High Absolute Coronary Disease Risk among Turks: Involvement of Risk Factors Additional to Conventional Ones

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Introduction

Turkish adults have been previously assessed in the Turkish Adult Risk Factor Study (TARFS) as demonstrating a high prevalence [1] of coronary heart disease (CHD) and a high rate of mortality from this disease; furthermore, a considerable excess absolute risk was detected based on prospective evaluation of the Framingham risk function in the original cohort [2]. It has been postulated that low-grade chronic inflammation associated with a prevailing metabolic syndrome might play a greater role in the atherothrombotic process in Turkish adults. Mean-
while, it was found that cigarette smoking protected Turkish adults, particularly women, from certain cardio-
metabolic disorders such as metabolic syndrome, type 2 diabetes [3] and hypertension [4]. Conversely and para-
doxically, at least 4 atheroprotective lipoproteins and peptides, namely high-density lipoprotein (HDL), apoli-
ipoprotein (apo)A-I and apoC-III, as well as adiponectin, were epidemiologically found to be dysfunctional in
terms of an absence of protection against diabetes or CHD [5, 6] and/or even proving to be diabetogenic [7, 8].

It is thus timely to prospectively evaluate a largely dif-
ferent cohort of the TARFS to determine whether excess absolute CHD risk based on the Framingham risk func-
tion [9] may be confirmed and to what extent some of the
protein dysfunctions may account for such an excess ab-
solute risk. The Framingham risk score (FRS) has been
used as a yardstick of cardiovascular risk in diverse pop-
ulations. In comparing 2 US cohorts [10], and in an Ita-
lian [11] and British population [12], the FRS was noted to
disclose a similar relative risk for the individual risk fac-
tors, but to overestimate the stated risk in the latter two
studies; in other words, the absolute risk might vary sub-
stantially across populations.

A comparison of this kind might provide benefits with
regard to delineating the absolute risk, as well as display-
ing the role of additional independent risk factors inher-
ent in Turkish adults. Therefore, in the present study we
aimed to compare the 10-year CHD risk assessed using
the FRS with the actual observed incident CHD risk in
participants of the TARFS, with the 1998 survey as base-
line and tracking the patients for up to 10 years.

Methods

Population Sample

The TARFS is a longitudinal population-based cohort study on
the prevalence of cardiac disease and risk factors in adults
in Turkey carried out biennially in 59 communities scattered
throughout all geographical regions of the country [13]. It involves
a random sample of the Turkish adult population, representa-
tively stratified for sex, age, geographical regions and rural/urban dis-
bution [13]. Participants were recruited from randomly selected
communities using a probability proportionate to size method.
Prespecified sex and age requirements had to be met, and recruit-
ment was carried out by door-to-door solicitation. The participa-
tion rate was greater than 82%. Combined measurements of waist
circumference and HDL cholesterol were first made at the follow-
up visit in 1997/1998; the latter examination provided the baseline
data. Participants 28 years of age or older at baseline were exam-
ined over a period of up to 10 years, until the survey of 2007/2008.
When individuals aged <30 or ≥75 years, the 113 cases with prev-
alent CHD and 146 individuals with missing values at baseline
were excluded, 3,440 participants remained. Follow-up was avail-
able in 3,027 participants (88%) free of CHD, who constituted the
cohort of the current study. The survey conformed to the princi-
iples embodied in the Declaration of Helsinki and was approved by
the Istanbul University Ethics Committee. Individuals from the
cohort gave written consent for participation. Data were obtained
from a history of the preceding years via a questionnaire, physical
examination of the cardiovascular system, sampling of blood and
recording of a resting 12-lead electrocardiogram (ECG).

