

Algorithm for predicting CHD death risk in Turkish adults: conventional factors contribute only moderately in women

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ABSTRACT

Objective: To assist the management strategy of individuals, we determined an algorithm for predicting the risk of coronary heart disease (CHD) death in Turkish adults with a high prevalence of metabolic syndrome (MetS).

Methods: The risk of CHD death was estimated in 3054 middle-aged adults, followed over 9.08±4.2 years. Cox proportional hazard regression was used to predict risk. Discrimination was assessed using C-statistics.

Results: CHD death was identified in 233 subjects. In multivariable analysis, the serum high-density lipoprotein-cholesterol (HDL-C) level was not predictive in men and the non-HDL-C level was not predictive in women. Age, presence of diabetes, systolic blood pressure ≥160 mm Hg, smoking habit, and low physical activity were predictors in both sexes. The exclusion of coronary disease at baseline did not change the risk estimates materially. Using an algorithm of the 7 stated variables, individuals in the highest category of risk score showed a 19- to 50-fold higher spread in the absolute risk of death from CHD than those in the second lowest category. C-index of the model using age alone was as high as 0.774 in men and 0.836 in women (p<0.001 each), while the incorporation of 6 conventional risk factors contributed to a C-index of 0.058 in males and 0.042 in females.

Conclusion: In a middle-aged population with prevalent MetS, men disclosed anticipated risk parameters (except for high HDL-C levels) as determinants of the risk of CHD death. On the other hand, serum non-HDL-C levels and moderate systolic hypertension were not relevant in women. The moderate contribution of conventional risk factors (beyond age) to the estimation of the risk of CHD death in women is consistent with the operation of autoimmune activation. (*Anatol J Cardiol* 2017; 17: 436-44)

Keywords: C-reactive protein, diabetes type 2, lipoproteins, metabolic syndrome, risk of CHD death, sex difference

Introduction

Evidence has been accumulated in the Turkish Adult Risk Factor study (TARF) that biologic rules governing coronary heart disease (CHD) and death exhibit deviations from conventionally recognized ones. This is particularly with reference to females in whom an algorithm to detect CHD revealed that high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) levels and smoking status are barely predictive of the new development of CHD (1). Factors closely linked to chronic subclinical inflammation, such as the presence of diabetes and systolic blood pressure (SBP), along with the inflammatory biomarker C-reactive protein (CRP), are significant predictors in both sexes. Such features are even more conspicuous in the recently derived algorithm to predict all-cause mortality in this adult population (yet unpublished).

Apart from the nonmodifiable factors such as sex and age, smoking status, presence of diabetes, physical activity, socioeconomic status, adiposity measures, SBP, and HDL-C and LDL-C levels are generally the risk factors related to CHD or cardiovascular mortality (2). A previous Dutch cohort (3) pointed out that age, smoking status, diabetes, and high blood pressure (BP) are independent determinants of cardiovascular and all-cause mortality in middle-aged subjects.

The validity of an algorithm is important as therapy, especially the administration of statins, is based on the finding related to circulating LDL-C levels and on an estimated cardiovascular risk that exceeds 5% or 7.5%, as recommended by the 2013 American College of Cardiology/American Heart Association practice guidelines (4).

The SCORE project, derived in 2003 from 12 European cohort studies, estimated the 10-year risk of fatal CHD and noncoro-

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nary cardiovascular disease in combination (5). Sex, age, smoking status, SBP, and total cholesterol (or total/HDL-C ratio) were used in the models. Separate estimate equations were calculated for high-risk and low-risk regions of Europe and displayed in risk charts. The model is intended to guide decisions with respect to interventions for patients without previous CVD events. The performance of the risk function, as judged by C-statistics, was not very high in persons aged 45 to 64 years, except in Germany. Much later, the risk chart SCORE Turkey was developed using the same risk factors, the basis of data for which has not been shared publicly.

Pro-inflammatory state, recognized by the Adult Treatment Panel-III as a component of metabolic syndrome (MetS) (6), is highly prevalent among in Turkish population (7). In addition, we have documented that autoimmune activation associated with enhanced subclinical inflammation is a major mechanism underlying diverse chronic diseases in this population (8).

The TARF study, having accumulated sufficient data on CHD deaths in the past 17 years, has been deemed suitable for developing an algorithm for predicting CHD mortality. Investigation of the factors determining CHD death in individuals aged 45 to 84 years is of particular relevance because the presence of diabetes is of paramount importance and because total cholesterol (or non-HDL-C) levels, HDL-C levels, and smoking habit for the risk of CHD has been shown to deviate (1, 9), particularly in women, from risk functions derived in Western populations. A secondary aim of this study was to compare the performance of the current risk score with that of SCORE Turkey, although the endpoints do not fully overlap.

Methods

Population sample

The TARF study is a longitudinal population-based cohort study on the prevalence of cardiac disease and risk factors in adults in Turkey. It is performed biennially in 59 communities scattered throughout geographical regions of the country (10). It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions, and rural–urban distribution (10). Participants were recruited from randomly selected communities using a probability proportionate to size method. Combined measurements of waist circumference and HDL-C levels were first made at the follow-up visit in 1997/1998; the latter examination formed the baseline. New random recruitments forming 15% and 10% of the study sample were performed in 2002/2003 and 2007/2008, respectively. Participants were examined over a period of up to 17 years, till the survey in 2014/2015.

