Low HDL-C in Turks: genetic/lifestyle interactions modulate plasma levels

Türklerde düşük HDL-C düzeyleri: Genetik/yaşam tarzı etkileşimleri plazma düzeylerini etkiliyor

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Objectives: Many studies have shown that extremely low high density lipoprotein cholesterol (HDL-C) levels (mean ~36 mg/dl in men; ~42 mg/dl in women) constitute a prime coronary heart disease (CHD) risk factor in Turks. We reviewed three separate cohorts of Istanbul residents surveyed over the past 14 years and evaluated trends in risk factors for CHD in men and women during this period.

Study design: The study subjects were healthy Turkish residents of Istanbul ≥20 years of age. Subjects recruited in 1996-2000 (n=828) and in 2003 (n=1100) were compared with the original Istanbul cohort (n=2686) of the Turkish Heart Study, recruited in 1990-1993.

Results: The mean HDL-C level increased from 45.3±9.5 mg/dl in 1990-1993 to 49.7±12.0 mg/dl in 2003 in women (p<0.0001). In 2003, university-educated women had markedly higher mean HDL-C levels than women with a primary school or less education (56±9 mg/dl *versus* 48±12 mg/dl, p<0.0001). Consistent with this difference, highly educated women with higher HDL-C levels had a lower body mass index (mean 25.6±4.9 kg/m^2 *versus* 29.7±5.1 kg/m^2), smaller waist circumference, smoked less, and exercised more. Among men, the HDL-C distributions were very similar in both the 1990-1993 and 2003 cohorts (38.3±8.3 mg/dl *versus* 39.3±9.8 mg/dl, respectively). There was no significant difference in terms of HDL-C distribution between men with higher and lower levels of education.

Conclusion: Data from the three cohorts show that, although genetically determined to a great extent, low HDL-C levels can be modulated by lifestyle factors. Higher levels of education are associated with a 10% to 15% increase in the HDL-C levels of women. However, the lack of an association between educational level and HDL-C in men remains to be explained.

Key words: Cohort studies; coronary disease/epidemiology; educational status; female; life style; lipoproteins, HDL cholesterol/blood; risk factors; socioeconomic factors; Turkey.

Amaç: Birçok çalışma, aşırı derecede düşük düzeydeki yüksek yoğunluklu lipoproteinin (HDL-C) (erkeklerde ort. ~36 mg/dl; kadınlarda ort. ~42 mg/dl) Türklerde koroner kalp hastalığı için temel bir risk faktörü oluşturduğunu göstermiştir. Bu çalışmada, 14 yıl içinde İstanbul'da yaşayan Türklerde yürütülen üç kohort çalışma incelenerek, erkek ve kadınlarda koroner kalp hastalığı risk faktörlerindeki eğilimler değerlendirildi.

Çalışma planı: Çalışmalara İstanbul'da yaşayan ve yaşı 20 veya uzerinde olan sağlıklı kişiler alınmıştı. 1996-2000 (n=828) ve 2003 (n=1100) yıllarında incelenen kişilerin verileri, 1990-1993 yıllarında Türk Kalp Çalışması kapsamında incelenen 2686 kişinin verileriyle karşılaştırıldı.

Bulgular: Kadınlarda 1990-1993 yıllarında 45.3±9.5 mg/dl olarak ölçülen ortalama HDL-C düzeyi 2003'te 49.7±12.0 mg/dl'ye yükseldi (p<0.0001). 2003 kohortunda üniversite eğitimi görmüş kadınlarda, ilkokul eğitimi görmüş veya daha düşük düzeyli eğitimli kadınlara göre ortalama HDL-C düzeyinde belirgin yükselme vardı (sırasıyla 56±9 mg/dl ve 48±12 mg/dl, p<0.0001). Bu farklılıkla uyumlu olarak, daha ileri eğitim gören ve HDL-C düzeyi daha yüksek olan kadınlarda beden kütle indeksi (sırasıyla ort. 25.6±4.9 kg/m^2 ve 29.7±5.1 kg/m^2) ve bel çevresi değerleri, sigara içme oranı daha düşük, egzersiz düzeyi daha yüksekti. Erkeklerde ise, 1990-1993 ve 2003 kohortlarındaki HDL-C dağılımları çok benzer bulundu (sırasıyla 38.3±8.3 mg/dl ve 39.3±9.8 mg/dl) ve yüksek ve düşük düzeyli eğitime göre anlamlı farklılık göstermedi.

