The Role of Atherosclerotic Cardiovascular Risk Enhancers in the Prediction of Cardiovascular Events: Tehran Lipid and Glucose Study

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Abstract

Background: To assess the effect of the atherosclerotic cardiovascular disease risk enhancing factors (ASCVD-REFs) on incident cardiovascular disease (CVD) events among non-diabetic individuals with borderline and intermediate ACC/AHA score during 10 and 15-year follow-up. Moreover, the added value of these ASCVD-REFs on the predictive power of the pooled cohort equations (PCE) was examined.

Methods: A total of 1204 adults aged 40-75 years, free from CVD at baseline with low-density lipoprotein cholesterol (LDL-C) between 70-189 mg/dl, were included. Unadjusted Cox regression analysis was used. The predictive ability of each significant ASCVD-REFs was estimated using the cut-point-free integrated discrimination improvement (IDI).

Results: During 10-year follow up, 181 CVD events (including 73 hard CVD) occurred. For hard CVD events, the high blood pressure (BP) component (i.e. ≥130/85 mmHg) of metabolic syndrome (Mets) (Hazard ratio: HR (95% CI; 1.67(1.03-2.70)) and positive history of preeclampsia (5.06(1.17-22.0)) were significant ASCVD-REFs. During the longer follow-up, Mets and its components of high waist circumference (WC) and high BP significantly increased the risk. As for CVD events, the Mets and its high BP and high WC components significantly increased the risk. However, in the ACC/AHA adjusted score, these covariates did not significantly improve the predictive power of the CVD or hard CVD.

Conclusions: The high BP was the most consistent and independent ASCVD-REFs in the prediction of all CVD and hard CVD, among the population with borderline/intermediate risk. Hence, considering pharmacologic therapies for patients with high BP and high LDL-C might be beneficial for preventive initiatives.

Background

Atherosclerotic cardiovascular disease (ASCVD) is one of the common non-communicable diseases (NCD) with high disability-adjusted life year (DALY) in the Middle East and North Africa (MENA) region. Mortality from metabolic risk factors has decreased in this region but disability due to metabolic diseases has increased drastically (1, 2). According to the Global Burden of Disease (GBD) estimates, lipid disorders are one of the main causes of morbidity and mortality in this region. DALYs due to high low-density lipoprotein cholesterol (LDL-C) have decreased by 46% during 1990–2017 in Iran, but it is still higher than the global estimate. This could be due to poor control of dyslipidemia despite increased medical therapy (1). It was shown that hypercholesterolemia had a population attributable fractions (PAFs) of 30% and 22% for premature cardiovascular disease (CVD) events in Iranian men and women, respectively (3). According to the last national study conducted in 2016 among the Iranian population aged over 25 years, more than 80.0% showed at least one lipid abnormality; among which the prevalence of high non-HDL-C and hypercholesterolemia were reported as 40% and 27%, respectively (4).

There are several previously suggested guidelines for lipid management. One of which is the guideline of 2013 American College of Cardiology/American Heart Association (2013 ACC/AHA) (5), which was validated for the Iranian population (6). This guideline was updated in 2018 (7). ASCVD risk is assessed in individuals using pooled cohort equations (PCE) (5, 8, 9). Based on the individuals' ASCVD risk score, non-diabetic individuals aged 40–75 years old with LDL-C ≥ 70 to < 190 mg/dl are then classified into low, borderline, intermediate, and high-risk. Low-risk individuals are advised to lifestyle modification. ACC/AHA recommends statin therapy for individuals with borderline and intermediate risk, in case of having risk enhancing factors (REFs), although the U.S Preventive Services Task Force (USPSTF) concluded: "current evidence is insufficient to assess the balance of benefits and harms of adding nontraditional risk factors to existing CVD risk assessment models" (10).

The association between the risk enhancers and CVD has been mentioned in several previously published studies among the general population (8, 11–17). However, to the best of our knowledge, no studies examined the impact of the REFs on hard CVD events among individuals with borderline and intermediate CVD risk. In the current study, we aimed to assess the

effect of the atherosclerotic cardiovascular disease risk enhancing factors (ASCVD-REFs) on incident all CVD and hard CVD in non-diabetic individuals aged 40–75 years old, with borderline and intermediate ASCVD risk during 10 and 15-year follow-up. Moreover, we evaluated the added value of these risk enhancers on the predictive power of the PCE for ASCVD risk assessment.

Materials And Methods

- study population

Tehran Lipid and Glucose Study (TLGS) is a community-based prospective cohort study carried out on an Iranian urban population in Tehran. The study aims to determine the prevalence and incidence of non-communicable diseases and related risk factors among people aged ≥ 3 years and encourage a healthy lifestyle and programs for the prevention of NCD. The study has been done in two phases including the first (1999–2001: n = 15005) and the second (2001–2005; n = 3550) and is planned to continue for at least 20 years with a three-year interval design. The design and methodology of the TLGS study have been reported elsewhere (18).

