

Review article

Risk factors and cardiovascular disease in Turkey

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Abstract

Cardiovascular risk factors as well as morbidity and mortality from coronary heart disease among Turkish adults are herein reviewed. Lipids and lipoproteins are in focus, but other relevant risk factors are also discussed. Turks have distinctively low levels of total and high-density lipoprotein (HDL)-cholesterol, associated with high levels of hepatic lipase and fasting triglycerides. In addition, physical inactivity is common in both genders; close to 60% of men have the smoking habit, while obesity is common among Turkish women leading to a high prevalence of hypertension and diabetes in them. These factors probably account for the unanticipated fact that Turkish adults have the pattern of causes of death similar to a developed population, although the process of industrialization is ongoing, the structure of its population is young and overall cholesterol levels are comparatively low. The age-standardized coronary heart disease death rate is estimated to rank among the highest in Europe. The leading independent predictors of coronary events and death [systolic blood pressure, total/HDL-cholesterol ratio, followed by diabetes and (central) obesity] are related to the metabolic syndrome, estimated to prevail in 3–4% of adults aged 30 or over, and to underlie one-eighth of cases of coronary disease. Since several adverse factors exhibit a rising trend, primary and secondary prevention of cardiovascular disease must assume a much higher priority in various issues in Turkey than it currently does. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Cardiovascular risk factors; Coronary heart disease; HDL-cholesterol; Lipoproteins; Metabolic syndrome; Serum lipids; Turkish adults

1. Introduction

This review describes cardiovascular risk factors as well as morbidity and mortality from coronary heart disease among Turkish adults. In the recently held European Atherosclerosis Society Workshop on Low HDL in Cardiovascular Diseases, it was emphasized that Turkish people had several distinctive features with respect to coronary risk factors compared with other European populations including low levels of total cholesterol and high-density lipoprotein-cholesterol (HDL-C). With the purpose of contributing to the question of whether conventional risk factors operate at the same levels of independent and interactive risks as in other populations [1], it would be of interest to attempt to put into context the state of the various risk

factors and its impact on cardiovascular morbidity and mortality in Turkey. A Balkan state and the biggest country in the Middle East, Turkey has a population of 65 million, composed of a relatively young structure. Rapid urbanization (leading to the residency of 65% of the population in urban areas) and a comparatively advanced stage of industrialization are the main features reflecting the social life. Although this review will focus on lipids and lipoproteins, other pertinent cardiovascular risk factors will also be discussed with the purpose of presenting a more complete assessment.

2. The Turkish Adult Risk Factor study

Apart from the Turkish Heart Study [2], which first disclosed the presence of low levels of HDL-C among Turks, most of the available data on cardiovascular risk factors, morbidity and mortality stem from the Turkish

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Adult Risk Factor Study, conducted under the auspices of the Turkish Society of Cardiology, in which coronary risk factors have been monitored since 1990. The survey on the prevalence of cardiac disease and risk factors in adults in Turkey comprised 3687 men and women 20 years of age or over residing in 59 communities scattered over all seven geographical regions of the country. Surveyed in the summer of 1990 was a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural–urban distribution [3,4]. In 1995, 1998, and 2000, the cohort was surveyed again. In a total follow-up of 28 800 person-years during 10 years, it was elicited that a total of 290 participants had died [5]. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system and recording of a resting electrocardiogram.

2.1. Definitions of coronary heart disease, deaths and new coronary events

Diagnosis of coronary heart disease (CHD) was based on the presence of angina pectoris, of a history of myocardial infarction with or without accompanying Minnesota codes of the electrocardiogram, a history of myocardial revascularization. In a total of 142 subjects, CHD was considered to have newly developed, in addition to those present at the baseline survey. The other studied two end-points were deaths and CHD deaths. The majority of 290 death cases were ascertained by the nurse or physician of the local health unit or by first-degree relatives. Deaths not classifiable as coronary or noncoronary were designated as indefinite. Barring the 36 instances of the latter, 42% of deaths with discernible origin were ascribed to coronary disease. In women, death below the age of 45 was generally considered of noncoronary origin. Coronary heart disease death comprised death from heart failure and fatal coronary event. Nonfatal new coronary events included nonfatal conditions occurring after the initial survey in 1990 and being consistent with predefined criteria [6].

2.1.1. Measurement of risk factors and validation

Blood pressure was measured appropriately, and the mean of two recordings 3 min apart was recorded. Plasma concentrations of cholesterol, HDL-C, fasting triglycerides and glucose were determined by the enzymatic dry method using a Reflotron apparatus. Plasma apolipoprotein A-I and B values were assayed by the turbidimetric method (Turbitimer; Behring), and plasma fibrinogen by Behring turbididensitometry. External quality control was made with a reference laboratory in a random selection of 5–6% of participants [4]. Adjustment of values by less than 3% was needed in most parameters except for the underestimation of HDL-C and triglycerides, and the overestimation of

glucose concentrations by the Reflotron, for which adjustments were in the range of 10%. Biochemical values were in general agreement with those obtained in the Turkish Heart Study [2]. With regard to smoking, current and past smokers and nonsmokers were evaluated. Anthropometric measurements included body mass index, waist circumference and waist-to-hip ratio. Each of the risk factors were stratified for sex and six age groups. For multivariate analysis, logistic and stepwise regression models were used.

