Modulation of High-Density Lipoproteins in a Population in Istanbul, Turkey, With Low Levels of High-Density Lipoproteins

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The extent to which high-density lipoprotein (HDL) cholesterol levels can be increased in patients with low HDL cholesterol is important because low HDL cholesterol levels increase the risk of coronary heart disease (CHD). During the past 14 years, we have assessed risk factors in Turks, a population in which extremely low HDL cholesterol levels (mean 36 mg/dl in men, 42 mg/dl in women) are a prime CHD risk factor. Although genetically determined to a significant extent, these low HDL cholesterol levels can be modulated by lifestyle factors, as in other populations. We measured the HDL cholesterol levels in men and women residing in Istanbul at 3 time points: 1990 to 1993, 1996 to 2000, and 2003. The mean HDL cholesterol levels increased from 45.3 ± 9.5 mg/dl in 1990 to 1993 to 49.7 ± 12 mg/dl in 2003 ($p < 0.0001$) in women, but were virtually unchanged in men (38 ± 8 vs 39 ± 10 mg/dl). In contrast to previous years, the HDL cholesterol levels in women in 2003 were markedly affected by education level and socioeconomic status, averaging 56 ± 9 mg/dl in those with a university education and 48 ± 12 mg/dl in those with a primary school education. Part of this difference could be explained by less smoking and more exercise and lower body mass index (average 25.6 ± 4.9 vs 29.7 ± 5.1 kg/m^2) of the highly educated women. It is important to note the increase in the prevalence of obesity between the 1990 to 1993 interval and 2003 in men and women, including a remarkable change from 9.4% to 45.2% among women with a primary school education. None of these factors affected the HDL cholesterol levels of men by >2 mg/dl at any of the 3 points. In conclusion, because CHD risk changes by as much as 2% to 4% per 1 mg/dl difference in HDL cholesterol level, the 8 mg/dl difference may reflect as much as a 20% to 30% reduction in CHD risk associated with the benefit of higher education in women. Why education failed to affect the HDL cholesterol levels in Turkish men remains unclear. **(Am J Cardiol 2005;96:547–555)**

Studies of the Turkish population have provided insights into the importance of the interaction of genetic and environmental factors in modulating high-density lipoprotein (HDL) cholesterol levels.[1–6] Turks have relatively low levels of total cholesterol and low-density lipoprotein (LDL) cholesterol and uniquely low levels of HDL cholesterol.[1] Despite their low LDL cholesterol levels, the prevalence of coronary heart disease (CHD) in Turkey is much higher than in the United States and is similar to that in Eastern European countries.[6–8] Low HDL cholesterol levels are independent predictors of CHD risk in Turks and undoubtedly contribute significantly to the high prevalence of CHD.[9] The high prevalence of low HDL cholesterol in Turks and the importance of a genetic component have been extensively documented by studies of Turks living in San Francisco[2] and Germany.[10,11] The Turkish Heart Study, originally conducted from 1990 to 1993 in ~9,000 Turks from 6 different regions of Turkey, demonstrated that the mean HDL cholesterol was ~36 mg/dl in men and 42 mg/dl in women,[1] or about 10 to 15 mg/dl lower than in the United States or Western European populations.[12,13] The consistently low HDL cholesterol levels in Turks was evident throughout Turkey, despite very significant differences in diet in the 6 regions surveyed. At least 1/2 of Turkish men and >1/4 of Turkish women have a HDL cholesterol level <35 mg/dl (~75% of men and 50% of women have a HDL cholesterol level of <40 mg/dl).[1] The cause of the high prevalence of low HDL cholesterol in Turks has been extensively studied.[1–9] HDL cholesterol levels are modulated by genetic and lifestyle (environmental) factors, including physical activity, body weight, cigarette smoking, ethanol

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Table 1
Istanbul study population characteristics

Variable	n	Mean age ± SD (yrs)	BMI (kg/m^2)		SBP ≥140 or DBP ≥90 (mm Hg)	Smokers		Exercise	Alcohol Consumption	
			≤25	>30		All	≥20 Cigarettes/d	>1 h/wk	Nondrinkers	>5 Drinks/Wk
Men										
1990–1993	2157	40 ± 10	46.3	8.4	17.6	47.7	22.9	39.4	38.4	13.7
1996–2000	403	41 ± 12	35.2	13.2	30.8	45.5	19.9	36.8	44.6	13.2
2003	452	42 ± 11	14.6	31.2	38.9	42.7	25.9	27.9	50.4	7.1
Women										
1990–1993	529	32 ± 10	69.2	7.2	11.5	41.8	5.5	25.3	76.9	2.9
1996–2000	425	38 ± 12	55.8	16.7	17.7	41.9	11.1	37.4	71.9	1.6
2003	648	44 ± 11	20.8	42.1	36.0	28.6	7.3	25.3	81.8	0.2

