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ORIGINAL RESEARCH

The Association of Metabolic Syndrome and Its Components with Electrocardiogram Parameters and Abnormalities Among an Iranian Rural Population: The Fasa PERSIAN Cohort Study

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Mohammad Hosein Yazdanpanah[1,2]
Sepideh Sayyadipoor[2]
Sayed Reza Hojati[2]
Amirreza Nikmanesh[2]
Mojtaba Farjam[1]
Reza Homayounfar[1,3]

[1]Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran; [2]Student Research Committee, Fasa University of Medical Sciences, Fasa, Iran; [3]National Nutrition and Food Technology Research Institute, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Background: Metabolic syndrome (MetS) as a set of cardiac risk factors and its growing prevalence is one of the major concerns in different societies. In this study, we aimed to investigate the relationship between Mets and electrocardiogram (ECG) parameters and abnormalities as indicators for subclinical cardiovascular diseases (CVD).

Methods: In this sub-analysis study, we used the data from Fasa PERSIAN Cohort Study which includes subjects age 35–70 years. Subjects with available ECG data included in the study (n=7002) and subjects with missing data on MetS components and non-sinus rhythm ECG were excluded (n=44). The MetS definition based on the Adult Treatment Panel (ATP) III guidelines and also a 12-lead ECG was obtained from all participants.

Results: Our study population (n=6958) showed a mean age of 48.60±9.34 years and also 1656 (24.2%) subjects had MetS. Except for P duration, PR interval and S amplitude in men and P amplitude, S amplitude, Sokolow-Lyon Index, and QT interval in women, other ECG parameters differ significantly between subjects with and without Mets ($P<0.05$). Also among ECG abnormalities, prolonged P duration (≥120ms), QRS duration (≥100ms), and QTc interval (>450ms in male, >470ms in female) had a significant association with MetS in the total population. Waist circumferences (WC) showed the most count of significant relationship with ECG parameters in both genders. In males, WC more than ATP cut-points had significant associations with prolonged P and QRS duration, and also blood pressure (BP) had significant associations with prolonged P and QRS durations and QTc interval. In females, the MetS component except triglyceride had at least a significant relationship with prolonged P and/or QRS duration.

Conclusion: MetS and its component especially WC and BP were associated with ECG parameters and abnormalities. These associations with ECG as a marker of subclinical CVD showed the importance of MetS and each component in our population to monitor in the further longitudinal studies.

Keywords: electrocardiogram, metabolic syndrome, P wave, QRS complex, QTc interval

Introduction

The metabolic syndrome (MetS) or X syndrome refers to a set of obesity, hypertension, hyperlipidemia, microalbuminuria, and impaired glucose metabolism risk factors[1] first defined by Reaven in 1988.[2] With a growing prevalence, the MetS affected 10–23% of the world population between 2002 and 2004.[3] From 2003 to 2012, the prevalence of MetS in the United States was approximately 33%.[4] Studies

Correspondence: Reza Homayounfar
Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran
Tel +989125140840
Email r_homayounfar@yahoo.com

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conducted in the Middle East between 2003 and 2014 showed that MetS had a prevalence of about 25% and rapid growth, even more than the American and European populations.[5] The prevalence rate of MetS was more than 30% in different studies in Iran.[6,7]

In another definition, this syndrome was defined as a set of cardiac risk factors[8] showing its role in developing cardiovascular disease (CVD). For example, MetS account for 25% of CVDs[9]. On the other hand, it increases the risk of CVD by 61%.[10] Each component of the MetS has a distinct role in the development of CVD; however, the distinct role of each component is greater than in the general.[11] CVD is the leading cause of premature mortality in the world with 17.9 million deaths in 2012, which is predicted to increase to 23 million deaths in 2030. Moreover, the low- and medium-income countries, specifically the Eastern Mediterranean countries, account for 50% of deaths and 80% of the global burden from this disease. The death from CVD in Iran increased from 26.6% in 1981 to 43.3% in 1995.[12] According to the GBD's reports, CVD has been the leading cause of mortality between 2010 and 2015 in Iran, accounting for more than 20% of all diseases and 46% of all deaths.[13]

Electrocardiogram (ECG) can be regarded as a simple comprehensive method to check the heart's activity history. As a test with a high prediction value, it can be used to predict the chance of CVD development.[14] It is worth noting that the majority of studies have investigated the effects of MetS only on one or few markers from the patients' electrocardiograms, such as aortic stiffness,[15] T-wave axis,[16,17] resting heart rate,[18] QT interval, ST segment, and Q-wave,[14] or assessed the effect of only one component of the MetS, such as blood glucose,[19,20] obesity,[21] and/or abdominal adiposity[22] on the majority of ECG markers. This suggests that there are few similar studies in the world and no similar study in Iran as comprehensive as the present study.

The genetic, cultural, and geographical differences, among many others, justify differences between various studies conducted in different geographic regions. In many areas, the cohort studies on metabolic subjects have investigated the effects of MetS and its components on the ECGs. It is worth noting that some of these studies produced different results, indicating that although a few relevant studies exist in the world, this relationship continues to remain unknown.[14,23] Besides, knowing the effects of MetS and its components on ECG can be helpful for CVD risk prediction, and used by health authorities and decision-makers to change its epidemic spread in Iran.[24]

Methods

Study Design and Population

In this sub-analysis of Fasa Cohort Study, as a part of the PERSIAN cohort study, near 11,100 people aged 35 to 70 years were included[25] Each participant has signed informed consent at the beginning of the study. All subjects with available data of ECGs and without reported or known CVD were included in the study (n=7002). All included subjects were at the same socioeconomic level, with the same ethnic and same residential region. Also, subjects with detected non-sinus rhythm ECG and missing data on Mets components haves been excluded (n=44,) and finally 6958 subjects remained in the study.

