</tbody>
</table>

Abbreviations: SE = standard error; see table 1 for others.
Behavior Pattern as a Risk Factor

The behavior pattern was then studied as an added risk factor. As shown in table 1, the estimated logistic coefficients for behavior pattern are 0.640 ($P = 0.0006$) and 0.743 ($P = 0.0015$) in the younger and older age decade groups, respectively. These correspond to 1.90 ($e^{0.640}$) and 2.10 ($e^{0.743}$) in terms of approximate relative risk (odds ratio) indicating that CHD risk is approximately 1.90 and 2.10 times higher in Type A than in Type B men in the younger and older decades, respectively. Since these estimates occur in a multivariate context, these values assess the predictive strength residing in the behavior pattern classification after adjustment for all of the other risk factors included in the analysis.

The separation in estimated risk that occurs in connection with behavior pattern is shown in figures 3 and 4. Numerical values on which these graphs are based can be obtained from information in table 3 using the method described in appendix 1. The upper curves in figures 3 and 4 show the pattern of estimated risk for Type A subjects sorted into deciles of risk. Similarly, the lower curve in figures 3 and 4 shows the corresponding results for Type B subjects. The separation between the upper and lower curves constructed in this way reflects not only the direct association between CHD incidence and behavior pattern but also some excess risk in Type A subjects due to their slightly elevated levels of the other risk factors.

In Appendix 1 an adjustment procedure is described which partitions the separation between the upper and lower curves into two parts. The partitioning is accomplished by removing the direct component of risk corresponding to Type A behavior from Type A subjects in each decile group to give the center curve. The spacing between the upper and middle curves in figures 3 and 4 reflects the CHD risk directly associated with Type A behavior. The residual separation between the middle and lower curves reflects the added CHD risk in Type A subjects that comes from their tendency to have somewhat elevated levels of other risk factors compared to Type B subjects. 18

The curves in figures 3 and 4 reveal a feature of multiple logistic risk analysis that may not be well known. When risk (R) is directly assessed, rather than indirectly assessed in terms of its logit transform, ln(R/(1-R)), the logistic model necessarily reveals interaction between risk factors. That is, the change in risk per unit change in one risk factor depends on the levels of the remaining risk factors. For example, the striking synergistic relationship between behavior pattern and the composite of the remaining risk factors is obvious in figures 3 and 4. For men aged 39–49, in the lowest risk decile, the excess CHD risk directly related to Type A behavior is 9.2/1,000 subjects, while in the highest risk decile the corresponding excess risk is 104.2/1,000 for Type A subjects. Similar results are found for men in the older age decade.

Discussion

Epidemiological studies have shown a significant relationship between the incidence of CHD and various prospective characteristics commonly termed risk factors. The prospective study at Framingham (FS) provided the basis for a multivariate risk equation$^3$ for CHD prediction based on intake age, serum cholesterol, systolic blood pressure, relative body weight, hematocrit, cigarette smoking, and ECG findings. It appeared important to test the generalizability of this equation for predicting the occurrence of CHD in another population, the Western Collaborative Group Study (WCGS). 4 As part of this effort, possible differences between these two studies, which could potentially diminish applicability of the FS equation to the WCGS population, were identified.

The definition of CHD, both for exclusion of subjects with CHD at intake and for identification of new CHD cases, could directly influence comparability of results, especially when considering absolute risk. At intake, subjects in the WCGS who manifested "silent" left-sided hemiblocks and complete left bundle branch block were considered CHD cases and were excluded from the subsequent incidence study. By comparison, these electrocardiographic entities were coded only as abnormal ECG at intake in the FS.

A second difference between the two studies occurs because at intake only subjects with "definite" and not those with "possible" LVH were coded abnormal ECG in the WCGS, whereas both of these were coded abnormal ECG in the FS. As might be anticipated from these differences in definition, an abnormal ECG was found to be a substantially weaker predictor of CHD in both age decades in the WCGS compared to the FS findings. However, the differences in the WCGS and FS logistic coefficients for ECG in each age decade failed to reach impressive statistical significance levels (see table 4).

For the other risk factors the differences in predictive strengths in the two studies, as measured by estimated logistic coefficients, are more difficult to interpret. Although some of the observed differences were sizable in a predictive sense, none were statistically significant at the $P = 0.05$ level. For example, for men in the younger age decade, the approximate relative risk per 100 mg/100 ml of serum cholesterol is 2.10 ($e^{0.1}$) in the FS and 3.32 ($e^{0.32}$) in the WCGS. However, the single comparison significance probability for this difference does not reach statistical significance ($P = 0.105$). In general, the observed differences can be reasonably ascribed to the substantial chance variation in the estimated coefficients. This variation is not surprising since the precision of an estimated logistic coefficient is determined by the number of CHD cases that occur rather than the total number of subjects.

