ORIGINAL ARTICLE

Tenth categories of total and HDL cholesterol fail to independently predict death risk in middle-aged Turkish adults

Orta yaşlı Türk yetişkinlerinde ölüm riski: Total ve HDL kolesterol ondabir dilimlerince bağımsız olarak öngörülmüyor

Altan Onat, M.D.,[1] Günay Can, M.D.,[2] Muhammed Keskin, M.D.,[3] Volkan Çamkıran, M.D.,[4] Ahmet Okan Uzun, M.D.,[3] Hüsniye Yüksel, M.D.[1]

[1]Department of Cardiology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
[2]Department of Public Health, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
[3]Department of Cardiology, Siyami Ersek Center for Cardiovascular Surgery, İstanbul, Turkey
[4]Department of Cardiology, Koç University Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Objective: The aim of this study was to delineate in detail the longitudinal association of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels with overall mortality in middle-aged participants of the biennial Turkish Adult Risk Factor study.

Methods: Baseline lipid variables were analyzed in sex-specific deciles. A baseline age of 45 to 84 years as an inclusion criterion led to the enrollment of 2121 men and women. Cox regression analyses were performed.

Results: Deaths were recorded in 237 and 306 women and men, respectively, during a mean 8.85±4.4 years of follow-up. After adjustment for age, smoking status, lipid-lowering and antihypertensive drug usage, prevalent diabetes, and coronary heart disease, and using the lowest decile as referent, neither TC (p trend=0.94 and 0.96, respectively), nor HDL-C categories (p trend=0.20 and 0.31, respectively) were significantly predictive of mortality in either gender. TC deciles exhibited a gender difference insofar as hazard ratios in females tended to be reciprocal to those in males in deciles 2 through 5.

Conclusion: The findings on TC deciles may be attributed to a comparatively higher death rate in the female (compared with male) bottom decile, reflecting the autoimmune process-induced elevated risk in the lowest decile. Observations on HDL-C confirmed presumed pro-inflammatory conversion in levels >50 mg/dL. These results have important clinical implications.

ÖZET

Amaç: Total kolesterol (TK) ile yüksek-yoğunluklu lipoprotein kolesterol (HDL-C) düzeylerinin TEKHARF Çalışması'nda kapsanan orta yaşlı katılımcılarda genel mortalite ile öne dönük ilişkisini ayrıntılı biçimde belirlemektir.

Yöntemler: Başlangıçtaki lipid değişkenleri cinsiyete özgü ondabir dilimlerde analiz edildi. Başlangıçtaki yaşın 45–84 olarak alınma ölçütü 2121 erkek ile kadının içerilmesine izin verdi. Cox regresyon analizleri uygulandı.

Bulgular: Ortalama 8.85±4.4 yıllık izlemede ölüm 237 kadın ile 306 erkekte saptandı. Yaş sigara içiciliği, lipid düşürücü ve antihipertansif ilaç kullanımı, başlangıçta diyabet ve koroner kalp hastalığına ayarlamadan sonra ve en alt ondabir dilim referent olarak alınınca, ne TK (sırasıyla, p trend =0.94 ve 0.96), ne de HDL-C kategorileri (sırasıyla, p trend =0.20 ve 0.31) iki cinsiyette de mortaliteyi anlamlı öngörmedi. TK dilimleri, kadınlardaki hazard oranlarının 2.–5. dilimlerde erkektekilere göre ayna halini sergileme eğilimleri ile ayrıştılar.

Sonuç: Total kolesterol ondabir dilimlerine ilişkin bulgular, erkektekine kıyasla, kadında en alt dilimde göreli yüksek ölüm oranına atfedilebilir ki bu da anılan dilimde otoimmün sürecin indüklediği yüksek riski yansıtır. Yüksek-yoğunluklu lipoprotein kolesterole ilişkin gözlemlerimiz >50 mg/dL düzeylerinin yangısal dönüşüme uğradığını desteklemektedir. Bu saptamalar önemli klinik çıkarımlar taşır.

Longevity is the single most important health parameter for an individual or a community. Worldwide, life expectancy has increased substantially in recent decades. The determinants of all-cause mortality are not established and include age, a high prevalence of type-2 diabetes, coronary heart disease (CHD), hypertension, a smoking habit, physical inactivity, abdominal obesity, and high total cholesterol (TC)

Received: February 17, 2017 *Accepted:* July 24, 2017

Correspondence: Dr. Altan Onat. İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Kardiyoloji Anabilim Dalı, İstanbul, Turkey.
Tel: +90 212 - 351 62 17 e-mail: alt_onat@yahoo.com.tr

© 2017 Turkish Society of Cardiology

Abbreviations:

BP	*Blood pressure*
CI	*Confidence interval*
CRP	*C-reactive protein*
CHD	*Coronary heart disease*
ECG	*Electrocardiogram*
HDL-C	*High-density lipoprotein cholesterol*
HR	*Hazard ratio*
HUNT	*Nord-Trøndelag Health Study*
IQR	*Interquartile range*
LDL	*Low-density lipoprotein*
Lp(a)	*Lipoprotein(a)*
MONICA	*Multinational Monitoring of Trends and Determinants in Cardiovascular Disease*
TARF	*Turkish Adult Risk Factor*
TC	*Total cholesterol*

or a low high-density lipoprotein cholesterol (HDL-C) level.[1–4] They vary between ethnicities. The use of prediction algorithms is recommended in the decision-making for therapies aimed at preventing cardiovascular diseases.[5] TC and HDL-C constitute 2 critical variables in fatal CHD, which ranks first among causes of death, and reduction of an elevated TC level has been the major single recommendation of prevention guidelines.

Cardiovascular risk factors have most often – though not uniformly – been predictors of death risk in other populations. Age, smoking, diabetes, and high blood pressure (BP) were independent determinants, not only of cardiovascular, but also of all-cause mortality in middle-aged Dutch subjects.[1] Among Norwegian men and women in the large Nord-Trøndelag Health (HUNT) Study,[2] intriguingly, an inverse association was found between TC and all-cause mortality in women, which assumed a U-shaped risk curve in men. A risk prediction algorithm in a general population was reported in the French Multinational Monitoring of Trends and Determinants In Cardiovascular Disease (MONICA) Study cohort.[3] Age, region of residence, educational level, and 4 traditional cardiovascular risk factors were detected as independent risk factors, while alcohol consumption, physical activity, antihypertensive drug treatment, diastolic BP, HDL-C, and triglycerides did not prove independent risk factors. Some gender differences[2] and age-specificity[6–9] in the associations between risk factors and the risk of death has been reported in other populations.

In a recent derivation of an algorithm for all-cause mortality in the Turkish Adult Risk Factor (TARF) study cohort, what was apparent from previous evaluations was confirmed: mechanisms involving risk factors beyond those conventionally recognized determined the risk of death to a substantial extent.[10] Baseline diabetes and severe systolic hypertension alone and, in men, current smoking, were major determinants consistent with the general knowledge. Yet with regard to lipid variables, non-HDL-C and HDL-C, each high HDL-C and low non-HDL-cholesterol category revealed a higher risk for death than the respective bottom and top categories in either sex, albeit insignificantly.[10]

This study was an assessment of the risk of overall mortality among Turkish adults with evidence of enhanced, low-grade inflammation and autoimmune activation operating as a major pathogenetic mechanism.[11] The focus here was specifically on the lipid parameters of TC and HDL-C using 10 categories, namely deciles, in each variable and the analyses were stratified by sex. A multi-adjusted Cox model was used.

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 carried out biennially in 59 communities scattered throughout all geographical regions of the country.[12] It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical region, and for rural and urban distribution.[12] Participants were recruited from randomly selected communities using a probability-proportionate-to-size method. Combined measurements of waist circumference and HDL-C first taken at the follow-up visit in 1997/98, C-reactive protein (CRP) from 2000, insulin from 2001 and lipoprotein(a) [Lp(a)] from 2003 formed the bulk of the baseline. Participants had median recruitment in year 2001 (interquartile range [IQR]: 2000–2003), and the 10th and 90th percentiles at baseline during the period 2000–2007. Participants were examined over a period of up to 18 years, through the survey of 2015/16.

Inclusion criteria for the current study were age of 45 to 84 years, no missing relevant values at baseline, and at least a 1 year of follow-up. The cohort of the current study comprised 2121 individuals. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University ethics committee. All individuals of the cohort gave written consent for participation. Data were obtained via a questionnaire, physical examination of the cardiovascular system, sampling of blood, and re-

cording a resting 12-lead electrocardiogram (ECG).

Measurement of risk variables

BP was measured using a sphygmomanometer (Erkameter; Erka Kallmeyer Medizintechnik GmbH & Co. KG, Bad Tölz, Germany) after 10 minutes of rest in the sitting position, and the mean of 2 recordings at least 3 minutes apart was documented. Plasma concentrations of TC and HDL-C, fasting triglycerides, and glucose were determined at baseline examination using the enzymatic dry chemistry method and a Reflotron apparatus (Roche Diagnostics, Basel, Switzerland). Since the 2001 survey, the stated parameters have been assayed in a single, central laboratory. Serum concentrations of CRP were measured with a Behring nephelometer (Behring Diagnostics, Marburg, Germany). External quality control in a random selection of 5% to 6% of participants was performed at a reference laboratory.