In the current study, we included 6275 adults aged 40–75 years who entered in the first or second phase of the TLGS study. According to the guideline, we excluded those with self-reported use of lipid-lowering medication (n = 364), hemodialysis (n = 1), missing data at baseline variables including total cholesterol (TC), HDL-C, triglycerides (TGs), fasting plasma glucose (FPG), 2-hour post-challenge plasma glucose (2 h-PCG), systolic blood pressure (SBP), current smoking (n = 313), and follow-up information on all CVD and hard CVD status (n = 495); leaving us with 5102 individuals. From this number, we excluded those with prevalent CVD (n = 387), LDL-C < 70 mg /dl (n = 69) as well as ≥ 190 mg/dl (n = 413) and those with type 2 diabetes (T2DM) (n = 687). Finally, of a total of 3546 non-diabetic individuals with LDL-C range 70–189 mg/dl, after excluding individuals with ACC/AHA score < 5% (n = 2109) and ≥ 20% (n = 233), 1204 individuals were eligible for the analysis of the further risk discussion on the primary prevention of all CVD and hard CVD during 10-year (20 Mach 2010) and 15-year follow-up (20 Mach 2016).

This study was approved by the Institutional Review Board (IRB) of the Research Institute for Endocrine Sciences (RIES), Shahid Beheshti University of Medical Sciences, Tehran, Iran, and all participants provided written informed consent.

- Clinical And Laboratory Measurements

Study participants were interviewed and a standard questionnaire was used to collect demographic information and subjects were questioned about their family history of CVD, premature menopause, preeclampsia, and smoking habits. Weight and height were measured to the nearest 100 grams while wearing light clothing and with shoes removed. Height was measured in a standing position, using a tape measure, while shoulders were in normal alignment. Waist circumference (WC) was measured with light clothing at the level of the umbilicus. Systolic blood pressure and diastolic blood pressure (DBP) were measured on the right arm after a 15-min rest in a sitting position. The mean of two measurements was considered as the subject's blood pressure.

Biochemical measurements including FPG, 2 h-PCG, TC, TGs, HDL-C, and creatinine were taken following a 12–14 hour overnight fasting from all study participants between 7:00 and 9:00 AM. More details have been described elsewhere (18). The modified Friedewald formula was used to calculate the LDL-C (19, 20).

- Variable Definition

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). A positive family history of premature CVD for the study participant was considered as having previously diagnosed CVD in first-degree male aged ≤55 and female ≤65 year's relatives. The current smoker was defined as who smokes cigarettes/pipe daily or occasionally. Chronic kidney disease (CKD) was defined as an Estimated Glomerular Filtration Rate (eGFR) of less than 60 mL/min per 1.73 m^2 for longer than 3 months (21). Type 2 Diabetes was defined if FPG was ≥ 126 mg/dl and/or 2-h PCG was ≥ 200 mg/dl or in case of using anti-diabetic medications. Applying the Joint Interim Statement (22), those who met at least three of the following five criteria were considered to have metabolic syndrome (Mets): (1) WC ≥ 95 cm for both sexes (23) ; (2) TGs ≥ 150 mg/dL or lipid-lowering medications (3) HDL-C < 40 mg/dL in males, < 50 mg/dL in females or lipid-lowering medications (4) SBP/DBP ≥ 130/85 mmHg or antihypertensive medication, and (5) FPG ≥ 100 mg/dL or using anti-diabetic medications. Definitions of risk enhancers are presented in Table 1.

Table 1
recommended ASCVD risk enhancing factors for individuals with borderline and intermediate-risk

- Family history of premature CVD
- Persistently elevated LDL-C ≥ 160 mg/dl
- Chronic kidney disease
- Metabolic syndrome
- Condition-specific to women (e.g. preeclampsia, premature menopause)
- Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g. south Asian ancestry)
Lipid biomarkers
- Persistently elevated triglycerides ≥ 175 mg/dl
In selected individuals, if measured
- hs-CRP ≥ 2 mg/dl
- LP(a) levels ≥ 50 mg/dl
- apoB ≥ 130 mg/dl
- Ankle-brachial index (ABI) < 0.9
CVD: cardiovascular disease, LDL-C: low density lipoprotein cholesterol, hs-CRP: highly sensitive C-reactive protein; LP (a): Lipoprotein (a).

- Outcomes

Cardiovascular outcomes details have been published elsewhere (24). In the TLGS study, each participant is followed-up for any medical event leading to hospitalization during the previous year by telephone call. They were questioned for any medical conditions by a trained nurse and later, a trained physician collected complementary data regarding that event during a home visit and by the acquisition of data from medical files. If required, the outcome assessment committee consisting of an internist, endocrinologist, cardiologist, epidemiologist, and other experts evaluated the collected data to assign a specific outcome for every event. In the current study, all CVD events were defined as a composite measure of any cases of definite and probable myocardial infarction (MI), unstable angina, angiographic proven chronic heart disease (CHD), CHD death, definite or possible stroke, transient ischemic attack or cerebrovascular death. Hard CVD was defined as a first non-fatal MI, CHD death, and fatal or non-fatal stroke.

