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Patterns of clustering of the metabolic syndrome components and its association with coronary heart disease in the Multi-Ethnic Study of Atherosclerosis (MESA): A latent class analysis

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ABSTRACT

Background: The Metabolic syndrome (MetS), refers to one of the most challenging public health issues across the world. The aim of this study was to explore the clusters of participants on the basis of MetS components and determine its effect on coronary heart disease (CHD).
Methods: This study used the information from Multi-Ethnic Study of Atherosclerosis (MESA). MESA was performed at 6 US sites and was a population-based cohort study of 6776 adults (3576 females; 3200 males), aged 45 to 84 years. The participants were free of clinical cardiovascular disease at baseline. Latent class analysis (LCA) was conducted to achieve the study's objectives. The outcome variable was CHD during the study period (2000−2012).
Results: The prevalence of all Mets components (except triglyceride (TG) and fasting blood glucose (FBS)) is more common in females than in males. Three latent classes were recognized: (1) Non-MetS, (2) low risk, and (3) MetS. Notably, MetS latent class included 29.88% and 35.38% in females and males, respectively. After adjustment for covariates (e.g. demographic, biomarker etc.), MetS latent class showed a positive association with CHD events in both genders.
Conclusions: Results showed that clustering pattern of the MetS components, as well as the association between latent classes and risk of incident CHD events, are different in females and males. Notable percentages of individuals are in the MetS class, which emphasizes the necessity of implementing preventive interventions for this subgroup of the population.

1. Introduction

Although clustering of some metabolic abnormalities was identified by Kylin in 1923 [1], the coining of the term “syndrome X” was extend by Reaven in 1988 [2]. According to National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATPIII) [3], the Metabolic syndrome (MetS) was defined as the presence of three or more of the following components: increased waist circumference (WC), dyslipidemia, hyperglycemia, and hypertension [4]. Metabolic syndrome (MetS), as a common clinical disorder, is characterized by the clustering of cardiovascular risk factors such as impaired glucose tolerance, dyslipidemia, central obesity, and hypertension [5,6]. MetS is a risk factor for cardiovascular diseases (CVD), type 2 diabetes (T2D), and cancer is becoming progressively important owing to the worldwide epidemic of

Abbreviations: LCA, latent class analysis; MetS, metabolic syndrome; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high density lipoprotein; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; MESA, Multi-Ethnic Study of Atherosclerosis; TG, Triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; AOR, adjusted odds ratios; GOF, goodness-of-fit; Med, medication; AAP, age-adjusted prevalence; T2D, type 2 diabetes.

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obesity [7]. MetS is a serious health problem around the world, for example, its prevalence in USA adults is estimated to be >25% [8]. So far, few studies have examined patterns and the clustering of MetS components by latent class analysis (LCA) among adults in worldwide [9,10]. Some studies have used traditional analysis methods, such as exploratory factor analysis and logistic regression to identify factors and the relationships between factors and MetS components [11]. Unlike these methods, LCA does not assume normal distribution, linearity, and homogeneity of variance [12]. LCA is a type of cluster analysis that recognizes unobservable subgroup (i.e., latent classes) profiles or categories of homogeneous individuals with regards to the observed variables [13,14]. In general, LCA is a subset of structural equation modeling (SEM), applied to find groups (subtypes) of cases in multivariate categorical data that these groups are called "latent classes" and within each subtypes, the observed variables are statistically independent. In our study MetS components defined by NCEP-ATPIII are categorical variables and LCA is appropriate for detection of latent classes. Previous studies have applied LCA to describe patterns (or "latent classes") of MetS components among adults>20 years of age. For instance, in a study in Iran showed that individuals in the Mets latent class had the highest prevalence of high WC, low high-density lipoprotein (HDL), high triglyceride (TG), and high fasting blood glucose [9]. LCA has been little used in medical investigation other than in the field of mental health. Based on the above background, the objectives of this study were (a) to explore latent classes and patterns of participants based on MetS components, (b) to determine membership percentage of individuals in each latent classes by gender (c) to determine visual agreement between the findings of LCA model and the NCEP-ATPIII criteria, and (d) to examine the association of latent classes with incident of coronary heart disease (CHD). Specification of MetS clustering components is important for implementing and developing more effective strategies to reduce the risk of many adverse health outcomes among adults >44 years of age such as cardiovascular disease. It also facilitates clinical and epidemiological studies which deal with preventive treatment approaches and improving lifestyle methods.

