Distributions of High-Sensitivity C-Reactive Protein, Total Cholesterol-HDL Ratio and 10-Year Cardiovascular Risk: National Population-Based Study

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Abstract- The present study aimed to evaluate the distributions of High-Sensitivity C-reactive protein, TC-HDL ratio and 10-year risk of cardiovascular diseases among Iranian adult population. We conducted a cross-sectional study on a total of 2125 adults aged 25 to 65. Data of the Third National Surveillance of Risk Factors of Non-Communicable Diseases (SuRFNCD-2007) was used. Anthropometric indices, blood pressure and biochemical measurements had been obtained. Ten-year risk of cardiovascular events was also calculated using different models. Median (interquartile range) and geometric means (95% CI) of hs-CRP were 5.1(3.9) and 4.1(4.38-4.85), respectively. Mean TC-HDL ratio±(SD) was 5.94±2.84 in men and 5.37±1.97 in women (P<0.001). In spite of risk scores (FRS and SCORE), no significant gender and age-related differences were observed in hs-CRP levels. Exclusion of CRP levels≥10 did not change the results. The proportion of high-risk categories using SCORE and FRS models were 3.6 % and 8.8 %, respectively. In comparison with other published data, greater means and median values of High-Sensitivity C-reactive protein were observed. Higher TC-HDL ratio and cardiovascular risk in men than in women were also demonstrated. The issue of screening for cardiovascular diseases has yet to be addressed due to considerable prevalence of elevated CRP and increased risk of cardiovascular events among various subgroups.

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Introduction

Development of atherosclerotic plaques usually plays a major role in the pathogenesis of most cardiovascular diseases (CVD) (1). Available evidence suggests that inflammation contributes to various stages of atherosclerosis. Thus, inflammatory biomarkers have been studied extensively to predict the risk of cardiovascular events especially coronary heart disease (CHD). C-reactive protein (CRP) is a downstream acute phase reactant and an indicator of low-grade inflammation, associated with future risk of CVD (2-4). Quantitative high sensitivity assays of CRP (hs-CRP) are able to determine minimal concentrations even below 0.3 mg/L. Therefore, CRP levels of asymptomatic individuals (<3mg/L) used for cardiovascular risk assessment are now detectable (5). Despite the probable associations, whether CRP is a direct participant in the progression of atherosclerosis and plaque rupture or a nonspecific marker increased during the inflammatory process is not well known (6). However, several meta-analyses have revealed a significant relationship between baseline levels of hs-CRP and subsequent cardiovascular events such as incident CHD (7). Although multiple observational studies suggest that hs-CRP adds only small incremental information to traditional risk factors in the general population (8), apparently it has the greatest predictive value in patients at intermediate risk for CVD. This category (10 to 20 % at 10 years by the Framingham risk score), is then reclassified according to hs-CRP cut points. So, It may help to determine the need for further evaluation and treatment in primary prevention (9).

In the present study, we aimed to describe the distribution of CRP values and prevalence of high-risk categories defined by CRP, cardiovascular risk scores

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(like FRS) and Total cholesterol to high-density cholesterol ratio (TC-HDL). Due to inadequate epidemiologic studies (in this field) among Iranian population (10), these observations help to achieve more reliable national estimates. We have also determined the prevalence of increased risk for first fatal cardiovascular events using Systematic Coronary Risk Evaluation model (SCORE) (11). Total cholesterol to HDL ratio which is associated with increased risk of cardiovascular events was also calculated among participants (12). These tools can help to find the patients with intermediate and high risk for CVD and CHD.