- Acc/aha Guideline

The 2013 ACC/AHA guideline according to the Pooled Risk Equations was used to calculate the 10-year risk of hard CVD for adults aged 40–75 years. Detail for risk equation was reported elsewhere (6, 25). According to this guideline, moderate to high-intensity statin therapy is recommended for individuals with prevalent CVD, those with LDL-C ≥ 190 mg/dl, diabetic patients, and non-diabetic individuals with LDL-C 70–189 mg/dl with risk score ≥ 5%. The ACC/AHA released an updated guideline on the 10-year ASCVD risk estimation in 2019 (26). According to the updated guideline, the 10-year risk score in non-diabetic individuals with LDL-C 70–189 mg/dl was classified into four risk groups; low:< 5%, borderline: 5% to < 7.5%, intermediate: ≥7.5% to < 20%, and high: ≥20%. Based on this guideline, for both borderline and intermediate-risk groups, a clinician-patient risk discussion about the defined risk enhancers is recommended to continue or initiate statin therapy. In the current study to reach full statistical power, we combined borderline and intermediate-risk groups as a single group.

Statistical analysis

Baseline characteristics of the study population were expressed as mean (95% confidence Intervals: CI) values for continuous variables, and as frequencies (%) for categorical variables. Comparison of the baseline characteristics of the study participants across two risk categories was done using the t-test for normally distributed continuous variables, the Chi-squared test for categorical variables and the Mann-Whitney test for skewed variables. Unadjusted Cox proportional hazards models were used to evaluate the associations of each risk enhancer including a positive family history of premature CVD, elevated LDL-C ≥ 160 mg/dl, elevated TGs ≥ 175 mg/dl, individuals with CKD, Mets (and its components separately), and conditions specific to women (e.g. preeclampsia and premature menopause) with the incidence of all CVD and hard CVD. The event date was defined as the date of the incident all CVD and hard CVD. Those who met the following criteria were censored: leaving the residential area, non-CVD related death, loss to follow-up, or end of follow-up. We further adjusted the significant risk enhancers to the ACC/AHA score. To evaluate the validity of these equations, Harrell´s concordance statistic (C-index) was calculated. Then, the cut-point-free Integrated discrimination improvement (IDI) was used as measures of predictive ability for incident all CVD and hard CVD added by significant risk enhancers (27). Bootstrapping method with 1000 replications was used to report bias-corrected 95% CI (27, 28). Using the above statistical approach, we repeated our data analysis for those with a 15-year follow-up. All analyses were conducted using STATA version 12 SE (StataCorp, TX, USA) and a two-tailed $p < 0.05$ was considered significant.

Results

The study population consisted of 1204 individuals at baseline with a mean (95% CI) age of 57.5 years (57.0–58.0). Baseline characteristics of the study population according to 10-year ASCVD risk categories are shown in Table 2. The prevalence of Mets, elevated TGs, elevated LDL-C, CKD, and positive family history of premature CVD among the total population and history of conditions specific to preeclampsia and premature menopause were 48.5%, 44.5%, 24.7%, 27.7%, 13.3%, 2.1%, and 3.0%, respectively. No significant differences were observed between the borderline-risk and intermediate-risk groups considering the prevalence of ASCVD risk enhancers.

Table 2
Baseline characteristics of the study participants according to the 10-year ASCVD risk categories: Tehran Lipid and Glucose Study 1999–2016)

		10-year ASCVD risk categories		
	Total (n = 1204)	Borderline risk (n = 401)	Intermediate risk (n = 803)	p
10-year ACC/AHA risk-related variables				
Female gender, n (%)	332(27.57)	152(37.9)	180(22.4)	
Age, years	57.5(57.0–58.0)	53.9(53.2–54.7)	59.3(58.7–59.8)	0.07
SBP (mmHg)	128.3(127.1-129.4)	123.9(122.1-125.6)	130.5(129.1–132.0)	0.001
DBP (mmHg)	80.5(79.8–81.1)	80.0(78.9–81.1)	80.7(79.9–81.6)	0.03
TC(mmol/L)	5.6(5.5–5.61)	5.56(5.47–5.64)	5.56(5.50–5.62)	0.42
HDL-C (mmol/L)	1.02(1.0-1.03)	1.02(1.0-1.05)	1.01(1.0-1.03)	0.11
LDL-C (mmol/L)	3.6(3.55–3.63)	3.57(3.51–3.64)	3.60(3.54–3.65)	0.28
FPG (mmol/L)	5.16(5.12–5.19)	5.15(5.10–5.21)	5.16(5.12–5.19)	0.71
2 h-PCPG(mmol/L)	6.38(6.28–6.48)	6.30(6.13–6.47)	6.42(6.29–6.55)	0.49
Current smoker, n (%)	381(31.64)	106(26.4)	275(34.2)	
Anti-hypertensive medication, n (%)	126(10.5)	46(11.5)	80(10.0)	
ASCVD risk enhancers				
METS, n (%)	583(48.5)	191(47.7)	392(48.9)	0.7
Elevated TG, n (%)	536(44.5)	180(44.9)	356(44.3)	0.85
Elevated LDL-C, n (%)	298(24.7)	91(22.7)	207(25.8)	0.24
Preeclampsia*, n (%)	7(2.1)	3(1.97)	4(2.22)	0.59
CKD, n (%)	333(27.7)	100(24.9)	233(29.0)	0.13
Family history premature CVD, n (%)	160(13.3)	62(15.5)	98(12.2)	0.12
Premature menopause*, n (%)	10(3.0)	5(3.29)	5(2.78)	0.26
Other variables				
BMI (kg/m^2)	26.9(26.6–27.1)	27.2(26.7–27.6)	26.7(26.4–27.0)	0.37
WC (cm)	92.3(91.7–93.0)	92.0(90.9–93.0)	92.5(91.8–93.3)	0.85
eGFR (ml/min/1.73 m^2)	67.4(91.7–93.0)	68.8(67.6–70.0)	66.7(65.9–67.5)	0.59
TG (mmol/L)	1.85(1.37–2.66)	1.86(1.38–2.64)	1.84(1.36–2.68)	0.73
10-year hard CVD event, n (%)	73(6.06)	16(4.0)	57(7.1)	0.03
15- Year hard CVD event, n (%)	138(11.46)	33(8.23)	105(13.1)	0.01
10-year all CVD event, n (%)	181(15.03)	39(9.73)	142(17.68)	< 0.001
15- Year all CVD event, n (%)	296(24.6)	70(17.46)	226(28.14)	< 0.001