Characteristics of Subjects

Basic data including age, sex, smoking status, alcohol consumption, and chronic diseases such as diabetes and hypertension were questioned and recorded by an internet-based questionnaire. All medication that was taken within 2 weeks before registration has been questioned and recorded. A list of drugs (selected medications) which has been provided by CredibleMeds, as an American organization, including drugs with known risk and drugs with a possible risk for Torsades de pointes, which counts 187 cardiac and non-cardiac drugs in total was used to recognize the drugs which have been known as effective factors in QT interval prolongation.[26] Physical activity was measured by a 20-item questionnaire that can measure routine physical activities of rural Iranians. The amount of each activity in hours and minutes was determined; the MET-value of each activity was multiplied by its duration, and MET-min of each activity was calculated. Finally, the sum of all activities was calculated as the total physical activity (MET/24h).

Measurements

For the anthropometry calculations, height was measured by a stadiometer with an accuracy of 0.1 cm and weight was measured by a digital scale with an accuracy of 0.1 kilograms. Body mass index (BMI) was calculated using weight divided by the square of height (kg/m2). Waist circumference (WC) was measured at the midpoint of the inferior border of the lowest ribs to the anterior superior iliac spine, using an inelastic tape. Hip circumference was

considered at the widest part of the participants' hip. Wrist circumference was measured just below the wrist bone.

For evaluating blood pressure (BP), participants first rested for 15 minutes, after which with an interval of five minutes, two consecutive BP's were measured from participants and reported by an average of systolic and diastolic pressure in mmHg. Triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and fasting blood sugar (FBS) all obtained from venous blood samples taken in a 10–14h fasting condition. TC and HDL measures were assayed by using the Mindray BS380 autoanalyzer (Mindray Medical International, Shenzhen, China) as the biochemical tests. Laboratory testing of FBS was done using glucose oxidize test. We used the Friedewald formula to calculate LDL.[27]

Electrocardiogram

A 12-Lead ECG was obtained from the participants using a computer-based paperless device (Cardiax®[28]) with a 2000 Hz sampling rate and 0.04 μV/bit (24-bit resolution). Patients were in the supine position 15 minutes before recording and were told to relax, breathe normally, refrain from moving and talking, but remain awake during the procedure. As this device provide us a more detailed value of the duration, amplitude, and axis of the ECG waves, we used ECG parameters such as Heart rate (bpm), P duration (ms), P amplitude II (mV), PR interval (ms), QRS duration (ms), R amplitude V5 (mV), S amplitude V1 (mV), QT interval (ms), QTc interval (ms), P axis (°) and QRS axis (°). All ECGs analyzed and reported Automatically by Cardiax software (version 3.50.2, International Medical Equipment Developing Co. Ltd., Budapest, Hungary) and exported to central data software. Also, prolonged PR interval was considered as PR interval≥ 200 ms, prolonged P duration was considered as P duration≥ 120 ms, prolonged QRS duration was considered as QRS duration ≥ 100 ms. Bazett's formula[29] was used to calculate heart-rate corrected QT interval (QTc) also we used clinical standard cut-offs for prolonged QTc interval (Man>450ms, Woman>470). Moreover, Sokolow-Lyon index was calculated as the sum of S amplitude V1 and R amplitude V5/6[30]

Metabolic Syndrome Definition

The MetS were assumed to be present provided that three or more of the following parameters are met, based on the NCEP ATP III guidelines:[31]

1. The WC more than 94 cm for men and more than 80 cm for women
2. HDL less than 40 mg/dL in men and less than 50 mg/dL in women or receiving drug therapy for reduced HDL
3. TG level ≥ 150 mg/dL or receiving drug therapy for hypertriglyceridemia
4. BP ≥ 130/85 mmHg or receiving blood pressure-lowering drugs
5. FBS ≥ 101 mg/dL or receiving glucose-lowering drugs

Data Analysis

Descriptive statistics were reported as number (percentage) or mean ± SD. Independent *T*-test was used to compare quantitative variables between the two groups. Also, both linear and logistic regression analyses performed for multivariate analysis. Regression adjusting was done with variables such as age, heart rate, smoking history, educational years, diabetes history, regular consumption of alcohol, physical activity, and selected medications (just for QT and QTc interval analysis). All the statistical analyses performed in SPSS 22.0 (IBM Corp., Armonk, N.Y., USA), Microsoft Excel 2019 software and for graphs, we used Prism version 8.00 (GraphPad Software, La Jolla California USA). Also, P-value<0.05 considered as statistically significant P-value.

Ethics Approval

Our study was following relevant guidelines and regulations of our regional and national research ethics committees, also the protocol of this study has the approval of regional and national research ethics committees (the equivalent of institutional review boards) of FUMS (reference number: IR.FUMS.REC. 1399.019).

Results

A total of 6958 participants, including 3001 (43.13%) male and 3957 (56.87%) female with a mean of age 48.60±9.34 years in total population were analyzed. Table 1 presents the demographic characteristics of the participants. According to this table, 1656 (24.2%) of the participants satisfied the MetS criteria. Participants with MetS had a significantly higher mean of age, anthropometrics variables, lipid profiles, and FBS. Physical activity was statistically significantly higher in those without MetS (p<0.001). Moreover, the majority of MetS subjects were

Table 1 Baseline Characteristics of the Population According to Metabolic Syndrome (n=6958)

	Without MetS (n=5302)	With MetS (n=1656)	P-value
Age (year)	47.61±9.16	51.72±9.24	**<0.001**
Waist circumference (cm)	90.57±11.14	101.86±9.55	**<0.001**
Hip Circumference (cm)	97.98±8.38	103.80±8.62	**<0.001**
Wrist Circumference (cm)	16.60±1.33	17.03±1.37	**<0.001**
BMI (kg/m^2)	24.64±4.63	28.85±4.32	**<0.001**
Physical activity (Met/24h)	42.07±11.48	38.38±7.88	**<0.001**
Diastolic Blood Pressure (mmHg)	72.48±10.81	79.57±12.28	**<0.001**
Systolic Blood Pressure (mmHg)	107.72±16.31	120.04±19.32	**<0.001**
FBS (mg/dL)	87.47±18.38	111.75±49.17	**<0.001**
Total Cholesterol (mg/dL)	182.18±37.38	192.87±44.17	**<0.001**
Triglyceride (mg/dL)	115.25±65.45	188.27±110.24	**<0.001**
HDL (mg/dL)	50.01±13.27	43.76±10.19	**<0.001**
LDL (mg/dL)	109.09±31.13	111.42±36.99	**0.010**
Education Years	5.01 ± 3.85	3.43 ± 3.40	**<0.001**
Sex (male)	2737 (50.9%)	343 (20%)	**<0.001**
Diabetes history	371 (6.9%)	524 (30.5%)	**<0.001**
Hypertension history	657 (12.2%)	786 (45.8%)	**<0.001**
Regular consumption of alcohol	128 (2.4%)	13 (0.8%)	**<0.001**
Active smoker	1600 (29.8%)	208 (12.1%)	**<0.001**