Inclusion criteria for the present study were age of 35 to 84 years, no missing relevant values at baseline, and partial or complete follow-up. In total, 3054 participants were included in the cohort of the present study. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved

by the Istanbul University Ethics Committee. All individuals in the cohort gave written consent for participation. Data were obtained by past history 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

BP was measured using a sphygmomanometer (Erka, Bad Tölz, Germany) after 10 min of rest in the sitting position, and the mean of 2 recordings at least 3 min apart was recorded. Plasma levels of total cholesterol and HDL-C, fasting triglycerides, and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus. From the survey in 2001, the stated parameters were assayed in a single central laboratory. Serum CRP levels were measured by Behring nephelometry (Behring Diagnostics, Marburg, Germany). External quality control was performed via a reference laboratory with a random selection of 5%–6% of participants.

Definitions and outcomes

Age was considered as a rounded figure assessed from year at birth. Individuals with self-reported cigarette smoking were categorized into nonsmokers [never smokers and former smokers (discontinuance for 3 months or more)] and current smokers (regularly smoking 1 or more cigarettes daily), as elicited in the interview during examination. Individuals with type 2 diabetes were diagnosed with the criteria of the American Diabetes Association (11), namely plasma fasting glucose level ≥ 7 mmol/L (or 2-h postprandial glucose level >11.1 mmol/L) and/or the current use of diabetes medication. Non-HDL-C was denoted as HDL-C subtracted from total cholesterol. Physical activity was graded by the participant into 4 categories of increasing order with the aid of a scheme (12), and low physical activity was herein classified into grades 1 and 2.

Information on the mode of death was obtained from first-degree relatives and/or the local health office. The cause of death was also assigned considering pre-existing clinical and laboratory findings elicited during biennial surveys. Non-fatal CHD was identified by the presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of ECG (13), or a history of myocardial revascularization. Typical angina and, in women, age > 45 years were prerequisite for diagnosis when angina was isolated. ECG changes of “ischemic type” of greater than minor degree (Codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia. CHD death included death from heart failure of coronary origin and fatal coronary event.

Data analysis

Descriptive parameters were shown as mean \pm standard deviation (SD) and in percentages. Pearson chi-square tests were

used to analyze the differences between proportions of groups. The significance between 2 groups was tested using Mann–Whitney U test for values with skewed distribution [serum triglycerides, Lp(a), and CRP].

In predicting the mortality risk from baseline examination, Cox proportional hazards regression was used to yield risk coefficients for each risk variable. Estimates [and 95% confidence intervals (CIs)] for hazard ratio (HR) of the independent categorized variables were expressed using a referent category. Before selecting the best fit model, we analyzed the complete sample including the variables waist circumference, CRP, physical activity grade, and antihypertensive drug usage. Scores were derived from multiple Cox regression models including all the listed factors. The regression coefficient β was used for each variable from the final model as weight for assigning risk points for which the risk magnitude and shape were examined across categories of the related variable. A coefficient of 0.296 or higher was assigned 1 point, a coefficient of 0.4 to 0.88 was assigned 2 points, and higher exponents were calculated using log-normal numbers. Score points were displayed for 7 risk

factors in the final algorithm model. A value of $p < 0.05$ on the 2-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, Ill).

Results

At the baseline examination, 3054 participants (1582 of whom were women) having a median [IQR] age of 49.5 [41.5; 60] years were available. The mean follow-up period was 9.08 ± 4.22 years, being similar ($p = 0.71$) in men and women (total 27,730 person-years). CHD death occurred in 233 subjects (8.1 per 1000 person-years). The mean age during CHD death was 70 ± 12.4 years in males and 71.9 ± 10.7 years in females ($p = 0.051$).

Baseline characteristics of the sample population are shown in Table 1, stratified to sex and survival. Of the listed parameters, as expected, most were significantly different across the survival groups in each sex. Serum levels of apoB and total cholesterol were higher in women who subsequently died, who were also fewer current smokers at baseline.

Table 1. Baseline characteristics (mean \pm SD; n, %) of 3054 men and women, stratified to survivorship

