Association of gender-specific risk factors in metabolic and cardiovascular diseases: an NHANES-based cross-sectional study

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ABSTRACT

In the present cross-sectional study, based on National Health and Nutrition Examination Survey (NHANES, 2007–2010) cohorts, various risk factors for metabolic syndrome (MetS) and cardiovascular diseases (CVDs) were analyzed (n=12,153). The variables analyzed include, demographics, comorbidities associated with MetS or CVD, behavioral and dietary factors, while the primary endpoints were the prevalence of MetS and CVD. The prevalence of MetS and CVD was slightly higher in males as compared with females (42.50% and 7.65% vs 41.29% and 4.13%, respectively). After controlling for confounding factors, advanced age, family history of diabetes mellitus (DM), overweight, and obesity were significantly associated with the likelihood of MetS, irrespective of gender differences. In males, the diagnosis of prostate cancer and regular smoking were additional risk factors of MetS, whereas, advanced age, family history of heart attack or angina, health insurance coverage, diagnosis of rheumatoid arthritis or depression, obesity and low calorie intake were identified as risk factors for CVD. In addition to the above risk factors, higher physical activity and vitamin D insufficiency were also found to increase the risk of CVD in females. Furthermore, obesity was a higher risk factor for MetS than CVD. Emerging risk factors for CVD identified in this study has major clinical implications. Of interest is the correlation of higher physical activity and the risk of CVD in women and the role of depression and lower calorie intake in general population.

Significance of the study

What is already known about this subject?

- After adjusting for age, the prevalence of metabolic syndrome is similar in men and women (22% and 24%, respectively).
- Patients with metabolic syndrome have a greater risk of developing diabetes mellitus and coronary heart disease later in life.
- The risk factors underlying metabolic syndrome and cardiovascular diseases are similar, and cardiovascular disease is often preceded by metabolic syndrome.

What are the new findings?

- The present analysis reveals risk factors that are not previously linked to cardiovascular disease, namely, the correlation of higher physical activity in women, and the role of depression and low calorie intake in the general population.
- Diagnosis of depression (adj. OR=2.46, 95% CI 1.13 to 5.36), higher physical activity (adj. OR=2.93, 95% CI 1.63 to 5.26), and low total calorie intake (adj. OR=2.40, 95% CI 1.07 to 5.67) were found to be highly associated with the development of cardiovascular disease in females, after controlling for confounding factors.
- In males, diagnosis of depression (adj. OR=1.80, 95% CI 1.09 to 2.92) and low total calorie intake (adj. OR=2.20, 95% CI 1.22 to 3.98) was shown to be strongly associated with the development of cardiovascular disease.

INTRODUCTION

Metabolic syndrome (MetS) is an important risk factor for the subsequent development of cardiovascular disease (CVD). MetS is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function.[1] Clinical manifestations of MetS include hypertension, hyperglycemia, hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), and abdominal obesity.

MetS is a growing health concern globally[2–5] and is equally prevalent in men (24%) and women (22%) after adjusting for age.[6] However, there are several factors that are unique to women, including pregnancy, use of oral contraceptives, postpartum breast feeding, polycystic ovarian syndrome and so on.[7] We hypothesized that these additional factors may increase the risk of CVD in women with MetS and assessed the role of gender in the development of MetS and CVD in the present study.

In addition to adipose dysfunction and insulin resistance,[8 9] psychological characteristics also play a major role in the development of MetS. Anger, depression, and hostility had been shown to be associated with increased risk for MetS.[10] Recent reports indicate that MetS is significantly associated with lifetime major depression and the presence of any anxiety

Significance of the study

How might these results change the focus of research or clinical practice?