Sonuç: Üç kohorttan elde edilen veriler, büyük ölçüde genetik olarak belirlenmiş olmakla birlikte, düşük HDL-C düzeylerinin yaşam tarzı faktörlerinden etkilenebildiğini göstermektedir. Eğitim düzeyi yüksek olan kadınlarda HDL-C düzeyi %10-15 kadar yüksek bulunmuştur. Bununla birlikte, erkeklerde eğitim düzeyi ile HDL-C arasında bir ilişki gösterilememesi araştırılması gereken bir durumdur.

Key words: Cohort studies; coronary disease/epidemiology; educational status; female; life style; lipoproteins, HDL cholesterol/blood; risk factors; socioeconomic factors; Turkey.

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Low plasma levels of high density lipoprotein cholesterol (HDL-C) are an important risk factor for premature coronary heart disease (CHD).[1-5] The relationship between low HDL-C and CHD is at least as strong as that of high levels of low density lipoprotein cholesterol (LDL-C).[6] Furthermore, approximately two-thirds of patients with CHD have low HDL-C.[7,8] Recently, the National Cholesterol Education Program Adult Treatment Panel III guidelines redefined low HDL-C, raising the cut point from 35 to 40 mg/dl.[9] Observational studies suggest that CHD risk increases by 2-4% for every 1-mg/dl decrease in HDL-C.[10]

Studies of the Turkish population have provided insights into the importance of the interaction of genetic and environmental factors in modulating HDL-C levels.[11-17] Turks have low levels of total cholesterol, LDL-C, and uniquely very low levels of HDL-C.[11] Despite their low LDL-C levels, the prevalence of CHD in Turkey is much higher than in the United States and is similar to that in eastern European countries.[16,18,19] Low HDL-C level is an independent predictor of CHD risk in Turks and undoubtedly contributes significantly to the high prevalence of CHD.[20]

The original cohort of the Turkish Heart Study, which was conducted in 1990 to 1993, comprising approximately 9000 Turks from six regions of Turkey, demonstrated that the mean HDL-C was about 36 mg/dl in men and 42 mg/dl in women,[11] or about 10-15 mg/dl lower than that estimated in the United States or western European populations.[21,22] At least half of Turkish men and more than one-quarter of Turkish women have HDL-C of lower than 35 mg/dl (about 75% of men and 50% of women have HDL-C <40 mg/dl).[11]

The cause of the high prevalence of low HDL-C in Turks has been extensively studied.[11-20,23,24] HDL-C levels are modulated by genetic and lifestyle (environmental) factors, including physical activity, body weight, cigarette smoking, ethanol consumption, and the proportion of calories consumed as carbohydrates.[25-32] Although these lifestyle factors are associated with variability in HDL-C levels in the Turkish population, these factors do not account for the disparity in HDL-C levels between the populations of the United States/western European and Turkey.[11-14] Previously, we showed that lifestyle factors modulate HDL-C levels in Turks by only 1-3 mg/dl.[11] In some populations, low HDL-C levels are associated with hypertriglyceridemia. However, in Turks, hypertriglyceridemia is not highly prevalent and HDL-C levels are much lower than in other populations across the spectrum of triglyceride levels from less than 50 mg/dl up to 300 mg/dl.[12,33]

Several lines of evidence suggest that the high prevalence of low HDL-C in Turks has a genetic origin. First, the HDL-C levels of Turkish adults are similar throughout the country despite substantial regional differences in diet that affect LDL-C levels, ranging from a Mediterranean-type diet high in monounsaturated fats to a diet very rich in saturated fat.[11] The consistency of low HDL-C levels in Turks (about 20% lower than that seen in western Europe) has been confirmed and extended in the Turkish Adult Risk Factor Study and other studies by Onat and associates.[16,18-20,23] In a survey of more than 2,000 subjects conducted in 1997-1998, HDL-C levels of 37 and 45 mg/dl were reported for Turkish men and women, respectively.[20] In addition, Tezcan et al.[34] conducted a cross-sectional survey of 1,210 Turkish men and women (25-64 years of age) in Ankara in 1999. The mean HDL-C levels were 36-39±8 mg/dl for men and 42-45±11 mg/dl for women (lipid analyses were performed in the reference laboratory in Giessen University, Germany). The prevalences of low HDL-C in Turkish men (<35 mg/dl) and Turkish women (<42 mg/dl) were five and eight times greater than those for Germans, respectively.