Materials and Methods

We used the data of the third national surveillance of risk factors of noncommunicable diseases (SuRFNCD) gathered in 2007. Details of the survey have been described elsewhere (13). In brief, a well-defined cluster sampling model was employed to have a representative sample of Iranian adult population. Random selection of addresses was done using postal codes across the country. Each cluster was comprised of 2 men and 2 women from each age group (5 ten-year categories aged 15-64 years). The number of clusters in provincial samples was proportional to the urban/rural size of the province in a country-wide scale. Participation in the survey was dependent on the standard considerations of the national committee of ethics in medical researches and CDC (Center for Disease Control) of Iran. Participants gave informed consent for 3 steps of the survey, separately. During the first step, general health characteristics and demographic data were collected by standardized questionnaires based on WHO STEPS instrument (core and expanded) (14). Trained health care professionals who were recommended by 40 collaborating medical schools conducted the interviews. In step 2, they performed a physical examination to determine weight, height, waist circumference, and blood pressure. Blood pressure was measured using a calibrated sphygmomanometer (Omron M7, HEM-780-E). The average of three measurements, recorded at 5-minutes intervals, was used for analysis. Participants were instructed to have an overnight fasting for 10-12 hours to prepare for the third step. Ten milliliters of venous blood was taken in sitting position and collected. After immediate centrifugation, samples were transferred to the central reference laboratory of the Ministry of Health of Iran (Tehran, Iran). Cold chain conditions were provided for the samples and standards of maintenance were met. Then, glucose oxidizes test with enzymatic colorimetric method was applied to determine fasting plasma glucose (FPG). Intra and inter-assay coefficients of variation (CV) were 2.1% and 2.6%, respectively. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were also measured using enzymatic methods (Parsazmun, Karaj, Iran). Serum concentrations of C-reactive protein were measured using high-sensitivity enzyme-linked immunosorbent assay (The quantitative CRP kit, Parsazmun, Karaj, Iran). The lower detection limit of the hs-CRP assay was 0.10 mg/l. The Intra and inter-assay coefficients of variation were 2.6% and 1.0%, respectively.

We selected a population sample consisted of 957 men and 1168 women, aged 25-65 years. Subjects enrolled in the present study had not a previous history of cardiovascular events including coronary heart disease. The other part of eligibility criteria had complete data records in three major domains of the survey. In addition, pregnant women (n=17) have been excluded even though they met the above criteria. To perform statistical analyses, we used the SPSS v.20 for windows (Chicago, IL, USA). Complex sample survey analysis and weighting were employed to extrapolate the results. Weighting for age, sex and residential area (urban and rural) was performed according to the adult population of Iran (national census, 2006). Continuous variables were expressed as mean±SD (with 95 % Confidence Interval) or mean±SE while the frequencies of categorical variables were shown in percentage (with 95 % CI). To assess the overall significance between the genders, Student's t-test was performed. A *P* less than 0.05 for a two-tailed test was considered statistically significant. A detailed percentile distribution of CRP concentrations for both genders, five age groups (25-65 years), and area of residence (urban-rural) was determined. Age- and sex-specific medians and interquartile ranges (IQR) were calculated to compare the results with other published data.

CRP values were categorized according to the known cut-off points for stratification of cardiovascular risk (9). Low, moderate, and high-risk levels of CRP were defined as <1, 1 to 3, and ≥3 mg/L, respectively. Since a skewed distribution (rightward) was expected, we determined the geometric means for subgroups as an additional observation. Therefore, CRP values were log-transformed, and then the back-transformed geometric means of hs-CRP (with 95 % CI) for age-, area- and sex-specific groups were calculated. Furthermore, we repeated the analyses after exclusion of 165 subjects

with hs-CRP levels≥10 (mg/l) in order to minimize the possible role of active infections (15). Total cholesterol to HDL ratio was also applied to identify low and elevated risk groups. Among men, a ratio of 6.4 or more was associated with an increased risk of CHD, while values of 5.6 or more were defined as high risk in women (16). The Weibull, proportional hazards model, has been applied to calculate the SCORE equation (11). This regression model estimates the 10-year risk of fatal cardiovascular events. In other words, the end-points of SCORE equation include 'hard' coronary heart disease (coronary death and non-fatal myocardial infarction) and 'hard' cardiovascular outcomes. Values were divided into 3 categories: low risk (under 1%), intermediate risk (2-5%) and high risk (5% and more). We have also estimated the prevalence of each group on a national scale. Similarly, the 10-year risk of non-fatal cardiovascular and coronary heart disease was calculated using Framingham risk score (17). Scores under 10%, 10-20% and above 20 (≥20%) refer to corresponding low, intermediate and high-risk categories. Age (in years), Total cholesterol(mg/dl), HDL (mg/dl), Systolic blood pressure, use of antihypertensive medications, history of current smoking and diabetes have been incorporated into risk assessment models. Definition of diabetes was made whether a positive personal history or fasting plasma glucose≥126 were found. The SCORE system provides separate coefficients and scores for higher and lower risk regions (11). The study population was considered to be representative of a high-risk region according to previously published data. Although the results of these studies are limited to some provinces, national estimates of incident CVD and CHD seem to be markedly greater than that of international reports (10).