3. High cardiovascular morbidity and mortality

Turkey, a developing country, has a high cardiovascular morbidity and mortality, despite relatively low general levels of plasma cholesterol [4]. The designation of the 290 instances of death in adults aged 20 years or older comprised 42% coronary deaths, far exceeding those due to cancer (20%), cerebrovascular accident (11%) and other suspected causes. Such a distribution is like the pattern observed in developed populations for more than half a century and is in sharp contrast to that seen in developing regions of the world [7]; this despite the fact that Turkish adults consist mostly of young people. In the age bracket 45–74 years, deaths considered to be due to CHD during 10 years of follow-up reflected an annual CHD mortality of 800 men and 470 women per 100 000 people [5]. Due to partly inadequate statistical power, these figures may be regarded with slight caution but, nonetheless, make Turks rank highest in Europe in regard to coronary mortality. As illustrated in Fig. 1, Turkish men's CHD

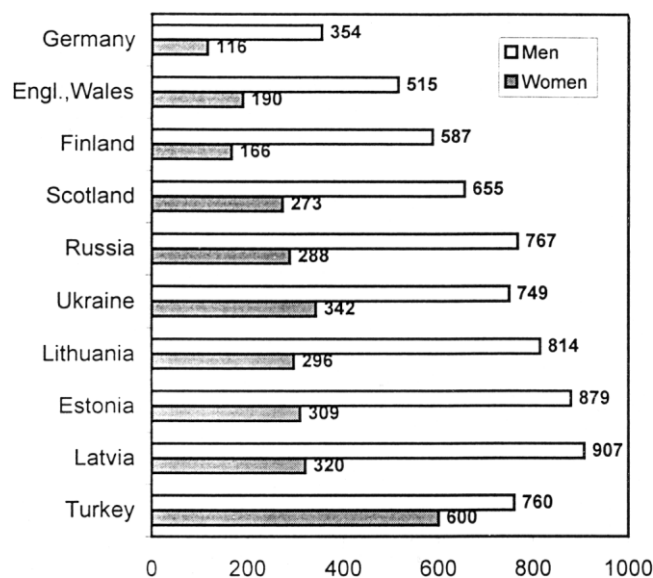


Fig. 1. Mortality from coronary heart disease per 100 000 men and women aged 45–74 years in selected countries of Europe. Compiled from Refs. [5,8].

Table 1
Comparison of lipid profile among Turkish men and women with that in Western populations (mean values, in mmol/l unless otherwise indicated)

	Turks (age 30–69)		Germans [10]		Americans [11–13]	
	Men	Women	Men	Women	Men	Women
Total cholesterol	4.7	4.9	5.9	5.9	5.4	5.4
LDL-cholesterol	2.93	3.13	3.8	3.7	3.4	3.3
HDL-cholesterol	1.01	1.22	1.22	1.55	1.20	1.44
Triglycerides (median)	1.46	1.25	1.53	0.9	1.13	1.13
Total/HDL cholesterol ratio (median)	5.18	4.25	4.6	3.5	4.5	3.8
Apolipoprotein A-I (mg/dl)	121	135	137	148	134	154
Apolipoprotein B (mg/dl)	115	119.5	111	104	103	96
Apoprotein C-III, nonHDL (mg/dl)	10.87	9.83	6.5	6	6	
Lipoprotein(a) (mg/dl) [2]	11.9	13.7				

mortality, similar to that of Scotland or Finland, is only exceeded by men from Russia and the Baltic countries [8], while CHD mortality of Turkish women seems not to be surpassed.

The prevalence of CHD adjusted for age 35–64 years among Turkish adults has been estimated as 5.8% in men and 5% in women [9] and to rise rapidly [5]. Relatively high coronary death and event rates in Turkish women have previously been pointed out [6]. The contrast between low total cholesterol levels and high coronary morbidity and mortality merits further investigation. The distribution of some conventional risk factors, the relative risk for CHD for each of them and the role of the metabolic syndrome are discussed in the following.

4. Lipids and lipoproteins

The lipid profile in Turkish adults is summarized in Table 1 along with mean relevant values for the German [10] and American [11–13] populations for comparison. It is apparent that levels of total, low-density lipoprotein (LDL)- and HDL-cholesterol and of apolipoprotein A-I are substantially low, and those of triglycerides, apolipoprotein B and C-III as well as of the total/HDL-cholesterol ratio are high.