Turks living outside of Turkey also have low HDL-C levels and a high prevalence of CHD. Two major studies have established that HDL-C levels are similarly low in Turks living in Germany and in those living in Turkey.[35,36] As part of the large and well-known PROCAM epidemiological study, Lüttmann and associates[35] reported that Turkish men and women living in northwestern Germany had HDL-C levels of 38±10 mg/dl and 46±12 mg/dl, respectively. In contrast, German men and women in the same study had HDL-C levels of 47±12 mg/dl and 60±15 mg/dl, respectively. Another study of Turks living in Germany for more than 10 years (average residence time after immigration was 21 years for males and 17 years for females) demonstrated a high prevalence of CHD and low HDL-C levels.[36] Most had adopted a German lifestyle. In Germany, the prevalence of CHD in Turks was as high as or even higher than in Germans of similar age (35 to 64 years). The mean HDL-C level was 32 mg/dl in Turkish men and 37 mg/dl in women (73% of men and 47% of women had HDL-C <35 mg/dl).

Similarly, we showed that the mean HDL-C levels of Turks living in the San Francisco Bay Area

were as low as those of Turks in Turkey (men, 37 mg/dl; women, 46 mg/dl).[12] Most had adopted a typical American lifestyle, including nutritional habits. Furthermore, the non-Turkish spouses of Turks in San Francisco had higher HDL-C levels typical of American/western European populations. All these studies demonstrate that Turks, regardless of where they live, have low HDL-C levels, indicating that there is a strong genetic factor modulating their HDL-C levels. This genetic susceptibility for low HDL-C is likely to be widespread throughout this part of the world and, of course, is possibly not confined to Turks. Recent extensive family studies have shown that the heritability of low HDL-C levels is 80% in Turks, a genetic predisposition far greater than reported for any population studied (unpublished data).

We explored polymorphisms in candidate genes involved in the regulation of HDL-C levels in Turkish subjects. Three genes were found to be of interest: hepatic lipase,[37,38] ATP binding cassette transporter A1,[39] and cholesterol ester transfer protein (CETP).[40] For example, four polymorphisms in the ATP binding cassette transporter A1 were associated with a 6-9% change in HDL-C. Furthermore, there was a striking interaction between the CETP *Taq*IB polymorphism and smoking in Turks. Men with the CETP B1B1 genotype, who smoked had markedly lower HDL-C levels (32.8±5.5 mg/dl) than men with the CETP B2B2 genotype, who did not smoke (37.1±6.9 mg/dl). Likewise, women with the CETP B1B1 genotype, who smoked had much lower HDL-C (35.5±4.0 mg/dl) compared with nonsmokers with the CETP B2B2 genotype (42.3±8.5 mg/dl).[40] Clearly, various genes are interacting to modulate HDL-C levels.

Low HDL-C levels in Turks are characterized specifically by low levels of either HDL_2 or the LpAI subfraction of HDL, which is 20% to 25% lower in Turks than in others.[13] High levels of these subclasses are typically associated with protection against CHD.[41-43] Consistent with the reduction of LpAI and HDL_2, Turks have an elevated level of hepatic lipase activity (25% to 30% higher than found in western Europeans).[13]

Interestingly, HDL-C levels in prepubescent Turkish children[14] are similar to those of prepubescent children in other populations of the world.[44-48] However, in Turks, HDL-C levels decrease markedly during adolescence, especially in those of higher socioeconomic status, after which they remain consistently low throughout adulthood.[14] This profound decrease in HDL-C at puberty (20 mg/dl in males and 13 mg/dl in females) may reflect alterations in the androgen/estrogen balance at puberty and a modulation of hepatic lipase affecting HDL-C levels. Hergenç et al.[49] have reported on hormonal changes in Turkish adults.

To evaluate population trends in plasma lipids, anthropometrics, and lifestyle factors, we recently compared three separate cohorts of Istanbul residents surveyed over the past 14 years.[50] In this review, we evaluated trends in CHD risk factors in men and women during this period.

MATERIALS AND METHODS

Study subjects. The study subjects were healthy Turkish residents of Istanbul ≥20 years of age. Subjects recruited in 1996-2000 (n=828) and in 2003 (n=1100) were compared with the original Istanbul cohort (n=2686) of the Turkish Heart Study, recruited in 1990-1993.[11] The study protocols were approved by the Committee on Human Research of the University of California, San Francisco. All the subjects gave informed consent. Those with acute or chronic illnesses or taking hypolipidemic drugs were excluded.

