SUMMARY The relationships of total cholesterol and the proportion of cholesterol in individual lipoprotein classes to coronary heart disease are complex. To help simplify these relationships, cholesterol values are often combined into one summary estimate to form a single risk factor with a relationship to disease that is more easily described. Although summary estimates result in convenient expressions relating cholesterols to coronary heart disease, there is the potential for sacrificing information by ignoring the joint configuration of cholesterols that make up these estimates. We investigated the extent of this possibility for the ratio of total cholesterol to high-density lipoprotein cholesterol and the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol. The findings suggest that the summary estimates are useful expressions for combining cholesterol information and are strong predictors of coronary heart disease. Clinicians who choose to use a summary estimate for screening purposes should recognize that a single ratio estimate is not always as informative as the joint configuration of the cholesterols that make up the estimate. This possibility is most clearly exhibited for the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol, and it may become more apparent in future studies as the capabilities of exploring lipoprotein cholesterol relationships improve.

TOTAL CHOLESTEROL (T-C) and the amount of cholesterol in individual lipoprotein density classes have been shown to be related to the development of coronary heart disease (CHD).1-4 With the discovery of these relationships, attempts have often been made to reduce the complex explanations of causality among the lipoprotein density classes. These attempts have resulted in the derivation of summary estimates, which combine information contained in more than one cholesterol value.5-10 The summary estimates are not intended to replace the need to jointly consider individual pieces of information concerning lipid profiles. Rather, they are convenient measures of disease risk because they provide a single value that quantifies the potential for developing CHD that can be compared to an easily remembered scale.

Although summary estimates of lipids have been used in studies of the epidemiology of cardiovascular disease, an assessment of how well they predict CHD compared with the joint configuration of individual lipoprotein cholesterol levels has not been provided. Combining cholesterol levels into one summary estimate might eliminate important information available when individual cholesterol values are considered together.

In this report, we analyze data from the Framingham Heart Study and evaluate how well two summary estimates predict total CHD when compared with the information available by jointly considering individual levels of the cholesterol values that make up these estimates. The issue considered in this presentation is not intended to emphasize the importance of individual lipoprotein cholesterols, but to examine the summary estimates and determine whether important information that could help describe CHD risk is lost. The summary estimates examined are the ratio of T-C to
Materials and Methods

The term "lipoprotein cholesterol" is used in this paper to describe cholesterol levels in individual lipoprotein classes. In the original Framingham cohort, concentrations of lipoprotein cholesterol were measured during the eleventh biennial examination of 2291 males and females.\(^\text{11}\) HDL-C levels were measured using a heparin–manganese chloride procedure following the protocol adopted by the Lipid Research Clinics.\(^\text{12}\) LDL-C levels were calculated by subtracting HDL-C from the bottom-fraction cholesterol, measured after reconstitution of the bottom fraction after preparative ultracentrifugation of EDTA plasma at serum density. T-C levels were measured using a manual Abell-Kendall procedure.\(^\text{13}\)

Data from the Framingham cohort are summarized in this presentation with an average follow-up of approximately 6 years. When the participants were initially examined for various lipid characteristics, they were 50–79 years old. Only participants who were free of CHD when lipids were measured are considered in this report.

Logistic regression models\(^\text{14}\) were used to help evaluate the performance of the summary estimates in predicting CHD relative to the information available by considering individual values of cholesterol together. Tests of significance are provided for the additional information supplied by the configuration of specific cholesterol values given the value of a summary estimate. The test is based on the likelihood ratio statistic and has an asymptotic chi-square distribution.\(^\text{15}\) The statistic used measures whether the increase in the likelihood ratio statistic attributed to additional cholesterol information given information on a summary estimate is significant. A significant indication means that the information provided by a single summary estimate is not sufficient in describing the risk to CHD if joint information about specific cholesterol levels is available.

Results

Standardized logistic regression coefficients for the various cholesterol measures in a model used to predict total CHD are given in table 1. Each line in table 1 gives the coefficient for the indicated variable from separate univariate and multivariate models. The results of the multivariate models confirm the findings that occur in other presentations of the Framingham data.\(^\text{3}\) Any differences between results can be attributed to the longer follow-up period used in this paper or to the use of a different set of covariates in the multivariate equations.

The univariate and multivariate coefficients for T-C are significant only for females (\(p < 0.05\)), and indicate a positive association with CHD. The significance of the coefficients for HDL-C and both summary estimates indicate a strong association between these variables and CHD for both sexes (\(p < 0.05\)), even when controlling for several covariates. The signs of the coefficients indicate that HDL-C is inversely related to CHD, whereas the relationship between CHD and either ratio is positive. The association of LDL-C with CHD is also positive for both males and females. In each sex, the univariate coefficients for LDL-C are significant at the 0.10 level. When other risk factors are included in the logistic model, the magnitude of the association remains about the same for females, but increases among males (\(p < 0.05\)).

