Relation of Family History and Reversible Risk Factors to Coronary Heart Disease Prevalence in an Afrikaner Community

Jacques E. Rossouw, Mary Lou Thompson, Pieter L. Jooste, Anne S.P. Swanepoel, and Peet C.J. Jordaan

In a cross-sectional study of an Afrikaner community (n=2,722 men and n=3,173 women aged 25–64 years), family history of coronary heart disease (CHD) was associated with an adverse risk factor profile and with prevalent CHD. Men with myocardial infarction (MI) and a family history of CHD had higher total minus high density lipoprotein cholesterol (TC-HDLC) levels than men with MI but no CHD family history. In preliminary multiple regression analyses, family history of CHD appeared to exert its effect partly independently of known risk factors and partly dependently through age, TC minus HDLC, and HDLC. Even though their association with MI was weakened after entering family history into the models, the reversible risk factors (particularly TC minus HDLC, HDLC, and uric acid levels) continued to contribute to CHD. For MI in men, there was an interaction between family history of CHD and TC minus HDLC, to the extent that raised TC minus HDLC levels were adverse only in the presence of a positive CHD family history. The findings suggest coinheritance of high blood cholesterol and increased susceptibility to CHD. If confirmed in prospective studies, the interaction between family history and TC minus HDLC will have implications for cholesterol screening and management.

(Family history of heart disease has repeatedly been shown to be predictive of future coronary events and to be associated with prevalent coronary heart disease (CHD). The heritability of CHD has been estimated to be 20–50% for men and 30–60% for women. The mechanisms by which family history influences CHD are not fully known. Most studies have suggested that family history operates largely independently of the standard risk factors (RFs). However, there is substantial evidence that at least part of the higher risk in family members of CHD cases is due to familial aggregation of hyperlipidemia, reduced high density lipoprotein cholesterol (HDLC) levels, hypertension, hyperglycemia, or psychosocial factors. Recently, Simons et al have described an interaction between family history and HDLC. They found that among Israelis, a low HDLC level was a significant predictor of prevalent CHD but only in the presence of a family history of CHD. This suggests a familial predisposition to the adverse effect of low HDLC on the heart. Afrikaans-speaking white South Africans have been shown to have an unusually high (1:71) prevalence of familial hypercholesterolemia. They also have a high prevalence of CHD and of the conventional RFs; thus, they are eminently suitable for examining the relations between family history of CHD, conventional RFs, and CHD prevalence. In this study, we report the simple- and multiple-regression associations of RFs with CHD in an Afrikaner population. In particular, we examined whether family history operates independently or dependently through conventional RFs and whether reversible RFs continue to contribute after family history has been taken into account. Finally, we investigated the extent to which family history interacts with other RFs in its impact on CHD prevalence.

Methods

The study population and methods have been described previously. Briefly, we studied 7,188 white males and females aged 15–64 years who were
living in three rural areas in the southwest Cape of South Africa. The response rate was 82%. Afrikaans was the home language of more than 95% of participants. In the age range of 15–64 years, the CHD mortality rate was 214/100,000 in the study areas. In common with many rural areas, the population contained a disproportionate number of older persons, so that the age structure was almost rectangular. We have previously described the high prevalence of hypercholesterolemia (30% of males and 34% of females had levels >250 mg/dl), hypertension (23% of males and 25% of females had a blood pressure reading ≥160/95 mm Hg or were on treatment), and of smoking (48% of males and 18% of females).12

For the purpose of the present analyses, only men and women in the age range 25–64 years were included because of the low prevalence of CHD at younger ages. Of the 2,722 men, 42.2% had a family history of CHD (in a first-degree relative, at any age), 4.2% had angina pectoris (AP) on Rose questionnaire, for which the participants had been seen by a physician and the diagnosis had been confirmed by a physician, and 7.9% had a history of myocardial infarction (MI) on Rose questionnaire that was confirmed by a physician or had pathological Q waves (Minnesota code 1.1–1.2). Among the 3,173 women, 52.0% had a family history of CHD, 4.0% had AP, and 4.6% had MI.