Definitions and outcomes

Cigarette smoking status was categorized into nonsmokers (never smokers and former smokers who had quit for 3 months or more) and current smokers (regularly, 1 or more cigarettes daily), and was self-reported in an interview during examination. Individuals with type-2 diabetes were diagnosed with criteria of the American Diabetes Association,[13] namely, plasma fasting glucose ≥7 mmol/L (or 2-hour postprandial glucose >11.1 mmol/L) and/or the current use of diabetes medication. Physical activity was graded by the participant into 1 of 4 categories of increasing level with the aid of a previously developed tool.[14] Low physical activity was defined as grades 1 and 2. Family income was categorized by the participant into 1 of 5 categories.

Information on mode of death was obtained from first-degree relatives and/or a local health office. Cause of death was assigned considering preexisting clinical and laboratory findings elicited during biennial surveys. Nonfatal CHD was identified by the presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the ECG,[15] or a history of myocardial revascularization. Typical angina was a prerequisite for a diagnosis when angina was isolated. ECG changes of "ischemic type" greater than minor degree (codes 1.1–2, 4.1–2, 5.1–2, 7.1) were considered myocardial infarct sequelae or myocardial ischemia.

Data analysis

Descriptive parameters were presented as mean±SD and percentages. Pearson chi-square tests were used to analyze the differences between proportions of groups. Significance between 2 groups was tested with the Mann-Whitney U test for values with skewed distribution (family income, serum triglycerides, Lp[a] and CRP).

In predicting mortality risk from the baseline examination, Cox proportional hazards regression was used to yield risk coefficients for each lipid or risk variable. Estimates (and 95% confidence intervals [CI]) for the hazard ratio (HR) of the independent categorized variables were expressed using a referent category. A model adjusted for age, smoking status, usage of statin or antihypertensive drugs, prevalent diabetes, and CHD was utilized. A value of $p<0.05$ in the 2-sided test was considered statistically significant. Statistical analyses were performed using SPSS for Windows, Version 10.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

At baseline examination, 2121 participants (1086 women) with a mean age of 58.9±9.0 [IQR 51–65.5] years were available. Mean follow-up constituted 8.85±4.38 (range: 1–18) years, and was similar ($p=0.25$) in men and women (total: 18,770 person-years). Death occurred in 543 subjects (33.8 and 24.4 per 1000 person-years in men and women, respectively). Mean age at death was 72.5±10.1 years in males and 73.4±9.3 years in females.

Baseline characteristics of the sample population are shown in Table 1, stratified by sex and survival. Of the listed parameters, greater age and systolic BP, shorter height, lower physical activity score and income bracket, antihypertensive drug usage, and diabetes and/or CHD prevailing at baseline were significantly different among non-survivors compared with survivors in each sex. In addition, fasting glucose and apolipoprotein B in women and CRP in men were significantly higher in those who subsequently died. Body mass index and triglycerides were lower in men. There were fewer current smokers among non-surviving women. It is noteworthy that, except for lower fasting triglycerides in males, all lipid fractions in each gender were similar across categories of survival.

Table 1. Baseline characteristics (mean±SD; n, %) of 2121 men and women, aged 45–84, stratified by survival