Young Turks appear to enter adulthood with very low cholesterol levels, yet their mean cholesterol concentration rises by 1 mmol/l in the two decades from age group 20–29 to 40–49 years (Fig. 2) — an appreciably steeper rate of rise than in available studies on other populations [4]. Nonetheless, only one-quarter of the adult population sample had hypercholesterolemia > 200 mg/dl. Data published later by Mahley et al. [2] on a larger number of Turkish participants substantiated this cholesterol profile.

Triglyceride levels in Turkish adults (at constant age) have deteriorated in the past decade, and currently exceed by about 0.2 mmol/l those of American and

European adults. Hypertriglyceridemia (> 200 mg/dl) prevailed in one out of each six adults aged 40–59 years.

In the Turkish Heart Study in which HDL-C levels were examined in over 9000 Turkish adults, 53% of men and 26% of women had values ≤ 35 mg/dl [2]. These strikingly low HDL-C levels were confirmed later in the Turkish Adult Risk Factor Study, which disclosed mean values of 37 ± 12 mg/dl in men and 45 ± 13 mg/dl among women [14]. The stated levels were 20% lower than those provided by NHANES III for the US white population [11] and for Germans [10].

In agreement with the Turkish Heart Study, which reported that 37% of men and 28% of women had values ≤ 130 mg/dl [2], our mean LDL-C concentrations were lower than the US adults by 13% in men and by only 4% in women — not enough to compensate the low HDL levels when one recalls that the LDL-C/HDL-C ratio was a powerful predictor of coronary disease in the PROCAM study [10]. The age-related rise in the concentrations of LDL-C was much steeper in females than in males.

The total cholesterol/HDL-C ratio was > 5.5, a range indisputably indicating high risk, in 22% of

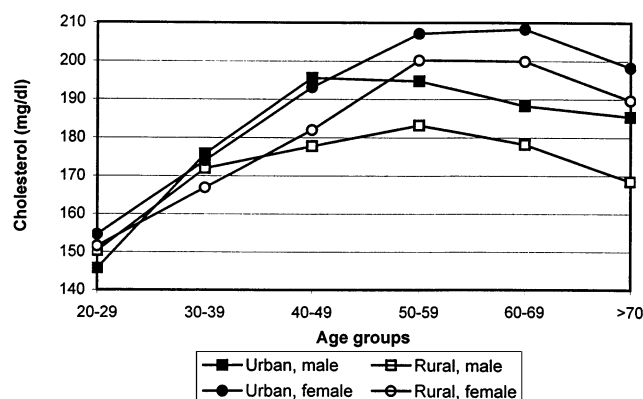


Fig. 2. Mean levels of plasma total cholesterol in Turkish men and women by age groups and urban–rural stratification [4].

women and in 42% of men. Median ratios presented in Table 1 demonstrate considerably higher ratios among Turkish adults, despite the fact that comparatively low LDL-cholesterol levels prevail.

Apolipoproteins A-I (apo A-I) levels (determined in a total of 1390 subjects) implied strikingly low levels of apo A-I in both genders (about 10% generally in Western populations). By contrast, slightly higher levels of apo B (assayed in 70% of the cohort) than generally in Western populations prevailed, with levels higher in women than among men. Expressed in milligrams per decilitre, they remained above the levels of LDL-cholesterol in both sexes throughout the age groups [14]. Apo B values were as highly correlated ($r = 0.63$) in both genders with levels of LDL-C as with apo C-III, suggesting as prominent an existence of apo B48 as of apo B100. Although total concentrations of apo C-III were not remarkable, the presence in excessive concentrations of nonHDL apo C-III and of grossly diminished HDL-linked apo C-III suggested, in Turks, a massive redistribution of apo C-III from HDL to very LDL and chylomicron remnants [15].

4.1. Lipoprotein(a)

In the 800 participants of the Turkish Heart Study, in whom Mahley et al. [2] determined Lipoprotein(a) levels, the range between the 25th and 75th percentiles were 3–19 mg/dl. An inverse association was observed between these values and the triglyceride levels.

4.2. Determinants of lipids

Mean total cholesterol values increased in both genders with diminishing grades of physical activity, and in younger adults with rising body mass index. Individual concentrations revealed a modest correlation with diastolic and, notably, with systolic blood pressure. Triglyceride values were significantly correlated with systolic and, particularly, diastolic blood pressure ($r = 0.24$) and more strongly with waist circumference, body mass index and with waist-to-hip ratio [16].