Data presented as percentages, unless otherwise noted.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

consumption, and the proportion of calories consumed as carbohydrates.[14–21] Although they are associated with variability in HDL cholesterol levels in the Turkish population, these factors do not account for the disparity in HDL cholesterol levels between the United States/Western European and Turkish populations.[1–4] Lifestyle factors modulate HDL cholesterol levels in Turks by only 1 to 3 mg/dl.[1] Likewise, hypertriglyceridemia is not widespread in Turks, and its effect in lowering HDL cholesterol in Turks is significantly less than in Americans.[2,22] In the present study, we analyzed the changes in CHD risk factors in Istanbul during the past 14 years.

Methods

Study subjects: Healthy Turkish adult volunteers were recruited at 3 different times to evaluate population trends in plasma lipids, anthropometrics, and lifestyle factors. Conducted in 1990 to 1993, the original Turkish Heart Study surveyed about 9,000 subjects from 6 different regions of Turkey.[1] The Istanbul cohort (n = 2,686) served as the base of comparison for the later studies.

The 1996 to 2000 (n = 828) and 2003 (n = 1,100) Istanbul cohorts were recruited from American Hospital employees, local advertisements, and neighborhood groups. The Committee on Human Research of the University of California, San Francisco approved the study protocols. All subjects >20 years old gave informed consent. The characteristics of the 3 cohorts are listed in Table 1. Subjects with acute or chronic medical problems and those taking hypolipidemic drugs were excluded.

The Turkish subjects were compared with non–Hispanic whites in the Third National Health and Nutrition Examination Survey of 1988 to 1994 (NHANES III),[23] a subgroup that included 1,721 men and 1,895 nonpregnant women. These subjects (age >20 years) had fasted for ≥8 hours before the examination, and data on their blood lipid and glucose levels, body mass index (BMI), and waist circumference were available.

Examination and laboratory procedures: Blood was collected from Turkish participants after a 10-hour fast. The iced samples were processed within 2 to 4 hours. Plasma, serum, and buffy coat aliquots were pipetted and stored at −70°C until the assays were conducted. For calculation of BMI, height was measured to within 0.5 cm and weight to within 0.1 kg. The waist circumference was measured to the nearest 0.5 cm according to standard guidelines.[24] All measurements were taken with shoes removed and with participants wearing light clothing.

The plasma total cholesterol, triglyceride, HDL cholesterol, and glucose concentrations were analyzed in the clinical laboratory of the American Hospital in Istanbul, which is certified as a reference laboratory by the Centers for Disease Control (Atlanta, Georgia).[1] The total cholesterol, triglyceride, and HDL cholesterol concentrations were measured enzymatically. The methods used to determine the HDL cholesterol level changed between 1990 and 2003. In the original Turkish Heart Study, HDL was separated from the other lipoproteins manually with phosphotungstic acid and magnesium chloride.[1] From 1990 to 1998, this precipitation technique was used to measure HDL cholesterol. Twice a year, frozen samples were transported to San Francisco and analyzed in the Gladstone Lipid Chemistry Laboratory using similar methods to establish comparability in results obtained with the United States and Turkish samples. After 1998, a direct, or homogenous, assay for measuring HDL cholesterol levels was used at the American Hospital Clinical Laboratory to automate the process.[25] The 2 methods were run in parallel for several months, and no significant differences were noted. Likewise, samples continued to be analyzed periodically in San Francisco.

To substantiate further the comparability of HDL cholesterol levels measured by the 2 techniques and to allow a comparison of results for the United States and Turkish populations, we sampled 66 patients in our Istanbul laboratory in 2002 and compared the results of the assays performed in 3 separate, standardized laboratories. The laboratory at the American Hospital in Istanbul used a

Table 2
Plasma lipids, lipoproteins, body mass index (BMI), and blood pressure for Istanbul survey population (age-adjusted)