The choice of RF variables was based on a prior exploration of the estimated odds ratios (ORs) for various definitions of the dichotomous variables and of the estimated ORs across quintiles of various definitions of the continuous variables. Of particular interest to the present analysis, the ORs for MI (by upper quintile relative to basal quintile) of total cholesterol (TC) were 2.83 in men and 1.63 in women, while the ORs of TC minus HDL cholesterol (TC–HDL cholesterol) were 3.30 and 2.29, respectively. Note that the lipids were measured while the individuals were in the nonfasting state, and triglycerides were not measured; hence, low density lipoprotein cholesterol (LDL cholesterol) could not be estimated. For those with a family history of CHD under the age of 50 years, the ORs for MI in men and women were 1.71 and 2.22, respectively; for those with a family history of CHD at any age, they were 1.74 and 2.21, respectively. TC minus HDL cholesterol was selected in preference to TC because it gave slightly higher ORs and because it excluded the opposing effect of HDL cholesterol on MI. Family history of CHD at any age was selected because it gave a more equal distribution of affected versus nonaffected individuals, and the ORs did not differ

<table>
<thead>
<tr>
<th>Variables</th>
<th>All participants</th>
<th>Family history (+)*</th>
<th>Family history (-)</th>
<th>MI (+)</th>
<th>MI (-)</th>
<th>MI (+)</th>
<th>MI (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N or n</td>
<td>1,151</td>
<td>1,571</td>
<td>124</td>
<td>1,027</td>
<td>91</td>
<td>1,480</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47±11</td>
<td>44±12</td>
<td>53±9</td>
<td>46±11</td>
<td>49±11</td>
<td>44±12</td>
<td></td>
</tr>
<tr>
<td>TC–HDLc (mg/dl)</td>
<td>212±54</td>
<td>201±53</td>
<td>238±59</td>
<td>209±53</td>
<td>214±49</td>
<td>200±53</td>
<td></td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>48±12</td>
<td>48±13</td>
<td>45±10</td>
<td>48±12</td>
<td>46±11</td>
<td>48±13</td>
<td></td>
</tr>
<tr>
<td>Smoking (yr)</td>
<td>19±14</td>
<td>17±13</td>
<td>26±14</td>
<td>18±14</td>
<td>22±15</td>
<td>16±13</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>31</td>
<td>26</td>
<td>48</td>
<td>29</td>
<td>36</td>
<td>26</td>
<td></td>
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<tr>
<td>Uric acid (mg/dl)</td>
<td>6.2±1.6</td>
<td>6.1±1.7</td>
<td>6.5±1.9</td>
<td>6.2±1.5</td>
<td>6.7±1.9</td>
<td>6.1±1.7</td>
<td></td>
</tr>
<tr>
<td>Diabetes history (%)</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.9±3.9</td>
<td>26.5±3.8</td>
<td>27.5±4.2</td>
<td>26.8±3.9</td>
<td>27.0±4.3</td>
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<td></td>
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<tr>
<td>Energy expenditure (kcal)</td>
<td>2,566±381</td>
<td>2,609±381</td>
<td>2,410±366</td>
<td>2,585±378</td>
<td>2,510±391</td>
<td>2,615±379</td>
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<tr>
<td>Alcohol (g/day)</td>
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<td>15±22</td>
<td>16±22</td>
<td>16±28</td>
<td>15±17</td>
<td>15±22</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N or n</td>
<td>1,651</td>
<td>1,552</td>
<td>98</td>
<td>1,553</td>
<td>48</td>
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<tr>
<td>Age (yr)</td>
<td>47±11</td>
<td>43±11</td>
<td>52±10</td>
<td>46±11</td>
<td>51±11</td>
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<td></td>
</tr>
<tr>
<td>TC–HDLc (mg/dl)</td>
<td>209±63</td>
<td>191±56</td>
<td>236±68</td>
<td>208±62</td>
<td>222±55</td>
<td>190±56</td>
<td></td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>59±15</td>
<td>60±15</td>
<td>55±14</td>
<td>60±15</td>
<td>56±15</td>
<td>60±15</td>
<td></td>
</tr>
<tr>
<td>Smoking (yr)</td>
<td>5±9</td>
<td>4±9</td>
<td>5±9</td>
<td>5±9</td>
<td>4±9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35</td>
<td>25</td>
<td>52</td>
<td>34</td>
<td>54</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.8±1.5</td>
<td>4.6±1.4</td>
<td>5.5±1.8</td>
<td>4.8±1.4</td>
<td>5.4±1.7</td>
<td>4.6±1.4</td>
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</tr>
<tr>
<td>Diabetes history (%)</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9±5.5</td>
<td>26.0±5.1</td>
<td>29.6±6.4</td>
<td>26.7±5.4</td>
<td>28.2±5.3</td>
<td>25.9±5.1</td>
<td></td>
</tr>
<tr>
<td>Energy expenditure (kcal)</td>
<td>1,744±301</td>
<td>1,753±249</td>
<td>1,702±247</td>
<td>1,747±304</td>
<td>1,652±194</td>
<td>1,756±250</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td>3±7</td>
<td>4±8</td>
<td>1±3</td>
<td>3±7</td>
<td>5±15</td>
<td>4±8</td>
<td></td>
</tr>
</tbody>
</table>