Notes: Data are presented as Mean± Standard Deviation or number (percentage). Significant results are bolded. P-value Results are based on independent samples *T*-Test and Chi-Square.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein.

women (80%) and being smoker and regular consumption of alcohol was higher in subjects without MetS.

In Table 2, As can be seen, male participants with MetS had a significantly higher heart rate, longer QRS duration, and QTc interval ($p<0.001$); whereas, their P amplitude II, R amplitude V_5, Sokolow-Lyon Index, QT interval, P axis, and QRS axis were lower ($p<0.001$). Among the female participants, those with MetS had a significantly higher heart rate ($p<0.001$), longer P duration ($p=0.002$), longer QRS duration ($p<0.001$), longer QTc interval ($p<0.001$), lower P axis ($p=0.017$), and lower QRS axis ($p<0.001$). Among the total population, 82 (1.1%) of subjects had prolonged PR interval, 670 (9.6%) had prolonged P duration, 2504 (35.98%) had Prolonged QRS duration, 691 (9.93%) had prolonged QTc interval. ECG abnormalities were more frequent in males. According to MetS, significantly higher frequency observed in prolonged P duration and prolonged QTc interval in males and prolonged P duration, QRS duration, and QTc interval in females ($p<0.001$).

Table S1 shows the association between EGC parameters and abnormalities with MetS in the males and females. The highest positive beta-coefficient and 95% CI was related to heart rate and the highest negative was related to the QRS axis in males and P axis in females. Among ECG abnormalities prolonged P and QRS durations odds ratios (95% CI) respectively were 1.561 (1.112–2.191) and 1.394 (1.095–1.774) with P-value<0.05 in male. In the female gender, the both mentioned abnormalities were still significant, also in addition to these abnormalities, prolonged QTc interval was in a significant association with MetS(P-value=0.003) in females. Table 3 represents the results of the linear regression model of the association of MetS components with ECG parameters in both genders. Among MetS components, WC was significantly related to all ECG parameters in males. In females, just the QT interval did not show any significant association with WC. In both genders, it seems that FBS had the lowest count of significant relationships but the highest positive relationship in females was related to FBS and heart rate and in males was related to SBP and Sokolow-Lyon Index with a standardized beta coefficient 0.189 and 0.182 (P-value<0.001) respectively. Also, the highest negative relationship was related to WC and P axis with −0.268 and WC and R amplitude V5 with −0.226 (P-value<0.001), respectively in males and females. Also, Table S2 represents the results of the linear regression model of MetS components as binary outcomes with ECG parameters in both genders.

Figure 1 represents a comparison of ECG parameters' means between different MetS scores in the total population. Overall, a significant increase of means was seen in multiple

Table 2 Baseline ECG Parameters of the Population According to Metabolic Syndrome in Both Gender

	Male (n=3001)			Female (n=3957)		
	Without MetS (n=2683)	**With MetS (n=318)**	**P-value**	**Without MetS (n=2619)**	**With MetS (n=1338)**	**P-value**
Heart rate (bpm)	65.29±10.653	71.64±11.252	**<0.001**	74.18±11.044	77.1±12.399	**<0.001**
P duration (ms)	99.97±25.319	101.15±30.585	0.428	98.97±22.108	101.26±23.336	**0.002**
PR Interval (ms)	140.5±35.878	140.77±42.605	0.898	136.12±31.802	138.6±33.155	**0.021**
P amplitude II (mV)	0.12±0.058	0.11±0.05	**<0.001**	0.12±0.05	0.12±0.05	0.202
QRS duration (ms)	98.23±10.525	100.81±11.779	**<0.001**	94.67±9.574	97.06±10.359	**<0.001**
R amplitude V_5 (mV)	1.20±0.53	1.07±0.50	**<0.001**	0.88±0.43	0.83±0.39	**0.001**
S amplitude V_1 (mV)	−0.59±0.36	−0.59±0.38	0.692	−0.57±0.35	−0.58±0.39	0.406
Sokolow-Lyon Index (mV)	1.84±0.72	1.66±0.73	**<0.001**	1.49±0.65	1.45±0.64	0.070
QT interval (ms)	405.01±36.695	394.99±32.169	**<0.001**	396.05±35.82	394.88±39.994	0.346
QTc interval (ms)	419.28±32.181	428.55±28.07	**<0.001**	437.45±33.006	443.92±34.521	**<0.001**
P axis (°)	50.84±25.767	40.34±24.601	**<0.001**	45.38±23.133	43.57±22.013	**0.017**
QRS axis (°)	40.58±42.867	22.06±42.465	**<0.001**	34.67±31.819	28.08±31.288	**<0.001**
Prolonged PR interval (≥ 200 ms)	43(1.6)	6(1.9)	0.705	22(0.8)	11(0.8)	0.953
Prolonged P duration (≥ 120 ms)	258(9.6)	53(16.7)	**<0.001**	193(7.4)	166(12.4)	**<0.001**
Prolonged QRS duration (≥ 100 ms)	1140(42.5)	156(49.5)	**0.025**	717(27.4)	491(36.7)	**<0.001**
Prolonged QTc interval [a]	260(9.7)	54(17)	**<0.001**	209(8)	168(12.6)	**<0.001**

Notes: Data are presented as Mean± Standard Deviation or number (percentage). [a]Prolonged QTc interval considered as >450ms in male and >470ms in the female. P-value Results are based on independent samples *T*-Test and Chi-Square. Significant results are bolded.
Abbreviation: MetS, metabolic syndrome.