HDL-C concentrations were inversely correlated significantly in both genders with plasma triglycerides ($r = 0.41$), smoking status, weight and waist circumference ($r = 0.27$). Thus, environmental factors predisposing to low HDL-C levels among Turks are not sparse: diabetes and physical inactivity prevail, a type of nutrition tending to raise plasma triglycerides is commonly consumed and, while menopausal women are generally obese, cigarette smoking is a widespread habit among men. In addition, based on the observation that HDL-C is consistently low among Turks regardless of the environment, Bersot et al. [17] suspect that Turks have a genetic anomaly, perhaps a hepatic lipase gene mutation that in fact leads to an (approximately 25%) ele-

Table 2

Independent predictors of death from CHD at 10-year follow-up among participants free of CHD at baseline in the Turkish Adult RF Study, by gender^a

Variable	Significance	Exp β	95% CI
<i>Men (n = 1016)</i>			
Systolic blood pressure (mmHg)	0.000	1.048	1.027–1.069
Diastolic blood pressure (mmHg)	0.052	0.961	0.924–1.000
Physical activity, grade 4 versus 1	0.029	0.179	0.039–0.835
Smoker versus nonsmoker	0.104	1.516	0.917–2.506
Total cholesterol (mg/dl)	0.205	1.005	0.997–1.012
<i>Women (n = 1028)</i>			
Systolic blood pressure (mmHg)	0.000	1.047	1.024–1.072
Physical activity, grade 1–4; trend	0.002		
Age (years)	0.077	1.039	0.996–1.084
Diastolic blood pressure (mmHg)	0.117	0.967	0.928–1.008
<i>Men and women (n = 2044)</i>			
Systolic blood pressure (mmHg)	0.000	1.048	1.033–1.064
Diastolic blood pressure (mmHg)	0.005	0.961	0.934–0.988
Physical activity, grade 4 versus 1	0.031	0.188	0.041–0.860
Age (years)	0.105	1.018	0.996–1.041
Total cholesterol (mg/dl)	0.106	1.005	0.999–1.010
Body mass index (kg/m ²)	0.139	1.039	0.988–1.093
Smoker versus nonsmoker	0.198	1.324	0.864–2.030

^a Included in the logistic regression model were, in addition, at baseline: in presence of diabetes, family income. Model comprised 80 deaths from CHD (male 45, female 35).

vated hepatic lipase activity, which underlies the very low HDL-cholesterol levels.

4.3. Predictors of coronary mortality

Nine baseline variables (stated in Table 2) were analyzed prospectively by logistic regression for death from coronary heart disease at 10-year follow-up among 2044 adults who were free of CHD at baseline. The model did not comprise HDL- and LDL-cholesterol, not having been determined at baseline, and fasting triglycerides, which were measured in only two-thirds of the cohort. Systolic blood pressure was the only significant independent determinant in men as well as in women. The relative risk of coronary mortality rose steeply (by 60%) with each 10 mmHg rise of systolic pressure. Absence in the model of a few of the aforementioned important parameters may well have augmented the relative risk. In addition, in men and when both genders were combined, decreasing diastolic pres-

sure and physical activity were further significant independent predictors of future death from CHD. The latter two parameters had borderline significance for excess coronary mortality among women, as had smoker or past smoker status in men, contrasted with smokers.

4.4. Relative risk for coronary heart disease

This was examined both in study participants free of coronary disease at baseline, prospectively followed up for 10 years, and (with the purpose of testing some additional parameters such as triglycerides and waist circumference) in the entire cohort of year 2000 cross-sectionally.

Among 1383 participants free of coronary disease at baseline, logistic regression analysis in a model comprising 12 risk parameters (Table 3) revealed presence of diabetes, ratio of total/HDL-cholesterol and smoking status (past smokers versus nonsmokers)

Table 3
Independent predictors of CHD risk at 10-year follow-up among participants free of CHD at baseline in the Turkish Adult RF Study, by gender^a

Variable	Significance	Exp β	95% CI
<i>Men (n = 676)</i>			
Age (years)	0.000	1.061	1.031–1.091
Presence of diabetes	0.027	1.63	1.058–2.510
Total/HDL cholesterol (at 1997–2000)	0.033	1.376	1.027–1.844
Body mass index (kg/m ²)	0.041	1.091	1.004–1.186
Past smokers (versus smokers)	0.051	1.68	0.998–2.810
Systolic blood pressure (mmHg)	0.150	1.017	0.994–1.042
<i>Women (n = 707)</i>			
Age (years)	0.000	1.063	1.033–1.093
Presence of diabetes	0.042	1.607	1.018–2.535
Diastolic blood pressure (mmHg)	0.122	1.030	0.992–1.070
<i>Men and women (n = 1383)</i>			
Age (years)	0.000	1.059	1.039–1.080
Presence of diabetes	0.005	1.548	1.142–2.097
Total/HDL cholesterol (at 1997–2000)	0.018	1.296	1.045–1.608
Past smokers (versus smokers)	0.042	1.60	1.017–2.515
Systolic blood pressure (mmHg)	0.122	1.012	0.997–1.027
Body mass index (kg/m ²)	0.141	1.037	0.988–1.088

^a Included in the logistic regression model were, in addition, at baseline: total cholesterol, HDL-C, smoking status, physical activity grade and family income. Model comprised 108 subjects with CHD (male 56, female 52).