	n	Men, n=1472		Women, n=1582	
		Survivors, n=1333	Deaths, n=139	Survivors, n=1488	Deaths, n=94
Age, years	3054	49.3 \pm 10.7	62.3\pm12	50 \pm 11	66.4\pm9.2
Waist circumference, cm	3054	94.3 \pm 10.8	95.3 \pm 10.8	90 \pm 12.4	97.3\pm13
Height, cm	3041	169.8 \pm 6.5	167.2\pm6.0	156.5 \pm 6.5	153.0\pm5.2
Systolic BP, mm Hg	3054	124.2 \pm 20.8	143.4\pm29.4	132.4 \pm 26	160\pm32.5
Diastolic BP, mm Hg	3053	79.6 \pm 12	83.9\pm15.4	82 \pm 13.7	92\pm18.4
Phys activity grade I-IV [†]	3021	2.60 \pm .95	2.12\pm1.01	2.18 \pm .68	1.56\pm0.64
Income bracket, I-IV*	2891	2.61 \pm 1.18	1.99\pm1.10	2.32 \pm 1.22	1.75\pm1.09
Fast. glucose, mg/dL	2705	99.2 \pm 37	117.5\pm58	99 \pm 34	118\pm52
Total cholesterol, mg/dL	3054	184.5 \pm 39	192 \pm 42	192.6 \pm 40	207\pm43.6
LDL-cholesterol, mg/dL	2065	110 \pm 33.5	120\pm33	116 \pm 36	125.4\pm36
HDL-cholesterol, mg/dL	3054	37.7 \pm 10.8	<i>38.6\pm11.1</i>	45.4 \pm 11.8	43.8 \pm 13.5
NonHDL-cholester., mg/dL	3054	146.8 \pm 39	<i>153.6\pm41.7</i>	147.2 \pm 39.9	163.0\pm43.8
F. triglyceride, med (IQR), mg/dL	2189	143.3 (96; 207)	147 (107; 217)	121 (54; 171)	157 (105; 243)
Apolipoprotein A-I, g/L	2627	1.327 \pm .24	1.292 \pm .24	1.464 \pm .27	1.437 \pm .35
Apolipoprotein B, g/L	2732	1.04 \pm .30	<i>1.144\pm.61</i>	1.057 \pm .35	1.26\pm.47
Lipoprotein(a), med (IQR), mg/dL	1605	10.05 (4.3; 23.5)	8.84 (5.6; 14)	12.8 (5.89; 28)	12.4 (5.15; 30)
Creatinine, mg/dL	2630	.98 \pm .48	1.15\pm.48	.782 \pm .36	.922\pm.34
C-react. protein, med (IQR), mg/L	2601	1.8 (0.9; 4.2)	3.05 (1.43; 7.8)	2.5 (1.1; 5.6)	3.9 (1.4; 13.1)
Antihypertensive drug, n, %	3054	99; 7.8	40; 19.6	46; 4.0	48; 10.8
Statin usage, n, %	3054	124; 9.1	15; 14.2	82; 6	12; 6.1
Curr. / former smoking, %	3054	47.3; 22.9	48.2; 22.3	17.7; 3.4	7.4; 5.3
Prevalent diabetes, n, %	3054	123; 9.0	28; 25	76; 5.2	21; 15.3
Prevalent CHD, n, %	3054	94, 6.9	57; 48	64; 4.3	33; 30

[†]t-test or chi-square in regard to percentages. Significantly different values are highlighted in bold, borderline significant values in italics. [†]Self-reported physical activity graded according to a scheme. *Self-reported monthly income, categorized. Phys - physical; Fast - fasting; Curr - current

Table 2. Cox regression analysis of risk factors at baseline (n=3015) for risk of 219 CHD deaths

Men per 1000 person years	Wald	β	HR	95%CI	β	HR	95%CI
	Whole sample, n=133/1457* 9.65				Free of CHD, n=79/1342* 6.3		
Age 50–59 years	16.1	1.211	3.36	1.86; 6.06	1.133	3.11	1.54; 6.28
60–69 years	38.2	1.838	6.29	3.51; 11.3	1.580	4.85	2.36; 10
≥70 years	77.0	2.814	16.7	8.9; 31.3	3.057	20.8	9.83; 44.2
Presence impaired f. glucose	.047	-0.061	0.94	0.54; 1.63	0.034	1.04	0.52; 2.07
Presence of diabetes	12.22	0.799	2.22	1.42; 3.48	0.484	1.62	0.82; 3.20
Systolic BP, 120–139 mm Hg	1.29	0.294	1.34	0.81; 2.23	0.464	1.59	0.84; 3.00
140–159 mm Hg	7.08	0.727	2.07	1.21; 3.54	0.811	2.25	1.12; 4.54
≥160 mm Hg	9.45	0.883	2.42	1.38; 4.25	1.046	2.85	1.32; 6.12
NonHDL-choL., 120–150 mg/dL	.047	-0.056	0.95	0.57; 1.57	-0.248	0.78	0.41; 1.50
>150 mg/dL	2.97	0.396	<i>1.49</i>	0.95; 2.33	0.430	1.54	0.87; 2.72
HDL-C 40–49/50–59 mg/dL	1.686	-0.296	0.74	0.48; 1.16	0.028	1.03	0.59; 1.79
>50/>60 mg/dL	.466	0.174	1.19	0.72; 1.96	0.419	1.52	0.82; 2.83
Low vs. high phys. activity	.532	0.146	1.16	0.78; 1.71	0.058	1.06	0.65; 1.73
Current vs. never-smokers	12.15	0.737	2.09	1.38; 3.16	1.017	2.77	1.56; 4.89
Former vs. never-smokers	.126	-0.089	0.92	0.56; 1.50	-0.014	0.99	0.50; 1.93
Women		n=86/1558* 5.95			n=55/1452 4.1		
Age 50–59 years	7.38	1.469	4.34	1.51; 12.5	1.161	<i>3.19</i>	0.89; 11.5
60–69 years	23.71	2.498	12.2	4.45; 33.2	2.635	7.68	4.56; 12.9
≥70 years	46.6	3.518	33.7	12.3; 92.6	3.385	29.5	9.1; 95.7
Presence impaired f. glucose	7.84	0.746	2.11	1.25; 3.56	0.784	2.19	1.14; 4.23
Presence of diabetes	10.9	0.955	2.60	1.47; 4.58	1.139	3.12	1.55; 6.30
Systolic BP, 120–139 mm Hg	.113	0.154	1.17	0.77; 2.01	0.106	1.11	0.38; 3.29
140–159 mm Hg	.190	0.207	1.23	0.48; 2.87	0.069	1.07	0.34; 3.39
≥160 mm Hg	5.82	1.044	2.84	1.22; 6.63	1.006	<i>2.73</i>	0.98; 7.64
NonHDL-choL., 120–150 mg/dL	.074	0.097	1.10	0.55; 2.21	-0.120	0.89	0.39; 2.04
>150 mg/dL	.006	0.027	1.03	0.54; 1.97	-0.116	0.89	0.41; 1.93
HDL-C 40–49/50–59 mg/dL	1.339	-0.366	0.69	0.37; 1.29	-0.374	0.69	0.31; 1.53
≥50/≥60 mg/dL	.890	-0.334	0.72	0.36; 1.43	-0.134	0.88	0.39; 1.95
Low vs. high phys. activity	2.49	0.821	2.27	0.82; 6.29	0.729	2.07	0.64; 6.77
Current vs. never-smokers	.68	0.337	1.40	0.63; 3.13	0.567	1.76	0.72; 4.32
Former vs. never-smokers	.306	0.294	1.34	0.47; 3.80	0.230	1.26	0.37; 4.32