Another feature which could spuriously influence comparability of the absolute risk levels from one study to another can be deduced from the formulas used to estimate logistic coefficients. It can be seen from the closed-form results available for the discriminant analysis approach to logistic estimation$^4$ that the coefficients which multiply risk factors depend on differences in average levels of risk factors in the CHD and the non-CHD subjects. Thus any shift in measurement procedure which uniformly influences all members of the study will not influence the estimation of these coefficients. On the other hand, the equation for estimating the intercept in the logistic model can be seen to depend on the sum of the average levels for the risk factor in the CHD and non-CHD subjects. Thus any spurious shift in the average levels of the risk factors from one study to another may significantly influence the constant, $B_0$, in the
logistic model, which to a large extent determines the overall level of risk. In view of the close agreement between the results obtained by discriminant analysis and maximum likelihood estimation, similar conclusions would be expected to apply to maximum likelihood estimates of the logistic coefficients. In the absence of a sample of subjects with dual measurements, it is impossible to determine whether differences in the average levels of risk factors are the results of measurement bias or reflect real differences in the populations.

A common logistic risk equation in both populations should be estimated in an unbiased way for large samples by the maximum likelihood method, even in the presence of real shifts in the average levels of risk factors from one population to another. Only the statistical efficiency of the estimation procedure, as reflected in standard errors, should be affected and only a population clustered around a portion of the risk factor range would lead to seriously diminished statistical efficiency. Thus differences in the age ranges in each decade group in the two studies as shown in table 1 should cause no difficulty when the results from one study are applied to the other.

A discrepancy between findings can be expected from differences in distributions of levels for strong risk factors which are not assessed in the risk equation. This bias in absolute risk levels is exemplified by the discrepancies between logistic results for European and American men, and probably also underlies the black-white differences observed in the Evans County study, since other major sources of potential shift in absolute risk levels would inherently be avoided in comparisons of subgroups of an over-all study in which measurement method, length of follow-up, and definition of CHD would be standardized.

Despite these possible difficulties, the CHD predictions for WCGS subjects, using the multiple logistic equations derived from the WCGS, and the FS findings, after adjustment for length of follow-up, show very good agreement for absolute risk levels. Also, good relative agreement was found between the WCGS and FS risk predictions except for a small proportion of the WCGS population represented by the outlying points in figures 1 and 2. This is a welcome confirmation in view of the widespread dissemination of the Framingham results. Important risk factors which are not included in the risk equations can be assumed to occur in about the same proportions in these two populations and bias in CHD definition and measurement of risk factors appears to be negligible. However, more elaborate situations with counterbalancing effects cannot be logically excluded as an explanation for the remarkable agreement between these two studies.

The results of the various statistical analyses in this report indicate that substantial CHD risk is directly associated with the Type A behavior pattern. Furthermore, such Type A behavior does not appear to diminish as a risk factor in older compared to younger men.

Despite its prevalence and apparent pathogenetic force, the addition of the behavior pattern to the logistic risk equation adds little improvement to effectiveness and efficiency of selection of CHD cases. If, for example, subjects in the 10th risk decile were chosen for intervention using the logistic risk equation without behavior pattern, 45.6 cases would be expected for WCGS men in the younger decade (table 2). Then the screening would be (45.6/145.0) × 100 = 31.4% effective and (45.6/224.9) × 100 = 20.3% efficient. Corresponding results (table 3) using the logistic risk equation including the behavior pattern as a risk factor are (47.5/145 × 100 = 32.8% and (47.5/224.9) × 100 = 21.1%, a small improvement.

It appears that similar results can be expected for any of the traditional risk factors when assessed as a last addition to a list of other risk factors. This observation raises important questions about the number and strength of additional independent risk factors that might be needed to substantially increase the effectiveness and efficiency of selection of subjects for intervention programs. It further suggests that the strength of a particular risk factor may not be as important from the point of view of intervention as the ability to safely and conveniently achieve even a moderate risk reduction in a large number of persons.

Epidemiological studies such as the WCGS and the FS can be used to find statistical associations between various risk factors and CHD incidence. However, such studies cannot establish cause and effect relationships. Reduction of risk factor levels and realization of corresponding reduction in CHD risk can only be demonstrated by primary and secondary intervention studies. Nevertheless, it is of interest to interpret the multivariate findings in the WCGS in order to assess the potential for CHD reduction that might be associated with behavior pattern intervention, assuming cause and effect pathways are both present and fully modifiable.

We can ask, what reduction might occur in the CHD incidence if all of the direct risk associated with Type A behavior were eliminated from the population. The CHD risk among Type B subjects would be unchanged but risk among Type A subjects would be reduced to the level given by the middle curves in figures 3 and 4. For this calculation only Type A behavior and not levels of other risk factors are assumed to be modified. Details of the calculation procedure are shown in Appendix 2. In the younger decade the estimated CHD risk per 1,000 subjects over a period of 8.5 years would be reduced from 64.5 to 46.1, which would give a 28.5% reduction in CHD cases with an estimated standard error of 7.6%. In the older decade the estimated CHD risk per 1,000 subjects in 8.5 years would be reduced from 123.8 to 81.5 which would give a 34.2% reduction with an estimated standard error of 9.9%. For both age groups combined, the estimated percentage reduction in CHD cases in the WCGS population, assuming removal of all of the direct risk associated with Type A behavior, is 31% with an estimated standard error of 6.6%. However, such intervention has not yet been formally achieved and the possible risk reduction that might be associated with successful behavior modification remains theoretical at this juncture.