	10-year ASCVD risk categories

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; 2 h-PCPG:2-hour post-challenge plasma glucose; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; Mets; Metabolic syndrome; Elevated TG: TG ≥ 2.0 mmol/L; Elevated LDL-C: LDL-C ≥ 4.1 mmol/L

Values are shown as Mean (95% CI) and number (%), (for continuous and categorical variables, respectively); for TG values are shown as median (Interquartile range);p, p-value.

*Reported only among females.

During the 10-year follow-up, the cumulative incidence of all CVD was 181(15.03%); the corresponding values for the 15-year follow-up were 296(24.6%). Considering the hard CVD, the cumulative incidence for the whole population was 73 (6.06%) and 138 (11.46%) during the 10- and 15-year follow-up, respectively. Adults in the intermediate-risk category experienced a higher incidence of all CVD and hard CVD.

Among the population with borderline/intermediate ASCVD risk, the unadjusted hazard ratios (HRs) with 95% CI of risk enhancers for hard CVD during 10-year follow-up are shown in Fig. 1.**A**. In the whole population, the high blood pressure component of Mets significantly increased the risk of hard CVD (1.67(1.03–2.70)). Moreover, among women, the positive history of preeclampsia increased the risk of hard CVD, however, the HR was unstably reflected by wide confidence intervals (5.06(1.17-22.0)). Figure 1.**B** demonstrates the unadjusted Cox regression of all ASCVD-REFs for the incidence of hard CVD during the 15-year follow-up. Mets (1.50(1.07–2.10)) per se and its components of high WC (1.41(1.01–1.98)) and high BP (1.62(1.15–2.29)) significantly increased the risk of hard CVD. As shown in Table 3, the C-statistics of discrimination for the model with and without significant risk enhancers were the same for incident hard CVD. Moreover, in the ACC/AHA adjusted score, high BP showed a moderate association with the event (1.53(0.94–2.48); p = 0.08). Preeclampsia and high blood pressure (for 10-year follow-up) and Mets, high WC and high BP (for 15-year follow-up) did not significantly improve the predictive power of the hard CVD. The maximum relative IDI of the mentioned risk enhancers was 0.6% for the prediction of hard CVD.

Table 3
Additional predictive power for Hard CVD by the ASCVD risk enhancers*: Tehran Lipid and Glucose Study (1999–2016).

Median 10-year follow-up				
	Traditional model HR† (95%)	**p-value**	**Enhanced model HR (95%)**	**p**
Model components¶ 1				
ACC/AHA Score	0.96(0.83–1.10)	0.53	0.95(0.82–1.10)	0.46
Preeclampsia			**5.35(1.22–23.38)**	**0.026**
Model predictive performance indexes 1				
C-index (95% CI)	0.52(0.42–0.61)	< 0.001	0.56(0.49–0.63)	< 0.001
IDI (95%CIs)			0.006(-0.03-0.04)	0.74
Model components 2				
ACC/AHA Score	**1.09(1.03–1.14)**	**0.001**	**1.08(1.02–1.14)**	**0.004**
High blood pressure			1.53(0.94–2.48)	0.08
Model predictive performance indexes 2				
C-index (95% CI)	0.60(0.58–0.62)	< 0.001	0.62(0.49–0.74)	< 0.001
IDI (95%CIs)			0.001(-0.002-0.006)	0.55
Median 15-year follow-up				
Model components 1				
ACC/AHA Score	**1.06(1.03–1.10)**	**0.001**	**1.06(1.025–1.11)**	**0.001**
METS			**1.47(1.05–2.06)**	**0.026**
Model predictive performance indexes 1				
C-index (95% CI)	0.58(0.55–0.62)	< 0.001	0.58(0.51–0.65)	< 0.001
IDI (95%CIs)			0.003(-0.003-0.01)	0.36
Model components 2				
ACC/AHA Score	**1.06(1.03–1.10)**	**0.001**	**1.06(1.02–1.10)**	**0.001**
High WC			**1.40(1.0-1.95)**	**0.05**
Model predictive performance indexes 2				
C-index (95% CI)	0.58(0.55–0.62)	< 0.001	0.58(0.51–0.65)	< 0.001
IDI (95%CIs)			0.002(-0.003-0.007)	0.46
Model components 3				
ACC/AHA Score	**1.06(1.03–1.10)**	**0.001**	**1.06(1.02–1.10)**	**0.004**
High blood pressure			**1.52(1.07–2.15)**	**0.02**
Model predictive performance indexes 3				

Median 10-year follow-up				
C-index (95% CI)	0.58(0.55–0.62)	< 0.001	0.58(0.51–0.65)	< 0.001
IDI (95%CIs)			0.002(-.004-00.008)	0.45

*Significant ASCVD risk factors

†Obtained from Weibull regression

¶ Only among female.