Variable	Total Cholesterol (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)	TC/HDL-C	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)
Men								
1990–1993	201 ± 48	135 ± 40	38.3 ± 8.3	142 ± 136	5.5 ± 2	25.6 ± 3.3	120 ± 18	77 ± 12
n	2,157	2,112	2,157	2,157	2,157	2,028	1,794	1,789
1996–2000	197 ± 51	126 ± 42	36.2 ± 8.8	174 ± 159	5.8 ± 2.2	26.5 ± 3.4	129 ± 19	82 ± 11
n	403	392	403	403	403	401	383	380
2003	186 ± 37	115 ± 32	39.3 ± 9.8	159 ± 108	5.0 ± 1.4	28.5 ± 3.5	135 ± 20	86 ± 11
n	452	444	452	452	452	452	445	445
p Value (1990–1993 vs 1996–2000)	NS	0.0001	<0.0001	<0.0001	0.0168	<0.0001	<0.0001	<0.0001
p Value (1990–1993 vs 2003)	<0.0001	<0.0001	0.0140	0.011	<0.0001	<0.0001	<0.0001	<0.0001
Women								
1990–1993	182 ± 63	116 ± 38	45.3 ± 9.5	98 ± 143	4.3 ± 4	24.1 ± 4.1	115 ± 19	72 ± 12
n	529	521	529	529	529	513	506	506
1996–2000	194 ± 59	125 ± 50	42.6 ± 9.8	133 ± 123	4.8 ± 1.9	26.2 ± 5.2	123 ± 18	80 ± 12
n	425	421	425	425	425	425	397	397
2003	188 ± 43	116 ± 37	49.7 ± 12	115 ± 62	4.0 ± 1.3	29.2 ± 5.2	132 ± 24	84 ± 13
n	648	648	648	648	648	648	645	645
p Value (1990–1993 vs 1996–2000)	0.0026	0.0016	<0.0001	<0.0001	0.023	<0.0001	<0.0001	<0.0001
p Value (1990–1993 vs 2003)	0.0299	NS	<0.0001	0.0069	0.0472	<0.0001	<0.0001	<0.0001

Data presented as numbers and mean ± SD.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; other abbreviations as in Table 1.

homogenous automated assay, the lipid laboratory of the Gladstone Institute of Cardiovascular Disease used phosphotungstic acid and magnesium chloride precipitation, and the Northwest Lipid Research Laboratories (Seattle, Washington) also used a precipitation technique. The mean HDL cholesterol values (±SD) in the 3 laboratories were not significantly different: 44 ± 12, 45 ± 14, and 46 ± 12 mg/dl, respectively. We concluded that the values obtained in 1990 to 1993, 1996 to 2000, and 2003 could be reliably compared. Kits from Boehringer-Mannheim (Mannheim, Germany) were used for lipid and glucose assays. A multichannel analyzer (Hitachi, Tokyo, Japan) was used for colorimetric enzymatic determinations of cholesterol (Monotest Cholesterol, CHOD-PAP), triglycerides (Peridochrom Triglyceride, GPO-PAP), and glucose (Glucose, GOD-PAP).[2,3] LDL cholesterol was calculated with the Friedewald[26] equation for patients with triglycerides <500 mg/dl.

An experienced interviewer collected detailed socioeconomic and lifestyle data and medical and family history data.[1] Socioeconomic factors included income (stratified into 4 categories and normalized to the United States dollar every 6 months, since the original survey of 1990 to 1993), occupation, and education level. For statistical analysis, alcohol consumption, cigarette smoking, and physical activity levels were placed into ordinal categories. A higher educational level was defined as university or higher and a lower educational level was defined as high school or less.

The examination and laboratory procedures have been reported in detail elsewhere for the Turkish Heart Study[1] and NHANES III.[23]

Statistical analysis: All continuous variables are reported as the mean ± SD. All parameters or their logarithmic transforms were normally distributed. The *t* test was used to compare the mean values. A p value <0.05 was considered significant. For the comparisons, cohorts were age-adjusted by the direct method,[27] stratifying men and women separately into 10-year age groups. Older subjects (≥60 years) in the Turkish cohorts were pooled to avoid overbiasing due to the relatively small sample size. Values for the NHANES III population were calculated using sampling weights to provide a representation of the United States population. The Statistical Package for Social Sciences, version 10.0 (SPSS Inc., Chicago, Illinois) and Microsoft Excel 97 (Microsoft, Redmond, Washington) were used for the statistical analyses.

Results

Characterization of the Istanbul study populations: The general characteristics of the Turkish participants in each survey population (1990 to 1993, 1996 to 2000, and 2003) are listed in Table 1. The mean age was ~40 years in the men (n = 3,012) and ~35 years in the women (n = 1,602). The percentage of subjects with a normal BMI (≤25 kg/m^2) decreased and the percentage of those classified as obese (>30 kg/m^2) increased in the decade after the initial survey in 1990 to 1993. In parallel, the percentage of men and women with elevated systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure increased. The percentage of smokers remained very high among men (~45%) but

Table 3
Distribution of plasma lipids and lipoproteins (age-adjusted)