*Number deceased/ number at risk. Significant values are highlighted in boldface. Physical activity values were missing in 1% of the sample comprising 14 CHD deaths. Reference categories were: age 30–49 (median 41) years (25 deaths/1541 subjects), normoglycemic (146/2446 deaths), nonHDL-choL. <120 mg/dL (44/748 deaths), HDL-C <40 mg/dL in men, <50 mg/dL in women (156/2023 deaths), SBP <120 mm Hg (34/1090 deaths), never smoker (123/1694), high physical activity (50/1099 deaths). Analysis of combined gender showed greater risk for male sex at an RR 1.82 (95% CI 1.31; 2.53)

Results of Cox proportional hazard regression analysis of 7 risk factors for the risk of CHD death are shown in Table 2, by sex. We included non-HDL-C rather than total cholesterol in the algorithm because the latter incorporates HDL-C, used in the current scoring. In men, apart from high HDL-C levels, low physical activity, and non-HDL-C levels of borderline significance, all variables were related to CHD mortality. In women, non-HDL-C levels and

modestly elevated SBP failed to predict risk of CHD death, while the remaining risk factor categories predicted the risk of CHD death.

CRP was significantly related to CHD death in men alone

When log-transformed CRP was added to the above-described models, HR for a 3-fold increment reached a significant

Table 3. Algorithm to predict risk of coronary disease mortality in the entire sample of Turkish men and women, aged 35–84 yrs (derived from the multiple Cox regression models)

Criterion	Category	Men	Women
Age, years	50–59	3	4
	60–69	6	12
	≥70	16	33
Impaired fasting glucose	Yes	0	2
Presence of diabetes	Yes	2	3
Systolic BP, mm Hg	120–139	0	0
	140–159	2	0
	≥160	2	3
NonHDL-cholesterol, mg/dL	120–150	0	0
	>150	1	0
HDL-cholesterol, mg/dL M/F	≥50/≥60	0	-1
	M/F 40–49/50–59	-1	-1
Current smoker	Yes	2	1
Former smoker	Yes	0	0
Low physical activity	Yes	0	2

Reference categories receive no points: age median 41 years, nondiabetic, SBP <120 mm Hg, nonHDL-C <120 mg/dL, HDL-C <40 mg/dL in men, <50 mg/dL in women, never smoker, high physical activity. BP - blood pressure; SBP - systolic blood pressure

level of 1.19 (95% CI 1.06; 1.35) in men but remained nonsignificant at 1.16 (95% CI 0.96; 1.40) in women.

Derived algorithm and risk prediction among Turkish adults

An algorithm to predict the risk of CHD mortality in the entire study sample is presented in Table 3. By applying the score to each study participant, we estimated the 9-year absolute risk of CHD death, as depicted in Figure 1 for the 5 selected categories. The computed 10-year CHD mortality for individuals at the age of 60, 70, and 80 years is depicted in Figure 2. In the 2 selected decades, the risk of CHD mortality increased from 3.7% to 27% in women and from 6.7% to 30% in men.

Risk discrimination (C-index) and validation of the algorithm

AROC (C-statistics) of the prediction model using age alone was 0.774±0.022 (95% CI 0.731; 0.818; p<0.001) in men and 0.836±0.021 (95% CI 0.795; 0.877; p<0.001) in women. Adding the 6 conventional risk factors increased this value to 0.832±0.016 (95% CI 0.800; 0.864; p<0.001) in men and 0.877±0.015 (95% CI 0.795; 0.877; p<0.001) in women (Fig. 3).

To validate the algorithm, we split the study sample in 2 by matching for sex, age, SBP, and diabetes; the latter was equally distributed by assigning every second participant to the validation set after having arranged the sample in increasing sequence. C-statistics for the male split samples were 0.823 (95% CI 0.776; 0.870; p<0.001) and 0.841 (95% CI 0.798; 0.885; p<0.001). These were 0.874 (95% CI 0.829; 0.918; p<0.001) and 0.880 (95% CI 0.839; 0.920; p<0.001) for the female split samples.