MI, myocardial infarction; TC, total cholesterol; HDLC, high density lipoprotein cholesterol; BMI, body mass index.

*Family history (+), history of coronary heart disease at any age in first-degree relative.
†MI (+), myocardial infarction by Rose questionnaire (confirmed by physician) or pathological Q waves on resting electrocardiogram.
greatly from those of subjects with a family history of CHD under age 50. The following variables were selected for further examination by means of single and multiple logistic regression analyses: age, family history of CHD at any age, TC minus HDLC (TC–HDLC), HDLC, hypertension (blood pressure >160 mm Hg systolic and/or 95 mm Hg diastolic, or on antihypertensive treatment), smoking years (i.e., duration of smoking, past or present), diabetes treatment, serum uric acid level, energy expenditure (work and leisure), body mass index (BMI), type A behavior, and alcohol consumption.

As a first step, the level and prevalence of the selected RFs were tabulated by the presence or absence of a positive family history of CHD and by the presence or absence of MI. Second, to obtain a visual impression of the residual effect of the reversible RFs on MI prevalence after age and also after age, reversible RFs, and family history had been accounted for, ORs were calculated and presented graphically. Logistic regression was used to adjust the OR of each RF for age and then for age, family history, and the other reversible RFs. The continuous RFs were categorized into quintiles except that duration of smoking and alcohol consumption were categorized into nonsmokers (or nondrinkers) and quartiles. The graphs illustrate ORs at the frequency midpoint of five levels of continuous RFs and of two levels of the dichotomous RFs.

Third, logistic regression analyses of AP and MI on the RFs were performed. The goodness of fit of each single continuous RF model was evaluated, and if the associated $p<0.05$, the corresponding variable was collapsed into two to five categories, the choice of the number of categories being guided by the values of the OR for each of the five original categories considered previously.

A stepwise multiple regression of AP and MI on age and the selected reversible RFs was performed, with entry and removal levels set at 0.05. With the fitted model resulting from this analysis, the nonre-

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**Figure 1.** Odds ratios for myocardial infarction by level or presence of TC–HDLC (mg/dl), HDLC (mg/dl), hypertension (status), and duration of smoking (years) after correcting for age in men (△—△) and women (○—○) and for other risk factors in men (△—△) and women (○—○). TC, total cholesterol; HDLC, high density lipoprotein cholesterol.
Rossouw et al Family History and Coronary Disease

Results

Descriptive Data

For the sake of brevity, only the results for MI will be presented in this section; those for AP did not differ in any major respect. A family history of CHD was present in 58% of men with MI (67% of women) and in 41% of men without MI (50% of women). The prevalence of hypertension was high due to the age structure of the study population. The mean TC was 253 ± 53 mg/dl (mean ± SD) in men and 260 ± 59 mg/dl in women. Further subgrouping by presence of MI showed that RF levels and prevalences were higher in cases than noncases, whether there was a family history of CHD or not (Table 1). Strikingly, male MI cases with a family history had a TC minus HDLC value 29 mg/dl higher than noncases; when there was no family history, the difference was only 14 mg/dl.

The graphs of adjusted ORs (Figures 1 and 2) indicate that a number of the categorized reversible RFs appeared to make additional contributions to

versible RF "family history of CHD" was then entered to assess whether it could be regarded as operating separately or dependently through the reversible RFs.

Finally, the extent to which family history interacts with other RFs in its impact on AP and MI prevalence was explored by including the pairwise second-order interactions of the form, family history \( \times (TC-HDLC) \), and so forth, in the variables used in the stepwise logistic model selection. A single higher-order interaction, family history \( \times (TC-HDLC) \times HDLC \), was also considered.