Variable	Original THS* (all 6 regions) (%)		Istanbul 1990–1993 (%)		Istanbul 2003 (%)		NHANES III Non-Hispanic Whites (%)	
	Men	Women	Men	Women	Men	Women	Men	Women
Total cholesterol (mg/dl)								
<175	43	49	30	52	40	40	24	25
<200	65	74	52	72	67	63	46	48
≥240	12	8	20	10	7	10	18	21
LDL-C (mg/dl)								
<100	31	38	19	37	34	34	19	26
<130	63	71	48	69	71	70	49	56
≥160	16	10	26	14	8	11	21	17
HDL-C (mg/dl)								
<40	72	45	63	30	56	20	37	13
<50	94	83	90	67	87	54	71	40
Triglycerides (mg/dl)								
<100	43	58	45	74	30	49	36	48
<150	69	82	69	89	61	80	64	75
≥200	15	8	15	5	24	9	20	14
Total cholesterol/HDL-C								
<3.5	10	25	9	37	12	42	18	40
≥4.5	65	43	68	31	62	32	57	31

Data presented as percentage.
* See Mahley et al.[1]
THS = Turkish Heart Study; other abbreviations as in Table 2.

decreased among women. Approximately 55% to 60% of male smokers consumed >1 pack of cigarettes/day. Ethanol consumption decreased in men. Women who consumed alcohol would be considered light drinkers. The exercise level appeared to be unchanged in men and women.

Blood levels and anthropometric parameters for study populations: A comparison of the lipid and lipoprotein levels for the 3 cohorts revealed small changes in total cholesterol (men ~7% decrease; women ~3% increase) and a decrease in LDL cholesterol, especially in the men (Table 2). The mean triglyceride levels increased in men and women (~12% to 17%) between the 1990 to 1993 interval and 2003. During the decade after the initial survey, the HDL cholesterol levels increased by approximately 1 mg/dl (~3%) in men and ~4 mg/dl (~10%) in women. The total cholesterol/HDL cholesterol ratio remained high in men (≥5.0) and women (≥4.0). The BMI increased by 11% in the men and 20% in the women, with a concomitant increase in blood pressure.

Turks tend to have relatively low total cholesterol and LDL cholesterol levels.[1] Table 3 lists the percent distributions of plasma lipids and lipoproteins in the original survey of the 6 different regions and in the 1990 to 1993 and 2003 Istanbul cohorts. Data from NHANES III (non-Hispanic whites) are given for comparison. Approximately 40% of Turkish men and women had total cholesterol levels of <175 mg/dl, and ~65% had levels <200 mg/dl. In contrast, only 25% of non–Hispanic white Americans (NHANES III) had plasma cholesterol levels <175, and 47% had levels <200 mg/dl. About 1/3 of Turks had a LDL cholesterol level of <100 mg/dl. The triglyceride levels were similar in Turks and non-Hispanic whites. However, Turks had very low HDL cholesterol levels.[1] This was most striking in the original survey and in the 1990 to 1993 Istanbul cohort (Table 3). Approximately 60% to 70% of men and 30% to 45% of women had HDL cholesterol levels <40 mg/dl. The HDL cholesterol levels were significantly lower than those of non-Hispanic whites. HDL cholesterol levels increased during the past decade, particularly in Turkish women (Tables 2 and 3). Triglycerides in the Turkish cohorts tended to be lower than those in non-Hispanic whites.

Education level associated with differences in plasma lipids and lipoproteins: Among men in the 1990 to 1993 and 1996 to 2000 cohorts, a higher educational level (university or higher) was associated with higher plasma total cholesterol and LDL cholesterol levels than in men with less education (high school or less; Table 4). The 2003 data did not show a difference associated with educational level. An increase in HDL cholesterol in the higher education group of men was statistically significant, but only represented a 1- to 2-mg/dl change between the 1990 to 1993 and 2003 cohorts. Education had little or no effect on BMI; however, the mean BMI increased during the decade. In all 3 cohorts, highly educated men were less likely to be obese and smoke and were more likely to exercise and have a higher salary (Table 4). In the 2003 cohort, highly educated men also had a significantly smaller waist circumference.

In women, the educational level did not affect the total cholesterol or LDL cholesterol levels but was associated

Table 4
Impact of educational levels on plasma lipids and lipoproteins and body mass index (BMI) (mean ± SD) (age-adjusted)