Measurements of Risk Variables

Blood pressure (BP) was measured on the right arm after 10
min of rest using a sphygmomanometer (Erka, Bad Tölz, Ger-
many) with the patient in a sitting position, and the mean of 2
recordings at least 3 min apart was recorded. Plasma concentra-
tions of total and HDL cholesterol and glucose were determined
at baseline examination by the enzymatic dry chemistry method
using a Reflotron apparatus. In the survey of 2002/2003, the stat-
ed parameters were assayed in a single central laboratory. Serum
concentrations of apoA-I and apoB, C-reactive protein (CRP) and
C3c were measured by Behring kits and nephelometry (Behring
Diagnostics, Marburg, Germany). External quality control was
performed with a reference laboratory in a random selection of
5–6% of participants. Plasma fibrinogen was assayed by the mod-
ified Clauss method using a Behring Fibrintimer II coagulometer
and Multifibren U kit. Serum apoC-III was measured in 2001 by
turbidimetric immunoassay (Apo C3-HA, Wako, USA), with the
help of a commercial precipitant reagent [8]. HDL apoC-III was
assayed similarly in the supernatant. Total adiponectin was as-
sayed in 2006 by a sandwich enzyme-linked immunosorbent
assay system (Adiponectin ELISA BioVendor, BioVendor Labo-
ratory Medicine Inc., Modrice, Czech Republic), Serum adipo-
nectin and apoC-III measurements were available only in an un-
selected 38 and 29% of the sample, respectively.

Definitions and Outcomes

Age was taken as a rounded figure assessed from the year at
birth. Self-reported cigarette smoking was categorized as never
smoked, former smokers (ceased smoking 3 months or more pre-
viously) and current smokers (regularly 1 or more cigarettes dai-
ly), as elicited in an interview during examination. Individuals
with type 2 diabetes were diagnosed using the criteria of the
American Diabetes Association [14], namely if plasma fasting
blood glucose was ≥7 mmol/l (2-hour postprandial glucose >11.1
mmol/l) and/or the current use of diabetes medication. In cases
of death, information on the mode of death was obtained from
first-degree relatives and/or health personnel of the local health
office. The cause of death was assigned also taking into consider-
ation preexisting clinical and laboratory findings elicited during
the biennial surveys. Nonfatal CHD was identified by the pres-
ence of angina pectoris, a history of myocardial infarction with
or without accompanying Minnesota codes of the ECG [15] or a
history of myocardial revascularization. Typical angina and, in
women, age ≥45 years were prerequisites for a diagnosis when an-
gina was isolated. ECG changes of the ‘ischemic type’ greater than
minor degree (codes 1.1–2, 4.1–2, 5.1–2, 7.1) were considered myo-
cardial infarct sequelae or myocardial ischemia, respectively.
CHD death comprised death from heart failure of coronary origin
and fatal coronary events.
Descriptive parameters are shown as means ± standard deviation (SD) and percentages. Due to skewed distribution, values derived from log-transformed (geometric) means and standard errors were used for serum triglycerides, CRP, apoC-III and adiponectin. Two-sided t tests with ANOVA were used to analyze the differences between means of multiple groups and Pearson χ² tests for differences between proportions of groups.

FRS points [9] were assigned to each study participant for age, total and HDL cholesterol, BP, status of diabetes and smoking according to the categories. The total FRS and the corresponding 10-year CHD risk of each participant were recorded. This predicted risk was compared with the observed CHD incidence by classifying the participants into quintiles. The sensitivity and specificity of the highest quintile were calculated. We further compared the observed CHD incidence with the CHD data of the new Framingham cardiovascular risk algorithm [16]; in this process, we multiplied the risk estimate corresponding to the identical Framingham quintile points by the sex-specific fraction of CHD events in total CVD events [16] (fig. 1).

To predict CHD from the baseline examination, Cox proportional hazards regression was used to yield risk coefficients for each risk variable. Estimates (and 95% confidence intervals) of the hazard ratio of the independent variables were expressed in terms of 1 SD of that variable. Before selecting the best-fitting model, we analyzed the entire sample with the variable waist circumference and other models in large or smaller subsets with CRP, apoA-I and complement C3. A value of p < 0.05 on the two-sided test was considered statistically significant. Statistical analyses were performed using SPSS 10 for Windows (SPSS Inc., Chicago, Ill., USA, No. 9026510).