Results

The mean age of the study population was 39.4 years (95% CI, 39.2-39.6) and 45% of them were male (957 of 2125). hs-CRP levels ranged from 0.1 to 54.0, and 7.77 % of the participants (n=165) had a value of 10 or more. Clinical characteristics and biochemical measurements of the subjects are summarized in Table 1. Table 2 shows the distribution of hs-CRP in the study sample, overall and by subgroups of age, sex, the area of resident and cardiovascular risk. Therefore, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} percentiles of hs-CRP concentration were determined in these subgroups. The median (interquartile range) of CRP values in men was not significantly different from that of women. Similar results were repeated with increasing age and after excluding high CRP values (≥10). Mean CRP values did not show significant differences between the genders and residential areas (urban versus rural regions) (*P* were 0.868 and 0.641, respectively). Geometric means of C-reactive protein were higher in the third age-group than the first one (45-55 against 25-35, *P*=0.039). An interesting finding was significantly increased the prevalence of high hs-CRP category (≥3mg/L) in all subgroups. In other words, only a small proportion of participants (3.0% of men and 5.1% of women) were in the low-risk group (CRP< 1 mg/L).

The average of total cholesterol to HDL ratio was greater in men and urban residential area (*P* were <0.001 and 0.017, respectively). TC-HDL ratio had an increasing trend of values following the FRS categories. In this way, mean±SD for low, intermediate and high-risk categories were calculated respectively (5.38±2.95, 6.34±1.81 and 7.05±2.78; *P*<0.001).

Among the age groups, younger subjects (25-35 y) had lower TC-HDL values than the others (*P*<0.001). The estimated 10-year risk of cardiovascular events by FRS and SCORE tools revealed similar patterns (Table 3). Mean calculated scores rise with increasing age using both risk assessment models (*P*<0.001 for both models). In addition, male participants had greater means than female ones (*P*<0.001). Mean FRS values were higher in the urban area of residence (versus rural), while mean SCORE values did not show such a significant difference (*P* were 0.008 and 0.504, respectively). Table 4 and 5 represents the prevalence of elevated TC-HDL, categorical FRS, and classified SCORE among the subgroups. The prevalence of high-risk category (FRS≥20%) was significantly higher in older subjects (*P* for trend between age groups: <0.001) and in men rather than women (*P*: <0.001). Prevalence of the intermediate FRS risk was higher in men and urban areas (*P*<0.001 and 0.021, respectively). Using the SCORE model, high-risk category (≥5%) was more common in men and among the highest age group (55-65y) compared with women and third age group (45-55y), respectively (both *P* were <0.001). In the same way, intermediate subclass was significantly more prevalent among men and higher age groups than their counterparts. Table 6 shows the comparison of mean values (for all variables) between the genders within each age group. Exclusion of high CRP concentrations (≥10 mg/l) did not change any of the results. Geometric means of CRP within the highest age group (55-65y) was greater in men than in women (5.17±1.71 against 4.21±2.88, *P*<0.001). This finding was repeated among the CRP levels under 10 (4.68±1.80

versus 3.87±3.01, *P*=0.001). Subjects who had higher TC-HDL values were at increased risk of cardiovascular events simultaneously. In other words, 10 y FRS was 10.10 % (9.29-10.92) in high TC-HDL subgroup vs. 5.33 %(4.99-5.67) in the other subgroup. Similarly, 10y SCORE was 1.05% (0.93-1.16) vs. 0.71% (0.64-0.77). These differences remained significant after the analysis was repeated in men and women.

Table 1. Clinical and laboratory characteristics of participants

Variables	Men (n=957)	Women (n=1168)	*P*	Total (n=2125)	N*
Age (year)	39.2 ± 4.6 (38.9-39.5)	39.6 ± 4.2 (39.3-39.8)	0.036	39.4 ± 4.45 (39.2 -39.6)	2125
BMI * (kg/m2)	25.72 ± 4.57 (25.43- 26.01)	27.55 ± 5.50 (27.23,27.87)	<0.001	26.64 ±5.07 (26.43 , 26.86)	2125
SBP (mmHg)*	124.7 ± 14.7 (123.8 ,125.7)	121.8 ± 15.7 (120.9 ,122.7)	<0.001	123.3 ±15.2 (122.6 , 123.9)	2125
DBP (mmHg)*	80.1 ± 10.6 (79.4 , 80.8)	80.9 ± 10.2 (80.33, 81.50)	0.077	80.5 ±10.5 (80.1 , 80.9)	2125
Hypertension (%)	23.9 (19.8 -28.6)	29.6 (26.7 -32.7)	0.003	26.8 (24.3 -29.5)	2125
On HTN medication (%)	4.4 (3.1 -6.2)	8.9 (7.7 -10.2)	<0.001	6.7 (5.7 -7.7)	2125
HDL-C * (mg/dl)	34.4 ± 8.3 (33.9 , 35.0)	39.6 ± 11.7 (38.9 ,40.3)	<0.001	37.0 ±10.0 (36.6 ,37.5)	2125
LDL-C * (mg/dl)	127.9 ± 30.5 (126.0, 129.9)	132.8 ± 33.2 (130.9, 134.7)	<0.001	130.4 ±31.8 (129.0 ,131.7)	2125
TC * (mg/dl)	192.8 ± 35.2 (190.6 , 195.1)	199.6 ± 38.3 (197.4 ,201.8)	<0.001	196.3 ±36.7 (194.7 ,197.8)	2125

*BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TC: Total Cholesterol
Variables are mean ± SD or frequency (percentage).