ASCVD: atherosclerotic cardiovascular disease; Mets; Metabolic syndrome; CVD: cardiovascular disease; AUC, area under the curve; IDI, integrated discrimination improvement; CI, confidence interval; p, p-value.

Focusing on all CVD events, during the 10-year follow-up, Mets (1.47 (1.09–1.97)) and its high BP component (1.46 (1.09–1.97)) significantly increased the risk (Fig. 2.**A**). The unadjusted HRs (95% CI) of ASCVD-REFs for a 15-year follow-up showed that high WC component (1.33(1.05–1.68)) also increased the risk in addition to the Mets (1.48 (1.17–1.86)) and its high BP (1.49 (1.18–1.88)) component (Fig. 2.**B**). The additional predictive power of ASCVD-REFs for all CVD is presented in Table 4. The C-statistics of discrimination for the model with and without significant risk enhancers were the same for incident all CVD. Moreover in the ACC/AHA adjusted score, high BP pressure showed a moderate association with the event (1.30(0.97–1.75); p = 0.08). Positive family history of premature CVD, Mets, and its high WC, and high BP components (for both 10-year and 15-year follow-up) did not significantly improve the predictive power for incident all CVD events. The maximum relative IDI of the aforementioned risk enhancers was 0.2% for the prediction of all CVD events.

Table 4
Additional predictive power for all CVD by the ASCVD risk enhancers*: Tehran Lipid and Glucose Study (1999–2016).

	Median 10-year follow-up				Median 15-year follow-up			
	Traditional model HR† (95%)	p-value	Enhanced model HR (95%)	p	Traditional model HR (95%)	p-value	Enhanced model HR (95%)	p
Model components 1								
ACC/AHA Score	**1.08(1.05–1.12)**	**< 0.001**	**1.08(1.05–1.12)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**
Family history premature CVD			**1.54(1.05–2.24)**	**0.025**			**1.42(1.05–1.93)**	**0.02**
Model predictive performance indexes 1								
C-index (95% CI)	0.6(0.56–0.63)	< 0.001	0.6(0.54–0.66)	< 0.001	0.59(0.57–0.62)	< 0.001	0.59(0.55–0.63)	< 0.001
IDI (95%CIs)			0.002(-0.005-0.01)	0.56			0.001(-0.002-0.03)	0.57
Model components 2								
ACC/AHA Score	**1.08(1.05–1.12)**	**< 0.001**	**1.08(1.05–1.12)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**
METS			**1.45(1.08–1.95)**	**0.013**			**1.45(1.15–1.82)**	**0.002**
Model predictive performance indexes 2								
C-index (95% CI)	0.6(0.56–0.63)	< 0.001	0.6(0.56–0.64)	< 0.001	0.59(0.57–0.62)	< 0.001	0.59(0.57–0.62)	< 0.001
IDI (95%CIs)			0.001(-0.005-0.008)	0.73			0.002(-0.004-0.008)	0.55
Model components 3								
ACC/AHA Score	**1.08(1.05–1.12)**	**< 0.001**	**1.08(1.05–1.12)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**
High WC			1.30(0.97–1.75)	0.08			**1.32(1.05–1.66)**	**0.02**
Model predictive performance indexes 3								
C-index (95% CI)	0.6(0.56–0.63)	< 0.001	0.6(0.53–0.66)	< 0.001	0.59(0.57–0.62)	< 0.001	0.59(0.56–0.62)	< 0.001
IDI (95%CIs)			0.002(-0.003-0.007)	0.48			0.002(-0.003-0.007)	0.5
Model components 4								
ACC/AHA Score	**1.08(1.05–1.12)**	**< 0.001**	**1.08(1.04–1.11)**	**< 0.001**	**1.07(1.04–1.10)**	**< 0.001**	**1.06(1.04–1.09)**	**< 0.001**
High blood pressure			**1.34(1.0-1.82)**	**0.05**			**1.38(1.09–1.75)**	**0.007**

	Median 10-year follow-up				Median 15-year follow-up			
Model predictive performance indexes 4								
C-index (95% CI)	0.6(0.56–0.63)	< 0.001	0.6(0.55–0.64)	< 0.001	0.59(0.57–0.62)	< 0.001	0.59(0.58–0.60)	< 0.001
IDI (95%CIs)			0.002(-0.004-0.007)	0.57			0.002(-0.003-0.008)	0.41

*Significant ASCVD risk factors

†Obtained from Weibull regression

ASCVD: atherosclerotic cardiovascular disease; Mets; Metabolic syndrome; CVD: cardiovascular disease; AUC, area under the curve; IDI, integrated discrimination improvement; CI, confidence interval; p, p-value.