Table 4

Estimates (*B*) of significant parameters of age-adjusted associations with prevalent CHD in the cohort in 2000 (*n* = 2453)^a

	Adults	Men	Women
Systolic blood pressure (mmHg)	1.011	1.014	1.012
Diastolic blood pressure (mmHg)	1.016	1.019	1.016
Waist circumference (cm)	1.018	1.013	1.023
Weight (kg)	1.020	1.016	1.023
Total cholesterol (mg/dl)	1.006	1.005	1.009
HDL-cholesterol (mg/dl)	0.986	NS	0.983
LDL-cholesterol (mg/dl)	1.008	1.008	1.008
Triglycerides (mg/dl) (<i>n</i> = 1494)	1.002	1.002	NS
Blood glucose (mg/dl) (<i>n</i> = 2340)	1.006	NS	1.010
Apolipoprotein B (mg/dl) (<i>n</i> = 937)	1.003	NS	1.005
Past smokers (versus nonsmokers)		1.718	

^a Nonsignificant (NS) in bivariate models were waist-to-hip ratio and physical activity grade.

as independent determinants of coronary disease in year 2000, while body mass index was so in men alone. Systolic pressure among men and diastolic pressure in women were additional independent determinants of borderline significance. Since HDL-C was not measured at baseline, values for total/HDL-cholesterol used in this model stemmed from 1997, wherein also all cases of diabetes ascertained in the period of 1990–2000 were included. Although diabetes displayed a relative risk of about 1.6 in either gender, that of a total/HDL-cholesterol ratio of 7 (instead of 3.5) placed an additional threefold risk in men. A difference of 3 U body mass index at baseline represented a relative risk of 1.3 among men.

Risk factors significantly associated with the likelihood of prevalent CHD in over 2400 participants, after age adjustment in a bivariate logistic analysis, are compiled in Table 4. Data are newly derived from the survey in year 2000, and indicate that ten parameters including systolic blood pressure, blood glucose, body weight and lipids and lipoproteins are significantly associated with CHD. Exponential parameter estimates (*B*) for each increment are provided.

Multiple stepwise forward logistic regression analysis among 1473 adults in the same model, this time comprising 13 risk parameters (Table 5), revealed systolic blood pressure, glucose, LDL- and HDL-cholesterol as independent determinants of coronary disease. However, systolic pressure among men and blood glucose in women were the only significant modifiable independent determinants. At a borderline significance, the four lipid and lipoprotein parameters were independent determinants in men, whereas total- and LDL-cholesterol as well as blood pressure, waist circumference and body weight emerged as independent determinants in women.

Table 5
Independent determinants of the likelihood of prevalent CHD in the cohort in 2000 in the Turkish Adult RF Study, by gender

Variable	Multivariate analysis ^a		
	Significance	Exp β	95% CI
<i>Men (n = 699)</i>			
Age	0.000	1.070	1.046–1.094
Systolic blood pressure	0.030	1.013	1.001–1.025
<i>Women (n = 774)</i>			
Age	0.000	1.077	1.053–1.102
Blood glucose	0.000	1.012	1.006–1.017
<i>Men and women (n = 1473)</i>			
Age	0.000	1.074	1.056–1.092
Systolic blood pressure	0.027	1.008	1.001–1.015
HDL-cholesterol	0.046	0.984	0.968–1.000
LDL-cholesterol	0.031	1.006	1.001–1.012
Blood glucose	0.002	1.007	1.003–1.011

^a Included in the forward stepwise logistic regression model were, in addition: diastolic pressure, total cholesterol, triglycerides, waist circumference, waist-to-hip ratio, weight, smoking, physical activity grade.

4.5. Predictors of and relative risk for coronary death and coronary heart disease

When the composite end-point of coronary mortality and morbidity was analyzed by logistic regression in a model comprising ten risk parameters at baseline of the survey among 1397 adults free of coronary disease (Table 6), systolic blood pressure, ratio of total/HDL-cholesterol and presence of diabetes were the significant independent predictors in adults of both genders combined. Total/HDL-C ratio (and perhaps diabetes) had a more predominant impact among women, while systolic pressure exerted a greater impact in men in whom body mass index also contributed independently, and past smokers had significantly higher excess risk as compared with never smokers.

4.6. Relative risk of further lipid factors

With the knowledge from the Framingham Offspring Study that an apo B value > 120 mg/dl defines a relatively high risk of CHD [18], we attempted to assess the role of apo B, determined only in the population of three regions of Turkey, in a model comprising 14 risk parameters including HDL- and LDL-cholesterol. Plasma fasting triglycerides and apo B were the sole independent age-adjusted determinants in step 1, and triglycerides remained the only significant determinant in step 2 when the association of apo B was resumed by triglycerides. This observation supports the atherogenic role of triglyceride-rich lipoproteins among Turks.