		Men (n=1035)		Women (n=1086)	
	n	Survivors (n=729)	Deaths (n=306)	Survivors (n=849)	Deaths (n=237)
Age, years	2121	56.5±7.6	**65.4**±9.4	56.8±7.8	**65.5**±9.1
Waist circumference (cm)	2121	95.8±10.7	*94.4*±11	92.7±11.8	*94.1*±13.4
Body mass index (kg/m^2)	2000	27.7±4.3	**26.5**±3.7	30.6±5.5	30.3±6.4
Height (cm)	2121	168.9±6.5	**167.0**±6.4	155.6±6.6	**153.0**±5.9
Systolic BP (mmHg)	2121	129±22	**140**±27.1	139±27	**153**±30
Diastolic BP (mmHg)	2113	81±12.3	82.5±14.3	84.3±14	**88.1**±15.2
Physical activity grade I-V	2107	2 (2; 3)	2 (1; 2)	2. (2; 2)	2 (1; 2)
Income bracket, 1-4	2034	2 (2; 4)	2 (1; 3)	2 (1; 3)	1 (1; 2)
Fasting glucose (mg/dL)	1789	104.6±44	*111.7*±48.5	101±34	**114.5**±54.8
Total cholesterol (mg/dL)	2121	187±39.5	183.6±38.5	201.3±40	203.2±43
LDL-cholesterol (mg/dL)	1439	111.6±34	113.8±33.5	121±37	125.6±38
HDL-cholesterol (mg/dL)	2121	38.6±10.6	39.4±11.7	46.3±12.2	46.1±13.1
Fasting triglyceride¶ (mg/dL)	1540	143 (97; 204)	122 (89; 181)	133 (95; 182)	129 (93; 187)
Apolipoprotein A-I (g/L)	1761	1.307±.25	1.284±.26	1.471±.28	1.424±.32
Apolipoprotein B (g/L)	1842	1.039±.30	1.094±.48	1.111±.35	**1.192**±.43
Lipoprotein(a)¶ (mg/dL)	1400	10.6 (4.7; 26)	8.88 (4.4; 19.5)	13.0 (5.6; 29.8)	13.4 (5.7; 34.2)
Creatinine (mg/dL)	1568	1.025±.53	**1.18**±.65	0.805±.21	**0.982**±.75
C-reactive protein¶ (mg/L)	1767	1.9 (1; 4.5)	2.5 (1; 6.8)	3 (1.4; 6.3)	2.9 (1.2; 7.7)
Antihypertensive drug, n, %	2121	135; 18.5	88; **29**	320; 37.7	116; **47.3**
Statin usage, n, %	2121	65; 8.9	30; 9.8	149; 17.6	30; 12.7
Current/former smoker, %	2121	36.4; 29.5	40.2; 29.7	11.3; 4.0	5.9; 3.8
Prevalent diabetes, n, %	2121	75; 10.3	53; **17.3**	89; 10.5	39; **16.5**
Prevalent CHD, n, %	2121	50; 6.9	86; **28.1**	64; 7.5	55; **23.2**

†Self-reported physical activity graded according to a scheme. *Self-reported monthly income, categorized.
Significantly different values are highlighted in bold, borderline significant (p=0.05-0.095) values are in italics.
†T-test or chi-square test was applied with regard to percentages.
¶Nonparametric variables: median (25%–75% percentile) values are provided. Significance using Mann-Whitney U test is indicated in bold.
BP: Blood pressure; CHD: Chronic heart disease; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation.

The distribution of mean serum TC and HDL-C values in each decile and sex, along with the respective number of deaths, are shown in Table 2, which also contains multivariable-adjusted HRs in Cox regression analysis for each decile with reference to the lowest decile. Neither TC (p trend=0.94 and 0.96, respectively), nor HDL-C categories (p trend=0.20 and 0.31, respectively) was significantly predictive of mortality in either gender.

Regarding TC categories among men, deciles 2 through 6 (135–194 mg/dL) exhibited an insignificantly (~20%) higher relative risk compared with the lowest decile, and higher TC levels had a risk similar to the reference category. Compared with the lowest TC decile, the remaining deciles in combination disclosed an HR of 1.12 (95% CI, 0.77–1.61; p=0.56). Among women, deciles displayed non-significantly lower multi-adjusted HRs (by just over one-tenth) than the lowest decile (HR: 0.89; 95% CI, 0.58–1.36; p=0.59). Interestingly, HRs in females were reciprocal to those in males, and formed a mirror image in deciles 2 through 5 (135–184 mg/dL and 150–198 mg/dL, respectively) (Figure 1).

With respect to HDL-C categories, non-significantly lower multi-adjusted HRs were observed in deciles 4 through 9 and 4 through 8 (range: 33–53 mg/

Table 2. Cox regression analysis of multivariable-adjusted¶ HDL and total cholesterol deciles at baseline (n=2121) for risk of 543 deaths

Men	HDL-cholesterol (n=305/1034)*				Total cholesterol (n=306/1035)*			
	Mean mg/dL	Deaths	HR	95% CI	Mean mg/dL	Deaths	HR	95% CI
Decile 1	23.2	30	1		123	33	1	
D 2	28.5	29	0.91	0.55; 1.53	147	38	1.25	0.78; 2.00
D 3	31.3	29	0.98	0.59; 1.64	160	34	1.12	0.69; 1.83
D 4	34	37	0.87	0.53; 1.43	169.5	30	1.24	0.75; 2.05
D 5	36.2	28	*0.63*	0.37; 1.06	179.4	27	1.11	0.66; 1.85
D 6	38.8	29	0.69	0.41; 1.16	188.7	35	1.27	0.79; 2.06
D 7	41.2	27	1.00	0.59; 1.68	199	24	1.04	0.61; 1.77
D 8	44.5	24	*0.60*	0.35; 1.03	210	27	0.88	0.52; 1.46
D 9	49.2	31	0.67	0.40; 1.11	226	30	1.14	0.68; 1.89
D 10	61.7	41	1.05	0.65; 1.71	259.9	28	1.04	0.63; 1.73
Total	38.8±11	305			188.2±39	306		
Women	**HDL-cholesterol (n=236/1080)***				**Total cholesterol (n=237/1086)**			
	Mean mg/dL	Deaths	HR	95% CI	Mean mg/dL	Deaths	HR	95% CI
Decile 1	27.9	28	1		139	24	1	
D 2	33.7	24	0.93	0.53; 1.63	162	25	0.94	0.54; 1.66
D 3	37.2	30	1.09	0.64; 1.85	174	22	0.84	0.46; 1.51
D 4	40.7	15	**0.48**	0.25; 0.91	184.3	22	0.85	0.48; 1.53
D 5	43.4	20	0.70	0.39; 1.25	193	24	0.81	0.46; 1.43
D 6	46.5	27	0.96	0.56; 1.64	203.3	23	1.11	0.62; 1.99
D 7	49	18	0.66	0.36; 1.19	211.6	19	0.82	0.45; 1.50
D 8	53.8	18	0.79	0.43; 1.45	225.5	25	0.77	0.43; 1.36
D 9	58.9	28	1.01	0.59; 1.73	243	23	0.88	0.50; 1.57
D 10	70.7	28	0.85	0.50; 1.45	281.2	30	1.05	0.60; 1.82
Total	46.3±12	236			201.7±41	237		