Results

At the baseline examination, there were 1,485 men (mean age 47.4 ± 11.4 years) and 1,542 women (47.5 ± 11.5 years) who were free of CHD. Mean follow-up was 7.24 years (total 21,920 person-years). During this period, 219 deaths occurred (9.7 per 1,000 persons/year), of which 88 (4.0/1,000) were due to CHD. CHD developed in 398 subjects (17.2 per 1,000 persons/year).

Baseline characteristics, not directly selected by inclusion in the Framingham risk function and presented in table 1, display with increasing risk quintiles significant progressive increases in age, waist girth, BMI, serum LDL cholesterol, triglycerides, apoB and CRP, as well as total and HDL-apoC-III. Noteworthy is that the protective serum protein concentrations of adiponectin and apoA-I did not decline, but rather increased significantly in women and reached a plateau in quintile 4 among the men; that the significant decline in HDL cholesterol was modest, and that non-HDL and total apoC-III levels in men already reached a plateau in quintile 2. The proportion of smoking females, in contrast to males, declined significantly with increasing risk quintiles. The prevalence of metabolic syndrome and diabetes increased significantly (8- to 47-fold) across the quintiles (not shown in detail).
Table 2 shows the outcomes of participants aged 30–74 years at baseline and the corresponding risk categories derived from the Framingham risk points in 5 categories of decreasing risk. The sensitivity of the highest quintile (making up 22.8% of the study sample) was 51%, while its specificity was 92%. Whereas CHD development would be anticipated in 153 men and 94 women, the time-standardized observed number was 2.2 times higher than that.

Figure 2 illustrates that males in the 3 lower quintiles exhibited risk levels similar to the anticipated (calculated) 10-year CHD risk, but these rose abruptly in the 2 highest quintiles to risk levels more than twice those anticipated. The threshold corresponded to 6 points in the Framingham risk function. Among females, only the lowest 2 quintiles had a CHD risk similar to that anticipated. This threshold corresponded to approximately 1 point. Women in higher-risk categories disclosed a uniformly higher (specifically 2.7-fold higher) CHD risk than anticipated.

Cox Regression Analysis with Conventional and Other Independent Factors

Age, presence of diabetes, total cholesterol and systolic BP were independent predictors of incident CHD in both genders, while current smoking and HDL cholesterol were independent predictors in men alone (table 3, model 1). Use of lipid-lowering drugs was reported by
Table 2. Observed versus anticipated 10-year incident CHD risk in 1998 TARFS participants aged 30–74 years

<table>
<thead>
<tr>
<th>Mean FRS risk points</th>
<th>n</th>
<th>CHD anticipated, n</th>
<th>CHD observed in 7.24 years, n</th>
<th>Incidence of CHD %</th>
<th>Adjusted1 incidence of CHD, %</th>
<th>CHD deaths n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.22</td>
<td>9.5</td>
<td>360</td>
<td>79</td>
<td>115</td>
<td>31.9</td>
<td>44.1</td>
</tr>
<tr>
<td>0.113</td>
<td>6.5</td>
<td>294</td>
<td>33</td>
<td>67</td>
<td>22.8</td>
<td>31.5</td>
</tr>
<tr>
<td>0.075</td>
<td>4.5</td>
<td>316</td>
<td>24</td>
<td>21</td>
<td>6.6</td>
<td>9.1</td>
</tr>
<tr>
<td>0.046</td>
<td>2.6</td>
<td>233</td>
<td>11</td>
<td>13</td>
<td>5.6</td>
<td>7.7</td>
</tr>
<tr>
<td>0.022</td>
<td>-0.4</td>
<td>282</td>
<td>6</td>
<td>21</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>0.099</td>
<td>4.9</td>
<td>1,485</td>
<td>153</td>
<td>218</td>
<td>14.7</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15</td>
<td>13.2</td>
<td>331</td>
<td>50</td>
<td>89</td>
<td>26.9</td>
<td>37.2</td>
</tr>
<tr>
<td>0.076</td>
<td>8.5</td>
<td>324</td>
<td>25</td>
<td>58</td>
<td>17.9</td>
<td>24.7</td>
</tr>
<tr>
<td>0.042</td>
<td>4.2</td>
<td>319</td>
<td>13</td>
<td>25</td>
<td>7.8</td>
<td>10.8</td>
</tr>
<tr>
<td>0.02</td>
<td>-1.4</td>
<td>290</td>
<td>6</td>
<td>8</td>
<td>2.8</td>
<td>3.9</td>
</tr>
<tr>
<td>0</td>
<td>-8.7</td>
<td>278</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.061</td>
<td>3.6</td>
<td>1,542</td>
<td>94</td>
<td>180</td>
<td>11.7</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Anticipated CHD risk was based on FRS [9].