The Turkish subjects were also compared with non-Hispanic whites in the Third National Health and Nutrition Examination Survey of 1988-1994 (NHANES III).[51] These subjects (1721 men and 1895 nonpregnant women ≥20 years of age) had fasted for at least eight hours before examination. Information on their blood lipid and glucose levels, body mass index (BMI), and waist circumference was available.

Examination and laboratory procedures. Blood was collected by venipuncture in the morning after a 10-hour fast, put on ice, and centrifuged within 2-4 hours. Aliquots of plasma, serum, and buffy coats were stored at -70°C until analysis. Height was measured to within 0.5 cm and weight to within 0.1 kg. Waist circumference was measured to the nearest 0.5 cm by standard methods.[52]

All biochemical assays were performed in the clinical laboratory of the Koç American Hospital in Istanbul, which is certified as a reference laboratory by the Centers for Disease Control and Prevention (Atlanta, GA, USA) since 1990 and by the College of American Pathologists since 1994. Total cholesterol, triglyceride, and HDL-C levels were measured enzymatically.[11,50,53] Kits from Boehringer-Mannheim

(Mannheim, Germany) were used for lipid and glucose assays. A multi-channel analyzer (Hitachi, Tokyo, Japan) was used for colorimetric enzymatic determinations of cholesterol (Cholesterol, CHOD-PAP), triglyceride (Triglyceride, GPO-PAP), and glucose (Glucose, GOD-PAP).[12,13] For subjects with triglyceride levels <500 mg/dl, LDL-C was calculated using the Friedewald equation.[54]

It is well known that HDL-C quantitation can be problematic, especially when HDL-C levels are measured with portable or bench-top analyzers.[53,55] The assays used to measure HDL-C underwent changes between 1990 and 2003.[11,50] To ensure the reliability of the HDL-C measurements of our Turkish Heart Study subjects, we transported annually, frozen samples to San Francisco to be analyzed in the Gladstone Lipid Chemistry Laboratory. Comparability of HDL-C levels was maintained, and results obtained in the laboratory in Istanbul were virtually identical to those obtained in San Francisco. This standardization allowed comparison of data obtained for Americans and Turks and of data for Turks from 1990 through 2003.

Socioeconomic and lifestyle data and medical and family histories were collected by an experienced interviewer using a detailed questionnaire.[11] The socioeconomic factors included income (stratified into four categories and normalized to the United States dollar every 6 months since the original survey of 1990-1993), occupation, and the level of education. For statistical analysis, alcohol consumption, cigarette smoking, and physical activity levels were analyzed as ordinal variables. Higher educational level was defined as a university or postgraduate education, while lower educational level as a high school education or less.

The examination and laboratory procedures were reported in detail for both the Turkish Heart Study[11,50] and NHANES III.[51]

Statistical analysis. Continuous variables were presented as the mean and standard deviation. All variables or their logarithmic transforms were normally distributed. The mean values were compared by the t-test and a p value of less than 0.05 was considered significant. For comparisons, cohorts were age-adjusted by the direct method,[56] with men and women stratified separately into 10-year age groups. To avoid over-biasing due to the relatively small sample size, older subjects (60+ years) in the Turkish cohorts were pooled. Values for the NHANES III population were calculated by using sampling weights to provide a representation of the U.S. population. SPSS v10.0 and MS Excel 97 were used for statistical analyses.

RESULTS

Characteristics of the Istanbul survey populations. The mean age of the subjects was about 40±11 years. As previously mentioned,[11] HDL-C levels are virtually unchanged throughout adulthood. The characteristics of men and women in all three surveys are shown in Fig. 1. The prevalence of obesity increased in both men and women in 2003, with 31% of men and 42% of women having a BMI >30 kg/m^2. Smoking appeared to have decreased in women but not men, and exercise levels did not increase in the 2003 survey.[50]

Among men, total cholesterol and LDL-C levels were lower in 2003 than in 1990-1993, but triglyceride levels were higher. HDL-C was slightly (1 mg/dl) higher in 2003 than in 1990-1993. Among women, total cholesterol increased slightly over the decade, but LDL-C did not. Triglyceride levels also increased, as did the mean HDL-C level, which was higher in 2003 (50 mg/dl) than in 1990-1993 (45 mg/dl) or 1996-2000 (43 mg/dl). The latter two values were not significantly different (for more detailed comparisons see reference 50).