- ► Increased total physical activity is thought to be associated with the reduced risk of coronary heart diseases, but in females, intense and strenuous exercise may have adverse effects.
- ► A low-calorie, high-fiber diet is often recommended to reduce the risk of metabolic syndrome and cardiovascular disease, but our results suggest that a low calorie intake may increase the risk. The underlying mechanism needs to be further investigated.
- ► Patients with depression need more support and attention, as it increases their risk in developing metabolic syndrome and cardiovascular disease.

disorder.[11 12] Furthermore, there is compelling evidence linking CVD with major depressive disorder and bipolar disorder.[13 14] In recent epidemiological studies in the USA, the prevalence of CVD among adults with major depressive disorder was nearly threefold greater than those without mood disorders.[15]

The association of traditional risk factors like family history, poor dietary habits, sleep disorders, and inadequate physical activity in the development of MetS and CVD had been well established. However, recent reports indicate that new risk factors that were not previously associated with CVDs are becoming apparent with drastic changes in lifestyle and dietary habits among the general population across the globe. In light of this, we undertook a cross-sectional analysis of the population by utilizing the National Health and Nutrition Examination Survey (NHANES) database of Centers for Disease Control and Prevention (CDC) in the USA. We believed that modern lifestyle and dietary habits may lead to an increased risk of MetS and CHD.

Furthermore, though the risk factors underlying the MetS and CVD are similar, CVD is tightly associated with a variety of other behavioral and genetic factors. The present study was undertaken to analyze the risk factors for both diseases separately in order to delineate the commonalities and differences in the behavioral and dietary factors leading to the emergence of one or the other. Recognizing the underlying risk factors may help healthcare providers in identifying individuals prone to CVD at routine clinic visits and to further improve the public health policy.

METHODS

Design, subjects, and endpoints

This cross-sectional study was performed using data stored in the NHANES, CDC, National Center for Health Statistics (NCHS), and the US Department of Health and Human Services (http://www.cdc.gov/nchs/nhanes/) (year 2007∼2010 cycles). All data from NHANES database were deidentified and hence, analysis of the data did not require Institutional Review Board approval or informed consent by subjects.

The present study sample consisted of NHANES participants above 20 years old (n=12,153). Subjects who were more than 80 years old was recorded as 80. Subjects with complete data for coronary heart disease, angina/angina pectoris, or heart attack were included in the analysis of CVDs (n=12,054). Individuals who did not participate in the fasting subsample were excluded from the analysis of the MetS (n=4920). The endpoints of the present study were the prevalence of MetS and CVDs. Criteria of MetS was based on guidelines developed by the 2001 National Cholesterol Education Program Adult Treatment Panel III (ATP III). ATP III MetS criteria were updated in 2005 in a statement from the American Heart Association/National Heart, Lung, and Blood Institute. Prevalence of CVDs included self-reported coronary heart disease, angina/angina pectoris, and heart attack in the questionnaire of 'Medical condition' section.

Study variables

The variables obtained for each disease group were patient demographics (age, gender, race/ethnicity, and marital status), family history (diabetes and heart attack/angina), socioeconomic status (education level, ratio of family income to poverty, and health insurance status), behavioral factors (body mass index (BMI), smoking history, alcohol use, physical activity, sleeping hours, postpartum breast feeding, and last childbearing age), dietary factors (vitamin D insufficiency, total daily calorie consumption, and total daily sugar consumption), and disease association (self-reported medical condition of rheumatoid arthritis, depression, asthma, osteoporosis, and prostate cancer). Details of each variable is discussed below.

Metabolic syndrome

Current ATP III criteria[16] define MetS as the presence of any **three** of the following five traits:

1. abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in).
2. serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides.
3. serum HDL-C <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) ,in women or drug treatment for low HDL-C.
4. blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure.
5. fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Demographic data

Subjects were administered the Family and Sample Person Demographics questionnaires at home by trained interviewers using a Computer-Assisted Personal Interviewing (CAPI) system. The CAPI system is programmed with built-in consistency checks to reduce data entry errors. CAPI also uses online help screens to assist interviewers in defining key terms used in the questionnaire.[17]

- ► Age, gender, race/ethnicity and marital status from the 'Demographic variables and sample weights' in the NHANES database were recorded.
- ► We separated the subjects by their gender into two categories, so as to identify the unique risk factors for each gender.
- ► Race/ethnicity was self-reported as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other race, including multiracial. We

further stratified them into three racial groups: non-Hispanic white, Hispanic, non-Hispanic black, and others (including Mexican American and other races).

