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Little contribution of conventional factors in an algorithm to predicting death risk in Turkish adults

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ABSTRACT

Objective: Determinants of risk of death are highly relevant for the management strategy of individuals. We aimed to determine an algorithm for predicting risk of death in Turkish adults who have a high prevalence of metabolic syndrome (MetS).

Methods: Nine-year risk of death was estimated in 3348 middle-aged adults, followed over 8.81 ± 4.2 years. Cox proportional hazard regression was used to predict risk of death. Discrimination was assessed using C-statistics. **Results:** Death occurred in 565 subjects. In multivariable analysis, high-density lipoprotein (HDL) and non-HDL cholesterol levels were not predictive in either sex; in women, current smoking was also not predictive. Age, presence of diabetes, systolic blood pressure ≥ 160 mmHg and low physical activity were predictors in both sexes, beyond smoking status in men. Exclusion of coronary disease at baseline did not change risk estimates materially. Using an algorithm of the stated 7 variables showed an 11- to 18-fold spread in the absolute risk of dying among individuals in the highest than in the lowest of 4 risk score categories. C-statistics of the model using age alone was 0.790 in men, 0.808 in women ($p < 0.001$ each), while the incorporation of 6 conventional risk factors contributed to C-index was > 0.020 in males and 0.009 in females.

Conclusions: In a middle-aged population with prevalent MetS, serum lipoproteins and, in women, smoking status, were not relevant for the risk of death. The contribution of conventional risk factors beyond age to estimating risk of death was modest among Turkish men, and little in women in whom autoimmune activation is operative.

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1. Introduction

Survival is of vital interest for the individual in question, and the risk of overall mortality is the ultimate endpoint against which developing cost-effective primary disease prevention is critical for society. Assessments of determinants of cardiovascular or coronary heart disease (CHD) mortality have been commonly reported and several prediction charts or algorithms were developed to estimate global risk of future cardiovascular events. The most important among these is the European SCORE project, which estimates the 10-year absolute risk of cardiovascular mortality [1]. Studies evaluating the value of a specific biomarker or condition to predict all-cause mortality [2], or assessing the risk of mortality in a specific disease [3] or group of diseases [4,5] are numerous.

The estimation of the risk of overall mortality relative to diverse potential determinants in a given population sample has not been frequently performed. Yet information on determinants of all-cause mortality is more relevant than of, say cardiovascular, mortality because of competing morbidity that may lead to death closely later, even if the former possibility is prevented.

Cardiovascular risk factors have not uniformly but most often been predictors of all-cause mortality in other populations. A previous Dutch cohort [6] pointed out that age, smoking, diabetes and high BP were independent determinants not only of cardiovascular but also of all-cause mortality in middle-aged subjects. Striking data for total cholesterol in relation to mortality risk were provided in Norwegian men and women in the large HUNT study [7], namely, an inverse association with all-cause mortality in women which followed in men a U-shaped risk curve. They, therefore, questioned the validity of related clinical and public health recommendations. The first risk prediction algorithm *par excellence* in a general population was published for the French MONICA cohort [8]. Age, region of residence, educational level and 4

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traditional cardiovascular risk factors were detected as independent risk factors, while alcohol consumption, physical activity, antihypertensive drug treatment, diastolic BP, HDL cholesterol and triglycerides did not prove independent risk factors on multivariable analysis.

Accumulating evidence generated in the Turkish Adult Risk Factor (TARF) study documented that standard risk factors (including LDL cholesterol, which is relatively low) failed to identify a large proportion of individuals at high CHD risk and that inflammatory markers (such as a high atherogenic index of plasma [9]) and type 2 diabetes were therein more pertinent, especially in Turkish women, than in Western populations [10]. Proinflammatory state, recognized by the Adult Treatment Panel-III as a component of the metabolic syndrome (Mets) [11], is highly prevalent among Turks [12]. These aspects documented striking features in a coronary disease risk prediction algorithm in this population [13], namely, that smoking status, HDL and LDL cholesterol levels were not predictive of CHD risk in women. Some gender difference [7] and age-specificity [14–17] of the associations between risk factors and the risk of death has also been reported in other populations.

Causality mechanisms of death may act differently in populations. Hence, the need for a risk algorithm to predict all-cause mortality in Turkish adults is evident in view of previous documentation of HDL dysfunction, sex-modulated effect of smoking status, and the operation of autoimmune activation in cardiometabolic outcomes. In a prospective Cox proportional hazard modeling of the ongoing population-based TARF study, we aimed to examine a series of conventional risk factors to develop a simple algorithm (consisting of 7 factors) for predicting the 9-year risk of mortality and investigated its accuracy. In addition to being a potential tool in identifying high-risk individuals to target for clinical intervention, this algorithm contributes to understanding the importance in this population of the proinflammatory state and autoimmune activation in mortality risk as well.