As for sensitivity analysis, when we replaced the BP cut off of 130/80 mmHg, the ACC/AHA definition of hypertension (29), with 130/85 mmHg, the results remained essentially unchanged (data not shown).

Discussion

In the current study conducted among a large population in the MENA region, we examined for the first time, the impact of ASCVD-REFs among participants with borderline/intermediate ASCVD score on incident all CVD and hard CVD events during more than a decade follow-up.

As for hard CVD, only preeclampsia showed a signal of significant risk during a 10-year follow-up while a family history of premature CVD and Mets remained significant ASCVD-REFs during the 15-year follow-up. As for all CVD events, a family history of premature CVD and Mets were the remaining ASCVD-REFs during the 10 and 15-year follow-up. Importantly among Mets components, high BP (i.e. BP ≥ 130/85 mm Hg) was the most consistent ASCVD-REFs in the prediction of all and hard CVD during both follow-up periods. Moreover, abdominal obesity as another component of Mets remained a significant ASCVD-REFs for all and hard CVD only during the 15-year follow-up. However, none of the above mentioned significant ASCVD-REFs had an added value for prediction of the model.

Preeclampsia remained significant ASCVD-REFs for hard CVD during a 10-year follow-up; however, it should be emphasized that this risk is not stable considering the limited number of events. This association is explained by endothelial dysfunction, vasoconstriction, and vascular resistance due to several causes including increased inflammatory and immunologic factors, reduced nitric oxide, and reactive oxygen species released from the ischemic and dysfunctional placenta(13). In a meta-analysis on 84 cohort studies, it was shown that gestational hypertension, moderate and severe preeclampsia were significantly associated with cardiovascular morbidity and mortality; however, the heterogeneity between included studies was high and quality of studies was adversely impacted by insufficient adjustment for the minimal set of confounders (30).

Focusing on family history of CVD, a meta-analysis on 26 studies, showed a pooled estimate of 1.31 (95% CI: 1.17–1.47; I^2 58%) for the paternal history of CVD and 1.48 (95% CI: 1.30–1.68; I^2 45%) for the maternal history of CVD, for incident CVD (31). In our study, this risk factor was associated with a significant incidence of all CVD over 10-year and 15-year follow-up, indicating its independent genetic role in the occurrence of CVD events, although its presence did not reclassify the population at borderline/intermediate risk to the higher risk category.

Mets was not remaining significant ASCVD-REFs for hard CVD during the 10-year follow-up, but it remained significant for hard CVD during the 15-year follow-up and all CVD during both follow-up periods in our borderline/intermediate-risk population. A meta-analysis of 87 studies showed that Mets is associated with a 2-fold increase in the risk of CVD, CVD mortality, MI, and stroke, and a 1.5-fold increase in the risk of all-cause mortality (32). Among the Iranian population, we

also showed that during 10 years of follow-up, the presence of Mets, independent of traditional risk factors, was associated with 97% and 120% increased risk of all CVD events in men and women respectively. Moreover, among Mets components, the high BP in both genders, high WC only among men and high FPG only among women, were independent risk factors for CVD events. Importantly we showed that adding Mets to the model including traditional risk factors and Mets components, had no added value in terms of model fitness and discriminative power (33).

Among different Mets components, we showed high BP had an independent and consistent role in the occurrence of cardiovascular events, although its presence did not reclassify the study population to the higher risk category. The 2017 guideline for the high BP of the ACC/AHA (29), updated the 2003 Seventh Report of the Joint National Committee (JNC7) (34) and the 2014 eight-panel member report (JNC8) (35) guideline in terms of the new definition for hypertension, candidates for pharmacotherapy and blood pressure target goals. Accordingly, the 2017 ACC/AHA guideline suggests a lower threshold of SBP/DBP for the definition of hypertension (130/80 mmHg vs. 140/90 mmHg, respectively), compared to the 2003 JNC7. Additionally, the 2017 AHA/ACC guideline-recommended antihypertensive medication at the level of SBP/DBP 130/80 mmHg for the elder population aged ≥ 65 years and those with high cardiovascular risk including cases with prevalent CVD or population with 10-year predicted cardiovascular risk ≥ 10% using PCE; the issues not addressed in previous guidelines. Our findings suggest that among the population with ASCVD risk between 5 to 20%, BP ≥ 130/85 mmHg or BP ≥ 130/80 mmHg can be associated with a higher risk of total and hard CVD. Hence, we speculate that these populations might benefit not only from anti-hypertensive mediation but also from statin therapy.

Improving risk prediction is not easy (36). C-reactive protein (hs-CRP) and ankle-brachial index (ABI) have great clinical potential as ASCVD-REFs, but their clinical significance in CVD prediction in terms of calibration, discrimination, and reclassification is yet uncertain (37). Unfortunately, we did not have data on novel atherosclerotic risk factors such as highly sensitive hs-CRP and measures of vascular damage that precede overt clinical CVD (i.e. ABI and coronary artery calcium score (CAC score)). We used a nested case-control study to assess the effect of hs-CRP in short-term prediction of cardiovascular disease outcomes in the Iranian population. Results showed that when traditional cardiovascular risk factors are known, measurement of hs-CRP has no additional value on the predictive power of the model(38).