2. Methods

2.1. Study design, participants & data source

We used the baseline information of the participants of the MESA study in our research. The MESA study design has been described in detail elsewhere [15]. Briefly, this study is a longitudinal observational study investigating the progression of subclinical atherosclerosis in a multi-ethnic sample free of clinical CVD, conducted at six field centers (Chicago, IL; Baltimore, MD; St. Paul, MN; Los Angeles, CA; Forsyth County, NC; New York City, NY). At baseline (Between July 2000 and August 2002), 6776 individuals aged 45 to 84 years, self-identified as African-American, white, Hispanic, or Chinese -Americans, were recruited. Approximately all individuals (99%; 3200 men and 3567 women) had complete data required for classification using NCEP-ATPIII definitions and were included in our analyses. Individuals with type I diabetes (n = 10), missing data on all MetS components (n = 28), or missing data on other variables included in logistic regression (n = 801) were excluded; 6776 participants were eligible for latent class analysis and 5975 were eligible for logistic regression analysis. Institutional review boards approved the study at all participating institutions; and each participant provided written informed consent.

2.2. Definition of metabolic syndrome components

In this study, the MetS was defined according to the NCEP-ATPIII definition which is the presence of three or more of the following components: [1] waist circumference (WC) >102 for males and >88 cm for females, [2] fasting blood glucose (FBS) ≥100 mg/dl or on antidiabetic medication, [3] high blood pressure (systolic blood pressure (SBP) >130 mm Hg or diastolic blood pressure (DBP) >85 or on antihypertensive medication, [4] low high-density lipoprotein-C (low HDL_C) ≤45 mg/dl for males and ≤55 mg/dl for females), and [5] high serum triglycerides (TG) ≥150 mg/dl [6].

2.3. Covariates

The following variables were used for adjustment in the logistic model. Sociodemographic variables including age, gender, race/ethnicity, and education were considered for adjustment. Additional potential risk factors for MetS including self-reported smoking and alcohol use, total physical activity assessed through the MESA Typical Week Physical Activity Survey [16], height, current aspirin use, family history of heart attack, height, LDL-c,and the use of any lipid-lowering medication were assessed too.

2.4. Outcome

MESA applies a standard adjudication protocol for classifying events. The main outcome of interest in this study was coronary heart disease (CHD) defined as CHD death, myocardial infarction, definite angina, probable angina (if followed by revascularization), and resuscitated cardiac arrest. Events were recorded during 12 years follow-up (2000–2012).

2.5. Statistical analysis

Crude and age-standardized prevalence rates of MetS and also its components according to the NCEP-ATPIII criteria were calculated. Age-standardization was done using WHO standard world population of 2000 [17].

2.5.1. Latent class analysis

Five dichotomous observable variables, including fasting blood glucose, HDL, WC, TG, and blood pressure were considered in LCA for clustering of individuals according to the latent variables behind the components of metabolic syndrome. We started with a two-class model and continuously increased the number of classes by one until the lowest sample-adjusted value of BIC was obtained. The number of classes was selected with regards to goodness-of-fit indices including Entropy, the likelihood ratio test statistic G2 (a statistics similar to $\chi 2$) and four information criteria, that can be calculated based on G2, including the Bayesian information criterion (BIC), Akaike information criteria (AIC), consistent AIC (CAIC), and ABIC (Adjusted BIC). Lower values of BIC, AIC, and CAIC and higher entropy revealed the better-fitted model [12,18]. For all above Indices except entropy, a Lower value indicates a more optimal balance of model fit and parsimony; in this way, a model with the smallest BIC, ABIC, AIC, or CAIC might be selected that considered better-fitted model [12,18].When the degrees of freedom are very large, the reference distribution for the G2 index is not known, therefore, we did not report *p*-values for tests of model fit.

2.5.2. Logistic regression model

After determination of the latent classes and the optimal number of latent classes, we generated latent class variable, and then we performed logistic regression model, by gender, to identify the association of this variable (latent classes), as main exposure, with CHD (outcome) during 12 years follow-up (2000–2012) adjusted for other covariates in the model. For this purpose, significant variables (at p-value <0.2) in univariable analyses were included in the multivariable analysis. All models were, therefore, adjusted for age, race, education, alcohol status, smoking status, current aspirin use, family history of heart attack, height, LDL-c, the use of any lipid-lowering medication. In logistic regression models, reference category of main exposure, for calculation of adjusted odds ratios (AOR), was considered the first latent class (Non-MetS). Finally, we present AOR and 95% confidence interval (CI) for each latent class by gender.