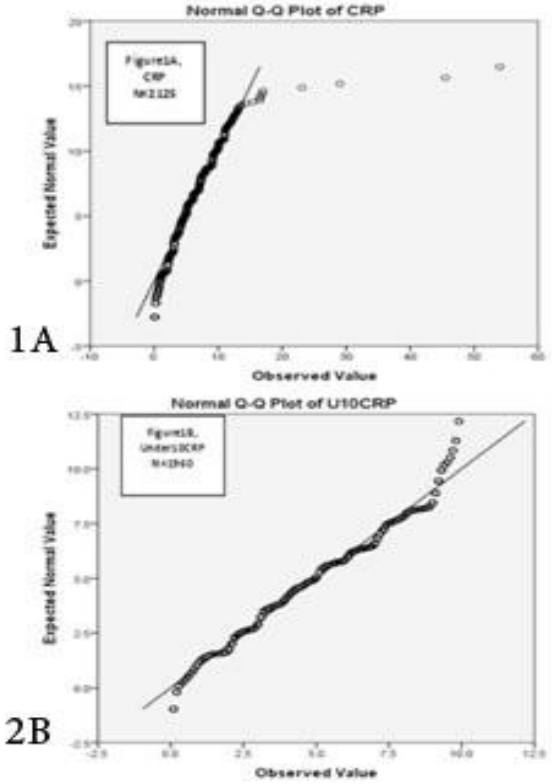

Figure 1 (1A, 1B). The distribution of CRP levels (total and under 10 values), plotted against a standard normal distribution (Q-Q plot)

Table 2. Distributions of hs-CRP and classification of subjects according to known cut points

		N	CRP(mg/l) Mean*± SD (95% CI)	Percentiles		Geometric means of CRP (95% CI)	Hs-CRP categories					
							Low (<1 mg/l ,n=82)		Moderate (1-3 mg/l ,n=228)		high (≥ 3 mg/l ,n=1815)	
				5	95		Prevalence** (%)	NE¶	Prevalence (%)	NE	Prevalence (%)	NE
Age (years)	25-35	558	5.50 ± 2.86 (5.26,5.75)	0.9	10.0	4.52 (4.21, 4.86)	5.0 (3.0, 8.4)	0.54	11.1 (7.8, 15.6)	1.20	83.8 (79.1- 87.7)	9.07
	35-45	535	5.49 ± 3.47 (5.18,5.79)	1.0	10.1	4.60 (4.22, 5.01)	3.6 (2.5, 5.3)	0.28	12.7 (9.3, 17.2)	0.99	83.6 (78.4- 87.7)	6.50
	45-55	552	5.57 ± 2.63 (5.34,5.79)	2.0	10.1	4.78 (4.54, 5.04)	2.6 (1.4, 4.7)	0.14	10.4 (8.1, 13.2)	0.58	87.0 (83.6- 89.7)	4.79
	55-65	480	5.71 ± 3.29 (5.41,6.02)	1.0	11.0	4.65 (4.32, 5.00)	4.5 (2.7, 7.5)	0.13	9.8 (7.2, 13.2)	0.29	85.7 (81.4- 89.1)	2.48
Sex	Male	957	5.52 ± 5.43 (5.16,5.87)	1.0	10.3	4.66 (4.21, 5.16)	3.0 (1.7, 5.2)	0.40	12.4 (8.3, 18.1)	1.66	84.6 (78.2- 89.4)	11.32
	female	1168	5.55 ± 3.33 (5.35,5.74)	0.9	10.1	4.56 (4.29, 4.85)	5.1 (3.5, 7.4)	0.70	10.2 (8.6, 12.1)	1.39	84.7 (81.8- 87.1)	11.52
Residential area	Urban	1467	5.51 ± 5.22 (5.23,5.78)	1.0	10.1	4.58 (4.28, 4.90)	4.3 (3.1, 5.9)	0.87	11.1 (8.1, 15.0)	2.24	84.6 (80.4- 88.1)	17.16
	Rural	658	5.61 ± 3.87 (5.31,5.92)	1.1	10.1	4.70 (4.47, 4.94)	3.4 (2.2, 5.4)	0.23	12.0 (10.0, 14.5)	0.80	84.5 (81.2- 87.4)	5.68
FRS categories	Low risk	1422	5.49 ± 3.80 (5.29,5.69)	1.0	10.1	4.55 (4.30, 4.82)	4.4 (3.1, 6.1)	0.92	11.9 (9.2, 15.3)	2.53	83.7 (79.9, 86.8)	1.77
	Intermediate	381	5.57 ± 3.52 (5.21,5.94)	2.0	10.0	4.76 (4.27, 5.30)	3.6 (1.8, 6.8)	0.12	7.9 (4.9, 12.6)	0.28	88.5 (82.5, 92.7)	3.09
	High risk	322	5.85 ± 4.00 (5.40,6.30)	2.0	11.0	4.92 (4.55, 5.33)	2.3 (1.1, 4.4)	0.05	10.6 (7.5, 14.8)	0.25	87.2 (82.1, 90.9)	2.07
Total		2125	5.53 ± 4.55 (5.33, 5.73)	1.0	10.1	4.61 (4.38, 4.85)	4.1 (3.1-5.4)	1.10	11.3 (8.9-14.3)	3.05	84.6 (81.4- 87.4)	22.85