Table 2 gives the increases in the likelihood ratio statistic attributed to additional information, given information on another cholesterol measure. The covariates used in the multivariate models described in table 1 are also included in another analysis in table 2. In table 2A, given values of T-C, both HDL-C and T-C:HDL-C, significantly improve the prediction of disease when they are considered as separate or joint pieces of additional information. This occurs for both sexes and regardless of whether covariates are included in the logistic model (\(p < 0.05\)).

Given information on HDL-C for males, T-C and T-C:HDL-C do not significantly improve the prediction of CHD when they are considered together. Separately, however, T-C and T-C:HDL-C improve the prediction of disease when covariates are added to the logistic model (\(p < 0.05\)). When the covariates are ignored, only T-C:HDL-C provides additional information in the presence of the information given by HDL-C (\(p < 0.10\)). For females, given information

### Table 1. Standardized Logistic Regression Coefficients for Various Cholesterol Measures

<table>
<thead>
<tr>
<th></th>
<th>Male Univariate</th>
<th>Male Multivariate</th>
<th>Female Univariate</th>
<th>Female Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-C</td>
<td>0.103</td>
<td>0.151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.451*</td>
<td>−0.473*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.183†</td>
<td>0.240*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-C:HDL-C</td>
<td>0.358*</td>
<td>0.400*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C:HDL-C</td>
<td>0.369*</td>
<td>0.411*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other risk factors in the multiple logistic regression model include age, diabetes, systolic blood pressure, Metropolitan relative weight, and left ventricular hypertrophy by ECG.

\(* p < 0.05.\)

\(† p < 0.10.\)

Abbreviations: T-C = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
on HDL-C, both T-C and T-C:HDL-C significantly improve the prediction of CHD when considered separately \((p < 0.05)\) or jointly \((p < 0.10)\) as additional information.

Given values of T-C:HDL-C, the additional predictive information contributed by HDL-C and T-C is not significant for either sex. This is true when HDL-C and T-C are considered jointly or separately, and it occurs in the presence or absence of the covariates in the logistic model.

In table 2B, additional information on HDL-C and the ratio LDL-C:HDL-C contribute significantly to the prediction of CHD given knowledge about values of LDL-C. As with T-C in table 2A, this contribution occurs for both sexes and regardless of whether the covariates are included in the logistic model \((p < 0.05)\).

Given information on HDL-C for males, when LDL-C:HDL-C is considered as a separate piece of information it improves the prediction of CHD significantly \((p < 0.05)\). This is also true when LDL-C is considered separately, although the additional information provided is slightly weaker \((p < 0.10)\). When LDL-C and LDL-C:HDL-C are considered jointly among males as additional information given information about HDL-C, the contribution is not significant when the covariates are ignored, but the information is significant when the covariates are added to the logistic model \((p < 0.05)\).

Given information about HDL-C among females, LDL-C does not provide significant additional information for the prediction of CHD. This also occurs when LDL-C is considered jointly with LDL-C:HDL-C. When LDL-C:HDL-C is considered as a separate piece of additional information, however, there is a slight improvement in prediction regardless of whether covariates are included in the logistic model \((p < 0.10)\).

Given values of LDL-C:HDL-C, the additional information contributed by LDL-C and HDL-C is not significant for females. This occurs whether LDL-C and HDL-C are considered jointly or separately, and it happens in the presence or absence of the covariates in the logistic model. A similar situation also occurs.