1 Adjusted for a 10-year period.

Fig. 2. Graph plot of the observed versus estimated Framingham CHD risk across quintiles at 10 years in men and women of the TARFS. Excess risk in men was only found in the top 2 quintiles, while the top 3 quintiles in women exhibited a factorial increase in the related estimated risk.
2.5% of participants, and this did not significantly predict incident CHD. In men, waist circumference was also an independent predictor (model 2), but was reduced to borderline significance when diabetes was included; similarly, the significance of HDL cholesterol was reduced when CRP and apoA-I or complement C3 were added in models 3 and 4. Among women, CRP and complement C3 were significant predictors of CHD, independent of diabetes or waist girth. apoA-I and, in any model, HDL cholesterol proved to be not protective. Current smoking was not predictive of CHD.

Selection of the best-fit model using 7 variables is compared in Table 4 with the identical model except for the exclusion of CRP. In these models, smoking status was categorized as having ever or never smoked. Mean follow-up amounted to 7.4 ± 2.4 years, with no significant difference between the sexes. Extrapolating to 10 years, the 10-year probability of remaining free of CHD was 81.1% for males and 84.8% for females.

The mean sex-specific risk equations using the covariate means were formulated as follows:

For males: \[0.056 \times 47.37 + 0.528 \times 0.033 + 0.016 \times 125.8 + (-0.021) \times 37.22 + 0.010 \times 113.87 + 0.378 \times 0.745 + 0.135 \times 1.887 = 5.4077\]

\[p = 1 - 0.8106 \exp(\sum \beta_i X_i - 5.4077)\]

For females: \[0.059 \times 47.46 + 0.882 \times 0.051 + 0.012 \times 131.56 + (-0.005) \times 44.745 + 0.004 \times 118.87 + (-0.168) \times 0.22 + 0.259 \times 2.27 = 4.8075\]

\[p = 1 - 0.848 \exp(\sum \beta_i X_i - 4.8075)\]

Tests showed that each variable (including CRP) contributed significantly to the equation in men, but that HDL and LDL cholesterol and smoking did not contribute significantly in women (in whom, besides age, diabetes and CRP levels were contributing factors). The 2-log likelihood in the models for the inclusion of CRP was 7.06 in men (p < 0.01) and 21.6 in women (p < 0.001); for the inclusion of HDL cholesterol, it was 16.12 in men (p < 0.001) and 0.92 in women (p = 0.33).

Table 3. Cox regression analysis of conventional and other risk factors for incident CHD at baseline

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Age (11 years)</td>
<td>1.82</td>
<td>1.59–2.10</td>
</tr>
<tr>
<td>Presence of diabetes</td>
<td>1.86</td>
<td>1.17–2.94</td>
</tr>
<tr>
<td>Total cholesterol (0.98/1.03 mmol/l)</td>
<td>1.46</td>
<td>1.30–1.70</td>
</tr>
<tr>
<td>Systolic BP (22/25 mm Hg)</td>
<td>1.33</td>
<td>1.17–1.55</td>
</tr>
<tr>
<td>HDL cholesterol (0.30/0.32 mmol/l)</td>
<td>0.77</td>
<td>0.65–0.90</td>
</tr>
<tr>
<td>Waist circumference (11/13 cm)</td>
<td>1.15</td>
<td>0.99–1.33</td>
</tr>
<tr>
<td>Current smoker vs. never smoked</td>
<td>1.74</td>
<td>1.22–2.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>HDL cholesterol (0.30/0.32 mmol/l)</td>
<td>0.77</td>
<td>0.65–0.90</td>
</tr>
<tr>
<td>Waist circumference (11/13 cm)</td>
<td>1.17</td>
<td>1.02–1.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 3</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>CRP (3 mg/dl)</td>
<td>1.10</td>
<td>0.99–1.24</td>
</tr>
<tr>
<td>Presence of diabetes</td>
<td>2.39</td>
<td>1.36–4.23</td>
</tr>
<tr>
<td>apoA-I (33 mg/dl)</td>
<td>1.14</td>
<td>0.91–1.39</td>
</tr>
<tr>
<td>HDL cholesterol (0.30/0.32 mmol/l)</td>
<td>0.81</td>
<td>0.67–1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 4</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Complement C3 (0.27 g/l)</td>
<td>1.15</td>
<td>0.89–2.13</td>
</tr>
<tr>
<td>HDL cholesterol (0.30/0.32 mmol/l)</td>
<td>0.84</td>
<td>0.64–1.10</td>
</tr>
<tr>
<td>Waist circumference (11/13 cm)</td>
<td>1.14</td>
<td>0.90–1.46</td>
</tr>
</tbody>
</table>