Family history

- Family history of diabetes and heart attack/angina were self-reported using interviewer-administered questionnaires (medical conditions) from NHANES database.

Socioeconomic status

- Education level, ratio of family income to poverty, and health insurance status were recorded using interviewer-administered questionnaires (demographic variables and sample weights) from NHANES database.
- Ratio of family income to poverty refers to the ratio of family income to poverty threshold. Range of values include 0–5. Value of 5 and greater were recorded as 5.

Behavioral factors

Body mass index

- BMI data were recorded based on 'Body Measures' of NHANES Examination Protocol.[18] The body measurement data were collected, in the Mobile Examination Center (MEC), by trained health technicians.
- We further categorized data based on WHO criteria into: underweight (BMI $<18.5\,kg/m^2$), normal (BMI$=18.5\sim24.9\,kg/m^2$), overweight (BMI$=25\sim29.9\,kg/m^2$), and obese (BMI $\geq30.0\,kg/m^2$).

Smoking history

- Smoking status was recorded using interviewer-administered questionnaires (smoking – cigarettes use) from NHANES database.
- We further categorized the subjects into current regular smoker and never regular smoker.

Risky alcohol use

- The National Institute on Alcohol Abuse and Alcoholism in the USA has estimated the amount of alcohol consumption that can increase health risks.[19]

For men under the age of 65:

- More than 14 standard drinks per week on average.
- More than four drinks on any day.

Women and adults 65 years and older:

- More than seven standard drinks per week on average.
- More than three drinks on any day.

Physical activity: metabolic equivalent of task (MET) score

- MET score[20] was calculated from the provided data using the interviewer-administered questionnaires (physical activity) from NHANES database.
- MET score at 600 MET-min/week is considered having a moderate intensity of physical activity based on WHO recommendation, and we set this as the cut-off value in our study.

Sleep duration

- Participants were asked using the CAPI system at the comfort of their home, 'How much sleep do you usually get at night on weekdays or workdays?' The numbers of hours of sleep were recorded.
- National Sleep Foundation has updated their recommendations for daily sleep amounts across the lifespan, clarifying that the average recommended amount of hours 'may be appropriate,' but varies significantly among subjects, and new ranges for each age group were given.[21]
- Based on the National Sleep Foundation recommendation, we further categorized data into normal sleep duration, short sleep duration, and long sleep duration.

Postpartum breast feeding

- These questions were administered at the MEC, by trained interviewers, using the CAPI system as a part of the MEC interview.
- Participants were asked, 'Did you breast feed your child or any of your children for at least one month?' in the questionnaire, and an answer of yes or no was obtained.

Last childbearing age

- These questions were administered at the MEC, by trained interviewers, using the CAPI system as a part of the MEC interview.
- Participants were asked, 'How old were you at the time of your last live birth?' in the questionnaire, and the range of age was recorded.
- We categorized the age range into 20s, 30s, and more than 40s.

Dietary factors

Vitamin D insufficiency

- Serum 25-hydroxyvitamin D (25 (OH)D) data were extracted based on 'Vitamin D' from NHANES Examination Protocol.
- There is no definite consensus on the value of vitamin D deficiency. After careful evaluation of literature, we set our cut-off value at <40 nmol/L.[22]
- The most widely used indicator of vitamin D status is the measurement of 25(OH)D in either serum or plasma. The National Institute of Standards and Technology (NIST) along with the National Institutes of Health's Office of Dietary Supplements developed a standard reference material for circulating vitamin D analysis and have suggested the use of liquid chromatography-coupled with tandem mass spectrometry (LC-MS/MS) measurement procedure developed by NIST.[23 24]