<table>
<thead>
<tr>
<th>Additional information</th>
<th>Given information</th>
<th>Male covariates</th>
<th>Female covariates</th>
<th>d.f.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>T-C</td>
<td>17.44*</td>
<td>18.59*</td>
<td>16.77*</td>
</tr>
<tr>
<td>T-C:HDL-C</td>
<td>T-C</td>
<td>16.70*</td>
<td>17.40*</td>
<td>17.96*</td>
</tr>
<tr>
<td>T-C</td>
<td>HDL-C</td>
<td>2.14</td>
<td>3.98*</td>
<td>4.25*</td>
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<tr>
<td>T-C:HDL-C</td>
<td>HDL-C</td>
<td>2.75†</td>
<td>4.31†</td>
<td>5.77*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>(T-C:HDL-C)</td>
<td>2.41</td>
<td>1.94</td>
<td>0.65</td>
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<tr>
<td>T-C</td>
<td>(T-C:HDL-C)</td>
<td>1.06</td>
<td>0.42</td>
<td>0.32</td>
</tr>
<tr>
<td>HDL-C and T-C:HDL-C</td>
<td>T-C</td>
<td>18.08*</td>
<td>19.20*</td>
<td>18.30*</td>
</tr>
<tr>
<td>T-C and T-C:HDL-C</td>
<td>HDL-C</td>
<td>2.78</td>
<td>4.59</td>
<td>5.78†</td>
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<tr>
<td>T-C and HDL-C</td>
<td>(T-C:HDL-C)</td>
<td>2.44</td>
<td>2.22</td>
<td>0.66</td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>LDL-C</td>
<td>16.53*</td>
<td>17.12*</td>
<td>14.51*</td>
</tr>
<tr>
<td>LDL-C:HDL-C</td>
<td>LDL-C</td>
<td>15.23*</td>
<td>15.07*</td>
<td>16.92*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>HDL-C</td>
<td>3.64†</td>
<td>5.96†</td>
<td>1.72</td>
</tr>
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<td>LDL-C:HDL-C</td>
<td>HDL-C</td>
<td>4.31†</td>
<td>6.16†</td>
<td>3.78†</td>
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<tr>
<td>HDL-C</td>
<td>(LDL-C:HDL-C)</td>
<td>3.19†</td>
<td>2.74†</td>
<td>2.03</td>
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<td>LDL-C</td>
<td>(LDL-C:HDL-C)</td>
<td>1.22</td>
<td>0.49</td>
<td>2.38</td>
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<td>HDL-C and LDL-C:HDL-C</td>
<td>LDL-C</td>
<td>17.26*</td>
<td>17.71*</td>
<td>17.16*</td>
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<tr>
<td>LDL-C and LDL-C:HDL-C</td>
<td>HDL-C</td>
<td>4.37</td>
<td>6.55*</td>
<td>4.37</td>
</tr>
<tr>
<td>LDL-C and HDL-C</td>
<td>(LDL-C:HDL-C)</td>
<td>3.25</td>
<td>3.13</td>
<td>2.62</td>
</tr>
</tbody>
</table>

Covariates in the multiple logistic regression model include age, diabetes, systolic blood pressure, Metropolitan relative weight, and left ventricular hypertrophy by ECG. The additional and given information are always included in the logistic models described in this table.

\* \(p < 0.05\)

\† \(p < 0.10\)

Abbreviations: d.f. = degrees of freedom (chi-square). See table 1 for other abbreviations.
among males, except that when HDL-C is considered as a separate piece of additional information given LDL-C:HDL-C, the prediction of CHD is improved ($p < 0.10$), with or without the covariates in the logis- 
cic model.

**Discussion**

Summary estimates of cholesterols that have been 
presented elsewhere have included the ratios of 
HDL-C to LDL-C,$^{5,6}$ T-C to HDL-C$^{1-9}$ and HDL-C to 
the various plasma lipoprotein subfractions.$^{10}$ We 
examined the ratios of T-C to HDL-C and LDL-C to 
HDL-C. The summary estimate involving LDL-C and 
HDL-C is the inverse of an expression previously re-
ported.$^{5,6}$ These ratios are considered here because 
lower the ratio, the greater the risk of developing 
CHD. This property of the two ratios merely adds to 
the convenience of the summary estimates, because 
high values of the ratio are of greatest interest and 
are not necessarily bounded, enabling the ratio to readily 
emphasize extreme combinations of cholesterols. 

The principal issue explored in this paper is how 
well summary estimates of cholesterols predict the de-
velopment of CHD when considered alone or in the 
presence of the joint information on individual levels 
of cholesterols. For example, does T-C:HDL-C predict 
the chance of developing CHD alone, and does the 
additional knowledge of specific values of T-C and 
HDL-C significantly improve this prediction? If the 
latter is true, then the ratio alone is not sufficient in 
describing the risk to CHD, and ignoring the exact 
levels of T-C and HDL-C would be inappropriate. If, 
however, knowledge of T-C and HDL-C does not 
significantly improve the prediction of disease given T-
C:HDL-C, then the summary estimate may be a conve-
nient shorthand for quickly describing disease risk. 