Age, total cholesterol, systolic BP and smoking status were used in all models, though specified in model 1 alone. In model 1, of the men, 810 were current smokers and 60 had diabetes, while of the women, 291 were current smokers and 86 had diabetes. Significant values are shown in bold. HR = Hazard ratio; CI = confidence interval.

1 Number of patients with CHD from the total number in each group.
Areas under the receiver operating characteristic curves in the models with and without CRP were 0.796 (p < 0.001) and 0.788 (p < 0.001) in men and 0.810 (p < 0.001) and 0.804 (p < 0.001) in women, respectively.

Comparison of ‘Own’ Data with the Framingham Data using Framingham CHD Risk Points

The observed 10-year CHD incidence classified into quintiles was also compared with the 10-year CHD risk data of the new Framingham cardiovascular risk algorithm [15] (fig. 1). The CHD incidence was twice as high in Turkish males in the top 2 quintiles and 4 times as high in Turkish females compared with the Framingham participants.

Discussion

In a representative sample of over 3,000 middle-aged Turkish men and women, the observed 10-year incident CHD risk was 3-fold that of Framingham study participants [16] in a similar age range. When the study population was divided into sex-specific, quintiles of increasing risk as assessed by the FRS [9], the top 2 risk quintiles (corresponding to ≥6 points) in men exhibited a sharp rise in CHD risk compared to the anticipated risk, and the 3 highest quintiles in women uniformly showed a 2- to 3-fold excess risk compared to that anticipated, implicating the existence of other major independent risk determinants involving nearly half of Turkish men and the majority of Turkish women. Cox regression analyses indicated that, compared with Framingham participants, our women not only had diabetes as a stronger CHD predictor and CRP as a contributing CHD predictor, but also showed lack of protection by HDL cholesterol and no risk conferred by current smoking or LDL cholesterol. Our men showed similarities to Framingham participants with regard to risk determinants, except for waist circumference and CRP contributing to CHD risk.

Liao et al. [10] compared the long-term CHD mortality of the Framingham risk model in 2 US cohorts. The rank order of the individual risk factors was similar in the 2 population samples. Prediction of the cumulative CHD mortality was in agreement with that of the Framingham equation among women, but it overestimated the absolute risk somewhat in men. A similar conclusion was reached in a validation attempt in subjects 55 years or older in the Rotterdam study [17]. In another, larger Dutch cohort, the ability to predict cardiovascular mortality was compared between the FRS and the Systematic Coronary Risk Evaluation system; neither was found sufficient in predicting absolute risks [18].