This study had some strength. Firstly, to the best of our knowledge, this is the first study to evaluate the added value of ASCVD-REFs on the ASCVD risk score of individuals with borderline/intermediate risk for all CVD and hard CVD events. Secondly, we assessed the risk score for an extended follow-up period of 15 years. Limitations of the study include 1) lack of information about other ASCVD-REFs such as lipoprotein (a) and Apo B, 2) given the limited number of events, we pooled borderline and intermediate-risk as a single group and no sex-stratified analysis was performed, 3) this study was conducted among the urban Tehranian population and might not be generalizable to other populations.

Conclusion

Among the population with baseline risk between 5 to 20%, the blood pressure ≥ 130/85 mmHg was the most consistent and independent ASCVD-REF in the prediction of all and hard CVD during follow-up periods of 10 and 15-years; however, it did not improve the predictive power of the model. Findings from this study suggest that among Iranian non-diabetic individuals aged 40-75 years old with borderline/intermediate risk, considering pharmacologic therapies for both BP ≥ 130/85 mmHg and LDL-C ≥70 to <190 mg/dl might be beneficial as a preventive measure, but the issue needs more investigation and randomized controlled trials to confirm the hypothesis.

Abbreviations

Atherosclerotic cardiovascular disease risk enhancing factors (ASCVD-REFs)

American College of Cardiology/American Heart Association (ACC/AHA)

Body mass index (BMI)

Confidence Intervals: (CI)

Cardiovascular disease (CVD)

Diastolic blood pressure (DBP)

Estimated Glomerular Filtration Rate (eGFR)

Fasting plasma glucose (FPG)

Hazard ratio (HR)

High-density lipoprotein cholesterol (HDL-C)

2-hour post-challenge plasma glucose (2h-PCG)

Low-density lipoprotein cholesterol (LDL-C)

Metabolic syndrome (Mets)

Middle East and North Africa (MENA)

Non-communicable disease (NCD)

Pooled cohort equations (PCE)

Systolic blood pressure (SBP)

Type 2 diabetes (T2DM)

Tehran Lipid and Glucose Study (TLGS)

Total cholesterol (TC)

Total cholesterol, triglycerides (TGs)

Waist circumference (WC)

Declarations

Ethics Approval and Consent to Participate: This study was approved by the Institutional Review Board (IRB) of the Research Institute for Endocrine Sciences (RIES), Shahid Beheshti University of Medical Sciences, Tehran, Iran, and all participants provided written informed consent.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: No competing interests.

Funding Sources: None

Author contributions: F.H and S.A contributed to the conception or design of the work, acquisition, analysis, or interpretation of data for the work. D.kh contributed to the interpretation of data for the work. F.H, S.A, F.M, and M.O drafted the manuscript. F.H and F.S critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figures

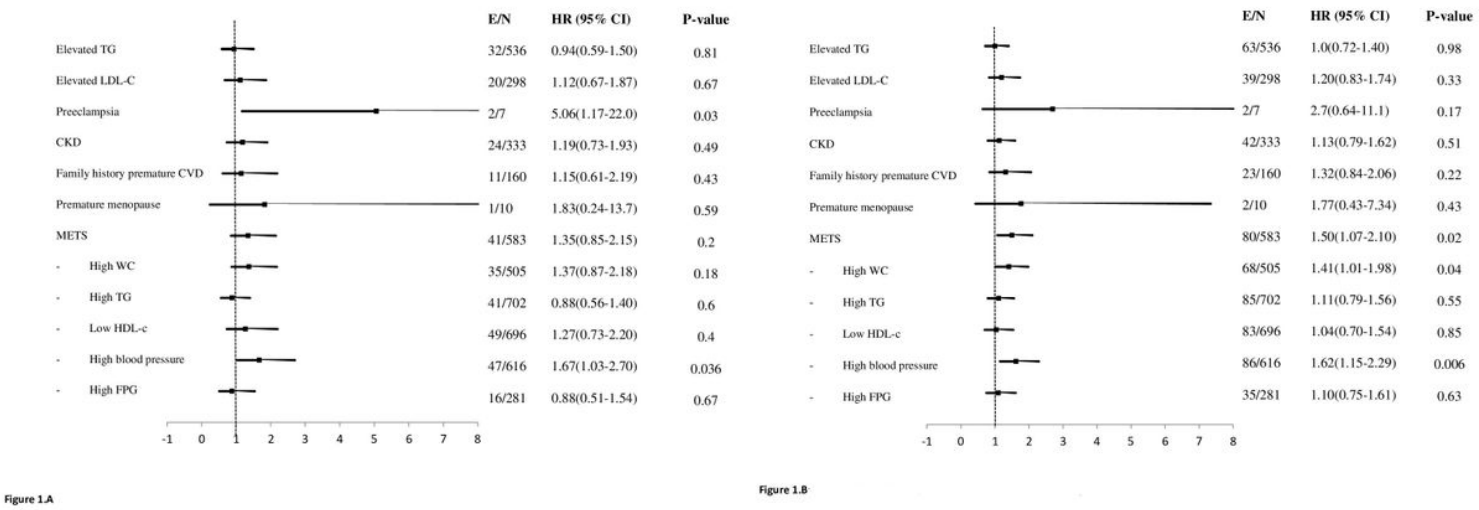

Figure 1

A: Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ASCVD risk enhancers for borderline/intermediate-risk groups according to the 2019 ACC/AHA guideline on the Primary Prevention of Cardiovascular Disease with incident all CVD during the median 10-year follow-up: Tehran Lipid and Glucose Study 1999–2014 ASCVD: atherosclerotic cardiovascular disease; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; CKD: chronic kidney disease; CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-