Effect of environment and lifestyle factors on HDL-C in Istanbul women. To identify associations that might help explain the recent increases in HDL-C, particularly among women, we examined several environmental and lifestyle factors (Fig. 2). Higher educational level was associated with a significant increase in HDL-C. Although nonexistent or weak in the earlier cohorts, this association was statistically and biologically significant in 2003, being 8-mg/dl higher in the most-educated women compared to the least-educated counterparts. A low BMI (≤25 kg/m^2) and an exercise level of more than 1 hour/week were also associated with higher HDL-C values. The characteristics of women in the 2003 cohort according to level of education are summarized in Table 1.

Factors that could explain the higher HDL-C levels in highly educated women were their lower prevalence of obesity, smaller waist circumference, increased exercise, and decreased smoking. Although women with a higher educational level had lower triglyceride levels, a stepwise multiple regression analysis incorporating all these factors demonstrated that the difference in triglyceride levels accounted for only a 2-mg/dl change in HDL-C levels. This is consistent with data from the Framingham study and the Turkish Heart Study, sug-

Table 1. Characteristics of women in the 2003 cohort according to level of education

	Lower education	Higher education	*p*
Total cholesterol (mg/dl±SD)	188±41	192±53	NS
LDL-C (mg/dl±SD)	115±35	118±50	NS
Triglycerides (mg/dl±SD)	118±64	89±41	0.0001
HDL-C (mg/dl±SD)	48±12	56±9	<0.0001
Body mass index >30 kg/m^2	45%	15%	
Waist circumference >88 cm	59%	23%	
Waist circumference <84 cm	26%	62%	
Exercise (>1 hour/week)	23%	37%	
Smokers (>1 cigarette/day)	29%	24%	

NS: Not significant

gesting that differences in triglyceride levels are too small to account for more than a 1-2-mg/dl difference in HDL-C values.[12,33] Smoking had no significant effect on HDL-C. These data are summarized in detail in Table 2.

HDL-C distribution. The HDL-C distributions in the 1990-1993 and 2003 cohorts according to the level of education are summarized in Fig. 3. Among Istanbul men, the HDL-C distributions were very similar in both the 1990-1993 and 2003 cohorts. Likewise,