Total daily calorie and sugar consumption

- The in-person interview was conducted in a private room in the NHANES MEC. A set of measuring guides (various glasses, bowls, mugs, drink boxes and bottles, household spoons, measuring cups and spoons, a ruler, thickness sticks, bean bags, and circles) was available in the MEC dietary interview room for the participant to use for reporting the amounts of foods.
- NHANES collected data on study participants' use of dietary supplements for 30 days during the Dietary Supplements Section in the household interview. In 2007–2008, additional information on supplement and antacid use for the previous 24 hours was collected to provide data of the same timeframe as the food and beverage intake. With a similar protocol, the 24-hour

dietary supplement interview was collected following the 24-hour dietary recall. All NHANES examinees responding to the dietary recall interview were eligible for the dietary supplement and antacid use questions. Information was obtained on all vitamins, minerals, herbals, and other dietary supplements that were consumed during a 24-hour time period (midnight to midnight), including the name and the amount of dietary supplement taken.[25]

- Data of total daily calorie and total daily sugar consumption were extracted.
- Based on the dietary guidelines for Americans in 2010,[26] we categorized data into recommended intake, higher intake, and lower intake based on age and gender differences.

Diseases association

- Different medical conditions were self-reported using the interviewer-administered questionnaires (medical conditions) from NHANES database.
- For identification of depression, we used 'Patient Health Questionnaire'[27] as our screener. Patient with score of 5 and greater is considered mild depression, while score of <five indicates no depression.
- The Depression Screener questions are from the Patient Health Questionnaire, a version of the Prime-MD diagnostic instrument. They are a self-reported assessment of the past 2 weeks, based on nine Diagnostic and Statistical Manual of Mental Disorders,Fifth Edition (DSM-IV) signs and symptoms from depression. The nine symptom questions are scored from '0' (not at all) to '3' (nearly every day). Depression severity can be defined by several cut points from the total score that ranges from 0 to 27.[28] A final follow-up question assesses the overall impairment of the depressive symptoms. The depression screener was conducted as part of the MEC interview questionnaire, using interviewer administered CAPI system in Spanish or English. No proxy or interpreters were permitted for these questions.

STATISTICAL ANALYSIS

Demographic data, basic characteristics, and dietary intake were expressed as mean (SE) for continuous variables, or unweighted counts (weighted %) for categorical variables. Univariate and multivariate logistic regression analyses were performed to determine the potential factors associated with MetS and CVD. Variables having a p value <0.05 in the univariate analysis were selected and further evaluated using multivariate logistic regression models with stepwise selection. All analyses included fasting subsample weight and stratum. Primary sampling units (PSUs) were per recommendations from NCHS to address oversampling, non-response, and non-coverage and to provide a nationally representative estimate. Statistic assessments were two sided and evaluated at the 0.05 level of significance. Statistical analyses were performed using the statistical software package SPSS complex sample module V.22.0.

RESULTS

Demographics, behavioral and dietary factors

Our study population comprised of participants aged 20 years and older, included in the 2007 to 2010 NHANES cohorts (n=12,153). Those with complete data for coronary heart disease, angina/angina pectoris, or heart attack were included in the analysis of CVDs (n=12,054). Individuals who did not participate in the fasting subsample were excluded from the analysis of the MetS (n=4920). Using NHANES fasting subsample weight, the analytic sample size was equivalent to a population-based sample size of 104,190,537 males and 110,589,267 females. Table 1 lists the characteristics, behavior and dietary intake of the participants according to gender differences. The mean age among the 2343 men was 45.84 years and among the 2577 women was 47.69 years. The prevalence of MetS and CVD were 42.50% and 7.65% for males and 41.29% and 4.13% for females, respectively.