| Table 4. Cox regression analysis of risk factors for incident CHD used for the risk equation at baseline |
|----------------------------------------------------------|----------------------------------------------------------|
| Men (160/1,055) | Women (142/1,189) |
| **Best-fit model** | **Best-fit model without CRP** |
| **β** | **HR** | **95% CI** | **β** | **HR** | **95% CI** |
| Age (11 years) | 0.056 | **1.86** | 1.57–2.19 | 0.059 | **1.92** | 1.59–2.31 |
| Presence of diabetes | 0.528 | 1.70 | 0.96–2.99 | 0.882 | **2.42** | 1.52–3.83 |
| LDL cholesterol (0.93 mmol/l) | 0.010 | **1.43** | 1.20–1.71 | 0.004 | 1.15 | 0.96–1.33 |
| Systolic BP (22/25 mm Hg) | 0.016 | **1.42** | 1.22–1.65 | 0.012 | **1.35** | 1.16–1.56 |
| HDL cholesterol (0.30/0.32 mmol/l) | -0.021 | **0.79** | 0.67–0.94 | -0.005 | 0.94 | 0.80–1.11 |
| Ever smoked versus never smoked | 0.378 | **1.46** | 0.999–2.13 | -0.173 | 0.84 | 0.50–1.44 |
| Ln CRP | 0.136 | 1.15 | 1.00–1.31 | 0.259 | **1.30** | 1.11–1.51 |

Significant values are shown in bold. HR = Hazard ratio; CI = confidence interval.

1 Number of patients with CHD from the total number in each group.
A recent meta-analysis reviewing 25 validation cohorts of different population groups showed a wide range from under- to overprediction of absolute risk by factors of 0.57 to 2.7 [19]. The investigators found the FRS to be well calibrated to predict coronary events in US, Australian and New Zealand populations but to overestimate absolute risk in European cohorts (odds ratio 0.58).

Evidence for and Determinants of Excess Absolute Risk

As assessed by survival analysis, CHD incidence in the current sample is over twice as high in men and 5 times as high as the CHD incidence in the new Framingham Study [16]. An observation supporting the validity of the present findings is that fatal and nonfatal CHD events in the 3 lowest quintiles in men and in the 2 lowest in women were in agreement with those estimated from the Framingham model. Thus, these findings indicate an excess absolute CHD risk in Turkish adults, concomitant with an elevated Framingham risk. The excess risk in men was independently associated with waist circumference, CRP and an insignificantly with apoA-I; the excess risk appeared to require the attainment of a certain level of conventional risk factors.

Excess risk in women started at perimenopausal ages, was higher than the concomitant risk by a factor of 3–5 and in Cox regression models disclosed a lack of protection by HDL or apoA-I, while the proinflammatory markers CRP and complement C3 were additive independent factors. In the best-fit model, the primary risk factors for CHD in women, barring age, were diabetes, CRP and systolic BP; the lack of protection by HDL cholesterol and LDL cholesterol and the fact that current smoking conferred little or no risk constituted notable dynamics. A similar rank order of diabetes and smoking for CHD risk was noted for Native Americans in the Strong Heart Study, and regarding smoking in Japanese American men in the Honolulu Heart Study [20].

It is reasonable to ascribe the male excess risk in part to abdominal obesity. The close parallelism between estimated Framingham risk by quintiles and waist circumference in each sex may be attributed to a close relationship between waist girth and circulating oxidized LDL [21], especially the susceptible small dense LDL particles. This risk may be assumed to be largely mediated by apoC-III in triglyceride-rich lipoproteins which regulates triglyceride metabolism. Partial lack of atheroprotection by HDL and a concomitant proinflammatory state, evidenced by levels of CRP, complement C3 and apoA-I, each positively associated with CHD risk, although not quite reaching significance, are likely further contributors.

Excess CHD risk among women may be ascribed to the coexistence of a proinflammatory state manifested by significantly predictive CRP and complement C3 levels and the dysfunction of several atheroprotective and/or antioxidative proteins, namely HDL, apoA-I and apoC-III in HDL. Increasing serum concentrations of each of these lipoproteins were previously shown in the TARFS to predict the risk of type 2 diabetes in women [5, 7, 8], and in the current study they were associated with a higher than usual CHD risk (hazard ratio 2.43), which may well have originated from the aforementioned proinflammatory constellation.