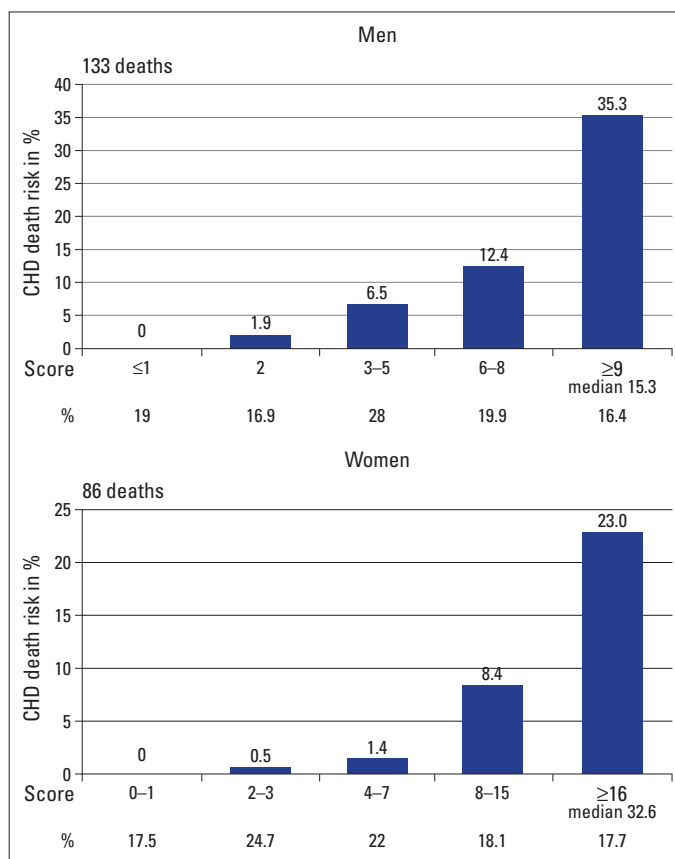


Figure 1. Graph depicting the 9-year absolute risk of CHD mortality in 1472 men and 1582 women corresponding to approximate score quintiles in the present algorithm. The lowest 2 categories include 528 men (median 1 pt) and 668 women (median 1 pt), while each of the highest category (≥9/≥16, median 15/33 pt) includes 267 men and 250 women. Each score corresponds in men to a mean of 1.25-fold in women to a mean of 1.21-fold absolute risk of CHD death

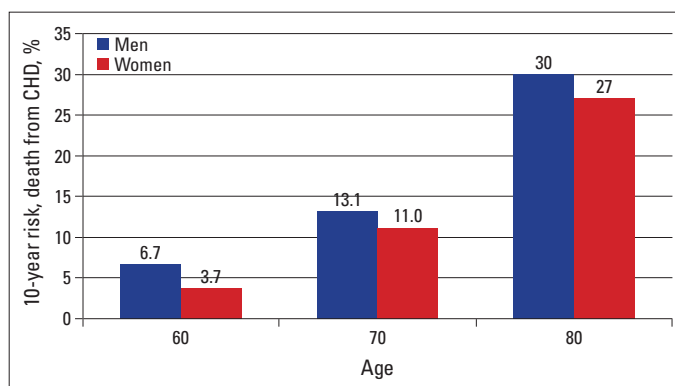


Figure 2. Mean 10-year risk of CHD death in Turkish males and females aged 60, 70, and 80 years. From 60 years onwards, the mean annual increase in the risk of CHD death is 7.8% in men and 10.5% in women. CHD - coronary heart disease

Discussion

In a middle-aged population with high MetS prevalence, anticipated risk factors proved largely to be determinants of the risk of CHD death only in men in this study. On the other hand, in women, serum non-HDL-C levels and moderate systolic hyper-