Potential risk factors for MetS and CVD in males

The results of multivariate logistic regression analysis examining potential factors associated with MetS or CVD in males are shown in figure 1. Data from the univariate analysis indicate age, race, family history of diabetes mellitus (DM) and heart attack or angina, marital status, education level, health insurance status, rheumatoid arthritis, prostate cancer, BMI, physical activity, regular smokers, sleep duration, and daily calorie consumption were associated with MetS (data not shown). After adjusting for all potential factors, the results of multivariate analysis demonstrated that elderly subjects (adjusted OR=1.05, 95% CI 1.03 to 1.07), having a family history of DM (adjusted OR=1.39, 95% CI 1.02 to 1.89), or prostate cancer diagnosis (adjusted OR=2.27, 95% CI 1.09 to 4.72), or overweight (adjusted OR=3.65, 95% CI 2.37 to 5.62), or obesity (adjusted OR=16.22, 95% CI 10.71 to 24.56) or regular smoking (adjusted OR=1.77, 95% CI 1.27 to 2.46) were significantly associated with the likelihood of MetS among the male participants (figure 1A).

According to univariate analysis, age, race, family history of heart attack or angina, marital status, education level, health insurance status, rheumatoid arthritis, depression, osteoporosis, prostate cancer, BMI, physical activity, regular smoking, and sleep duration were associated with the likelihood of CVD in males. Moreover, elderly (adjusted OR=1.09, 95% CI 1.08 to 1.11), having family history of heart attack or angina (adjusted OR=2.36, 95% CI 1.30 to 4.29), health insurance coverage (adjusted OR=0.40, 95% CI 0.17 to 0.93), diagnosis of rheumatoid arthritis (adjusted OR=2.45, 95% CI 1.32 to 4.55), depression (adjusted OR=1.80, 95% CI 1.09 to 2.92), obesity (adjusted OR=1.86, 95% CI 1.02 to 3.41), and low total calorie intake (adjusted OR=2.20, 95% CI 1.22 to 3.98) were likely to be more associated with the development of CVD in males after controlling for potential factors (figure 1B).

Potential risk factors for MetS and CVD in females

The results of multivariate logistic regressions examining potential factors associated with MetS and CVD in females are shown in figure 2. After adjustment for all potential factors, the results of multivariate analysis demonstrated that elderly subjects (adjusted OR=1.08, 95% CI 1.06 to 1.10), having family history of DM (adjusted OR=1.70, 95% CI 1.20 to 2.41), overweight (adjusted OR=4.77,

Table 1 Characteristics of subjects (males, n=2343, weighted n=104,190,537; and females n=2577, weighted n=110,589,267) included in the NHANES database between 2007 and 2010