All logistic regressions in this study were performed with the BMDP routine PLR. For the multiple logistic regression analyses, the results are expressed in terms of the \( \beta \) coefficient, the \( Z \) score (\( \beta \) coefficient/SEM), and the associated \( p \) value. Because of the multiple comparisons involved in the analysis, an RF was considered to be significantly associated with a CHD end point if \( p < 0.01 \) and marginally associated if \( p < 0.05 \).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Odds ratios for myocardial infarction by level or presence of diabetes history (status), uric acid (mg/dl), body mass index (Kg/m\(^2\)), and alcohol consumption (g/day) after correcting for age in men (△—△) and women (○—○) and for other risk factors in men (△—△) and women (○—○).}
\end{figure}
MI prevalence, after other RFs, age, and family history had been included. Particularly in women, the ORs were markedly reduced when adjusted for other RFs (except duration of smoking). They illustrate why TC minus HDLC values in women and hypertension in both sexes were not significantly associated with MI in the multiple logistic regression analyses discussed next. The "protective" alcohol intake level appears to be very low (<5 g/day).

**Regression Analyses**

Single regression analyses indicated that age, family history of CHD, TC minus HDLC, HDLC (negative association), hypertension, duration of smoking (men), diabetes (women), uric acid level, energy expenditure (negative association), BMI, and alcohol consumption (negative association) were significantly (p<0.01) associated with AP, MI, or both.

Tables 2 (men) and 3 (women) show the results of stepwise multiple logistic regression analyses of AP and MI on the reversible RFs, first without and then with family history. The entry of family history into the fitted models for AP and MI demonstrated that it made a significant further contribution in both sexes. There were small but consistent decreases in the Z scores for age and TC minus HDLC (and in women, for HDLC as well) when family history was entered. The Z scores for other RFs were little affected, but in women, the partial "taking up" of the contributions of age, TC minus HDLC, and HDLC by family history allowed marginally significant contributions from alcohol, duration of smoking, and energy expenditure to emerge. Certain reversible RFs remained significantly (p<0.01) associated with CHD after entering family history, thus confirming the impressions gained from the OR graphs. For male AP, these were TC minus HDLC, and for male MI, they were uric acid level, TC minus HDLC, HDLC, and duration of smoking. For female AP, significant associations remained for HDLC and total hypertension, and for MI, with uric acid level, diabetes, and BMI.

Exploration of the second-order effects of family history×RFs showed that there was a significant interaction between family history and TC minus HDLC (p=0.009, Table 4) for MI in men, and the predictive power of the model was enhanced by entering the interaction term. The presence of the interaction term means that the coefficient of TC minus HDLC is 0.002 in the absence of family history and 0.009 (i.e., 0.002+0.007) in the presence of family history. The model indicates that TC minus HDLC was a significant RF only in the presence of a positive family history. This was confirmed by separate, multiple logistic regression analyses of MI on TC minus HDLC in the presence and absence of family history (β=0.009, Z=5.12, p<0.001 in the presence of family history; β=0.003, Z=1.21, p=0.128 in the absence of family history). There were no significant interactions of family history with HDLC, and no higher-order interactions of the form, family history×(TC−HDLC)×HDLC.

**Discussion**

The reversible RFs that appeared to contribute most consistently to CHD even after allowing for family history were TC minus HDLC, HDLC, and uric acid level. In women, TC minus HDLC appeared less potent than HDLC, a finding that is concordant with the limited available data from prospective studies. The persistent impact of
TABLE 3. Effect of Family History on Multiple Logistic Regression of Prevalent Angina Pectoris and Myocardial Infarction on Risk Factors in Women Aged 25–64 Years (N=3,173)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Angina pectoris (n=127)</th>
<th>Excluding family history</th>
<th>Including family history*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>Z</td>
<td>p</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.044</td>
<td>4.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>TC–HDLC (mg/dl)</td>
<td>0.005</td>
<td>2.94</td>
<td>0.003</td>
</tr>
<tr>
<td>HDLC (mg/dl)</td>
<td>−0.027</td>
<td>−3.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>0.637</td>
<td>3.10</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>0.484</td>
<td>1.68</td>
<td>0.007</td>
</tr>
<tr>
<td>Alcohol (g/day)^†</td>
<td>0.884</td>
<td>2.96</td>
<td>...</td>
</tr>
<tr>
<td>Smoking (yr)^§</td>
<td>...</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Constant</td>
<td>−5.572</td>
<td>−7.53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Myocardial infarction (n=215)