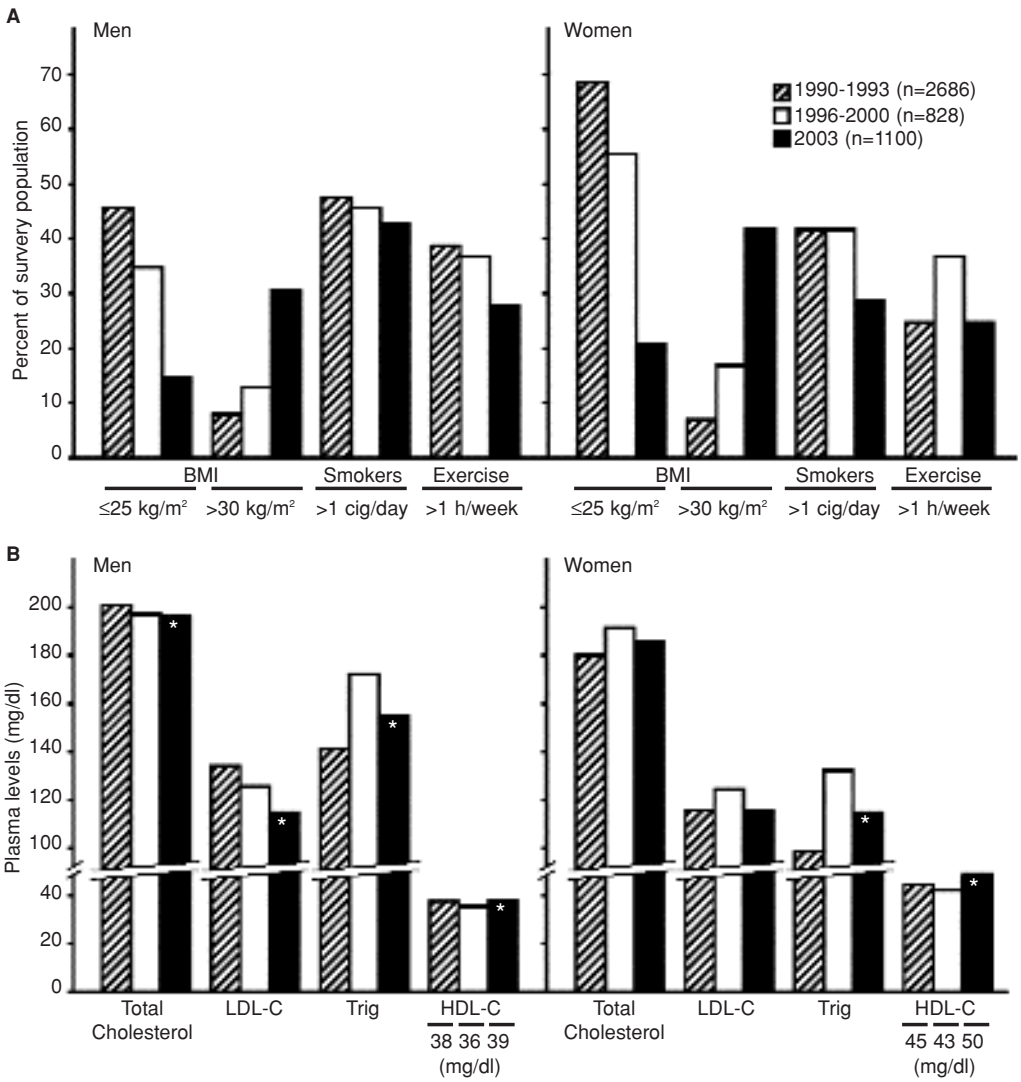

Fig. 1. (A) BMI, smoking, and exercise and **(B)** plasma lipid and lipoprotein levels in Istanbul men and women in the three survey populations. *Significant difference between 1990-1993 and 2003 values (p<0.01).

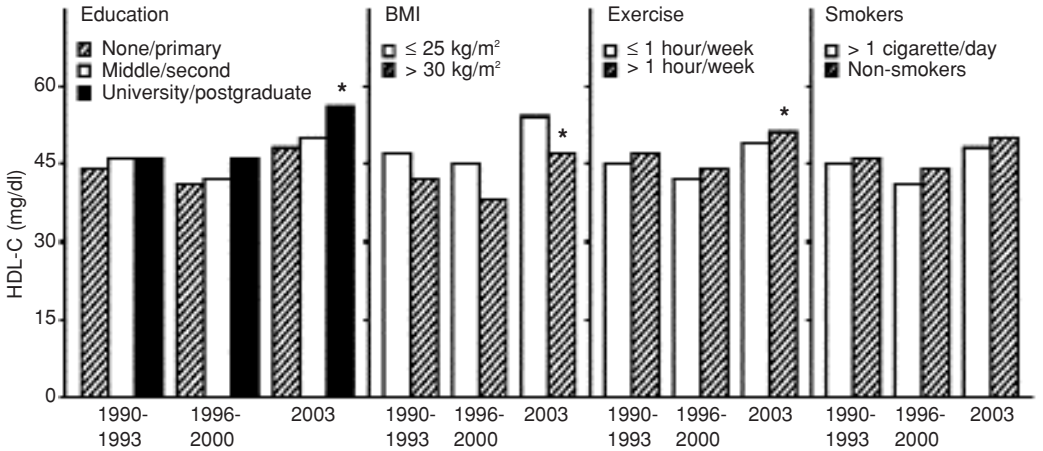

Fig. 2. Effect of environment and lifestyle factors on HDL-C levels in Istanbul women in the three survey populations. Mean age-adjusted values are shown. *Significant difference between values from the lower *versus* higher educated women ($p<0.01$).

there was no significant difference in terms of HDL-C distribution between men with higher and lower levels of education. The peak HDL-C values were about 35-39 mg/dl (Fig. 3a, top panels). The lack of an association between educational level and HDL-C in men remains to be explained.

Among Istanbul women, HDL-C levels increased significantly between the 1990-1993 and the 2003 population surveys. Educational level had little or no effect on the HDL-C distribution in the 1990-1993 cohort (peak occurred at about 40-44 mg/dl) or in the 1996-2000 cohort (data not shown). In 2003, however, education had a striking effect (Fig. 3a, bottom panels), with the peak HDL-C values being 45-49 mg/dl and 55-59 mg/dl in women with lower and higher education levels, respectively.

HDL-C distribution data derived from NHANES III show that non-Hispanic white women in the U.S. had significantly higher HDL-C values than Turkish women in the 2003 survey. HDL-C values were ≥60 mg/dl in about 34% of the U.S. women but in less than 10% of Turkish women (Fig. 3b). Therefore, despite a recent increase in HDL-C levels, a large proportion of Turkish women still possess undesirably low HDL-C levels. It remains to be determined if Turkish women can have higher HDL-C levels like those typical of U.S. and other European populations by significant lifestyle modifications.