ECG parameters including heart rate, P duration, QRS duration, QTc interval, and P amplitude II. Also, a significant decrease of means was seen in the QT interval, P axis, QRS axis, R amplitude V_5, and Sokolow-Lyon Index.

In ECG abnormalities, in males, just three of the MetS components including WC, BP, and HDL were significantly associated with prolonged P duration with odds ratios (95% CI), 1.849 (1.352–2.528), 1.323 (1.006–1.739) and 1.286 (1.013–1.631) respectively. Also, WC was related to prolonged QRS duration with 1.552 (1.231–1.956) and P-value<0.001, and BP was related to prolonged QT interval with 1.421 (1.067–1.893) and prolonged QRS duration with 1.215 (1.011–1.459) P-value<0.05. But in females, just prolonged P duration and prolonged QRS duration were in significant associations with MetS components, prolonged P duration with WC, FBS and BP, and prolonged QRS duration with WC, BP, and HDL. Among these variables, the highest OR was related to BP and prolonged P duration with 1.758 (1.392–2.221) and P-value<0.001 (Table 4).

According to Table 5, it seems that WC and BP are the two MetS components (as binary outcomes) which have significant associations with having single or multiple ECG abnormalities. In male, WC with odds ratios (95% CI) 1.381 (1.095–1.742) and 1.571 (1.149–2.147) was related to having single or multiple ECG abnormalities (P-value<0.05) respectively. In females, such relationships observed with smaller odds ratios. Also, BP with an odds ratio (95% CI), 1.628 (1.265–2.094) and P-value<0.001, was related to having multiple ECG abnormalities in males but there was not any significant association between BP and having single abnormality (P-value=0.468) while in females it was significant with 1.356 (1.169–1.573) and P-value<0.001.

In total, 707 (35.8%) of subjects with MetS score of 1, 693 (35.5%) of subjects with MetS score of 2, 445 (41%) of subjects with MetS score of 3, 167 (37.0%) of subjects with MetS score of 4, 49 (40.8%) of subjects with MetS score of 4 had one ECG abnormality which was an insignificant difference (P=0.021). Also, 171 (8.6%) of subjects with MetS score of 1, 183 (9.4%) of subjects with MetS score of 2, 108 (10%) of subjects with MetS score of 3, 60 (13.3%) of subjects with MetS score of 4, 24 (20%) of subjects with MetS score of 4 had multiple ECG abnormalities which were insignificant difference (P<0.001). ECG abnormalities' frequency in different MetS scores has been

Table 3 A Multivariate Linear Model of Association of ECG Parameters with Metabolic Syndrome Components in Both Genders

	Male (n=3001)						Female(n=3957)					
	WC	FBS	BP		TG	HDL	WC	FBS	BP		TG	HDL
			DBP	SBP					DBP	SBP		
Heart rate (bpm)	**0.157** [a]	**0.178** [a]	**0.149** [a]	**0.136** [a]	**0.152** [a]	**−0.081** [a]	**0.057** [a]	**0.189** [a]	**0.125** [a]	**0.131** [a]	**0.099** [a]	−0.027
P duration (ms)	**0.080** [a]	0.006	0.001	−0.011	**0.057** [b]	−0.004	**0.044** [c]	0.012	**0.036** [c]	**0.036** [c]	0.003	0.008
PR Interval (ms)*	**0.092** [a]	0.017	0.021	0.012	**0.054** [c]	0.012	**0.044** [c]	0.027	0.030	**0.034**[c]	0.008	0.012
P amplitude II (mV)	**−0.219** [a]	−0.024	**−0.081** [a]	**−0.081** [a]	**−0.068** [a]	**0.102** [a]	**−0.080** [a]	**−0.017**	0.001	0.004	−0.014	**0.051** [a]
QRS duration (ms)	**0.136** [a]	0.018	**0.054** [c]	**0.067** [a]	**0.037** [c]	**−0.045** [c]	**0.126** [a]	0.026	**0.051** [c]	**0.060** [a]	−0.005	**−0.041** [b]
R amplitude V_5 (mV)	**−0.146** [a]	**−0.043** [c]	**0.136** [a]	**0.144** [a]	**−0.041** [c]	**0.113** [a]	**−0.226** [a]	**−0.060** [a]	**0.083** [a]	**0.097** [a]	**−0.076** [a]	**0.082** [a]
S amplitude V_1 (mV)	**0.052** [b]	−0.016	**−0.130** [a]	**−0.158** [a]	0.010	**−0.103** [a]	**0.069** [a]	−0.030	**−0.168** [a]	**−0.158** [a]	0.016	**−0.074** [a]
Sokolow-Lyon Index (mV)	**−0.146** [a]	−0.025	**0.165** [a]	**0.182** [a]	**−0.040** [c]	**0.137**	**−0.182** [a]	−0.028	**0.156** [a]	**0.163**	**−0.056** [a]	**0.086** [a]
QT interval (ms)**	**0.054** [a]	−0.021	**0.049** [a]	0.030	−0.002	0.007	0.015	−0.017	**0.054** [a]	**0.048** [a]	**0.033**[c]	−0.035
QTc interval (ms)**	**0.065** [a]	−0.030	**0.065** [a]	**0.037** [c]	−0.004	0.001	0.021	−0.025	**0.064** [a]	**0.052** [a]	0.043	**−0.044** [b]
P axis (°)	**−0.268** [a]	−0.032	**−0.103** [a]	**−0.108** [a]	**−0.065** [c]	**0.082** [a]	**−0.164** [a]	−0.030	**−0.055** [a]	**−0.057** [a]	**−0.054** [a]	**0.038** [c]
QRS axis (°)	**−0.222** [a]	**−0.050**[c]	**−0.106** [a]	**−0.101** [a]	**−0.077** [a]	**0.046** [c]	**−0.122** [a]	−0.020	**−0.075** [a]	**−0.070** [a]	**−0.038**[c]	0.027

Notes: Data are presented as standardized beta coefficient [P-value]. The analysis was adjusted for age, heart rate, smoking history, educational years, diabetes history, regular consumption of alcohol, and physical activity. *P duration was added to analysis plus previously mentioned adjusted variables **QRS duration and selected medications were added to analysis plus previously mentioned adjusted variables. Significant results are bolded. P-value reference: a <0.001, b <0.01, c <0.05.