Variable	1990–1993			1996–2000			2003		
	Lower*	p Value†	Higher‡	Lower*	p Value†	Higher‡	Lower*	p Value†	Higher‡
Men									
n	435		1676	211		192	241		211
Total cholesterol (mg/dl)	185 ± 52	<0.0001	210 ± 44	192 ± 52	0.0420	202 ± 50	185 ± 37	NS	189 ± 36
LDL-C (mg/dl)	121 ± 39	<0.0001	143 ± 39	120 ± 39	0.0035	133 ± 44	114 ± 32	NS	119 ± 32
HDL-C (mg/dl)	37.1 ± 8.4	<0.0001	38.9 ± 8.1	35.3 ± 7.5	0.0340	37.2 ± 10	38.8 ± 9.8	0.0360	41 ± 9.6
Triglycerides (mg/dl)	136 ± 161	NS	145 ± 119	179 ± 174	NS	169 ± 140	162 ± 104	NS	152 ± 120
Total cholesterol/HDL-C	5.2 ± 2.3	<0.0001	5.6 ± 1.7	5.7 ± 2.4	NS	5.8 ± 2	5 ± 1.5	NS	4.8 ± 1.2
BMI (kg/m^2)	25.4 ± 3.5	NS	25.6 ± 3.2	26.7 ± 3.3	NS	26.2 ± 3.5	28.6 ± 3.4	NS	28.2 ± 3.9
Waist (cm)							101 ± 11	0.0099	99 ± 9
BMI >30 kg/m^2 (%)	9.2		7.8	15.2		13.1	113 (34.0)		25.5
Smokers (>1 cigarette/wk) (%)	57.2		40.6	43.9		36.5	131 (39.2)		36.5
Exercise (>1 hr/wk) (%)	34.7		44.9	25.8		43.6	94 (28.1)		37.9
Upper salary (%)	40.2		96.4	49.1		89.7	111 (33.3)		84.0
Waist >102 cm (%)							158 (47.5)		36.0
Waist <98 cm (%)							114 (34.2)		52.1
Women									
n	141		364	331		93	431		218
Total cholesterol (mg/dl)	179 ± 71	NS	188 ± 42	195 ± 57	NS	188 ± 63	188 ± 41	NS	192 ± 53
LDL-C (mg/dl)	112 ± 37	0.0007	124 ± 39	126 ± 49	NS	121 ± 54	115 ± 35	NS	118 ± 50
HDL-C (mg/dl)	44.9 ± 9.7	NS	46.2 ± 9	41.8 ± 9.5	0.0008	45.6 ± 10.3	48.8 ± 12.1	<0.0001	56 ± 9.4
Triglycerides (mg/dl)	102 ± 171	NS	89 ± 58	141 ± 133	0.0197	107 ± 73	118 ± 64	0.0001	89 ± 41
Total cholesterol/HDL-C	4.4 ± 4.8	NS	4.2 ± 1.4	4.9 ± 1.9	0.0130	4.4 ± 1.9	4 ± 1.3	0.0013	3.6 ± 1.3
BMI (kg/m^2)	24.4 ± 4.5	0.0164	23.5 ± 3.2	27 ± 5.3	<0.0001	23.4 ± 3.9	29.7 ± 5.1	<0.0001	25.6 ± 4.9
Waist (cm)							92 ± 12	<0.0001	82 ± 11
BMI >30 kg/m^2 (%)	9.4		4.7	25.1		10.6	45.2		14.5
Smokers (>1 cigarette/wk) (%)	42.5		37.6	44.0		33.9	29.2		23.9
Exercise (>1 hr/wk) (%)	21.4		35.4	32.9		49.4	22.7		36.5
Upper salary (%)	55.8		93.1	59.1		90.7	28.2		70.5
Waist >88 cm (%)							58.9		22.6
Waist <84 cm (%)							25.9		62.0

* High school and below.
† p values determined by *t* test.
‡ University and postgraduate studies.
Abbreviations as in Table 2.

with significant changes in HDL cholesterol in the 1996 to 2000 and 2003 populations (Table 4). The highly educated women in the 1996 to 2000 and 2003 cohorts had a 4- to 7-mg/dl (10% to 15%) increase in HDL cholesterol level. However, in the 1990 to 1993 cohort, the educational level had little or no effect on any of the plasma lipid or lipoprotein levels. The most dramatic change in HDL cholesterol was found among the highly educated women. It was 21% higher in the 1990 to 1993 and 1996 to 2000 cohorts than in the 2003 cohort (~46 vs 56 mg/dl). Although the BMI increased in highly educated women in 2003, a much higher percentage of the less educated women were obese (45%; Table 4). Likewise, in the 2003 cohort, many more highly educated women than less-educated women with high HDL cholesterol had a waist circumference <84 cm (62% vs 26%). They also tended to exercise more and were predominantly in the upper socioeconomic status group. The mean triglyceride levels were lowest in the highly educated women. Thus, the striking increase in HDL cholesterol among highly educated women was associated with changes in lifestyle and socioeconomic factors that raise HDL cholesterol levels. The magnitude of these beneficial changes within a decade suggests that education is reducing the risk of CHD specifically in Turkish women, but not so strikingly in Turkish men.