Turkish adults are prone to metabolic syndrome [22], far more than Western or East Asian populations, and the CHD risk conferred by it is greater [23] than that obtained in a meta-analysis of these clustered risk factors [24]. It is postulated that in an environment of prevailing metabolic syndrome and concomitant systemic low-grade inflammation or excess oxidative stress, some enzymes of the protective lipoproteins either lose their activity or even induce them to become diabetogenic or atherogenic risk factors. Vascular cell adhesion molecules may mediate or contribute to this process. apoA-I has newly been reported to be combined with LDL during oxidation, which could be a more accurate marker of coronary artery disease in a cross-sectional study than CRP [25]. Hypertriglycerideremia, with concomitant modification of the HDL lipid core and conformational alteration of apoA-I, was recently identified as a driving force in the dysfunction of HDL particles in type 2 diabetes [26].

A recent multislice CT study among 185 Turkish non-diabetic women with low or moderate CHD risk reported that coronary disease was detected in the majority of the women; the study concluded that obese women, especially those with hypertension and dyslipidemia, may be candidates for further stratification [27]. Collectively, these observations further support the concept that there is a major source of CHD risk inherent among Turks in excess of the conventional factors.

We believe that the previously documented severe dysfunction of HDL [6] and of its major apoproteins A-I [7], A-II and C-III [8], as well as of serum adiponectin [5], which are related to enhanced low-grade inflammation associated with but independent of (central) obesity, very likely accounts for the excess risk. The topic of dysfunctional HDL as a diagnostic and therapeutic target was recently reviewed by Smith [28]. High concentrations of HDL in patients with coronary artery disease were shown
in coculture assays to possess less anti-inflammatory activity than in healthy controls, thus documenting that HDL was dysfunctional in these patients [29]. An evaluation of the significance for cardiovascular risk of HDL cholesterol levels, particle size and apoA-I in 2 prospective studies found that very high serum HDL levels as well as the highest categories of HDL particle size were positively associated with cardiovascular risk [30]. High HDL cholesterol did not protect against coronary artery disease when associated with combined cholesterol ester transfer protein and hepatic lipase gene variants in the Regression Growth Evaluation Statin Study [31].

The clinical implications of these findings are huge. The following estimates may be made with regard to the magnitude of the problem. Since conservative estimates of the current annual incidence of CHD in Turkish men and women are 240,000 and 150,000, respectively, an excess of newly developing fatal and nonfatal CHD in 50,000–60,000 women may be considered to arise from risk factors other than conventional ones. Prevention and management strategies should incorporate – in addition to the conventional ones – measures including physical exercise to stem the tide of the epidemic of male abdominal obesity and overall obesity in women with much greater emphasis than is currently employed. Since the balance between obesity and smoking with regard to the impact on health is greatly different among Turks compared to most Westerners, campaigns against smoking need not include Turkish women. Targeting those individuals at high risk with anti-inflammatory agents seems to be indicated. In addition, further biomedical and biochemical research is urgently required in individuals with evidence of dysfunctional serum proteins.

The fact that there was a high prevalence of metabolic syndrome in our population sample may limit the ability to generalize these conclusions to other populations who do not have a background of insulin resistance, though the present findings may well have validity in South Asian Indians [32], Native Americans and Middle Eastern populations, as well as certain subsets of many other populations. Accurate identification of CHD in females is difficult and may have led to some misclassification. However, obtaining congruent observed risk with low-risk FRS quintiles, as well as the elicited magnitude of an excess absolute risk constituting a multiplicative factor in the upper quintiles, may be cited against this possibility. The accumulated number of 398 CHD cases is of sufficient size for statistical power in each sex. The study’s large sample size, and the fact that it was based on a representative sample of a general population of both sexes, in which the range of obesity measures were wide and adjustments were made for markers related to chronic inflammation, form the strengths of the study.

We conclude that Turkish men who exhibit ≥6 Framingham risk points have a CHD risk more than twice that anticipated by the Framingham risk function. Women in the 3 highest quintiles of CHD risk also uniformly showed a risk of CHD 2–3 times in excess of that anticipated. It is postulated that the previously documented severe dysfunction of HDL and of its major apoproteins A-I, A-II and C-III, as well as of serum adiponectin, presumably arising from (central) obesity, very likely accounts for the excess risk. Awareness of this excess risk is critical if the cardiovascular health of Turkish adults is to be improved by appropriate preventive measures and management.

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