Abbreviations: WC, waist circumference; FBS, Fasting Blood Sugar; BP, Blood Pressure; TG, triglyceride; HDL, High Density Lipoprotein Cholesterol.

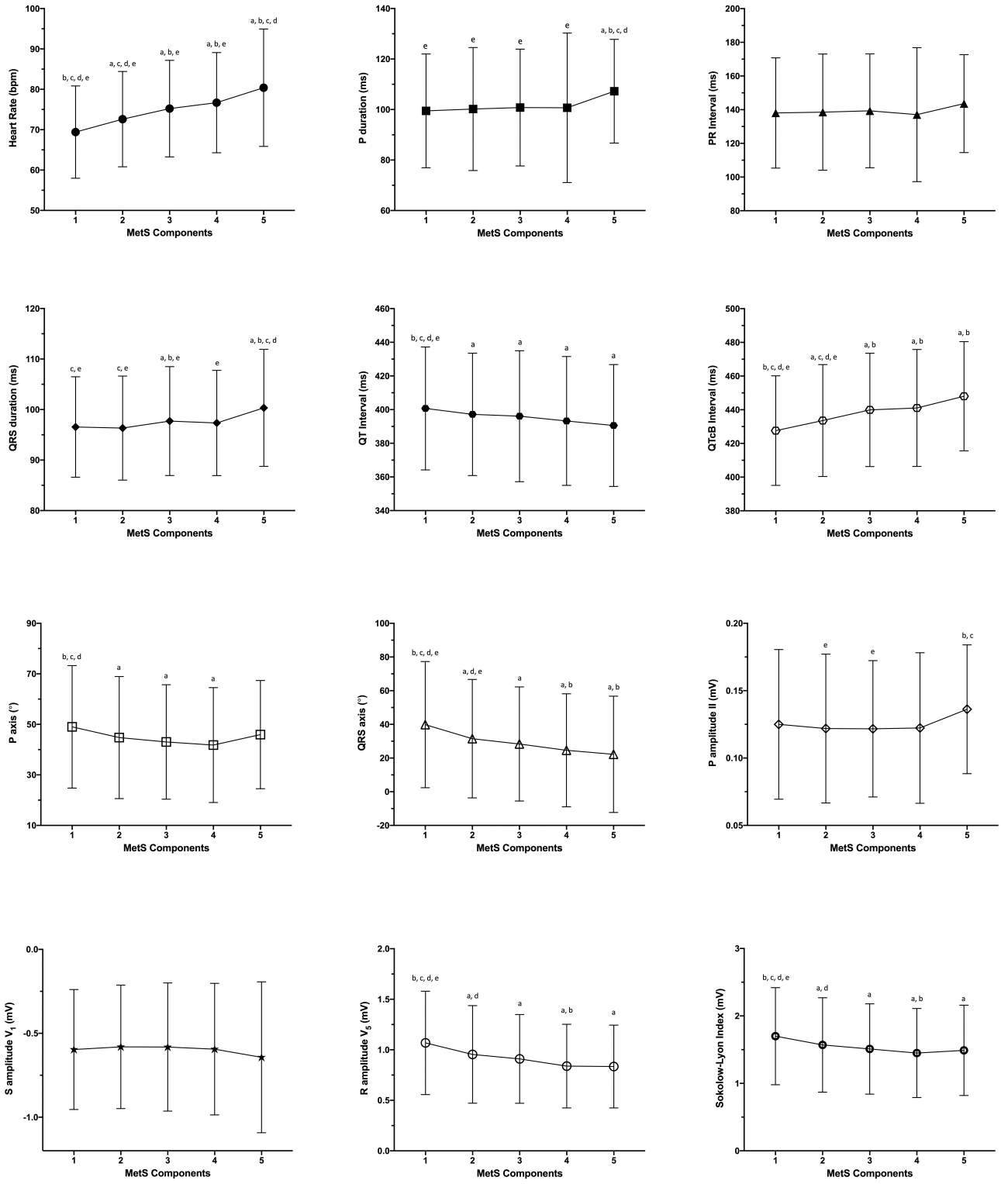

Figure 1 Comparison of ECG parameters' means in different metabolic syndrome scores in the total population. a: significant difference to subjects with score 1, b: significant difference to subjects with score 2, c: significant difference to subjects with score 3, d: significant difference to subjects with score 4, e: significant difference to subjects with score 5.
Abbreviations: MetS, Metabolic syndrome.

presented in Figure 2 according to gender. Significant differences among different MetS scores in men were related to the frequency of multiple ECG abnormalities while both single/multiple ECG abnormalities showed significant differences in women (P<0.001). Also, Table S3 shows the odds ratios of having different MetS scores with

Table 4 A Multivariate Model of Association of ECG Abnormalities with Metabolic Syndrome Components According to Gender