| Risk factors       | β          | Z          | p       | β          | Z          | p       |
|--------------------|------------------------|--------------------------|---------------------------|
| Age (yr)           | 0.043      | 4.50       | <0.001  | 0.033      | 3.27       | 0.001  |
| Uric acid (mg/dl)  | 0.177      | 3.35       | 0.001   | 0.196      | 3.64       | <0.001  |
| Family history     | ...        | ...        | ...     | 0.444      | 2.36       | 0.017   |
| HDLC (mg/dl)       | −0.015     | −2.27      | 0.023   | ...        | ...        | NS      |
| Diabetes (%)       | 1.855      | 5.25       | <0.001  | 1.866      | 5.21       | <0.001  |
| Energy expenditure (kcal)^† | ... | ... | NS | −0.784 | −2.46 | 0.044 |
| BMI (kg/m^2)       | 0.545      | 2.15       | 0.007   | 0.562      | 2.22       | 0.006   |
| Alcohol (g/day)^‡   | 0.858      | 3.15       | ...     | 0.863      | 3.15       | ...     |
| Smoking (yr)‡       | ...        | ...        | NS      | −0.861     | −2.28      | 0.031   |
| Constant           | −5.686     | −8.89      | <0.001  | −6.145     | −10.91     | <0.001  |

β, multiple logistic coefficient; Z, coefficient/SEM; TC, total cholesterol; HDLC, high density lipoprotein cholesterol; BMI, body mass index.

*Family history of coronary heart disease in a first-degree relative at any age.
†BMI categorized levels 1–2, 3–4, and 5.
‡Alcohol categorized levels 1–2, 3–4, and 5 for angina pectoris model, and levels 1–2, 3, 4, and 5 for myocardial infarction model.
§Duration of smoking categorized levels 1, 2, and 3–5.
‖Energy expenditure categorized levels 1–2, 3–4, and 5.

these and other reversible RFs indicates possible benefit from risk reduction, even in this population which has a high prevalence of positive family history and of familial hypercholesterolemia.

The descriptive data show that the presence of a family history of CHD is associated with a higher prevalence of MI and of reversible RFs. Aggregation of RFs in family members of CHD cases is well recognized and is one of the possible mechanisms through which family history exerts its effect.10

Our observation that levels of TC minus HDLC were disproportionately high in men with the combination of MI and a family history raised the possibility that blood cholesterol was a mediator of the effect of family history on CHD. This possibility was enhanced by the logistic multiple regression analysis, which indicated that the strength of association of age and TC minus HDLC (and HDLC in women) was decreased by the entry of family history into the models. However, the initial models also indicated that family history appeared to have an additional impact on CHD other than being associated with a higher age, higher TC minus HDLC, or lower HDLC. This finding is in agreement with the "independent" effect of family history described in previous studies.1,3,5,7,8

Such an additional or independent effect could be exerted either through an association of family history with an unknown RF with no relation to any of the reversible factors measured in this study or through a greater susceptibility of individuals with a family history to the adverse effects of a known RF.16

The results of the final models suggest that the second mechanism is more likely since there was no evidence for any further adverse effect of family history, once the interaction term family history×
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presumably lower the high risk attached to its inter-
disturbance that are amenable to treatment will
management of those components of lipoprotein
population, where a similar interaction (for family
rigating the existence and mechanism of familial
action with family history. Prospective studies inves-
tire effect through Lp(a). 18
model, indicating that family history exerted its en-
substituted for parental history in the multivariate
control study of British men with MI, Lp(a) could be
may not be limited to populations with a high prev-
ealence of familial hypercholesterolemia; in one case-
control study of British men with MI, Lp(a) could be
ferredent for part of the interaction of
family history and TC minus HDLc. The mechanism
not be limited to populations with a high prev-
ealence of familial hypercholesterolemia; in one case-
control study of British men with MI, Lp(a) could be
substituted for parental history in the multivariate
model, indicating that family history exerted its en-
tire effect through Lp(a).18
The present results differ from those in an Israeli
population, where a similar interaction (for family
history and HDLc) was described.8 It is possible that
in different populations, any interaction of family
history with lipoproteins may differ, depending, for
example, on the nature of the responsible apo
photonpe. Nevertheless, the present findings suggest
that the characterization of family history as a "non-
reversible" RF needs to be reconsidered. Aggressive
management of those components of lipoprotein
disturbance that are amenable to treatment will
presumably lower the high risk attached to its inter-
action with family history. Prospective studies investi-
gating the existence and mechanism of familial
predisposition to the adverse effects of lipoproteins
are needed to confirm and expand our findings. If
confirmed, greater emphasis on family history in
deciding who should be screened and treated for
lipoprotein disturbances will enable resources to be
more effectively targeted.