*Number deceased/ number at risk. Significant values are highlighted in boldface. ¶Adjusted for age, smoking status, lipid and antihypertensive drug usage, prevalent diabetes, and coronary heart disease. CI: Confidence interval; HR: Hazard ratio; HDL: High-density lipoprotein.

dL and 39–56 mg/dL, respectively), rising in the higher categories. Evidence for reciprocal behavior in the shape of the risk curve was lacking. Women showed an increase in HR in deciles 6 and 9 (Figure 1).

With respect to independent variables in the model significantly associated with risk of death, age (1 SD: 8.8 years), prevalent diabetes, and CHD revealed the following HRs in men and women: 2.13 (95% CI, 1.87–2.35) and 2.19 (95% CI, 1.95–2.55); 1.63 (95% CI, 1.19–2.25; p=0.003) and 1.53 (95% CI, 1.06–2.19; p=0.022); 1.99 (95% CI, 1.51–2.62; p<0.001) and 1.82 (95% CI, 1.31–2.52; p<0.001), respectively. Furthermore, current smoking in men (HR: 1.93; 95% CI, 1.46–2.57; p<0.001) and lipid-lowering drug usage in women (HR: 0.68; 95% CI, 0.45–1.01; p=0.057) were similarly associated. Lipid-lowering drugs were used at baseline in 9.2% and 16.5% of men and women, respectively, and antihypertensive drugs in 21.5% and 39.8%, respectively.

DISCUSSION

In a middle-aged Turkish adult sample, we investigated whether the 2 lipid risk factors commonly used as treatment targets, TC and HDL-C concentrations,

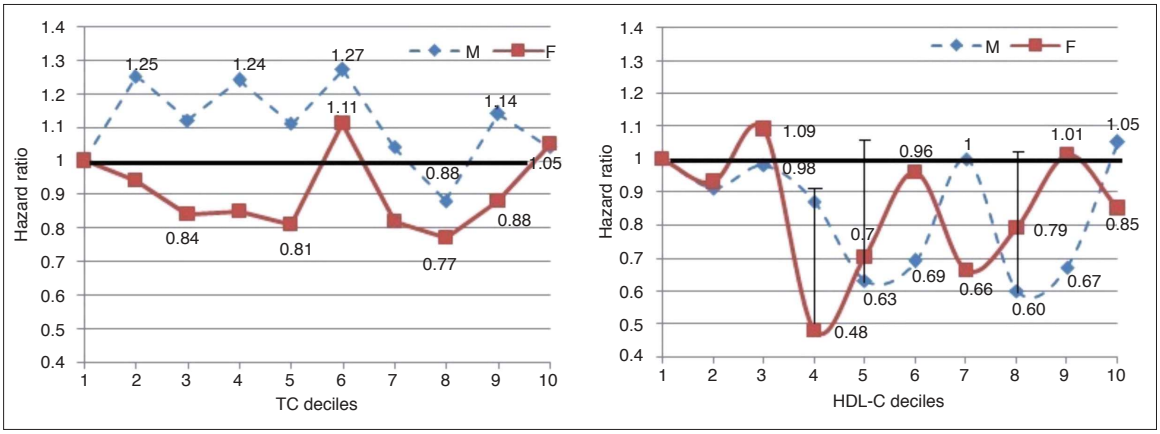


Figure 1. Graph depicts hazard ratios for risk of death of total (upper panel) and HDL cholesterol deciles (lower panel) in women and men. The generally anticipated significant trend in HR in regard to TC increments and HDL-C decrements is clearly lacking. A tendency to lower HRs in deciles 4-8 is apparent, yet rising in the 2 highest deciles. Men and women appear to show reciprocal changes in HR in the lower half of total cholesterol categories (see comment in Discussion).

HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol.

are significantly related to survival/mortality. Using categories of tenths, and adjusting for age, smoking status, lipid and antihypertensive drug usage, prevalent diabetes or CHD, and TC and HDL cholesterol levels did not predict mortality risk in either gender, and did not even display a significant trend. Baseline diabetes, CHD, and age were important determinants, added to a smoking habit in men.

Sex only marginally modulates the association of lipids with the risk of death

Though the TARF study has disclosed that several major risk factors diverge between the sexes,[16] this study did not find a disparity between women and men in the predictive value of TC and HDL-C for mortality risk. The only difference related to TC deciles was that HRs in females tended to be reciprocal to those in males in deciles 2 through 5. This may be attributed to a comparatively higher death rate in females in the lowest decile, reflecting the effect of elevated risk due to autoimmune activation in the lowest TC decile.

Lipoproteins did not confer greater risk of death

Our main finding was the lack of association with mortality risk of both TC and HDL-C in both sexes. It is pertinent to point out the findings of 2 large meta-analyses. For worldwide deaths due to cardiovascular diseases, chronic kidney disease, and diabetes in 2010, high BP formed the leading risk factor.[17]By 2010, the relative importance of high cholesterol fell, and its mortality burden was fourth greatest (after excess weight and hyperglycemia), being responsible for just more than 10% of deaths. In the meta-analysis of the Emerging Risk Factor Collaboration examining the impact of multimorbidity (diabetes, stroke, and myocardial infarction), baseline total cholesterol was lower (205 mg/dL) in 541 subjects with all 3 conditions than in over 25,600 subjects with diabetes alone (219 mg/dL), or some 6000 with a combination of 2 diseases (225 mg/dL).[18] This suggests that multimorbidity was more likely in patients with a lower TC level.

With respect to serum HDL-C, the highest and lowest 2 to 3 deciles were associated with a non-significantly higher mortality risk in each sex, compared with the intermediate categories (deciles 4 to 8/9). This is consistent with previous prospective outcome studies in Turkish adults indicating that serum HDL-C provided only partial protection against cardiometabolic risk.[19] Current findings are also in agreement with a failure of HDL-cholesterol to prove an independent risk factor in the algorithm of the French MONICA cohort.[3] Similarly, no association was found prospectively between HDL-C and all-cause mortality in Japanese-American men aged over 70 years.[8] Our HDL-C findings are also in line with a systematic review of 108 randomized trials that disclosed no association between treatment-induced

change in HDL-C level and risk ratios for cardiovascular disease morbidity and mortality when controlled for low-density lipoprotein (LDL) cholesterol.[20]

Neither TC nor HDL-C was reported to be an independent significant factor in predicting long-term all-cause mortality in the study conducted by Mannan et al.,[21] who used the Framingham cohorts. Among publications reporting on the death risk with respect to TC, the largest of which, the HUNT-2 study, analyzed 2490 deaths, documented a linearly inverse association with TC in women, and one that pursued a U-shaped risk curve in men.[2] A review of observational studies and randomized controlled trials on TC and mortality in people 80 years old or more did not find that lipid-lowering treatment had a beneficial effect on mortality.[8] After multivariable adjustment, an inverse association was found between TC and stroke or cardiovascular mortality in a Japanese cohort of over 16,000 participants tracked over a mean of 10.9 years.[22] Furthermore, a predictive value of cholesterol level for mortality was lacking in Swedish peri- and postmenopausal women, in contrast to premenopausal women.[6] Thus, our observations are far from confined to Turkish adults and are supported by previous reports studying diverse ethnicities.

Potential explanation of elicited findings

Current findings on TC, supported by the previously reported findings discussed above, are of note due to 2 shallow U-shaped risk curves in Turkish women divided by decile 6 (~198–208 mg/dL), somewhat paralleled in the top 4 deciles in men. This is consistent with parallel serum Lp(a) aggregation in deciles 8 and 7 and in deciles 5 to 2. Though these were not analyzed herein due to missing Lp(a) assays, a recent TARF study, which examined the role of a macrophage migration inhibitory factor genotype, provided some evidence that lower Lp(a) values may disclose an association with the risk of death.[23] Lp(a) quintiles in men tended to be inversely associated with incident metabolic syndrome and all-cause mortality, and a significant HR for overall mortality was found in quintile 2. No association with mortality emerged in women, which was attributed to a more complex autoimmune activation.[23] Lp(a) and LDL-cholesterol may be linked via the LDL-receptor. The reciprocal risk association in females vs males, particularly in the lowest 5 TC deciles, is indicative of Lp(a) protein aggregation operating in women but only little in men. This hypothesis is consistent with the results of a large population-based study from Japan with 830 deaths recorded during 12½ years of follow-up, which reported that a low (<8 mg/dL) Lp(a) level was a significant, 1.5-fold risk factor for all-cause death. Low Lp(a) level significantly and independently also predicted cancer and non-cardiovascular deaths.[24]