	Waist Circumference Male > 94 cm Female > 80 cm	Fasting Blood Glucose ≥101 mg/dL	Blood Pressure ≥130/85 mm/Hg	Triglyceride ≥150 mg/dL	High-Density Lipoprotein Male <40 mg/dL Female <50 mg/dL
Males (n=3001)					
Prolonged PR interval (≥ 200 ms) *	0.598 (0.197–1.812)	0.399 (0.085–1.880)	1.023 (0.464–2.258)	1.369 (0.678–2.766)	1.046 (0.543–2.017)
Prolonged P duration (≥ 120 ms)	**1.849 (1.352–2.528)** [a]	1.009 (0.686–1.486)	**1.323 (1.006–1.739)** [b]	1.127 (0.870–1.460)	**1.286 (1.013–1.631)** [b]
Prolonged QRS duration (≥ 100 ms)	**1.552 (1.231–1.956)** [a]	1.131 (0.876–1.462)	**1.215 (1.011–1.459)** [b]	1.156 (0.983–1.360)	1.091 (0.941–1.264)
Prolonged QTc interval (>450 ms) **	0.908 (0.634–1.301)	0.803 (0.541–1.194)	**1.421 (1.067–1.893)** [b]	0.925 (0.703–1.217)	0.985 (0.762–1.272)
Females (n=3957)					
Prolonged PR interval (≥ 200 ms)	0.937 (0.381–2.302)	0.706 (0.240–2.075)	1.400 (0.623–3.149)	0.903 (0.378–2.156)	0.921 (0.434–1.955)
Prolonged P duration (≥ 120 ms)	**1.365 (1.033–1.805)** [b]	**1.351 (1.009–1.810)** [b]	**1.758 (1.392–2.221)** [a]	1.151 (0.908–1.458)	1.005 (0.807–1.250)
Prolonged QRS duration (≥ 100 ms)	**1.536 (1.299–1.816)** [a]	1.123 (0.920–1.371)	**1.514 (1.301–1.763)** [a]	0.906 (0.775–1.059)	**1.175 (1.024–1.347)** [b]
Prolonged QTc interval (>470 ms) **	1.147 (0.889–1.480)	1.052 (0.771–1.435)	1.075 (0.846–1.365)	0.953 (0.749–1.213)	1.183 (0.956–1.463)

Notes: Data are presented as odds ratio (95% Confidence Interval) [P-value]. The analysis was adjusted for age, heart rate, smoking history, educational years, diabetes history, regular consumption of alcohol, and physical activity. *P duration was added to analysis plus previously mentioned adjusted variables **QRS duration and selected medications were added to analysis plus previously mentioned adjusted variables. Significant results are bolded. P-value reference: a <0.001, b <0.05.

ECG abnormalities according to gender comparing to the reference group of subjects (MetS score=0).

Discussion

In this study with a large number of Iranian population main findings of the study were i) In overall, the mean of Heart rate, P duration, PR Interval, QRS duration S amplitude, and QTc interval was higher in subjects with MetS but the mean of P amplitude, R amplitude, Sokolow-Lyon Index, QT interval, P axis, and QRS axis was lower in the subject with MetS. ii) ECG abnormalities including prolonged PR interval, P duration, QRS duration, and QTc interval frequencies were higher in subjects with metabolic syndrome. However, just prolonged P duration and QTc interval in men and prolonged P duration, QRS duration, and QTc interval in women were at a significant difference. iii) The MetS were associated with prolonged P duration and QTc interval in males. This association in female subjects was seen with all ECG abnormalities except prolonged PR interval. iv) Among MetS components, WC had the highest count of significant relationship with ECG parameters in both genders, and the highest positive relationship in females was related to FBS and heart rate and in males was related to SBP and Sokolow-Lyon Index. Also, the highest negative relationship was related to WC and P axis and R amplitude V5 respectively in males and females. v) Among relationships between MetS components and ECG abnormalities, WC had significant associations with prolonged P and QRS duration and BP had significant associations with prolonged P and QRS duration and QTc interval in males. Also, prolonged P and HDL had a significant association. In females, the MetS component except TG had at least a significant relationship with prolonged P and/or QRS duration. vi) Considering ATP cut-points for MetS components, Subjects with WC and BP more than cut-points seem to be more prone to have single/multiple ECG abnormalities which were higher in males than females. Also, MetS may increase the frequency of having multiple ECG abnormalities near 80% and 30% respectively in men and women significantly.

It should be mentioned that these findings were independent of other risk factors such as age, heart rate, smoking history, educational years, diabetes history, regular consumption of alcohol, and physical activity.

Metabolic Syndrome and ECG Parameters

Our results showed that it seems MetS is in a significant positive association with heart rate as first ranked and following by QRS duration in men and QTc interval in women. Queen et al,[14] reported that the odds ratio in having MetS in

Table 5 A Multivariate Model of Association of ECG Abnormalities with Metabolic Syndrome and Its Components as Binary Outcomes According to Gender

		Male (n=3001)		Female (n=3957)	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Without ECG abnormalities	Metabolic syndrome	**0.706 (0.552–0.903)**	**0.006**	**0.674 (0.585–0.777)**	**<0.001**
	Waist Circumference	**0.595 (0.468–0.756)**	**<0.001**	**0.677 (0.581–0.788)**	**<0.001**
	Fasting Blood Glucose	0.881 (0.681–1.140)	0.336	0.851 (0.704–1.028)	0.094
	Blood Pressure	**0.829 (0.690–0.997)**	**0.046**	**0.640 (0.554–0.739)**	**<0.001**
	Triglyceride	0.895 (0.761–1.053)	0.181	1.051 (0.909–1.215)	0.504
	High-Density Lipoprotein	0.900 (0.777–1.042)	0.159	**0.874 (0.770–0.993)**	**0.039**
With one ECG abnormality	Metabolic syndrome	1.104 (0.864–1.410)	0.430	**1.420 (1.228–1.642)**	**<0.001**
	Waist Circumference	**1.381 (1.095–1.742)**	**0.006**	**1.342 (1.146–1.572)**	**0.001**
	Fasting Blood Glucose	1.208 (0.932–1.566)	0.153	1.110 (0.914–1.349)	0.293
	Blood Pressure	0.933(0.774–1.125)	0.468	**1.356 (1.169–1.573)**	**<0.001**
	Triglyceride	1.076 (0.913–1.268)	0.382	0.983 (0.846–1.142)	0.822
	High-Density Lipoprotein	1.060 (0.913–1.230)	0.446	1.100 (0.964–1.255)	0.157
With multiple ECG abnormalities	Metabolic syndrome	**1.561 (1.141–2.135)**	**0.005**	1.242 (0.961–1.605)	0.097
	Waist Circumference	**1.571 (1.149–2.147)**	**0.028**	**1.410 (1.038–1.915)**	**0.005**
	Fasting Blood Glucose	0.866 (0.603–1.244)	0.437	1.206 (0.871–1.669)	0.260
	Blood Pressure	**1.628 (1.265–2.094)**	**<0.001**	**1.664 (1.290–2.147)**	**<0.001**
	Triglyceride	1.118 (0.878–1.423)	0.366	0.901 (0.689–1.179)	0.447
	High-Density Lipoprotein	1.131 (0.603–1.416)	0.284	1.165 (0.917–1.480)	0.211