Analyses were conducted by using proc. LCA in SAS 9.2 software (SAS Institute Inc. Cary, NC, USA) and Stata version 12 (STATA Corp., Texas, USA).

3. Results

3.1. Baseline characteristic

Gender-specific baseline characteristics of the study population are illustrated in Table 1. There were 3576 females and 3200 males aged 44–84 years in this study. The mean (SD) age in women and men was 62.12 ± 10.25 and 62.20 ± 10.19 years, respectively. The majority of participants were Caucasian-Americans (37.89% in females, 39.16% in males). Females had lower levels of WC, DBP, FBS, and TG, but levels of HDL-C and SBP were higher than males. There were significant gender differences between all variables presented in Table 1. The crude and age-standardized prevalence of each MetS components (using ATPIII definition) by gender are shown in Supplementary Table 1. The results show that the prevalence of all MetS components except TG and FBS were more common in females than males. The age-adjusted prevalence of the MetS in females and males were 39.60% and 34.21% by the ATPIII definition, respectively.

3.2. Identification of optimal number of latent classes

With the five dichotomous variables, 32 possible response patterns can be found. For selecting the optimal model, we fit LCA models with classes ranging from 1 to 5 (Supplementary Table 2). The goodness-of-fit (GOF) indices like G2, AIC, BIC, CAIC, ABIC and Entropy were

Table 1
Characteristics of the study populations by gender, Multi-Ethnic Study of Atherosclerosis (MESA) baseline examination (2000−2002).

Item	Total (n = 6776)	Female (n = 3576)	Male (n = 3200)	*P*-value*
N (%)				
Race				
Caucasian-Americans	2608(38.49)	1335(37.89)	1253(39.16)	0.08
Chines-Americans	803(11.85)	414(11.58)	389(12.16)	
African-American	1874(27.66)	1036(28.97)	838(26.19)	
Hispanic-Americans	1491(22.00)	771(21.56)	720(22.50)	
Education				
Less than high school diploma	1221(18.08)	703(19.73)	518(16.24)	<0.001
High school diploma or some college	2812(41.64)	1584(44.44)	1228(38.51)	
College degree or higher	2720(40.28)	1277(35.83)	1443(45.25)	
Alcohol status				
Never	1381(20.53)	1056(29.78)	325(10.22)	<0.001
Former	1614(24.00)	757(21.35)	857(26.95)	
Current	3731(55.47)	1733(48.87)	1998(62.83)	
Smoking status				
Never	3401(50.36)	2108(59.15)	1293(40.53)	<0.001
Former	2475(36.64)	1040(29.18)	1435(44.98)	
Current	878(13.00)	416(11.67)	462(14.48)	
Current aspirin use (at least 3 days/wk)				
No	5200(80.11)	2850(83.48)	2350(76.37)	<0.001
Yes	1291(19.89)	564(16.52)	727(23.63)	
Family history of heart attack				
No	3643(57.30)	1830(54.21)	1813(60.80)	<0.001
Yes	2715(42.70)	1546(45.79)	1169(39.20)	
Mean (SD)				
Age, y	62.16(10.22)	62.12(10.25)	62.20(10.19)	0.62
Height, cm	166.36(9.96)	159.94(7.06)	173.53(7.56)	<0.001
Total Physical activity (MET-min/wk)	12,116.35(7197.6)	12,231.6(6670.3)	11,987.6(7742.9)	0.16
LDL-C, mg/dl	117.23(31.46)	117.72(31.85)	116.67(31.01)	0.17
HDL-C, mg/dl	50.95(14.81)	56.24(15.25)	45.03(11.77)	<0.001
Waist circumference, cm	98.14(14.37)	97.12(16.00)	99.28(12.21)	<0.001
Systolic blood pressure, mm Hg	126.60(21.49)	127.09(23.24)	126.04(19.33)	0.044
Diastolic blood pressure, mm Hg	71.92(10.26)	69.12(10.18)	75.05(9.42)	<0.001
Median [Interquartile Rang]				
Triglyceride, mg/dl	111[78–161]	110[77–157]	113[79–165]	<0.007
Fasting blood glucose, mg/dl	90[83–99]	88[81–97]	92[85–101]	<0.007