As concerns the relative impact of LDL-cholesterol, it could be computed exponentially from the data pre-

sented in Table 4 that an increment of 50 mg/dl in LDL-cholesterol was associated with a 35% rise of coronary risk. Since the stated increment corresponds roughly to a 43% increase in Turkish adults, each 1% increase in LDL-cholesterol would represent an increase of CHD risk by 0.82% — marginally less than the generally accepted 1:1 relationship in risk increment. The shallowness of the slope of the curve related to LDL-cholesterol coronary risk (mean LDL-cholesterol, 3 mmol/l in adults) might account for the slightly low risk increment elicited. In fact, in the Framingham study, the relative risk for CHD of a 60 mg/dl increment in LDL-cholesterol (from category 160–190 mg/dl to that of 100–129 mg/dl) was reported as 1.7 in multivariate analysis [19].

HDL-C constituted in the 1998 cohort a significant independent marker for CHD risk in Turkish women, but not in men. Fig. 3 illustrates graphically the CHD risk distribution in each quintile of HDL-C concentration. In a multiple logistic regression model that com-

Table 6
Independent predictors at baseline of future coronary death and prevalent CHD in the cohort in year 2000, by gender^a

Variable	Significance	Exp β	95% CI
<i>Men (n = 684)</i>			
Age (years)	0.001	1.044	1.018–1.071
Systolic blood pressure (mmHg)	0.023	1.024	1.003–1.045
Exsmoker versus nonsmoker	0.023	1.759	
Body mass index (kg/m ²)	0.039	1.087	1.004–1.177
Total/HDL-cholesterol (at 1997–2000)	0.071	1.295	0.978–1.714
Presence of diabetes (1990–2000)	0.100	1.428	0.934–2.183
<i>Women (n = 713)</i>			
Age (years)	0.000	1.060	1.031–1.090
Total/HDL-cholesterol (at 1997–2000)	0.050	1.295	1.001–1.676
Presence of diabetes (1990–2000)	0.071	1.521	0.965–2.398
Systolic blood pressure (mmHg)	0.156	1.014	0.995–1.034
<i>Men and women n = 1397</i>			
Age (years)	0.000	1.049	1.030–1.069
Systolic blood pressure (mmHg)	0.003	1.021	1.007–1.035
Total/HDL-cholesterol (at 1997–2000)	0.006	1.296	1.076–1.560
Presence of diabetes	0.020	1.429	1.058–1.930
Past smokers (versus nonsmokers)	0.014	1.703	

^a Included in the logistic regression model were, in addition, at baseline: total cholesterol, HDL-C, diastolic pressure, physical activity grade and family income. Model comprised 122 subjects with composite endpoint (male 64, female 58).

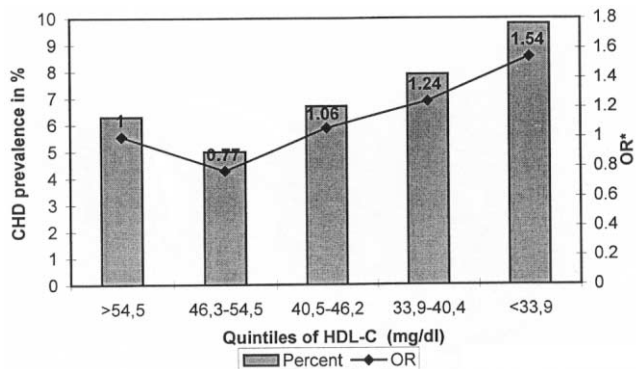


Fig. 3. Prevalence of coronary heart disease and odds ratio in different quintiles of HDL-cholesterol adjusted for age, total cholesterol, blood pressure, anthropometric measures, smoking and physical activity.

prised age, total and HDL-cholesterol, blood pressure, three anthropometric measures, cigarette smoking and grade of physical activity, apart from age, HDL-C was independently associated with CHD risk ($P < 0.04$). When odds ratio (OR) of 1 was assigned to the highest quintile, OR increased gradually to 1.54 in the lowest quintile with HDL-C values ≤ 34 mg/dl [14]. A greater risk gradient was observed in the PROCAM study [14] when the cohort, predominantly men, was categorized into tertiles. The probability over 8 years of the development of a coronary event in the lowest HDL-C tertile was reported as 2.7-fold as compared with the highest tertile.

Aside from systolic pressure, total/HDL-cholesterol ratio appeared to be the most reliable predictor of future coronary events in Turkish adults (in association with low general cholesterol levels), surpassing the role of diabetes and of obesity. The cholesterol ratio was a reliable and, in the presence of high cholesterol levels, the most effective predictor of CHD in the Framingham study [19].

The hypothesis that plasma triglyceride levels may better reflect coronary risk if a selected elevated range is taken into account rather than levels in excess of 200 mg/dl was tested in the Turkish Adult Risk Factor Study [20]. For this purpose, participants were divided into four categories depending on their fasting triglyceride levels. After adjustment for age, HDL-C, LDL-C, smoking and body mass index by logistic regression analysis, and having assigned the CHD risk of 1 to category I, the OR in women rose gradually to 1.78 ($P < 0.025$) in category III (140–212 mg/dl), only to decline in category IV (> 212 mg/dl; Fig. 3). The relative risk for men and women combined rose to a significant 1.42, while it diminished to about 1 in category IV. This observation was interpreted as suggesting that high risk for CHD in subjects with slightly elevated or normal cholesterol levels is better reflected by modest elevations of fasting triglycerides, which serve better

as marker of triglyceride-rich lipoprotein particles. A similar observation was described in the discussion of the report from the Copenhagen Male Study [21]. An increased proportion of small, dense LDL particles is known to be associated with elevated triglyceride and apo B concentrations and reduced HDL-C levels [22,23].