Notes: Data are presented as odds ratio (OR) 95% Confidence Interval (CI). The analysis was adjusted for age, heart rate, smoking history, educational years, diabetes history, regular consumption of alcohol, and physical activity. Waist Circumference: Male >94, Female >80 cm, Fasting Blood Glucose: both gender ≥101 mg/dL, Blood Pressure: both gender ≥130/85 mm/Hg, Triglyceride: both gender≥150 mg/dL, High-Density Lipoprotein: Male <40, Female <50 mg/dL. Significant results are bolded.

subjects with HR more than 72 bpm in comparison to those with HR lower than 65.6 bpm is 2.38. They have also reported that the odds ratio in having MetS in subjects with QTcB more than 422 ms in comparison to those with QTc lower than 396 ms is 1.69. However, they had a different study design but it supports our result in the case of association of HR, QTc, and MetS. In a recent study with a smaller sample size, the PR interval had the strongest association with metabolic syndrome.[21] Surprisingly PR interval in our study was not at a significant relationship with metabolic syndrome. A cross-sectional analysis in the Netherlands[23] reported the mean of P and QRS axis 44.2 and 23.0 respectively in non-obese subjects which were near our results. Also, the same as our results, they observed a negative significant relationship between P and QRS axis with metabolic syndrome. In our study P axis was the first and QRS was the second parameter in having the highest negative relationship with MetS in women while vice versa was

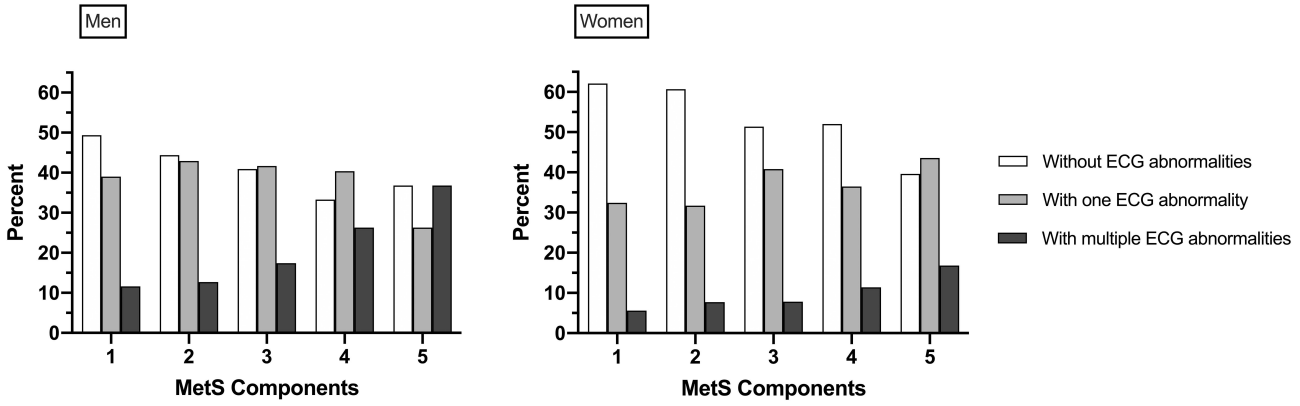

Figure 2 Frequencies of ECG abnormalities in different metabolic syndrome scores in both gender.
Abbreviation: MetS, Metabolic syndrome.

seen in men. A few studies are focusing on different ECG wave amplitudes with metabolic syndrome. A study that has been performed just on men, reported that a lower mean of P, R, and S amplitudes in subjects with MetS.[32] Among these amplitudes, just R amplitude was in the significant differences between the two groups. Our findings also have shown almost the same results.

Metabolic Syndrome and ECG Abnormalities

Our findings suggested that prolonged P duration in men and prolonged QRS in women among ECG abnormalities had the strongest significant association with metabolic syndrome. There was just another significant association in men among ECG abnormalities which were related to prolonged QRS duration. Also, the three statistically significant associations in women from highest to lowest association respectively were prolonged QRS duration, prolonged QT interval, and prolonged P duration. Ebong et al,[33] in a study on 6765 subjects aged from 45–84, reported that among those with MetS, 65.1% of men and 50% of women had abnormalities in their ECG. Although we had very different criteria for ECG abnormalities, in our study 61.8% of men and 49.9% of women which was near the previously reported results. Also, having multiple ECG abnormalities seems to have a higher significant association than having one ECG abnormality in both genders. In men, MetS seem to prone subjects to have multiple ECG abnormalities more than 78% as subjects without MetS. Also, female subject with Mets had a higher significant association (near more than 35%) with having one ECG abnormality which did not apply to men.

Each Metabolic Syndrome Component and ECG Parameters

Waist circumference in men was at a significant positive association with all ECG parameters except P and R amplitude, Sokolow-Lyon index, P, and Q axis. The same relations were seen in females except for QT and QTc intervals and waist circumference which was not at a significant association which may be due to heart rate variability. Elffers et al,[22] reported that waist circumference positively was associated with QRS duration, P duration, and negatively was associated with the QRS axis and without any associations with the P axis. Their results support our findings however in the case of the P axis there was a negative association in our study.