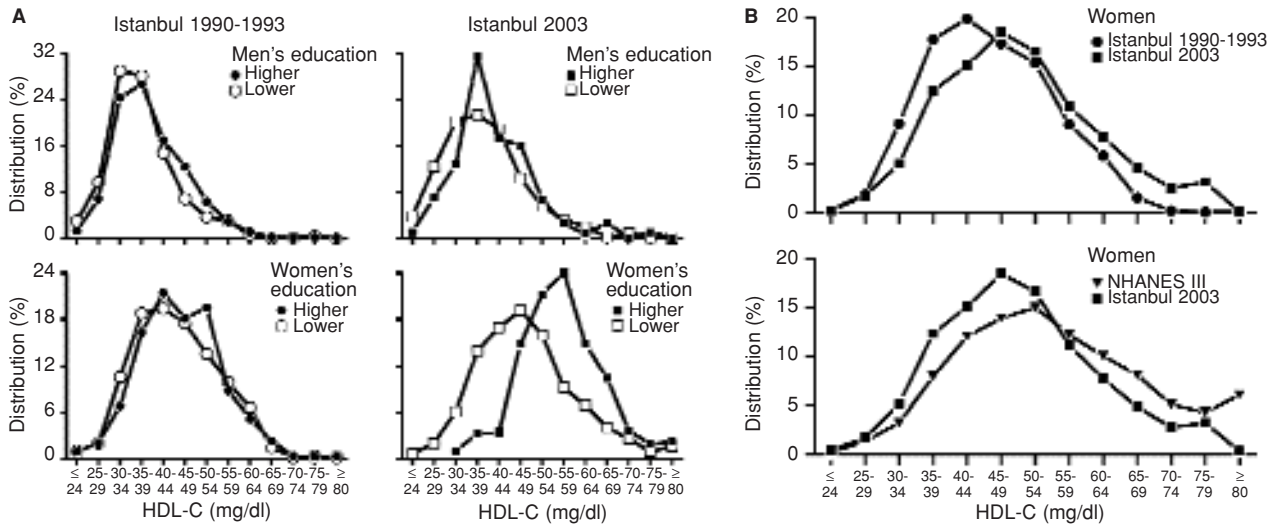

Fig. 3. (A) HDL-C distribution in Istanbul men and women in the 1990-1993 and 2003 cohorts according to level of education. **(B)** HDL-C distributions in Istanbul women and non-Hispanic white women from NHANES III.

Table 2. Impact of environment and lifestyle on HDL-C levels (mg/dl, mean±SD) in the Turkish population (age-adjusted)

	Istanbul cohorts			Lower *vs.* upper values		
	1990-1993	1996-2000	2003	1990-1993	1990-93 vs. 2003	2003
	Men / Women	Men / Women	Men / Women	Men / Women	Men / Women	Men / Women
Education						
None/primary	37±8 / 44±10	36±7 / 41±9	39±10 / 48±12	<0.0001 / 0.02	0.001 / <0.0001	NS / <0.0001
n	368 / 158	96 / 141	162 / 343			
Middle/secondary	38±9 / 46±10	35±8 / 42±10	38±9 / 50±13		NS / 0.0008	
n	427 / 193	115 / 190	171 / 223			
University/postgraduate	39±8 / 46±9	37±10 / 46±10	41±10 / 56±9		0.01 / <0.0001	
n	1362 / 178	192 / 93	119 / 81			
Salary/income						
Lower (<$500/month)	37±8 / 44±9	37±8 / 42±9	39±9 / 48±11	0.0004 / NS	0.03 / 0.0001	NS / 0.0002
n	512 / 165	125 / 143	241 / 430			
Upper (≥$500/month)	39±8 / 46±10	36±9 / 43±10	40±10 / 52±13		0.01 / <0.0001	
n	1609 / 354	274 / 277	211 / 218			
Body mass index						
≤25 kg/m^2	40±9 / 47±10	38±9 / 45±10	43±12 / 54±12	<0.0001 / 0.003	0.006 / <0.0001	0.0003 / <0.0001
n	951 / 339	134 / 207	71 / 155			
>30 kg/m^2	36±7 / 42±7	34±6 / 38±7	37±8 / 47±11		0.02 / 0.004	
n	169 / 41	57 / 92	144 / 268			
Smoking						
Nonsmoker	39±8 / 46±10	37±9 / 44±10	41±10 / 50±12	<0.0001 / NS	0.0001 / <0.0001	<0.0001 / 0.009
n	1149 / 313	240 / 247	278 / 462			
Smoker	37±8 / 45±9	35±9 / 41±9	36±8 / 48±12		NS / 0.005	
n	1008 / 216	163 / 178	174 / 186			
Alcohol						
Non-drinker	37±8 / 45±9	36±8 / 42±10	39±10 / 49±12	<0.0001 / 0.005	0.0117 / <0.0001	NS / 0.04
n	830 / 384	191 / 273	229 / 519			
Drinker (any amount)	39±9 / 47±10	36±10 / 44±10	40±10 / 52±14		NS / 0.004	
n	1289 / 134	204 / 103	223 / 128			
Waist circumference (cm)						
<102 cm			38±9 / –			0.004 / –
n			176 / –			
<98 cm			42±11 / –			
n			201 / –			
>88 cm			– / 47±11			– / <0.0001
n			– / 352			
<84 cm			– / 54±12			
n			– / 197			
Exercise						
≤1 hour/week	38±8 / 45±9	36±9 / 42±10	39±9 / 49±11	0.024 / 0.006	NS / <0.0001	0.03 / 0.06
n	1263 / 389	233 / 209	313 / 489			
>1 hour/week	39±8 / 47±10	37±10 / 44±10	41±11 / 51±14		0.009 / 0.006	
n	883 / 136	123 / 121	139 / 158			