5. Blood pressure, smoking and diabetes

Systolic blood pressure was the most prominent risk factor in CHD mortality in both genders prospectively at 5 years [6] and in a multivariate analysis at 10-years' follow-up. The impact of systolic pressure on CHD mortality was greater in Turkish adults than in the male cohort of the Seven Countries Study, recently examined by van den Hoogen et al. [24], in which the conclusion was reached that not the absolute, but the relative risk of a given increment in blood pressure was similar in different populations. Overall, a 10 mmHg increase in systolic pressure in that study raised the CHD risk by 17% and, after adjusting for intra-individual variability of blood pressure, raised it by 28%. In line with the experience of Benetos et al. [25] on French men was, in Turkish men, the adverse effect of low diastolic blood pressure on coronary mortality, reflecting rising pulse pressure.

Although not among women, systolic blood pressure was an independent determinant of coronary morbidity among men. For every increment of 10 mmHg, CHD risk increased by 14%. During the baseline survey of the Study, hypertension defined as a systolic pressure ≥ 140 mmHg, or diastolic ≥ 85 mmHg, or being treated with antihypertensive medication, was noted to prevail in one-third of the adults. In the age bracket 40–69 years, current prevalence of hypertension reaches one-half of subjects, namely 43% in men and 56% in women [26]. Mean systolic and diastolic blood pressures standardized for age 35–64 years were 125/80 mmHg in men and 133/82 mmHg in women in 1990. In the last survey in 2000, after allowance made for 10 years of ageing, mean blood pressure measurements exhibited a net rise of 7/4 mmHg in women and 5/3 mmHg among men. Blood pressures were significantly associated with indices of obesity and central obesity. Highest correlation coefficients were observed with waist circumference in regard to systolic ($r = 0.37$ or over) as well as diastolic pressure values ($r \approx 0.35$), followed by body mass index ($r \approx 0.31$) [26], and by triglycerides.

Smoking cigarettes is the most widespread risk factor in Turkey. Among adults, 58% of men and 22% of women are currently smokers. The relative risk of smoking at baseline on subsequent coronary mortality, not significant in women, was 1.53 among men ($P <$

0.07; Table 2). This finding is not in disagreement with present knowledge for the American population [27]. In multivariate analysis, smoking proved to be the most significant independent marker of elevated plasma fibrinogen levels among Turks of either gender. Not current smoking, but past smoking independently predicted coronary morbidity or a composite outcome of coronary mortality and morbidity.

Like in many other developing countries [7], the prevalence of diabetes and glucose intolerance is rapidly increasing in Turkey too. It is estimated that the prevalence of diabetes mellitus [28], diagnosed according to the WHO criteria, has doubled within a decade to 2 million in year 2000. Women are affected (8.9% of female aged 30 or over) slightly more than men (8.3%); these rates indicate a higher share of diabetes than the 4% given for adults worldwide in 1995 [7]. Significantly elevated plasma fibrinogen levels were associated with diabetic women. In multivariate analysis, the relative risk for CHD in diabetics was no more than 1.6-fold that of nondiabetics in each sex ($P < 0.05$).

6. Other risk factors for CVD

6.1. Obesity

Obesity is highly prevalent in Turkish postmenopausal women [29]. At present, 14% of men and 30% of women aged 20 or over are estimated to have a body mass index ≥ 30 kg/m², implying that young and middle-aged men have put on considerable weight (approximately an average of 3.5 kg) in the past 8 years. For comparison, it may be recalled that age-adjusted prevalence rates of obesity for US men and women are 19.5 and 25.0%, respectively [30].

Body mass index was a strong independent marker of systolic and diastolic pressures in women, while in men waist-to-hip ratio was equivalent to body mass index in this regard [31]. Among indices of central obesity, waist circumference displayed in both genders, as did body mass index, moderate and significant correlations ($r = 0.2$ – 0.4) with plasma triglycerides, total cholesterol, total cholesterol/HDL-C ratio and, particularly, with systolic and diastolic blood pressure, and inversely with HDL-C [16]. Correlations with waist-to-hip ratio were slightly weaker. In an adult cohort with a mean age of 49 ± 14 , average waist circumference in men and women were 92.4 and 90.8 cm, respectively.