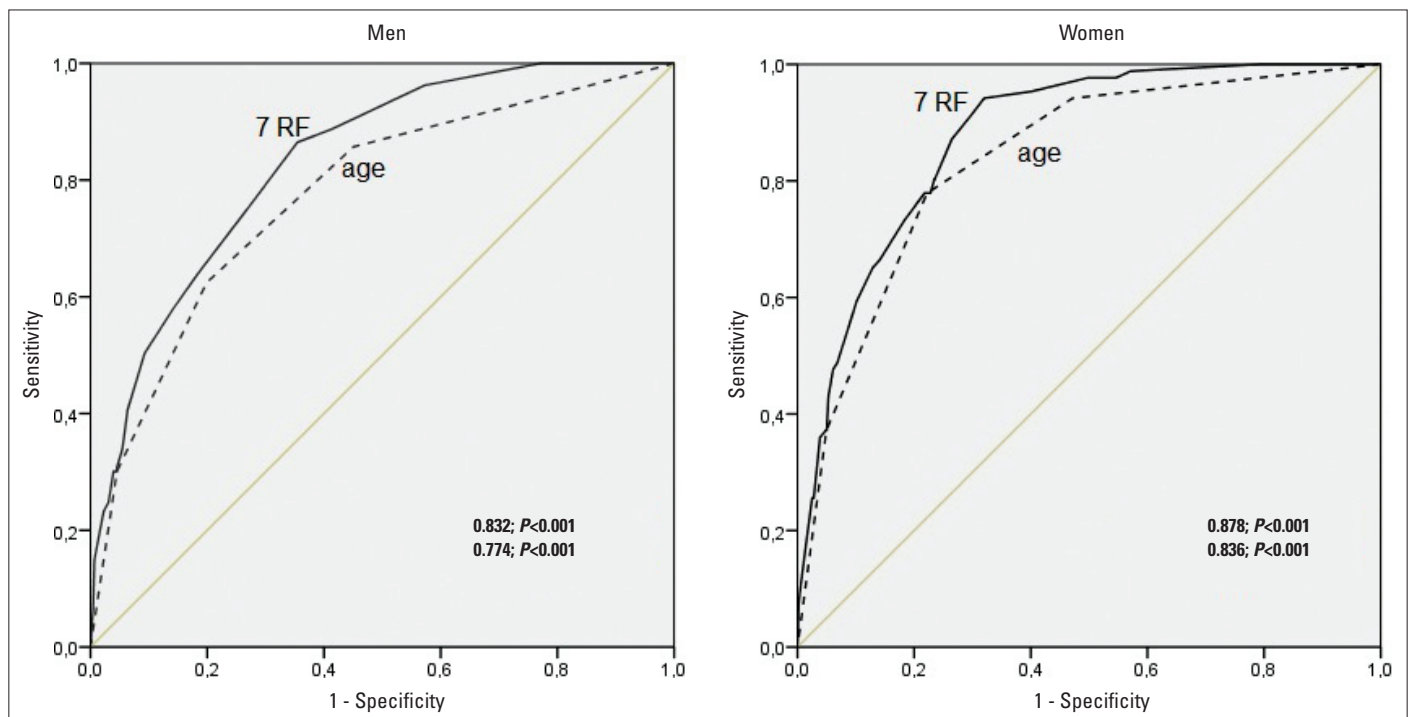


Figure 3. Receiver operation curve areas (AROCs) for CHD mortality. Panels on left for men. Dashed lines indicate AROC for age alone, while dark lines indicate that for the full model with 7 risk factors. The use of age alone provided a C-statistic as high as 0.774 in men and 0.836 in women. The incorporation of 6 conventional risk factors contributed a C-statistic of 0.058 in males and 0.042 in females

tension were not associated with this risk, and age was of paramount importance. Impaired glucose regulation, including diabetes, was an important determinant, in addition to severe systolic hypertension, smoking habit, low HDL-C levels, and low physical activity. The use of age alone provided a C-index as high as 0.774 in men and 0.836 in women. The incorporation of 6 conventional risk factors contributed to a C-index of 0.058 in men and 0.041 in women. The moderate contribution of conventional risk factors other than age to the estimation of the risk of CHD death in women supports the operation of autoimmune activation in them.

Risk scores and their accuracy

In the recent Kaiser Permanente Northern California health care delivery system, the 10-year CVD risk score was estimated for over 300,000 cohort members aged 40–75 years. They showed that the ACC/AHA Pooled Cohort Risk Equation substantially overestimated in adults not treated with statin therapy actual 5-year risk within adults without diabetes and with LDL-C levels of 70 to 189 mg/dL in men and women and in ethnic groups (14). The study also demonstrated suboptimal accuracy in subjects with diabetes. It has been expressed that the weight of the most current evidence appears to tilt toward systematic overestimation with the Pooled Cohort Risk Equation, potentially implicating overtreatment (15). Risk scores need to be fine-tuned every few years to best reflect the populations in which they are meant to be used (15).

During a 7.4-year follow-up of the Framingham Heart study, 169 participants had a first major cardiovascular event (16). C-

statistics were 0.68 with age and sex as predictors and 0.76 with additional conventional risk factors as predictors, yielding a contribution of 0.08 for factors beyond age. The contribution of the latter in our study was by 25% lower in males and 50% lower in females, although the current overall C-index was markedly higher than that in the Framingham study or that in the Australian risk prediction chart for CVD mortality in men (0.76) and women (0.71) (17). This suggests that age reflects another group of predictors (more prominent in women than in men), which may be included within the pro-inflammatory state and autoimmune activation.

The SCORE project performed moderately in high risk regions of Europe (such as UK, Scotland, Sweden, and Russia), and ROC areas were reported to be between 0.70 and 0.72 (0.67; 0.75) (5). In determining the vascular age from the SCORE project in high-risk countries, Cuende et al. (18) demonstrated the absolute 10-year risk of fatal cardiovascular disease for men and women with a vascular age of 60 years to be 3.55% and 1.32%, respectively. For men and women with a vascular age of 70 years, these rates were 7.55% and 3.76%, respectively. The stated rates were conspicuously (1.7-fold and 2.9-fold) higher among Turkish men and women at the age of 70 years, respectively.

Comparison of risk with SCORE Turkey

It is to be underlined at the outset that the SCORE project assesses the risk of fatal cardiovascular events, whereas the current algorithm only assesses the risk of CHD mortality. Nonetheless, comparisons may be attempted. Overall advantages of the

current algorithm over the SCORE function are applicability to adults with CHD; the presence of a greater focus on individuals aged over 60 years in whom mortality estimates are required to a greater extent; and the inclusion of type 2 diabetes, physical activity grade, and HDL-C among risk factors in the model. SCORE Turkey charts indicate the absolute death risk; the hazard ratio in the present study is converted to absolute risks. Among risk factors that are mutually applied in both projects, the following differences emerge.

The mean risk ratios in SCORE Turkey across 4 categories of rising total cholesterol levels varied in each sex by 2.0- to 1.85-fold; these were substantially greater than those in males and were not at all increased in females in this study. Although the risk in male smokers largely overlapped, the 2-fold increased risk in female smokers contrasted to the low and equal risk in former smokers conferred in the present algorithm. The risk of mild hypertension was not increased in women. The mean 10-year increase in age in SCORE Turkey (2.5- to 3.2-fold in men and women, respectively) was slightly higher than that in the algorithm (2.0- to 2.4-fold in men and women, respectively). Part of these differences may be explained by the lack of consideration of diabetes in SCORE Turkey.