With respect to our findings that HDL-C lacks predictive value for mortality risk in either sex, it is pertinent to note that deciles 5 through 9 in women and deciles 6 through 10 in men displayed (unexpectedly) a tendency for a rising HR. This is in agreement with a pro-inflammatory conversion of such high HDL contributing to increasing risk.

Strengths and limitations The present study's large end-point and relatively large sample sizes, based on a representative general population sample of each sex, are strengths. Analysis of the lipid variables by tenths, adjusted for major determinants of risk of death, allowed for detailed characterization of the associations in a sex-stratified manner. Findings may have limited applicability among younger Turkish adults, as age was shown to be a strong effect modifier, with 3- to 4-fold higher excess risk in middle age than in individuals >70 years old.[25]

The population sample prone to impaired glucose tolerance/metabolic syndrome[26] may limit the ability to generalize conclusions to other populations who do not have a background of insulin resistance, though the present findings may have validity in similar subsets of many other populations.[27] The use of only 1 baseline measurement may have led to a regression dilution effect and underestimation of the predictive value of the lipid variables.

Guidelines on TC and HDL-C A systematic review of guidelines on cardiovascular risk assessment found they were lacking a stated consensus on the recommended age of screening for target populations.[28] Furthermore, the recommendation, "Adults 40–75 years of age with LDL-C 70–189 mg/dL, without clinical atherosclerotic CVD [cardiovascular disease] or diabetes, and with an estimated 10-year atherosclerotic CVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy",[29] is in conflict with our results, which coincide with both the age and the LDL-C brackets of individuals, harboring even a quadruple risk of mortality.

Clinical implications We agree with the HUNT study investigators[2] questioning the validity of related clinical and public health recommendations, with the notable limitation of this question with respect to certain subsets of the population, namely, individuals prone to impaired glucose regulation, and aged over 50 to 60 years. Placebo-controlled trials that enrolled individuals with high absolute risk in the settings of heart failure or renal failure found little evidence of event reduction with statin therapy despite large reductions in LDL-cholesterol.[30,31] We documented that appropriately instituted statin therapy in population subsets with metabolic syndrome or enhanced inflammation –such as in Turks- may increase CHD risk in a primary prevention setting.[32]

We conclude that TC and HDL-C levels in each sex were not relevant to mortality risk. These findings support the operation in this population of the previously epidemiologically documented excess cardiometabolic risk via the pathogenic process of enhanced pro-inflammatory state, HDL dysfunction and autoimmune activation. Together with current practice guidelines and recommendations related to diverse cardiometabolic risks, this finding should guide clinical practitioners in the prevention of multimorbidity in adults aged over 50 years.

Acknowledgement

We acknowledge the support of the Turkish automotive firm, TOFAŞ, and the Turkish Society of Cardiology, Istanbul, Turkey, for the recent TARF surveys.