*Mean CRP is expressed using mg/L** Prevalence of CRP categories is shown by percent.¶NE: National Estimates are rounded to the nearest millions

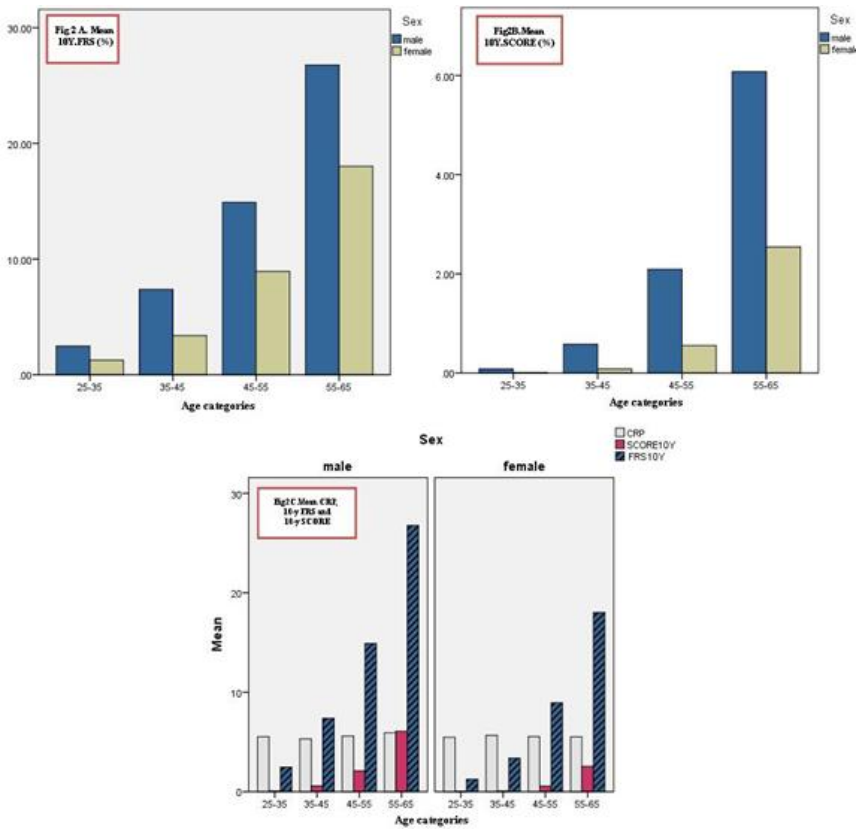

Figure 2(A, B and C). Ten year risk of subsequent CVD (via FRS and SCORE prediction models) and hs-CRP (mg/L) among age categories

Table 3. Description of TC-HDLc ratio, 10Y-FRS and 10Y-SCORE among subgroups of the study population