* *P* values from $\chi 2$ tests, *t*-tests or Mann-Whitney, as appropriate, are for comparisons of the gender differences of baseline variables.

computed for each class. As shown in Supplementary Table 2, based on the interpretability of GOF indices of the models, we concluded the three-class latent model was more suitable for these individuals. Table 2 presents the results of latent classes by gender in MESA baseline examination. The second part of this table included the conditional probabilities of the "Yes" response to each MetS components. The probability of a "No" response for each component of MetS can be calculated by subtracting each item-response probabilities from one. The first latent class, named "Non-MetS," described 42.72% and 42.46% of individuals in females and males, respectively, and characterized by individuals who have healthy MetS components status. The second latent class, named "low risk," described 27.39% and 22.16% of individuals in females and males, respectively, and is characterized by individuals who exhibit relatively healthy status of MetS components with the exception of blood pressure and WC in females and TG and low-HDL-C in males. The third latent class, named "MetS" described 29.88% and 35.38% of individuals in females and males, respectively, and is characterized by individuals showing clinically raised levels across most metabolic syndrome components (With the exception of fasting blood glucose in females and low-HDL-C in males).

Table 2
The three Latent Classes Model of components of MetS by gender in MESA baseline examination (2000–2002).

	Latent class (C) Membership probability (standard error)		
Gender	**(C1) Non-MetS**	(C2) Low-risk	**(C3) MetS**
Female	42.72(2.83)	27.39(2.35)	29.88(1.19)
Male	42.46(4.61)	22.16(5.37)	35.38(4.74)
Female	Probability of a "**Yes**"*		
Waist circumference	43.52	**85.72**	**89.03**
Triglyceride	16.72	43.01	**63.85**
Low-High density lipoprotein	17.08	0.00	**99.96**
Blood pressure	30.22	**86.98**	**69.09**
Fasting blood glucose	3.41	33.95	40.46
Male			
Waist circumference	19.63	37.49	**59.65**
Triglyceride	16.93	**58.79**	**63.16**
Low-High density lipoprotein	2.21	**80.68**	46.37
Blood pressure	45.29	27.62	**88.22**
Fasting blood glucose	13.82	22.80	**54.98**

Note. The probability of a "No" response for each component can be calculated by subtracting the item-response probabilities from one.
* Item-response probabilities higher than 0.5 are presented in bold font to simplify interpretation.

3.3. Visual agreement between the finding of LCA model and number of the NCEP components of the MetS definition

The visual agreement between the results of LCA model and NCEP components of the MetS criteria in MESA participants is shown in Tables 3. As mentioned earlier in Section 2.2, MetS was defined as the presence of three or more of each component. In the first latent class, Non-MetS, all participants had less than three components in both sexes, as well as in the third latent class, MetS, all participants had more than three components in both sexes (With the exception of 11persons in females that had two component). The majority of disagreement cases observed in the second latent class reported 529 and 184 individuals in females and males, respectively. In general, in females, unexpected classification of individuals happened in 14.8% (518 individuals in the second latent class had more than three components and 11 individuals in the third latent class had less than three

Table 3
Visual agreement between the finding of LCA model and Number of the NCEP-defined components of the metabolic syndrome definitions by gender, MESA baseline examination (2000–2002).

Latent class	Number of the NCEP component of MetS						Total
	Zero N (%)	One N (%)	Two N (%)	Three N (%)	Four N (%)	Five N (%)	
Female							
Non-MetS	427(27.21)	725(46.21)	417(26.58)	0(0)	0(0)	0(0)	1560(100)
Low-risk	0(0)	0(0)	471(47.62)	405(40.95)	113(11.43)	0(0)	989(100)
MetS	0(0)	0(0)	11(1.08)	404(39.69)	404(39.69)	199(19.55)	1018(100)
Total	427(11.94)	725(20.27)	899(25.14)	809(22.62)	517(14.46)	199(5.56)	3576(100)
Male							
Non-MetS	459(27.70)	676(40.80)	522(31.50)	0(0)	0(0)	0(0)	1657(100)
Low-risk	0(0)	106(18.93)	270(48.21)	145(25.89)	39(6.96)	0(0)	560(100)
MetS	0(0)	0(0)	0(0)	523(53.20)	347(35.30)	113(11.50)	983(100)
Total	459(14.34)	782(24.44)	792(24.75)	668(20.88)	386(12.06)	113(3.53)	3200(100)

components). Furthermore, in males, unexpected classifications of individuals happened in only 5.75% (529 individuals in the second latent class which had more than three components).