With regard to SBP, we found women to deviate from men in that moderate hypertension was not associated but severe hypertension was somewhat highly associated with fatal CHD. A meta-analysis of 124 cohort studies demonstrated a broadly similar impact of SBP increments on the risk of ischemic heart disease in both sexes (19). On the other hand, in the Atherosclerosis Risk in Communities study (20), this risk was significantly, albeit slightly, higher in females.

The risk of fatal CVD in Turkey is estimated to be nearly 1.4-fold that of CHD mortality (21). For 60-year old men and women in the SCORE Turkey chart, the 10-year risk is estimated to be approximately 13% and 8%–9%, while the 10-year CHD mortality risk is 7% and 4%, respectively, in the present algorithm.

Serum cholesterol and CHD mortality

We had previously documented in the algorithm on the risk of all-cause mortality that an association between non-HDL-C (which encompasses LDL-C and triglyceride) categories was lacking in each sex. In the present study on CHD death, similarly, non-HDL-C levels did not confer an independent risk of fatal CHD, barring the modest risk observed in the highest male category. These are consistent with findings of diverse works in the literature. In contrast to a positive association of cholesterol levels in premenopausal women, in peri- and postmenopausal women, a predictive value for myocardial infarction or mortality is lacking (22). In the large HUNT-2 study (23) analyzing 2490 overall deaths, a linearly inverse association with total cholesterol levels in women and an association following a U-shaped risk curve were documented in men. In a cohort of over 16,000 participants of a general Japanese population followed up over a mean of 10.9 years, an inverse association was observed be-

tween total cholesterol levels and mortality from cardiovascular disease or CHD after multivariable adjustment (24).

The U-shaped risk curve of coronary mortality for HDL-C in men has not been surprising because impaired protection of elevated and presumably pro-inflammatorily converted HDL-C from cardiometabolic risk has been repeatedly demonstrated in Turkish adults (1, 8, 9). This concept has been supported by the finding that risk is related to overloading with cholesterol of MR spectroscopy-determined HDL particles (25).

Danish investigators (26) have modified the SCORE model to allow the estimation of both CVD-specific and all-cause mortality using a competing risk approach and expressed their results for the expected residual lifetime, together with expected benefits from statin treatment. Notably, they have documented that for a man aged 65 years, the increased gains due to cholesterol lowering by statins for the expected residual lifetime do not exceed 2 months, and for smokers, these do not exceed 1 month, regardless of the total cholesterol level. This is in congruence with a review of observational studies and randomized controlled trials on total cholesterol levels and mortality in ≥ 80 -year-old individuals, failing to find a beneficial effect lipid-lowering treatment on mortality (27).

The contribution of CRP levels to the independent prediction of CHD mortality was modest and significant only in men. This may be due to the mediation effects of diabetes and smoking habits and stands at variation to the meta-analysis by the Emerging Risk Factors Collaboration (28), in which the risk ratio for vascular mortality per 3-fold higher CRP was 1.55 (95% CI 1.37; 1.76) when adjusted for sex, age, and conventional risk factors.

Role of autoimmune activation in the modest contribution of conventional risk factors

The hypothesis of pro-inflammatory state and autoimmune activation that we have put forward (8) can considerably explain the high risk discrimination in the present algorithm solely by age in each sex and the modest contribution of conventional risk factors in Turkish adults, particularly women.

Implications for public health and clinical practice: Evidence from the present work implies that, with regard to the risk of death from CHD, the prevention of type-2 diabetes should be a major aim, particularly in women. In pursuing this aim, campaigns urging the discontinuance of cigarette smoking, to be continued in men, should be directed to a lesser extent or in moderation toward women. Rather than targeting normotension in women, the amelioration of severe hypertension appears essential. Based on findings of a previous prospective TARF study (29) and on present findings, it seems rational to apply guideline recommendations for lipid-lowering medication among middle-aged Turkish individuals in their 40s and 50s but much less so and with caution among elderly adults aged over 60 years. V. Fuster called for a personalized approach for each individual patient rather than seeking an ideal BP (or LDL-C) target (30). HDL-C levels of ≥ 50 mg/dL among males should not lead to a feeling of reassurance or complacency in clinicians.

Study limitations

A major limitation of the present study was the relatively limited number of CHD deaths which, however, did not preclude the emergence of significant findings in relation to numerous risk factors. The use of only a single baseline measurement may overlook intraindividual variations and may have led to a regression dilution effect with consequent underestimation of the predictive value of the included determinants. Present findings may have validity in similar subsets of many other populations (31). The inclusion of diabetic patients and measurement of diverse biochemical and anthropometric markers clearly form strengths of the present study.

Conclusion

In middle-aged Turkish individuals, anticipated risk parameters (except for high HDL-cholesterol) largely proved to be determinants of CHD death risk only in men. In contrast, in women, serum non-HDL-C levels and moderate systolic hypertension were not relevant, and beyond the paramount important age, impaired glucose regulation, severe systolic hypertension, low HDL-C levels, and low physical activity were important determinants of the risk. The incorporation of 6 conventional risk factors added to age contributed to C-statistics of 0.058 in males and 0.041 in females. These observations in estimating the risk of CHD death in women are consistent with the operation of autoimmune activation.