		N	TC-HDLc Mean*±SD (95% CI)	10y-CVD risk .FRS Mean*±SE (95% CI)	10y-CVD risk. SCORE Mean*±SE (95% CI)
Age (years)	**25-35**	558	5.30 ± 2.40 (5.10,5.51)	1.86 ± 0.07 (1.72, 2.01)	0.04 ± 0.003 (0.037, 0.049)
	35-45	535	5.79 ± 3.19 (5.51,6.07)	5.39 ± 0.25 (4.89, 5.90)	0.33± 0.02 (0.29, 0.37)
	45-55	552	5.95 ± 1.76 (5.80,6.10)	11.87 ± 0.33 (11.21, 12.53)	1.31± 0.05 (1.22, 1.40)
	55-65	480	6.00 ± 1.69 (5.85,6.16)	22.20 ± 0.68 (20.83, 23.57)	4.23 ± 0.16 (3.91, 4.55)
Sex	**Male**	957	5.94 ± 2.84 (5.75,6.12)	8.93 ± 0.28 (8.37, 9.49)	1.25 ± 0.05 (1.15, 1.36)
	female	1168	5.37 ± 1.97 (5.25,5.48)	5.31 ± 0.14 (5.03, 5.58)	0.42 ± 0.02 (0.39, 0.45)
Residential area	**Urban**	1467	5.72 ± 2.80 (5.57,5.87)	7.32 ± 0.20 (6.92, 7.71)	0.84 ± 0.03 (0.79, 0.89)
	Rural	658	5.45 ± 1.23 (5.35,5.54)	6.46 ± 0.21 (6.04, 6.87)	0.81 ± 0.04 (0.74, 0.88)
Total		2125	5.65 ± 2.95 (5.52,5.78)	7.10 ± 0.17 (6.76, 7.45)	0.83 ± 0.02 (0.79, 0.88)

Table 4. Prevalence of categorical TC-HDLc ratio, 10Y-FRS among subgroups of the study population

			High TC-HDLc- n=841		10y-CVD risk .FRS					
					Low (<10%)- n=1422		Intermediate(10–20%) n=381		High (≥ 20%)- n=322	
		N	Prevalence*	NE	Prevalence	NE	Prevalence	NE	Prevalence	NE
Age (years)	**25-35**	558	28.7 (23.5,34.6)	3.11	99.5 (98.5,99.8)	10.77	0.3 (0.1,1.3)	0.04	0.2 (0.0, 1.2)	0.02
	35-45	535	39.6 (31.1,48.7)	3.08	89.8 (85.5,92.9)	6.98	8.6 (5.7,12.6)	0.67	1.6 (0.8,3.6)	0.13
	45-55	552	45.6 (41.7,49.5)	2.51	51.4 (46.8,55.9)	2.83	33.3 (29.3,37.5)	1.84	15.3 (12.9,18.1)	0.85
	55-65	480	46.3 (42.0,50.7)	1.34	19.3 (15.7,23.6)	0.56	32.8 (27.6,38.4)	0.95	47.9 (42.5,53.4)	1.39
Sex	**Male**	957	35.4 (30.5,40.7)	4.75	70.2 (67.0,73.3)	9.41	17.8 (15.2,20.6)	2.38	12.0 (10.3,14.0)	1.61
	Female	1168	38.9 (35.8,42.2)	5.30	86.2 (84.5,87.7)	11.73	8.2 (6.7,9.9)	1.11	5.6 (4.7,6.7)	0.77
Residential area	**Urban**	1467	38.4 (34.6,42.4)	7.79	77.1 (75.1,79.0)	15.64	13.8 (12.1,15.8)	2.80	9.1 (8.0,10.3)	1.84
	Rural	658	33.5 (31.4,35.6)	2.25	81.8 (79.1,84.2)	0.55	10.2 (7.8,13.3)	0.69	8.0 (6.4,9.9)	0.54
Total		2125	37.2 (33.9,40.6)	10.04	78.3 (76.4,80.1)	21.14	12.9 (11.5,14.5)	3.49	8.8 (7.8,9.9)	2.38

*Prevalence is expressed as percentages with 95% Confidence Interval. ,¶
NE: National Estimates are rounded to the nearest millions. NS: not estimated

Table 5. Prevalence of categorical TC-HDLc ratio and 10Y-SCORE among subgroups of the study population