The findings in the WCGS are consistent with the hypothesis that Type A behavior may also have an additional, indirect risk component that operates through elevation of traditional risk factors. As can be seen by comparison of the middle and bottom curves in figures 3 and 4, a small portion of the excess risk in Type A subjects is explained by their higher levels of other risk factors. If conver-
sion from Type A to Type B behavior can be accomplished and this leads to reduction in levels of traditional risk factors, then some CHD risk reduction may also occur by this mechanism. For example, in a recent study it was found that modification of Type A behavior was associated with a fall of serum cholesterol levels in CHD patients.14

Despite the provisional nature of these intervention projections the findings suggest that behavior intervention studies are fertile ground for further research in CHD prevention.

Appendix 1

If \( r_j \) is the estimated CHD risk for the jth subject in a risk decile group which consists of n Type A subjects, then \( R_A = \Sigma r_j n \) is the expected CHD rate in the group. For example, in the 10th risk decile of Type A men, aged 39–49, there are \( n = 107 (\approx 1067/10) \) subjects at risk. For this group there are 28.0 (\( \Sigma r_j \)) expected CHD events computed using the estimated logistic model for WCGS men, aged 39–49, so the expected CHD rate in this group is

\[
R_A = \Sigma r_j / n = 28.0 / 107 = 261.7 / 1000.
\]

Let \( r_i \) be the risk for the jth Type A subject when the direct risk associated with Type A behavior is removed. Then, using the linearized form of the logistic model, \( r_j \) and \( r_i \) are related by

\[
\ln \left( \frac{r_j}{r_j + r_i} \right) = \ln \left( \frac{r_j}{r_j + r_i} \right) - B
\]

where B is the estimated logistic coefficient for behavior pattern (coded 0 = Type B, 1 = Type A).

Equivalently,

\[
r_i = \frac{1}{1 + \left( \frac{1 - r_j}{r_j} \right) e^B}
\]

Then the adjusted expected CHD rate in the group after removal of the direct Type A risk can be expressed by

\[
R_j = (1/n) \Sigma r_i = (1/n) \Sigma \left[ \frac{1}{1 + \left( \frac{1 - r_j}{r_j} \right) e^B} \right]
\]

For values of the logistic coefficient for behavior pattern, B, estimated from the WCGS data, the function of \( r_j \) over which summation occurs has been studied empirically and found to be nearly linear over the ranges of values of \( r_j \) encountered in each risk decile group. Therefore, for each group, \( R_A \) can also be very closely approximated by

\[
R_j \approx \frac{1}{1 + \left( 1 - (1/n) \Sigma r_j \right) e^B} = \frac{1 + \left[ 1 - R_A \right] e^B}{1 - (1/n) \Sigma r_j} e^B
\]

which provides the adjustment procedure used to obtain the center curves in figures 3 and 4.

Appendix 2

The following definitions are needed to specify the procedure for assessing the reduction of CHD risk that would be expected if the direct risk associated with Type A behavior could be completely eliminated from the population. Let \( N \), \( N_A \) and \( N_B \) be the numbers of total, Type A and Type B subjects, respectively, in a particular age decade group (see table 3). Let \( R_{A,i} \) represent the expected CHD rate for Type B subjects in the ith risk decile and \( R_{A,i+1} \) represent the expected CHD rate for Type A subjects in the ith decile after removal of the direct risk associated with Type A behavior (see appendix 1). Then the adjusted, expected CHD rate (AR) after removal of Type A risk is

\[
AR = \frac{\Sigma [(N_i/10)R_{A,i+1}] + \Sigma [(N_i/10)R_{A,i}]}{N}
\]

By comparison, when \( R_{A,i} \), the CHD rate for Type A subjects in the ith decile is substituted for \( R_{A,i} \) in the above equation, then the unadjusted, expected CHD rate (UR) is obtained. This unadjusted rate need not be computed, however, since it necessarily coincides with the observed CHD rate when the maximum likelihood method is used to fit the logistic model.11

The estimated percentage reduction in CHD rate (or cases) when Type A risk is eliminated is given by \( (UR-AR)/UR \times 100 \). This method for measuring the importance of a dichotomous risk factor combines information on both the prevalence of the risk factor and the strength of the risk factor as measured by its estimated logistic coefficient. This measure does not appear to be highly sensitive to the degree of risk separation accomplished by other risk factors included in the logistic analysis.

References

Multivariate prediction of coronary heart disease in the Western Collaborative Group Study compared to the findings of the Framingham study.
R J Brand, R H Rosenman, R I Sholtz and M Friedman

_Circulation._ 1976;53:348-355
doi: 10.1161/01.CIR.53.2.348

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/53/2/348

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ 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 _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/