	Males (n=2343)	Females (n=2577)		Males (n=2343)	Females (n=2577)
Metabolic syndrome, n (%)	1108 (42.50)	1210 (41.29)	Prostate cancer, n (%)		
Cardiovascular diseases, n (%)	237 (7.65)	140 (4.13)	Yes	75 (2.21)	
Coronary heart disease	147 (4.98)	62 (1.70)	No	1483 (57.41)	
Angina/angina pectoris	78 (2.50)	54 (1.64)	Missing	785 (40.38)	
Heart attack	150 (4.66)	84 (2.57)	*Behavioral factors*		
Age (years)	45.84 (0.52)	47.69 (0.42)	BMI, n (%)		
Race, n (%)			Underweight	20 (1.09)	47 (2.16)
Mexican American	429 (9.41)	486 (7.64)	Normal weight	587 (26.40)	723 (33.14)
Other Hispanic	253 (5.11)	314 (5.06)	Overweight	910 (38.45)	774 (28.66)
Non-Hispanic white	1141 (68.81)	1202 (69.22)	Obese	790 (32.84)	1011 (35.26)
Non-Hispanic black	409 (10.13)	457 (11.89)	Missing	36 (1.23)	22 (0.78)
Other race-including multiracial	111 (6.55)	118 (6.19)	Physical activity, n (%)		
Family history–DM, n (%)			MET scores <600	777 (27.33)	1264 (43.94)
Yes	877 (36.18)	1067 (37.20)	MET scores >600	1561 (72.50)	1309 (55.86)
No	1404 (61.40)	1458 (60.82)	Missing (%)	5 (0.18)	4 (0.21)
Refused/don’t know	62 (2.43)	52 (1.98)	Cigarettes smoking, n (%)		
Family history–heart attack/angina, n (%)			Regular smokers	1211 (48.70)	941 (38.01)
Yes	265 (10.85)	371 (13.60)	Non-regular smokers	1126 (51.16)	1630 (61.80)
No	2012 (86.54)	2139 (84.23)	Missing (%)	6 (0.14)	6 (0.19)
Refused/don’t know	66 (2.60)	67 (2.17)	Alcoholism, n (%)		
Marital status, n (%)			Yes	55 (2.22)	26 (0.99)
Married/living with partner	1588 (68.36)	1408 (60.59)	No	1688 (76.18)	1884 (76.47)
Widowed/divorced/separated	368 (12.18)	759 (23.29)	Missing	600 (21.60)	667 (22.55)
Never married	387 (19.46)	409 (15.98)	Sleep duration, n (%)		
Refused/don’t know	0 (0.00)	1 (0.13)	Short sleep duration	960 (39.13)	980 (34.32)
Education level, n (%)			Normal sleep duration	1276 (57.92)	1479 (61.85)
Less than ninth grade	311 (6.66)	325 (6.22)	Long sleep duration	107 (2.95)	117 (3.81)
9~11thgrade	379 (12.62)	411 (12.27)	Missing	0 (0.00)	1 (0.03)
High school grad/GED or equivalent	576 (23.92)	587 (23.41)	Postpartum breast feeding, n (%)		
Some college or AA degree	571 (28.07)	742 (30.00)	Breast fed any child		1090 (40.60)
College graduate or above	505 (28.72)	505 (28.00)	Not breast fed any child		812 (29.60)
Refused/don’t know	1 (0.02)	7 (0.10)	Never pregnant		322 (16.07)
Family poverty income ratio*	3.12 (0.05)	2.90 (0.06)	Missing		353 (13.74)
Health insurance status, n (%)			Last childbearing age, n (%)		
Covered by health insurance	1691 (77.16)	1994 (83.01)	Never pregnant		322 (16.07)
Not covered by health insurance	647 (22.72)	582 (16.90)	Age at last live birth within 20 s		952 (36.75)
Refused/don’t know	5 (0.12)	1 (0.09)	Age at last live birth within 30 s		731 (26.27)
Rheumatoid arthritis, n (%)			Age at last live birth more than 40 s		90 (2.61)
Yes	114 (3.42)	172 (4.81)	Missing		482 (18.31)
No	1998 (88.22)	2126 (85.45)	*Dietary factors*		
Missing	231 (8.35)	279 (9.73)	Vitamin D insufficiency, n (%)		
No	1998 (88.22)	2126 (85.45)	Serum 25-hydroxyvitamin D <40	450 (14.16)	562 (16.96)
Depression, n (%)			Serum 25-hydroxyvitamin D >40	1712 (77.78)	1816 (75.51)
Yes	331 (13.51)	594 (20.75)	Missing	181 (8.05)	199 (7.53)
No	1878 (81.10)	1745 (70.77)	Total daily calorie consumption, n (%)		
Missing	134 (5.39)	238 (8.48)	Higher total calorie intake	577 (29.11)	515 (21.96)
Asthma, n (%)			Recommended total calorie intake	677 (29.92)	665 (26.66)
Yes	131 (5.70)	246 (9.56)	Lower total calorie intake	1030 (38.27)	1325 (48.66)

Continued

Table 1 Continued

	Males (n=2343)	Females (n=2577)		Males (n=2343)	Females (n=2577)
No	2201 (93.57)	2320 (89.97)	Missing	59 (2.70)	72 (2.72)
Missing	11 (0.73)	11 (0.47)	Total sugar daily consumption, n (%)		
Osteoporosis, n (%)			Higher total sugar daily intake	1622 (70.91)	1905 (74.81)
Yes	34 (1.11)	275 (9.59)	Recommended total sugar daily intake	256 (10.74)	256 (9.96)
No	2307 (98.77)	2287 (89.79)	Lower total sugar daily intake	406 (15.65)	344 (12.51)
Missing	2 (0.12)	15 (0.61)	Missing	59 (2.70)	72 (2.72)

*205 of males and 231 of females did not fill in family poverty income status.
AA, associate degrees; BMI, body mass index; DM, diabetes mellitus; GED, tests of general educational development; MET, metabolic equivalent of task; NHANES, National Health and Nutrition Examination Survey.