			High TC-HDLc- n=841		10 y-CVD risk. SCORE					
					Low (< 2 %)- n=1662		Intermediate (2– 5 %)- n=313		High (≥ 5 %)- n=150	
		N	Prevalence*	NE	Prevalence	NE	Prevalence	NE	Prevalence	NE
Age (years)	25-35	558	28.7 (23.5,34.6)	3.11	100.0	10.82	0.0	NS	0.0	NS
	35-45	535	39.6 (31.1,48.7)	3.08	99.0 (96.6,99.7)	7.69	1.0 (0.3,3.4)	0.08	0.0	NS
	45-55	552	45.6 (41.7,49.5)	2.51	80.2 (76.9,83.0)	4.42	18.0 (15.1,21.3)	0.99	1.8 (0.9, 3.7)	0.10
	55-65	480	46.3 (42.0,50.7)	1.34	24.3 (20.7,28.4)	0.71	45.7 (41.5,49.9)	1.33	30.0 (25.1, 35.4)	0.87
Sex	Male	957	35.4 (30.5,40.7)	4.75	81.2 (79.7,82.7)	10.88	12.6 (11.2,14.2)	1.69	6.2 (5.0, 7.6)	0.82
	Female	1168	38.9 (35.8,42.2)	5.30	93.7 (92.9,94.5)	12.76	5.2 (4.6,5.8)	0.71	1.1 (0.7, 1.6)	0.15
Residential area	Urban	1467	38.4 (34.6,42.4)	7.79	87.3 (86.4,88.1)	17.71	9.3 (8.2,10.5)	1.88	3.4 (2.8, 4.2)	0.70
	Rural	658	33.5 (31.4,35.6)	2.25	88.3 (86.7,89.7)	5.93	7.7 (6.6,8.8)	0.51	4.1 (3.2, 5.2)	0.28
Total		2125	37.2 (33.9,40.6)	10.04	87.5 (86.8,88.2)	23.64	8.9 (8.0,9.8)	2.40	3.6 (3.0, 4.3)	0.97

*Prevalence is expressed as percentages with 95% Confidence Interval. ,¶
NE: National Estimates are rounded to the nearest millions. NS: not estimated

Table 6. Age adjusted comparison of mean values between the genders

Age (years)	N		CRP (mg/l) Mean ± SD (95% CI)		*P*	TC-HDLc Mean ± SD (95% CI)		*P*	10y-SCORE (%) Mean ± SD (95% CI)		*P*	10y-FRS (%) Mean ± SD (95% CI)		*P*
	Male	Female	Male	Female		Male	Female		Male	Female		Male	Female	
25-35	243	315	5.5±3.6 (5.1,5.9)	5.5±3.0 (5.1,5.8)	0.845	5.7±2.4 (5.4,6.0)	4.9±1.8 (4.7,5.1)	<0.001	0.08±0.07 (0.07,0.09)	0.006±0.005 (0.005,0.007)	<0.001	2.5± 2.0 (2.2,2.7)	1.3±0.9 (1.1,1.4)	<0.001
35-45	238	297	5.3±4.0 (4.8,5.8)	5.7±2.9 (5.3,6.0)	0.228	6.1±2.8 (5.8,6.5)	5.5±2.4 (5.2,5.7)	0.003	0.58±0.49 (0.51,0.64)	0.08± 0.07 (0.07,0.09)	<0.001	7.4± 6.1 (6.6,8.2)	3.4±1.9 (3.2,3.6)	<0.001
45-55	251	301	5.6±2.4 (5.3,5.9)	5.5±2.7 (5.2,5.9)	0.845	6.1±1.8 (5.9,6.4)	5.8±2.2 (5.5,6.0)	0.028	2.09±1.44 (1.91,2.27)	0.55± 0.34 (0.52,0.59)	<0.001	14.9±8.8 (13.8,16.0)	8.9±7.7 (8.1, 9.8)	<0.001
55-65	225	255	5.9±2.8 (5.6, 6.3)	5.5±4.1 (5.0,6.0)	0.210	5.9±1.8 (5.7,6.2)	6.0±1.5 (5.8,6.2)	0.702	6.08±3.51 (5.60,6.55)	2.54± 2.03 (2.29,2.80)	<0.001	26.8±14.8 (24.8,28.8)	18.0±11.6 (16.6,19.5)	<0.001

Discussion

Major advantages of this study were the application of a high-sensitivity CRP assay and multi-ethnic polycentric feature of sampling design. Furthermore, our sample subjects were representative of Iranian adult population. Compared with previous reports from other populations, our means (arithmetical/geometric) and median (IQR) values were significantly higher (8,18). Ye *et al.*, have also found a low median level and the geometric mean of CRP among healthy Chinese population without a significant difference between the genders. Median CRP was 0.68 mg/L in their research and geometric means with 95%CI were 0.70 (0.66-0.74) for men and 0.71(0.68-0.75) for women (19). In the third National Health and Nutrition Examination Survey (NHANESIII), mean CRP concentrations (SD) were 0.41±0.64 and 0.46±0.62 among men and women, respectively. The median CRP levels were 5.1 in our study (versus 0.21 in NHANES) for both genders (20). In the same way, all age categories of the present study (even 25-35 years) had greater means and median values than previous reports. In results of a nested case-control research from Tehran Lipid and Glucose Study (TLGS), median (IQR) CRP concentrations were 1.74 mg/l (0.76–3.19) and 0.94 mg/l (0.52–2.25) for cases and controls respectively (21). We observed higher CRP concentrations in women than in men, but the difference was not significant except for a subset of obese participants (30<BMI<35, *P*=0.002). Moreover, hs-CRP progressively increased with BMI in women (although P value for trend was greater than 0.05). Although higher BMI found in women may in part explain this result, it was not persisted after adjustments. On the other hand,

the lack of data about using OCP medications and Hormone Replacement Therapy may influence the comparison of CRP levels between male and female subjects. This justification for gender-based difference had been demonstrated in some investigations (19,20,22).