Effects of lifestyle and environmental factors on HDL cholesterol levels in Turkish population in Istanbul—1990 to 1993: In men, lifestyle and socioeconomic factors had a minimal impact on the HDL cholesterol levels. As presented in Table 4, the HDL cholesterol levels were only 1 to 2 mg/dl higher in men with higher education (university and postgraduate studies) or higher income than in those with a lower education or lower income. Salary (<\$500 vs ≥\$500 per month) was associated with a small increase in HDL cholesterol (37 vs 39 mg/dl, respectively). Likewise, the HDL cholesterol levels were higher (1 to 2 mg/dl) in nonsmokers, those who consumed alcohol, and those who exercised (data not shown). These results are consistent with data previously published for Turkish men.[1] The greatest difference in the mean HDL cholesterol levels (4 mg/dl) was between men with a BMI of ≤25 kg/m^2 (HDL cholesterol 40 mg/dl) and a BMI >30 kg/m^2 (36 mg/dl).

In women, the HDL cholesterol levels were ~2 mg/dl higher in those who were better educated (Table 4) and exercised (≤1 hour/week, 45 mg/dl; >1 hour/week, 47 mg/dl) or consumed alcohol (nondrinker, 45 mg/dl; drinker of any amount, 47 mg/dl). The mean HDL cholesterol level was 4 mg/dl higher in women with a BMI ≤25 kg/m^2 (47 mg/dl) than in those with a BMI >30 kg/m^2. Likewise, a lower versus upper income level was associated with a 2-mg/dl difference in HDL cholesterol.

1996 to 2000: The HDL cholesterol levels in 1990 to 1993 differed little from those in 1996 to 2000 (Table 4). None of the lifestyle and socioeconomic factors were associated with higher HDL cholesterol levels.

2003: Among men in the 2003 cohort, the mean HDL cholesterol value was slightly higher than in men in the 1990 to 1993 cohort (1- to 2-mg/dl increase in men who were highly educated [Table 4], had a high income, had a lower BMI, were nonsmokers, and consumed alcohol [data not shown]). Men with a BMI ≤25 kg/m^2 had the highest mean HDL cholesterol (43 mg/dl) (6-mg/dl difference compared with those who had a BMI >30 kg/m^2 [37 mg/dl]). Consistent with the BMI data, HDL cholesterol was higher in men with a waist circumference <98 cm than in those with a waist circumference >102 cm (42 vs 38 mg/dl).

The highly educated women had a 10-mg/dl increase in mean HDL cholesterol during the decade (46 vs 56 mg/dl). In 2003, the women who were nonsmokers, consumed alcohol (any amount), and exercised (>1 hour/week) had an increase in HDL cholesterol of 4 mg/dl (1990 to 1993, 46 mg/dl; 2003, 50 mg/dl). Pronounced differences in HDL cholesterol levels were also noted among subgroups of the 2003 cohort. Women with a BMI of ≤25 kg/m^2 had a HDL cholesterol level that was 7 mg/dl higher than those with a BMI >30 kg/m^2 (54 vs 47 mg/dl, respectively). Similarly, HDL cholesterol was 7 mg/dl higher in women with a waist circumference of <84 cm than those with a waist circumference >88 cm (54 vs 47 mg/dl).

Effects of education on HDL cholesterol levels in Turks and non-Hispanic whites: In Turkish men, the distribution of HDL cholesterol levels showed little or no significant change between the 1990 to 1993 cohort and the 2003 cohort (Figure 1). Turkish men had much lower HDL cholesterol levels than non-Hispanic whites in NHANES III (peak ~35 to 39 vs 40 to 45 mg/dl), and the distribution had shifted quite markedly to lower levels in Turks (Figure 1). In Turkish women, however, the HDL cholesterol levels increased (Table 2), and the distribution shifted toward higher values (Figure 1). Nevertheless, the HDL cholesterol peak and distribution in the Turkish women were markedly lower than in non-Hispanic whites in NHANES III (peak 40 to 44 vs 50 to 54 mg/dl; Figure 1). More than 1/3 of American women but <10% of Turkish women have HDL cholesterol values ≥60 mg/dl.