density lipoprotein cholesterol; TG: triglyceride; Mets; Metabolic syndrome; CVD: cardiovascular disease. Elevated TG: TG≥2.0 mmol/L; Elevated LDL-C: LDL-C≥4.1 mmol/L *Preeclampsia and Premature menopause Reported only among females. Figure 1.B: Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ASCVD risk enhancers for borderline/intermediate-risk groups according to the 2019 ACC/AHA guideline on the Primary Prevention of Cardiovascular Disease with incident all CVD during the median 15-year follow-up: Tehran Lipid and Glucose Study 1999–2014 ASCVD: atherosclerotic cardiovascular disease; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; CKD: chronic kidney disease; CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; Mets; Metabolic syndrome; CVD: cardiovascular disease. Elevated TG: TG≥2.0 mmol/L; Elevated LDL-C: LDL-C≥4.1 mmol/L *Preeclampsia and Premature menopause Reported only among females.

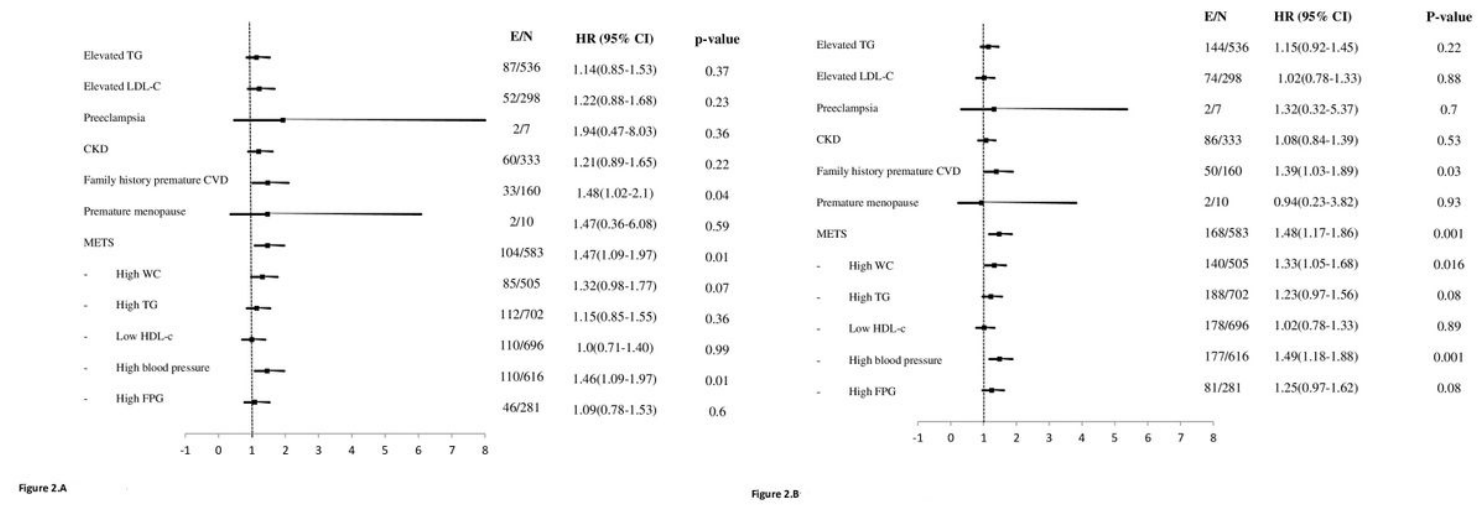

Figure 2

A: Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ASCVD risk enhancers for borderline /intermediate-risk groups according to the 2019 ACC/AHA guideline on the Primary Prevention of Cardiovascular Disease with Incident Hard CVD during the median 10-year follow-up: Tehran Lipid and Glucose Study 1999–2014 ASCVD: atherosclerotic cardiovascular disease; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; CKD: chronic kidney disease; CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; Mets; Metabolic syndrome; CVD: cardiovascular disease. Elevated TG: TG≥2.0 mmol/L; Elevated LDL-C: LDL-C≥4.1 mmol/L *Preeclampsia and Premature menopause Reported only among females. Figure 2.B: Hazard Ratios (HR) and 95% Confidence Intervals (CI) of ASCVD risk enhancers for borderline/ intermediate-risk groups according to the 2019 ACC/AHA guideline on the Primary Prevention of Cardiovascular Disease with incident Hard CVD during the median 15-year follow-up: Tehran Lipid and Glucose Study 1999–2014 ASCVD: atherosclerotic cardiovascular disease; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; CKD: chronic kidney disease; CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; Mets; Metabolic syndrome; CVD: cardiovascular disease. Elevated TG: TG≥2.0 mmol/L; Elevated LDL-C: LDL-C≥4.1 mmol/L. *Preeclampsia and Premature menopause Reported only among females.