In spite of some other published studies (23), the observed increase in CRP means from lower to higher age-groups did not show statistical significance. The increasing trend of CRP concentrations from low to high FRS categories was another finding in agreement with previous reports (24,25).

Estimated proportion of individuals with high plasma CRP levels≥3 mg/L among the study population was 84.6 % (81.4-87.4) that describes high prevalence of increased cardiovascular risk. The category of high CRP accounts for 21.4% (95% CI 18.7-24.0) of the Nunavic study (Marie-Eve Labonte´ *et al*.,) (26), Whereas Ajani *et al*., reported higher prevalence among the subgroups (33.5% against 34.2% before and after excluding>10 values in subjects with normal lipid profile) (18). In the present study, exclusion of CRP concentrations≥10 did not change the results of primary analyses. It may reflect a nearly homogenous distribution of C-reactive protein (<10 vs.≥10 mg/L) along with a low proportion of markedly elevated values (7.7 % had CRP≥10 mg/L). However, the average of two CRP assays optimally two weeks apart would provide a stronger estimate (9).

Total cholesterol to HDL ratio among the participants was not considerably different from previous investigations. Linn *et al*., have reported similar mean values, 5.06 and 4.30 for white men and women, respectively (27). Arsenault *et al*., have also shown similar figures (5.07±1.54 and 4.22±1.43 among men and women without CHD) (28). However, the estimated prevalence of high TC-HDL ratio (37.2%) was significantly higher in our study than above studies. Male subjects had greater TC-HDL ratio than their female counterparts, which is concordant to previous studies (27-29).

Mean estimated cardiovascular risk using Framingham equation was significantly higher than some of the previously published data (for both of genders). As an example, P. Marques-Vidal *et al*., observed lower mean FRS values (original and recalibrated scores were 1.8 and 0.8 in women and 7.4 vs. 3.4 in men, respectively). In comparison with mentioned reports, we have illustrated the greater prevalence of high risk category (12 % of men and 5.6 % of women had FRS≥20 %). The 10-year CHD risk results in NHANES III included 82, 16 and 3 percent of patients pertaining to low, intermediate and high risk categories, respectively. Male subjects were also at increased risk of CHD events as demonstrated in these reports (30-32). On the other hand, a large scale meta-analysis consisted of 16 studies showed greater mean values (10-y FRS) in both genders compared with the present study. The estimated means (SD) of 10-year risk of CHD varied across studies from 11.0% (6.1%) to 31.6% (14.1%) in men and from 7.1% (6.1%) to 14.5% (10.1%) in women (33). Although the latter may be the result of enrolling late middle aged and older participants (mean ages from 47 to 78 years). Calculated risk by SCORE model predicted similar incidence rate for fatal and nonfatal cardiovascular events to the available literature. Bhopal *et al*., in the Newcastle Heart Project described the calculated 10-y risks among different ethnic groups as follows: fatal events varied from 1.26 to 1.58 in men and from 0.20 to 0.30 in women (31). The distribution pattern of mean SCORE values was the same as Framingham model in mentioned reports. In other words, greater average risks were observed in men and higher age groups compared with their counterparts (31). This study described the distribution of CRP in the Iranian general population. Compared with literature, greater means and median values were observed with no significant difference among genders and residential area. Similar concentrations in various age categories may also extend the recommended ranges for the application of hs-CRP in risk assessment for asymptomatic individuals. However, we need further studies to determine the appropriate cut-points of CRP and modify the recommendations in risk prediction of CVD. Higher TC-HDL ratio and cardiovascular risk in males than their female counterparts should warrant more attention and intervention plans. We also recommend other researchers to show if in Iranian population higher TC-HDL and CRP values can increase the risk of subsequent cardiovascular events (both fatal and non-fatal outcomes via SCORE and FRS models). Considering high prevalence of elevated CRP, High TC-HDL and increased risk of cardiovascular events (using both risk scores) among various subgroups, a national version of screening guidelines may be required.

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