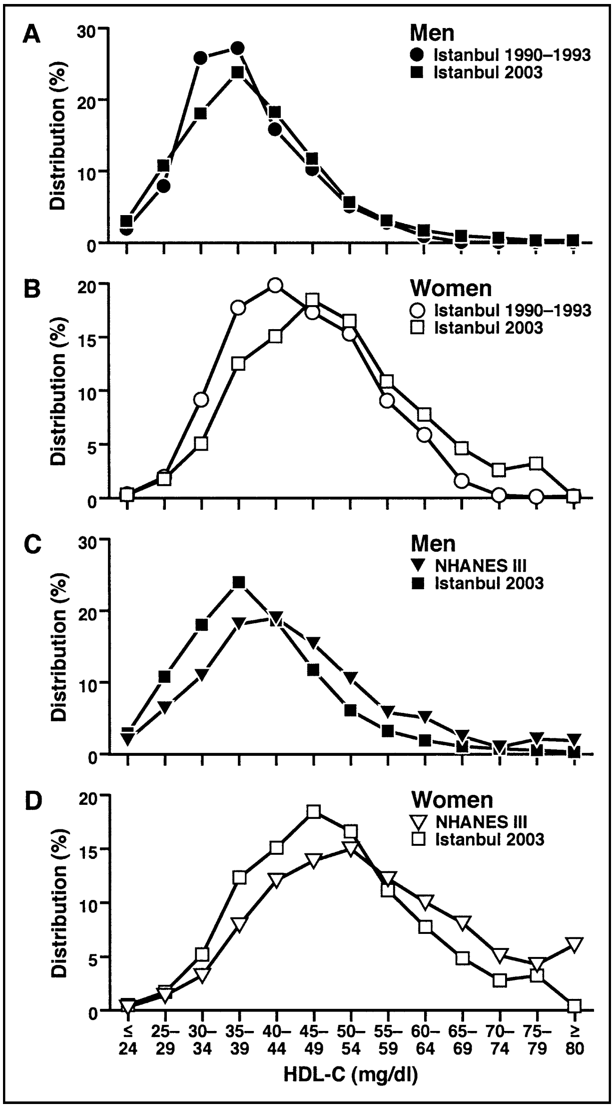

Figure 1. Distribution of plasma HDL cholesterol levels. *(A and B)* Distribution of HDL cholesterol for Istanbul men and women in 1990 to 1993 versus 2003. HDL cholesterol distribution compared in *(C)* Istanbul men (2003) with that of non-Hispanic white men (NHANES III) and (D) Istanbul women (2003) with that of non-Hispanic white women (NHANES III).

The educational level had little or no effect on the distribution of HDL cholesterol in non-Hispanic whites, Turkish men in 1990 to 1993 or 2003, or Turkish women in 1990 to 1993 (Figure 2). However, the education level markedly affected the HDL cholesterol distribution in Turkish women in 2003 (Figure 2).

Discussion

The past decade has seen significant socioeconomic changes in Turkey, especially in large urban areas. The present study