Both ratios have strong associations with CHD for 
each sex. For females, information from both ratios 
used to predict CHD is not significantly improved by 
considering specific levels of cholesterols that make 
up these ratios. This is also true among males for 
T-C:HDL-C. For LDL-C:HDL-C, specific levels of 
HDL-C significantly improves CHD prediction among 
males given the level of LDL-C:HDL-C, even though 
by some this may be considered to be a slight improve-
ment ($p < 0.10$). Nevertheless, this latter finding is 
important because it indicates that a single ratio esti-
mate may not always be as informative as the config-
uration of the cholesterols that make up the estimate. 
This possibility should not be ignored, for it may be 
become manifest in future studies that use improved 
procedures for exploring the heterogeneity of lipoprotein 
particles. Indeed, the information given by the ratio 
estimates is only as good as the measurements of T-C, 
HDL-C, and LDL-C that go into the ratio computation, 
and any quantification of disease risk, be it in relative 
or absolute terms, should be undertaken with specific 
attention to the laboratory procedures used in these 
determinations. While there may be reason to believe 
that some laboratory biases may be canceled out by use 
of the ratio estimates, demonstration of such a phe-
nomenon would require further study.

For some segments of a population, use of a ratio 
estimate may even be meaningless. For example, in-
dividuals with certain lipoprotein abnormalities like 
Tangier disease are characterized by high ratios but not 
an excessive risk to CHD.$^{11}$ Abbott et al.$^{11}$ emphasized 
the importance of considering the relationships among 
lipoprotein cholesterols in a general population. 

Despite these caveats, both ratios are useful expres-
sions for combining cholesterol information. In par-
icular, for males and females, T-C:HDL-C, appears to 
be a useful summary of CHD risk. Both ratios are also 
scaled in such a way as to be easily remembered (table 
3). Quantiles of each ratio are given and suggest that 
T-C:HDL-C exceeding 6 and LDL-C:HDL-C exceeding 
4 indicate a high risk of CHD.

Table 4 describes average levels of both ratios 
among selected groups. Vegetarians,$^{18}$ marathon run-
ers,$^{1}$ and persons who are free of CHD have an average 
T-C:HDL-C lower than 5.2 and an average 
LDL-C:HDL-C lower than 3.4. For patients who fall 
into the Fredrickson classes of hyperlipidemia$^{19}$ and 
are characterized by excessive rates of CHD, the average 
T-C:HDL-C is 6 or greater and the average 
LDL-C:HDL-C is 3.5 or greater. 

As a quick summary of disease risk, the ratios are 
useful. These can be easily computed and the risk of 
disease evaluated without referring to cumbersome 
tables. Patients considered at high risk of developing 
CHD can then be immediately identified, and features 
that would better describe the patient's health more 
fully explored. However, neither ratio by itself may be 
as informative about the risk of developing CHD as the 
information contained in the configuration of the spe-
cific values of cholesterols. Since this is the case, 
clinicians who choose to use a summary estimate for

<table>
<thead>
<tr>
<th>Table 3. Quantiles for T-C:HDL-C and LDL-C:HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantiles</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>5%</td>
</tr>
<tr>
<td>10%</td>
</tr>
<tr>
<td>25%</td>
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<tr>
<td>50%</td>
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<tr>
<td>75%</td>
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<tr>
<td>90%</td>
</tr>
<tr>
<td>95%</td>
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<tr>
<td>Female</td>
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<tr>
<td>5%</td>
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<td>10%</td>
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<td>25%</td>
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<td>50%</td>
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<tr>
<td>75%</td>
</tr>
<tr>
<td>90%</td>
</tr>
<tr>
<td>95%</td>
</tr>
</tbody>
</table>

Abbreviations: See table 1.
### Table 4. Selected Groups According to Increasing Average Levels of T-C:HDL-C and LDL-C:HDL-C

<table>
<thead>
<tr>
<th>Group</th>
<th>T-C:HDL-C</th>
<th>LDL-C:HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetarians</td>
<td>2.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Boston Marathon runners</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Average among females without CHD</td>
<td>4.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Average among males without CHD</td>
<td>5.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Average among females with CHD</td>
<td>5.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Average among males with CHD</td>
<td>5.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Type IIA hyperlipidemia among females</td>
<td>6.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Type IV hyperlipidemia among females</td>
<td>6.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Type IV hyperlipidemia among males</td>
<td>6.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Type IIA hyperlipidemia among males</td>
<td>7.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Type IIB hyperlipidemia among males</td>
<td>7.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Type IIB hyperlipidemia among females</td>
<td>8.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Abbreviations: CHD = coronary heart disease. See table 1 for other abbreviations.

screening purposes should realize that limitations of the estimate may emerge in future studies with the improved precision of laboratory procedures.

**References**
Summary estimates of cholesterol used to predict coronary heart disease.
W P Castelli, R D Abbott and P M McNamara

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