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References

- Onat A, Can G, Hergenç G, Uğur M, Yüksel H. Coronary disease risk prediction algorithm warranting incorporation of C-reactive protein in Turkish adults, manifesting sex difference. *Nutr Metab Cardio Dis* 2012; 22: 643-50. [CrossRef]
- Huynh QL, Reid CM, Chowdhury EK, Huq MM, Billah B, Wing LM, et al, on behalf of the Second Australian National Blood Pressure Management Committee. Prediction of cardiovascular and all-cause mortality at 10 years in the hypertensive aged population. *Am J Hypertens* 2015; 28: 649-56. [CrossRef]
- Hoes AW, Grobbee DE, Valkenburg HA, Lubsen J, Hofman A. Cardiovascular and all-cause mortality, a 12 year follow-up study in the Netherlands. *Eur J Epidemiol* 1993; 9: 285-92. [CrossRef]
- Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2889-934. [CrossRef]
- Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al.; SCORE Project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J* 2003; 24: 987-1003. [CrossRef]
- National Cholesterol Education Expert Panel. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-97. [CrossRef]
- Onat A, Ceyhan K, Başar Ö, Erer B, Toprak S, Şansoy V. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels – a prospective and cross-sectional evaluation. *Atherosclerosis* 2002; 165: 285-92. [CrossRef]
- Onat A, Can G. Enhanced proinflammatory state and autoimmune activation: a breakthrough to understanding chronic diseases. *Curr Pharm Des* 2014; 20: 575-84. [CrossRef]
- Onat A, Can G, Ayhan E, Kaya Z, Hergenç G. Impaired protection against diabetes and coronary disease by high-density lipoproteins in Turks. *Metabolism* 2009; 58: 1393-9. [CrossRef]
- Onat A. Risk factors and cardiovascular disease in Turkey. *Atherosclerosis* 2001; 156: 1-10. [CrossRef]
- Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus: The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; 26: 3160-7. [CrossRef]
- Onat A, Şurdum Avcı G, Şenocak M, Örnek E, Gözükar Y. Plasma lipids and their interrelation in Turkish adults. *J Epidem Community Health* 1992; 46: 470-6. [CrossRef]
- Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular Survey Methods*, 2nd edn. Geneva, World Health Organization, 1982. p. 124-7.
- Rana JS, Tabada GH, Solomon MD, Lo JC, Jaffe MG, Sung SH, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary multiethnic population. *J Am Coll Cardiol* 2016; 67: 2118-30. [CrossRef]
- Blaha MJ. The critical importance of risk score calibration. Time for transformative approach to risk score validation? *J Am Coll Cardiol* 2016; 67: 2131-4. [CrossRef]
- Wang TJ, Gona P, Larson MG, Tofler JH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006; 355: 2631-9. [CrossRef]
- Chen L, Tonkin AM, Moon L, Mitchell P, Dobson A, Giles G, et al. Recalibration and validation of the SCORE risk chart in the Australian population: the AusSCORE chart. *Eur J Cardiovasc Prev Rehabil* 2009; 16: 562-70. [CrossRef]
- Cuende JI, Cuende N, Calaveras-Lagartos J. How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation. *Eur Heart J* 2010; 31: 2351-8. [CrossRef]
- Peters SAE, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke* 2013; 44: 2394-401. [CrossRef]

20. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC Investigators. *Am J Epidemiol* 1989; 129: 687-702. [\[CrossRef\]](#)
21. 24 Years of the TARF: Health of Turkish Adults and Pioneering to the Approach of Medicine to Chronic Diseases. Istanbul, Logos Publ. 2015. p.23. ISBN: 978-975-349-078-8
22. Lindqvist P, Bengtsson C, Lissner L, Björkelund C. Cholesterol and triglyceride concentration as risk factors for myocardial infarction and death in women, with special reference to influence of age. *J Intern Med* 2002; 251: 484-9. [\[CrossRef\]](#)
23. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TIL, Getz L. Is the use of cholesterol in mortality risk algorithms in clinical guidelines valid? Ten years prospective data from the Norwegian HUNT 2 study. *J Evaluat Clin Pract* 2012; 18: 159-69. [\[CrossRef\]](#)
24. Tsuji H. Low serum cholesterol level and increased ischemic stroke mortality. *Arch Intern Med* 2011; 171: 1116-30. [\[CrossRef\]](#)
25. Qie Y, Fan J, Liu J, Wang W, Wang M, Sun J, et al. Cholesterol-overloaded HDL particles are independently associated with progression of carotid atherosclerosis in a cardiovascular disease-free population: a community-based cohort study. *J Am Coll Cardiol* 2015; 65: 355-63. [\[CrossRef\]](#)
26. Støvring H, Harmsen CG, Wisløff T, Jarbøl DE, Nexøe J, Nielsen JB, et al. A competing risk approach for the European Heart SCORE model based on cause-specific and all-cause mortality. *Eur J Prev Cardiol* 2013; 20: 827-36. [\[CrossRef\]](#)
27. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. *Age Ageing* 2010; 39: 674-80.
28. Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010; 375: 132-40.
29. Onat A, Aydın M, Köroğlu B, Can G, Kaya H, Ademoğlu E. Statin therapy and increased coronary heart disease risk in primary prevention of people with enhanced low-grade inflammation. *Türk Klin J Cardiovasc Sci* 2014; 26: 118-27.
30. Fuster V. No such thing as ideal blood pressure: a case for personalized medicine. *J Am Coll Cardiol* 2016; 67: 2014-5. [\[CrossRef\]](#)
31. Dodani S. Excess coronary artery disease risk in South Asian immigrants: Can dysfunctional high-density lipoprotein explain increased risk? *Vasc Health Risk Managem* 2008; 4: 953-61. [\[CrossRef\]](#)



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