Body mass index (≥ 30 kg/m²) proved to be associated with CHD in women alone, both at the baseline survey (with an odds ratio of 1.76 [32]) and in the survey 1998 being independently associated with CHD ($P < 0.02$), whereby each unit of body mass index added a CHD risk by 11%. It proved to be an independent predictor in men of the composite end-point of

future coronary events and death, conferring 40% excess risk for every 4 U body mass index.

6.2. Physical activity

Physical inactivity, considered a major target in preventive medicine in the US [33], is evidently difficult to evaluate accurately. In a combined assessment of leisure-time and work activity, it was categorized into four grades of increasing activity via a questionnaire in which the participant, assisted by the survey physician, assigned a grade for his/her activity. Such an assessment, rather than providing information on the absolute situation, is of use for the trend in a longitudinal study and for associations with other risk factors and presence of CHD.

Decreasing physical activity exhibited a significant trend as an independent predictor not of coronary morbidity, but of coronary mortality when two genders were combined. In multiple regression analysis that included eight risk factors, physical activity was independently and inversely associated with diastolic pressure and (at a borderline significance) with blood glucose, and positively with waist-to-hip ratio in both genders.

6.3. Pro-inflammatory markers

C-reactive protein (CRP): In a population sample of three regions in western Turkey, C-reactive protein (CRP) was recently determined in 1046 participants. Blood fibrinogen, waist circumference, total cholesterol and grade of physical activity were found independently associated with log CRP concentrations by multivariate analysis. Among many risk variables in a logistic regression analysis, quartiles of CRP and systolic blood pressure were, beside age and gender, the only significant independent determinants of CHD [34]. The age-adjusted OR for CHD in the upper as opposed to the lower quartile exceeded 4 ($P < 0.001$). Even after adjustment for the five determinants of CRP, a twofold discrimination on the CHD likelihood still persisted between the upper and lower quartiles. Thus, the associated increased likelihood was in part via the intermediary effects of some indicators of insulin resistance, but interaction due to inherent inflammation beyond these effects was also suggested.

An established cardiovascular risk factor in Western populations [35], plasma fibrinogen values have been determined by the turbidimetric method in approximately 1600 Turkish adults aged 48 ± 12 years. Overall, the mean fibrinogen value was higher in women (2.88 g/l), in whom it was not age dependent; in men, this value (2.68 g/l) rose independently by 0.21 g/l for each decade on multivariate analysis. When age is taken into account, levels among Turks are similar in women and

slightly higher in men than in compared three populations. Plasma triglycerides and waist circumference were independently and positively associated with fibrinogen levels in women. Our sample size was not adequate to evaluate statistically the association between fibrinogen and CHD.

In a case–control study in Turkey comprising a limited number of individuals in the control group, mean homocysteine levels were found to be 15.6 $\mu\text{l/l}$ [36]. A concentration over 15 $\mu\text{l/l}$ was a significant risk factor for the presence and extent of coronary artery disease. The TT genotype of methylene tetrahydrofolate reductase gene was a predictor of the extent of coronary atherosclerosis and of plasma homocysteine, especially in the presence of low plasma folate values [36].

6.4. Estimated prevalence of metabolic syndrome

An attempt was made to assess the prevalence of the metabolic syndrome and of atherogenic dyslipidaemia in the cohort of Turkish Adult Risk Factor Study, which appear to have a distinct place in regard to underlying CHD among Turks. When criteria are used for atherogenic (metabolic or nonmetabolic) dyslipidaemia as a ratio of total/HDL-cholesterol of > 5 in men and > 4.5 in women, a waist circumference ≥ 94 and 80 cm, respectively, a systolic blood pressure of ≥ 130 mmHg, and glucose intolerance or diabetes as the other three features of the metabolic syndrome, and nonmetabolic dyslipidaemia as a dyslipidaemia unaccompanied by the other full triad, then following prevalences of metabolic syndrome and associated CHD may be estimated among Turks. One out of 30 adults should be designated as having the full metabolic syndrome who have substantially excess coronary risk as compared with the remainders, regardless of gender. The morbidity associated with it constitutes one-eighth of the CHD cases. Nonmetabolic dyslipidaemia (in which LDL-cholesterol levels do not differ significantly from those of the metabolic syndrome) is uncommon among women, yet is encountered in over 50% of men. Forty percent of Turkish men and 60% of women belong to the normolipidaemic subset who may have these or other individual factors for risk. This distribution probably differs considerably from that in Western populations.

7. Conclusion

In the 1990s, it became apparent that incidence of and mortality from coronary heart disease had a greater impact among Turkish adults than would be anticipated from the youthful structure of population, stage of industrialization and low levels of plasma cholesterol. The leading independent predictors of fu-

ture coronary events and death are related to the insulin resistance syndrome, namely systolic blood pressure, total/HDL-cholesterol ratio, followed by diabetes and (central) obesity. Conventional risk factors appear to operate at the same levels of independent and interactive risks as in other populations, although the relative role of LDL, pattern A and pattern B, presumably is weighted towards the latter. A huge effort of preventive medicine is required in Turkey to reverse the tide of coronary disease epidemic.

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