FBS in men was only associated with heart rate, R amplitude, and QRS axis. In women, FBS had a significant relation with heart rate, P, and R amplitudes. A few studies are focusing on blood glucose and ECG parameters but Paudyal et al on 100 participate, indicated a possible association between Impaired and left axis deviation.[34] Our negative association between FBS and QRS axis can indicate the same somehow but, this relationship was not significant. Another study reported a slight increase in PR interval in subjects with higher FBS.[35] We observed this association in both genders however it was one of the smallest and again insignificant.

Both Systolic and diastolic BP in men were associated with ECG parameters except P duration and PR interval. Systolic BP also did not show a significant relationship with the QT interval. These exceptions in women were P amplitude. Also, Systolic BP did not show a significant relationship with the PR interval in addition to the previous one. Alonso et al, on 3180 participate from the MESA study suggested that Systolic and diastolic BP were not strongly associated with PR interval or P duration which can support our results in men.[36] In other studies, with focusing on QT interval and QRS duration, the authors observed that central aortic blood pressure can be a risk factor for QTc prolongation and longer QRS durations.[37,38] It seems BP after WC had the highest count of significant relationships especially diastolic blood pressure in both genders.

TG in our study was the most different variable in having a significant relationship with ECG parameters between men and women. In men, TG was related to ECG parameters except for QTc interval and S amplitude but in women, it had significant associations with heart rate, R amplitudes, Sokolow-Lyon index, QT interval, P and QRS axis. Although we did not find any correlation between TG and PR interval in women and a slight significant relationship in men but Adegoke et al,[39] reported that triglyceride had a positive correlation with the PR interval ($r = 0.3$). This difference may be due to their different population and age because they have studied children with sickle cell anemia. In another study on 69 men,[32] TG was related to the P axis and QRS axis negatively with $r=-0.374$ and -0.363 respectively which was higher than our result which may be due to their small sample size and unadjusted results.

HDL as another lipid profile among MetS components was at a significant association with heart rate, P amplitudes, QRS duration, R and S amplitudes, Sokolow-Lyon index, P and QRS axis in men. In women, P, R and S amplitudes, Sokolow-Lyon index, P axis, and QTc interval indicated a

significant relationship with HDL. A Previous population-based study reported a J-shaped association between QTc interval and HDL[40] which can be as a support for our results. In another study,[32] HDL was related to the P axis and QRS axis positively with r=0.426 and 0.219 respectively which was much higher in comparison with our result. Also, it should be mentioned that in their study HDL and QRS axis were not statistically significant while our results showed a significant positive relationship in men.

Each Metabolic Syndrome Component and ECG Abnormalities

In subjects with WC and BP more than ATP cut-points, it seems the chance of having prolonged P and/or QRS duration may be significantly higher. Moreover, HDL and BP had significant relationships with prolonged P duration and prolonged QTc interval. In males, WC had a higher value in comparison with BP and HDL in having ECG abnormality. In females, BP increases the frequency of prolonged P duration near 75% and increases the frequency of prolonged QRS duration near 50%. Interestingly HDL in our study show just a significant association in subjects without ECG abnormalities which can represent its protective effect on ECG abnormalities. Overall, it can be interpreted that MetS can increase the chance of having single or multiple ECG abnormalities, especially multiple ECG abnormalities in men.

Possible Mechanism

There are several possible mechanisms of components of MetS and electrical status and heart's structure which may manifest as ECG abnormalities. These effects of MetS on ECG variables may be direct, indirect, or interrelated with each other. Waist circumference as a representative of central obesity could result in increased sympathetic activity, diaphragm elevation, and increased cardiac output.[41,42] Hypertension also can result in elevated cardiac output and this elevation may cause increased left ventricular (LV) wall stress, which stimulates myocardial hypertrophy.[43] Also, the interrelation between obesity with an increased predisposition to hypertension is another point. Other studies have suggested leftward shifts of P and QRS axis were related to obesity.[44,45] Obesity also may increase cardiac loading and lead to remodeling of the heart muscle and finally PR prolongation. These effects of obesity may be due to hormones produced by the adipose tissue which can result in electrophysiological changes.[46] Higher FBS levels are associated with hypertension, hyperlipidemia, and a prothrombotic state which can interact synergistically to increase cardiac and ECG changes.[47] Also, as it is known atherosclerosis can increase myocardial ischemia which can lead to scarring and heart dysfunction and ultimately ECG changes.[43]

Strengths and Limitations

A strength in our study was our large study population (n=6960). Data collection of digital ECGs were done under highly standardized conditions and enabled us to report more detailed ECG data. Another strength was the extensive measurements of confounding factors in the Fasa PERSIAN Cohort Study which made us examine the relationship of MetS and its component with ECG parameters more accurately and independent from effective factors. In this study, we used ECG as a predictor for future CVD risks and examined the role of MetS and its components separately for better screening. Also, to our knowledge, this is the first study that aimed to investigate the relationship between metabolic syndrome, its components, and ECG parameters in an Iranian population.

Our study is not free from limitations. First, as this study has a cross-sectional design, it limits our ability to infer any causality. For sure longer follow-ups in our study and other populations can reveal more results in case of these relationships. Second, our study was based on a rural population. As the subject we assessed may differ from a rural to urban subjects and the modernized urban population increasing in both developed or developing countries, it should be investigated in further studies with an urban Iranian population. Third, our study subjects were aged from 35–70 and we may not apply our findings to a younger Iranian population.

Conclusion

In conclusion, our study indicated that MetS and its components may have several different relationships on ECG parameters or abnormalities, and also, we suggest WC and BP as the two MetS components which had more and stronger associations with ECG parameters or abnormalities. Our results support this idea that MetS as an effective role player in ECG which is representative of subclinical CVD should be considered and screened to maintain subjects in a healthier lifestyle.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request to the corresponding author.

Ethics Approval and Consent to Participate

The study protocol was following the Helsinki Declaration and confirmed by the Ethics Committee of Fasa University of Medical Sciences (Approval Code: IR.FUMS.REC. 1399.019). The participants were informed about the research objectives and the written informed consent was obtained from the subjects before starting the survey.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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