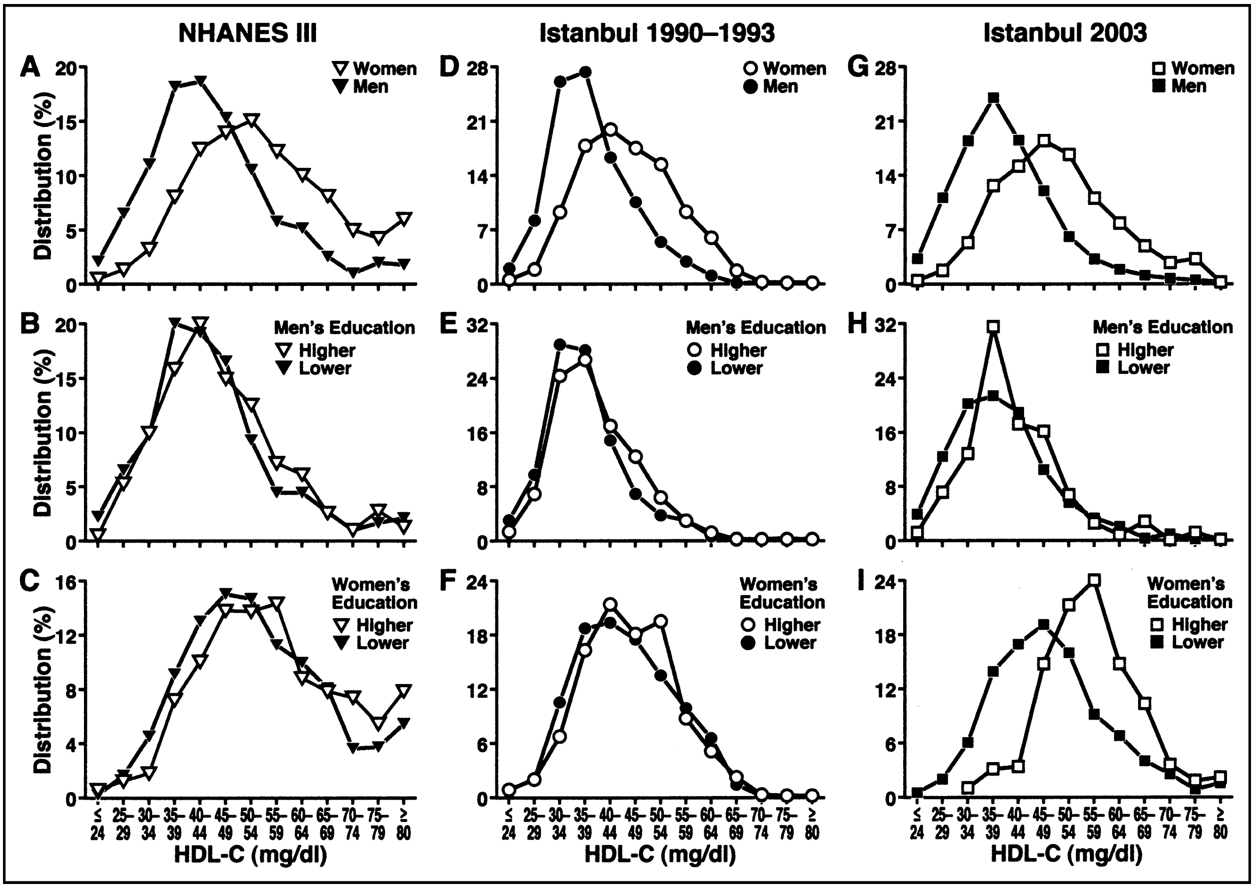

Figure 2. Effect of educational level on HDL cholesterol levels. *(A to C)* Comparison of HDL cholesterol distribution in higher educated (university or above) versus lower educated (high school or lower) non-Hispanic white men and women (NHANES III). *(D to F)* Comparison of HDL cholesterol distribution versus educational level in Istanbul 1990 to 1993 cohort. *(G to I)* Comparison of HDL cholesterol distribution versus educational level in Istanbul 2003 cohort.

focused on changes in lipids, lipoproteins, anthropometrics, and lifestyle factors in Istanbul (population ~12 million) in 1990 to 1993, 1996 to 2000, and 2003. As in other populations around the world, the mean BMI increased significantly, as did the percentage of overweight or obese subjects.[28] Smoking rates among Turkish men remained high, and exercise among Turkish men and women, except for the highly educated women, did not increase significantly.

The plasma total cholesterol and LDL cholesterol levels remained rather low throughout the decade spanning these surveys. However, the HDL cholesterol levels increased significantly in highly educated Turkish women, but not in men, suggesting that knowledge of heart disease risk factors can affect a population characterized by very low HDL cholesterol levels. In particular, Turkish women significantly altered their HDL cholesterol levels through lifestyle changes. The genetic background responsible for the low HDL cholesterol levels in Turks is associated with differences in responses to interventions, such as statin therapy and lifestyle changes. Previously, we showed that Turkish men with very low HDL cholesterol levels (~31 mg/dl) and elevated total cholesterol/HDL cholesterol ratios (despite low LDL cholesterol) are very sensitive to low-dose simvastatin (10 mg/day). The total cholesterol levels decreased by 30% to 40% and HDL cholesterol levels increased by 20%.[29]

The lifestyle modifications that accounted for the increased HDL cholesterol in the highly educated Turkish women are difficult to identify precisely. The increase probably reflects a complex interplay among diet, exercise, body weight, and smoking. The women with the highest HDL cholesterol levels in 2003 were highly educated, much less overweight, more likely to exercise, and in the upper socioeconomic class. However, only a very small fraction of Turkish women are highly educated.

The dramatic association between a higher education level and higher HDL cholesterol levels in Turkish women in the 2003 survey appears to be recent (Figure 2). No such association was observed in the 1990 to 1993 survey, and only a weak effect was observed in the 1996 to 2000 survey (Figure 2 and Table 4). Nevertheless, Turkish women still had lower HDL cholesterol levels than non-Hispanic white women (NHANES III; Figure 2). It remains to be determined whether HDL cholesterol levels in Turkish women can be elevated by lifestyle changes to the levels seen in American and Western European women.

Highly educated men were predominantly in the upper socioeconomic class, but their BMI levels did not differ from those of men with less education. The HDL cholesterol levels were statistically higher in the more highly educated men in 2003, but the difference was only 2 mg/dl (41 vs 39 mg/dl; Table 4). The HDL cholesterol levels in men changed little throughout the decade (Table 4 and Figure 2) and remained ~10 mg/dl lower than in non-Hispanic white men (Figure 2).

Among non-Hispanic white adults, educational level did not significantly affect the distribution of HDL cholesterol values (Figure 2). In general, most studies of white adults showed a small positive association between educational achievement and HDL cholesterol level.[30–32] Heiss et al[30] demonstrated that most of the positive association among these factors in women reflected lower BMI, alcohol consumption, less smoking, and the use of sex hormones (sex hormone use is very limited among Turks). Freedman et al[33] extended these observations in whites and blacks using NHANES II data. They demonstrated little or no association between education and HDL cholesterol levels in white men but a positive association in white women. In contrast, a negative association was found in black men and no association in black women. In the Multiple Risk Factor Intervention Trial, a positive association was observed in white men and a negative association in black men.[34] Clearly, racial and gender differences in lipid levels exist.

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