3.4. Association of the latent classes variable with CHD

For assessing the association of the latent classes with CHD, We conducted logistic regression by gender. Fig. 1. illustrates the strength of association for second and third latent classes, generated by LCA, with incident CHD events compared to the Non-MetS latent class (reference category). After adjustment for demographic and traditional CHD risk factors, only MetS latent class showed a positive association with incident CHD events in both sexes. The AOR for CHD events were 1.97 (95%CI: 1.19–3.26) and 2.24 (95%CI: 1.63–3.10) in females and male, respectively.

4. Discussion

This investigation was the first study in MESA population to be conducted for identifying patterns of MetS components by latent class analysis (LCA). The age-standardized prevalence of the MetS was more prevalent in females than in males (39.60% vs. 34.21%). In general, the most common component of MetS was WC with the adjusted prevalence rate of 52.79%, and FBS was uncommon with the prevalence rate of 20.83%. Our results showed that the adjusted prevalence of all components of MetS- except TG and FBS were more common among women compared to men. The result of our study is similar to another study in United States (US) [19]. The finding in our study showed that only one latent class (the third latent class) was consistently associated with many features of metabolic syndrome. This latent class may demonstrate a specific clinical status generating the observed features of MetS [9]. The understanding of how the components of metabolic syndrome cluster together can help clinicians that interpret the pathophysiology of MetS and develop effective and valuable approaches for recognizing and preventing the inherent risk of CHD and type 2 diabetes [11]. Clinicians believe that determinants of cardiovascular disease tend to accumulate, and thus the risk of developing CVD goes up along with increments in their clustering abilities [20]. In our study, Patterns of clustering of the MetS components examined by the new method of LCA and explored three latent classes. These latent classes were as follows: [1] Non-MetS, [2] low risk, and [3] MetS.

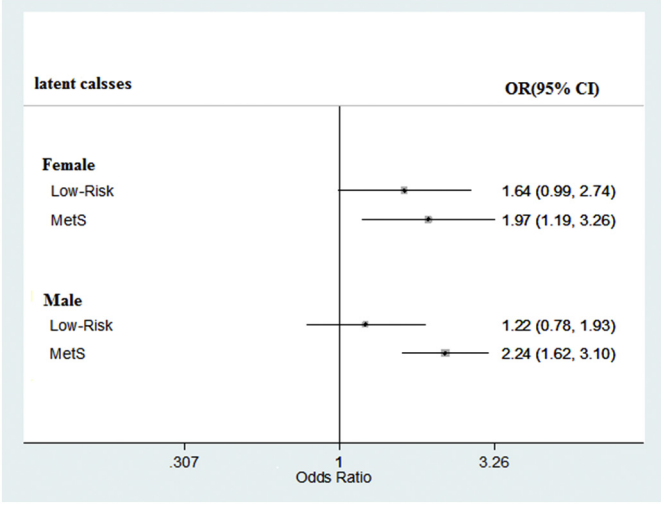

Fig. 1. Logistic regression analysis for identifying Association of the latent classes of NCEP components with CHD. All models were adjusted for Age, Race, Education, Alcohol status, Smoking status, Current aspirin use, height, and Family history of heart attack, LDL-c,the use of any lipid-lowering medication. Reference category in logistic regression models was considered the first latent class (Non-MetS class).

Our results indicated that participants in the third latent class-MetS were more likely to have most of the MetS components. In contrast, those in the first latent class, non-MetS, were likely not engaged in any of the components of MetS. The second Latent class shows individuals who have a low risk of having MetS components. This latent class had a high probability of having two MetS components in both sexes (BP and WC in females; TG and low-HDL-C in females). It seems that these individuals in the female group have obesity feature along with hypertension and has no other components of MetS. In contrast, in the male group dyslipidemia features were more observed. With consideration of this description, we named it "Low risk" latent class. These individuals are likely to be at low risk for incident CHD, and in this study, we assessed the strength of this association. In general, clustering of components of MetS can be helpful and valuable in reinforcing the hypothesis that underlying pathophysiological mechanisms are engaged in this process [21]. The most important findings in our LCA were that: (a) combination patterns of MetS components varied between females and males. (b) We found that among participants of latent class three, some of MetS components did not play an influential role (i.e. FBS in females; low HDL-C in males). This result, i.e. (b), was a discrepancy with previous similar study in which blood pressure have no influential role [9]. Some previous studies reported that obesity feature plays a fundamental role in the pathophysiological mechanism of MetS [22,23]. the present study illustrated that this pattern may be different in both sexes. Abdominal obesity (WC) in females and high TG in males play an essential role in two latent classes of MetS. In general, it seems that combination of MetS components among individuals may be varied based on different societies. We recommend that additional investigation is performed on clustering of MetS components in different societies in the future.