NS: Not significant

DISCUSSION

Our findings suggest that lifestyle changes can positively affect HDL-C levels even in a population characterized by low HDL-C levels with a strong (80% heritability) genetic component. The strongest factor associated with an increased HDL-C level was higher education, specifically in women. The lack of a similar association in men may reflect a strong negative biological factor, making them resistant to the effects of lifestyle modifications. Alternatively, men may have modified lifestyle factors to a lesser extent than women, which may merit consideration of gen-

der-specific educational approaches. The increase in HDL-C among Istanbul women in the 2003 survey could be highly protective against premature CHD. Considering that each 1-mg/dl increase in HDL-C is associated with a decrease by 2-4% in the CHD risk, this 8-mg/dl increase in HDL-C could translate to a 20-30% risk reduction.

Previous studies have shown that education level, which is also an indicator of social class, acts upon many lifestyle, behavioral, psychological, and economic factors that affect risk factors for heart disease.[57-59] There is an association with hypertension, smoking, and obesity but little or no effect on cholesterol.[60-67] Physical activity is less common among the less educated,[68] and is positively associated with HDL-C and socioeconomic status in white adults.[69,70] The impact of education on disease risk factors may arise from reinforcement of positive health behavior and habits encouraged by supportive social milieu associated with higher education.[71] The Whitehall II study indicated that HDL-C rises in parallel with increasing social status[59] and that "feelings of well being," which could be associated with higher social status and educational level, may affect CHD risk.[72] Regardless of how higher education promotes positive changes in coronary risk factors, the evidence clearly establishes that intervention strategies targeting education can result in beneficial changes.

More detailed studies in a larger cohort need to be undertaken to identify the most important lifestyle factors and to assess their relative contributions to the variability of HDL-C in Turkish women. It is hoped that this approach will lead to elucidation of the metabolic pathways involved. It remains to be seen whether further improvements in lifestyle will result in increased HDL-C levels in Turkish men as they do in women.

Recently, two large population studies in Turkey have found higher HDL-C values for both men and women (personal communications: ICEBERG study, Dr. Barış İlerigelen; Metsar study, Dr. Aytekin Oğuz) than we and several others have published.[11-13,15-17,20,23,35,36,50] While these studies provide very valuable data on hypertension and the metabolic syndrome, the methodology for the measurement of HDL-C must be considered.[55] If one is to compare values among populations worldwide, then it must be ensured that the methodology provides values that are comparable. The Koç American Hospital was established as a standardized reference laboratory by the Centers for Disease Control and Prevention (Atlanta, GA, USA) in 1990.[11] Even though the methodology for measuring HDL-C has evolved over the past 15 years, we have frequently checked the consistency of all lipid biochemical parameters by conducting parallel assays in our laboratory in San Francisco. As reviewed here and elsewhere,[50] strict comparability of the results for HDL-C has been maintained, allowing comparison of values in the U.S. and Turkey and those within Turkey over more than a decade.

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