The present study had certain limitations, and the
results should be regarded as preliminary. The inter-
action could only be demonstrated for MI in men but
neither for MI in women nor for AP in either sex.
The less impressive findings in women may be due to
the much lower risk attached to TC minus HDLc; in
female MI, TC minus HDLc was not a significant
contributor to the multivariate models, so that the
interaction could not be tested. The lipids were
measured in the nonfasting state, and it would have
been preferable to measure LDLc rather than the
surrogate TC minus HDLc. The cross-sectional
study design meant that only CHD survivors were
studied, which may have weakened some of the RF
associations with CHD. Our methods of identifying
CHD prevalence were relatively crude although their
specificity was improved by requiring a physician's
confirmation of chest pain.13 In a Utah population
where family ties are strong, recall of family history
of CHD at any age or at a young age was used as
the definition.6 Afrikaners in a rural community
setting have similarly strong family ties, and we
believe (although we did not perform validation
studies) that the recall of CHD in first-degree rela-
tives is likely to be accurate. In a recent publication
from Framingham, a 35% misclassification of family
history of CHD (mostly underreporting) was found.
In men, family history of CHD after 65 years had an
adjusted OR of 1.4, whereas before 65 years it was
1.3.21 In our study, it is unlikely, in view of the lack of
difference in the ORs of family history at any age
rather than at a young age (<50 years) for MI in
men, that using the latter definition would change
our results. If biases exist in our study, they would be
more likely to be operating in the direction of

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>( \beta )</th>
<th>( Z )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.035</td>
<td>4.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>0.100</td>
<td>2.65</td>
<td>0.007</td>
</tr>
<tr>
<td>Family history</td>
<td>-1.070</td>
<td>-1.72</td>
<td>0.080</td>
</tr>
<tr>
<td>TC-HDLc (mg/dl)</td>
<td>0.002</td>
<td>0.89</td>
<td>0.367</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>-0.021</td>
<td>-3.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking (yr)</td>
<td>0.020</td>
<td>3.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Energy expenditure (kcal)</td>
<td>-0.428</td>
<td>-2.44</td>
<td>0.013</td>
</tr>
<tr>
<td>Family history ( \times ) TC-HDLc</td>
<td>0.007</td>
<td>2.55</td>
<td>0.009</td>
</tr>
<tr>
<td>Constant</td>
<td>-4.699</td>
<td>-6.42</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( \beta \), multiple logistic coefficient; \( Z \), coefficient/SEM; TC, total cholesterol; HDLC, high density lipoprotein cholesterol.

When TC-HDLc as a main effect was allowed to leave the model, the \( Z \) score for family history increased to -3.39 \( (p<0.001) \) and that for family history \( \times \) TC-HDLc increased to 5.08 \( (p<0.001) \).
weakening the associations between RFs and CHD. A possible exception is that recall of family history may have been improved by prevalent CHD.

We conclude that family history of CHD in a population with a high prevalence of familial hypercholesterolemia exerts its influence partly independently of reversible RFs and partly through TC minus HDLC and HDLC. The interaction with TC minus HDLC is complex, but the results indicate that the risk attached to TC minus HDLC (and, by inference, LDLC) is greatly enhanced in the presence of a family history of CHD. Nevertheless, even in this population, management of the reversible RFs offers considerable potential for improvement in CHD outcome.

References

Key Words • coronary disease • lipoproteins • genetics • epidemiology • risk factors • adult • male • female • logistic regression • South Africa
Relation of family history and reversible risk factors to coronary heart disease prevalence in an Afrikaner community.

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