2. Methods

2.1. 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 carried out biennially in 59 communities scattered throughout all geographical regions of the country [18]. It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural-urban distribution [18]. Participants were recruited from randomly selected communities using a probability-proportionate-to-size method. Combined measurements of waist circumference and HDL cholesterol having been 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 made in 2002/2003 and 2007/2008. Participants were examined over a period of up to 17 years, till the survey in 2014/2015.

Inclusion criteria for the current study was individuals' aged 35 to 84 years, no missing relevant values at baseline, and having at least 2 years of follow-up. Few individuals who reported an inflammatory disease during the previous month ($n = 9$) were excluded. Participants numbering 3348 composed the cohort of the current 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 history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting 12-lead electrocardiogram.

2.2. Measurements of risk variables

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

2.3. Definitions and outcomes

Age was considered as a rounded figure assessed from year of birth. Self-reported cigarette smoking was categorized into non-smokers [never smokers and former smokers

(discontinuance of 3 months or more)] and current smokers (regularly 1 or more cigarettes daily), as elicited in interview during examination. Individuals with type 2 diabetes were diagnosed using criteria from the American Diabetes Association [19], namely, when plasma fasting glucose was ≥ 7 mmol/L (or 2 h postprandial glucose > 11.1 mmol/L) and/or the current use of diabetes medication. Non-HDL cholesterol denoted HDL cholesterol measure subtracted from total cholesterol. Physical activity was graded by the participant himself into four categories of increasing order with the aid of a scheme [20], and low physical activity was defined as grades 1 and 2.

Information on the mode of death was obtained from first-degree relatives, the local health office and/or from records of the nationwide Identity Participation System. Nonfatal CHD was identified by presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the ECG [21] or a history of myocardial revascularization. Typical angina and, in women, age > 45 years were prerequisite for a 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, respectively. CHD death comprised death from heart failure of coronary origin and fatal coronary event.

2.4. Data analysis

Descriptive parameters were shown as mean \pm standard deviation (SD) and in percentages. Due to skewed distribution, values derived from log-transformed (geometric) means were used for serum triglycerides and CRP. Pearson chi-square tests were used to analyze the differences between proportions of groups. In predicting mortality risk from baseline examination, Cox proportional hazards regression was used to yield risk coefficients for each risk variable whereby proportionality of hazards was assumed via significant log rank of Kaplan-Meier survival curves. Estimates (and 95% confidence intervals) for relative risk (RR) of the independent categorized variables were expressed using a referent category. We analyzed in the complete sample the independent risk estimates for the variables waist circumference, body mass index (BMI), CRP, physical activity grade, serum creatinine and antihypertensive drug usage as well (Suppl. Table 1) and selected the best fitting model. Scores were derived from multivariate Cox regression models including all the factors listed in Table 2. The regression coefficient β was used for each variable from the final model as weights for assigning risk points for which risk magnitude and shape were examined across categories of the related variable. Though only 5 independent indicators yielded positive points (excess risk), score points were displayed for 7 risk factors in the final algorithm model aiming to emphasize that the two parameters recommended as treatment indicators and generally considered to be risk-conferring did not prove to be so. 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, IL).

3. Results

At baseline examination, 3348 participants (of whom 1697 were women) having a median [IQR] age 49.5 [41.5; 60] years, were available. Mean follow-up constituted 8.81 ± 4.25 years, similar ($p = 0.86$) in men and women (total 29,558 person-years). CHD prevailed in 146 men and 124 women at baseline. Death occurred in 565 subjects (20 per 1000 person-years). Mean age at death was 70 ± 12.4 years in males and 71.9 ± 10.7 years in females ($p = 0.051$). CHD death led the causes of death with 41%; followed by cancer with 20% and cerebrovascular disease with 11%.

Baseline characteristics of the sample population are shown in Table 1 stratified to sex and survivorship. Of the listed parameters, only HDL cholesterol and triglycerides were similar and current smokers were significantly fewer among non-surviving women. Only waist circumference, smoking status and total cholesterol were similar across survivorship in men in whom triglycerides tended to be lower and HDL cholesterol levels to be higher in men who eventually died.

Results of Cox proportional hazard regression analysis of 7 risk factors for risk of death are presented in Table 2 by sex. We selected to include in the algorithm non-HDL cholesterol rather than total cholesterol since the latter incorporates HDL cholesterol, used in the current scoring. Age-adjusted relative risks were basically similar to multivariable-adjusted ones, except for the protective effect of physical activity in females which appeared only to be mediated by diabetes and BP. Age proved of paramount relevance insofar as 1 decade corresponded to 2.4- to 2.7-fold relative risk in men and women. Prevalent diabetes and systolic BP ≥ 160 mmHg were risk indicators in each gender, emerging with RRs of approximately 1.7. Low physical activity and current smoking were significant determinants in men alone. HDL cholesterol and non-HDL cholesterol categories were not related to the mortality

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