REFERENCES

1. Hoes AW, Grobbee DE, Valkenburg HA, Lubsen J, Hofman A. Cardiovascular risk and all-cause mortality; a 12 year follow-up study in The Netherlands. Eur J Epidemiol 1993;9:285–92.
2. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TI, 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 Eval Clin Pract 2012;18:159–68.
3. Bérard E, Bongard V, Arveiler D, Amouyel P, Wagner A, Dallongeville J, et al. Ten-year risk of all-cause mortality: assessment of a risk prediction algorithm in a French general population. Eur J Epidemiol 2011;26:359–68. [CrossRef]
4. Song X, Jousilahti P, Stehouwer CD, Söderberg S, Onat A, Laatikainen T, et al; DECODE Study Group. Cardiovascular and all-cause mortality in relation to various anthropometric measures of obesity in Europeans. Nutr Metab Cardiovasc Dis 2015;25:295–304. [CrossRef]
5. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39. [CrossRef]
6. Lindquist 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]
7. Volpato S, Leveille SG, Corti MC, Harris TB, Guralnik JM. The value of serum albumin and high-density lipoprotein cholesterol in defining mortality risk in older persons with low serum cholesterol. J Am Geriatr Soc 2001;49:1142–7. [CrossRef]
8. Koropatnick TA, Kimbell J, Chen R, Grove JS, Donlon TA, Masaki KH, et al. A prospective study of high-density lipoprotein cholesterol, cholesteryl ester transfer protein gene variants, and healthy aging in very old Japanese-american men. J Gerontol A Biol Sci Med Sci 2008;63:1235–40. [CrossRef]
9. 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. [CrossRef]
10. Onat A, Can G, Ademoğlu E, Kaya A, Tusun E, Ural D. Little contribution of conventional factors in an algorithm to predicting death risk in Turkish adults. Int J Cardiol 2017;230:542–8.
11. Onat A, Can G. Enhanced proinflammatory state and autoimmune activation: a breakthrough to understanding chronic diseases. Curr Pharm Des 2014;20:575–84. [CrossRef]
12. Onat A. Risk factors and cardiovascular disease in Turkey. Atherosclerosis 2001;156:1–10. [CrossRef]
13. 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. Diabetes Care 2003;26:3160–7. [CrossRef]
14. Onat A, Avcı GŞ, Şenocak M, Örnek E, Gözükara Y. Plasma lipids and their interrelation in Turkish adults. J Epidem Commun Health 1992;46:470–6. [CrossRef]
15. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular Survey Methods. 2nd ed. World Health Organization Monograph Series, No 56. Geneva: p. 124–7.
16. Onat A, Karadeniz Y, Tusun E, Yüksel H, Kaya A. 2016 Mar 2. Advances in understanding gender difference in cardiometabolic disease risk. Expert Rev Cardiovasc Ther 2016;14:513–23. [CrossRef]
17. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. Lancet Diabetes Endocrinol 2014;2:634–47. [CrossRef]
18. Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, et al. Association of Cardiometabolic Multimorbidity With

Mortality. JAMA 2015;314:52–60. [CrossRef]
19. Onat A, Can G, Ayhan E, Kaya Z, Hergenç G. Impaired protection against diabetes and coronary heart disease by high-density lipoproteins in Turks. Metabolism 2009;58:1393–9.
20. Briel M, Ferreira-Gonzalez I, You JJ, Karanicolas PJ, Akl EA, Wu P, et al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. BMJ 2009;338:b92. [CrossRef]
21. Mannan HR, Stevenson CE, Peeters A, McNeil JJ. A new set of risk equations for predicting long term risk of all-cause mortality using cardiovascular risk factors. Prev Med 2013;56:41–5. [CrossRef]
22. Boumendil A, Latouche A, Guidet B; ICE-CUB Study Group. On the benefit of intensive care for very old patients. Arch Intern Med 2011;171:1116–7. [CrossRef]
23. Onat A, Can G, Çoban N, Dönmez İ, Çakır H, Ademoğlu E, et al. Lipoprotein(a) level and MIF gene variant predict incident metabolic syndrome and mortality. J Investig Med 2016;64:392–9. [CrossRef]
24. Sawabe M, Tanaka N, Mieno MN, Ishikawa S, Kayaba K, Nakahara K, et al. Low lipoprotein(a) concentration is associated with cancer and all-cause deaths: a population-based cohort study (the JMS cohort study). PLoS One 2012;7:e31954.
25. Sawabe M, Tanaka N, Mieno MN, Ishikawa S, Kayaba K, Nakahara K, et al; JMS Cohort Study Group. Low lipoprotein(a) concentration is associated with cancer and all-cause deaths: a population-based cohort study (the JMS cohort study). PLoS One 2012;7:e31954. [CrossRef]
26. Onat A, Ceyhan K, Başar O, Erer B, Toprak S, Sansoy 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.
27. Dodani S. Excess coronary artery disease risk in South Asian immigrants: can dysfunctional high-density lipoprotein explain increased risk? Vasc Health Risk Manag 2008;4:953–61. [CrossRef]
28. Ferket BS, Colkesen EB, Visser JJ, Spronk S, Kraaijenhagen RA, Steyerberg EW, et al. Systematic review of guidelines on cardiovascular risk assessment: Which recommendations should clinicians follow for a cardiovascular health check? Arch Intern Med 2010;170:27–40. [CrossRef]
29. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1–45. [CrossRef]
30. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231–9.
31. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395–407. [CrossRef]
32. Onat A, Aydın M, Can G, Cakmak HA, Köroğlu B, Kaya A, et al. Impaired fasting glucose: Pro-diabetic, "atheroprotective" and modified by metabolic syndrome. World J Diabetes 2013;4:210–8.

Keywords: High-density lipoprotein cholesterol; mortality risk; sex; Turkish Adult Risk Factor study; total cholesterol.

Anahtar sözcükler: Yüksek-yoğunluklu lipoprotein kolesterol; ölüm riski; cinsiyet; Türk Erişkinlerinde Kalp Hastalığı ve Risk Faktörleri çalışması; total kolesterol.