So far, many studies have been conducted to classify the metabolic syndrome according to NEPP-ATPII criteria, but no one has been

examined whether this classification is correct or not [24,25]. In the current study, we presented a visual agreement between the finding of LCA model and Number of the NCEP-defined components of the metabolic syndrome criteria. Our results indicated that visual agreement was better in males than in females (95.25% vs. 85.20%), which it may be due to the various cut-points of some components in both sexes (such as HDL and WC). A study conducted by Sandra Slagter et al. shown that the MetS definitions should be used more cautiously, and suggested to use age-specific values for elevated blood pressure as well as to establish new thresholds for abdominal obesity [26].

The findings of this study indicate that the risk of developing CHD varies from one class to another. "MetS" latent class showed a strong positive association with the incident of CHD events compared to "Non-MetS" latent class in both genders so that this association was stronger in males than females (Adjusted odds ratio; 2.24 vs. 1.97). Moreover, it seems that the membership of individuals in "low risk" latent class also increases the incidence of CHD. However, the effect is not statistically significant, most likely as a result of observing so few events and lower power for the analysis. Prior studies reported that cardiovascular risk factors and determinants tend to cluster [20,27]. Therefore, the chance of CVD goes up in line with increments in the mentioned determinants clustering ability [28]. In addition, some cohort studies have reported that there are variations in the risk of mortality based on the various combination patterns of MetS components. [29–31] Another study also showed that the metabolic syndrome is associated with higher incident CVD risk through many various paths such as dyslipidemia, insulin resistance (IR), and enteral obesity [27]. Specially, the three components of MetS atherogenic dyslipidemia (such as increased LDL, decreased HDL and high TG concentrations) are individually associated with high incident CVD risk, whereas IR significantly increases the risk of developing type 2 diabetes which is an important risk factor for developing CVD [27]. Generally, it should be noted that we could not examine the pathophysiological mechanism of MetS, but the clustering of MetS components together indicates the importance of those features in combination patterns of MetS.

5. Limitations

There are several points that should be considered when interpreting the results of this study. The main limitation of this study was its cross-sectional observational nature. Considering the rising trend in the prevalence of some MetS components over the time in US [19], tables reported in the current study might well be an underestimation. Moreover, our data in some behavioral variables (such as smoking, alcohol status, Physical Activity, and current aspirin use) were based on individual self-reports and may thus be subject to recall and social desirability bias. In spite of these limitations, the outstanding strength of this study was using a large population-based cohort study which augments the validity of our findings. Also, we conducted LCA by gender and presented separated patterns for each one.

6. Conclusion

Results showed that clustering patterns of the MetS components, as well as the strength of associations between latent classes and risk of incident CHD events, are different in females and males. Besides, notable percentages of individuals exist in the MetS class, which emphasizes the necessity and importance of implementing preventive interventions for this sub-group of the population.

Authors' contributions

Conception and design: Seyed Mohammad Riahi, Seyed Saeed Hashemi-Nazari.

Cleaning of data: Seyed Mohammad Riahi.

Data analysis and interpretation: Seyed Mohammad Riahi, Seyed Saeed Hashemi-Nazari, Mahshid Namdari.

Manuscript writing: All authors.

Final approval of manuscript: All authors.

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Dr. SS. Hashemi-Nazari and SM. Riahi had full access to all data and take responsibility for the integrity and accuracy of the data and analyses. We thank researchers, staff, and participants of MESA study for their valuable contributions. A full list of participating MESA investigators and institutions is at http://www.mesa-nhlbi.org.

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Ethical approval

For this study, we did not require ethical approval because the data were acquired under the National Heart, Lung, and Blood Institute (NHLBI)—Research Materials Distribution Agreement (RMDA) V02 1d20120806.

Conflicts of interest

The authors declare no conflicts of interest and are responsible for the content and writing of the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.05.080.

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