95% CI 3.30 to 6.89), and obesity (adjusted OR=17.77, 95% CI 10.88 to 29.03) were significantly associated with the likelihood of MetS in female patients (figure 2A). Moreover, elderly subjects (adjusted OR=1.09, 95% CI 1.06 to 1.11), having family history of heart attack or angina (adjusted OR=2.11, 95% CI 1.15 to 3.88), diagnosis of depression (adjusted OR=2.46, 95% CI 1.13 to 5.36), obesity (adjusted OR=2.56, 95% CI 1.18 to 5.54), having higher physical activity (adjusted OR=2.93, 95% CI 1.63 to 5.26), vitamin D insufficiency (adjusted OR=2.68, 95% CI 1.40 to 5.13), and low total calorie intake (adjusted OR=2.40, 95% CI 1.07 to 5.67) were likely to be more associated with the development of CVD in females after controlling for confounding factors (figure 2B).

In a subgroup analysis, women were grouped by their MET score (MET <600 vs MET ≥600), and the results are shown in table 2. For the risk factors associated with CVD, age, rheumatoid arthritis, BMI, postpartum breast feeding, last childbearing age and vitamin D insufficiency may change the OR value for physical activity in women (from less than 1 in the univariate analysis to more than 1 in the multivariate analysis). We further tried to determine if these variables were associated with physical activity. The results indicate that rheumatoid arthritis, obesity, breast feeding, pregnancy and vitamin D insufficiency can alter the OR of MET score. The risk of CVD in women with higher physical activity (MET ≥600) is minimal; however, in the presence of the above risk factors, higher physical activity may in turn increase the risk of CVD (table 2).

Comparison of risk factors for MetS and CVD

Participants who were obese had a greater risk of developing MetS than CVD when compared with those with normal weight, after controlling for confounding factors (16.22 (95% CI 10.71 to 24.56) vs 1.86 (95% CI 1.02 to 3.41) in males and 17.77 (95% CI 10.88 to 29.03) vs 2.56 (95% CI 1.18 to 5.54) in females). Results indicate that obesity is a greater risk factor for MetS than CVD in both females and males.

DISCUSSION

In the present study, the prevalence and risk factors of MetS and CVD were evaluated using deidentified data extracted from the 2007–2010 NHANES database. Though not significantly different, the prevalence of MetS and CVD was slightly higher in males as compared with females (42.50% and 7.65% vs 41.29% and 4.13%, respectively). Our results indicate that advanced age, family history of DM, overweight, and obesity were significantly associated with the likelihood of MetS in both males and females, after controlling for all potential confounding factors. Additionally, men diagnosed with prostate cancer (adjusted OR=2.27, 95% CI 1.09 to 4.72) or who were regular smokers (adjusted OR=1.77, 95% CI 1.27 to 2.46) also had a high risk for MetS. However, advanced age, family history of heart attack or angina, health insurance coverage, diagnosis of rheumatoid arthritis or depression, obesity, and low calorie intake were identified as risk factors for CVD in males (figure 1). Apart from these, higher physical activity (adjusted OR=2.93, 95% CI 1.63 to 5.26) and vitamin D insufficiency (adjusted OR=2.68, 95% CI 1.40 to 5.13) were also linked to an increased risk of CVD in females (figure 2). The increase in the risk of CVD is especially harmful in women with MET ≥600 and having other risk factors, like age, incidence of rheumatoid arthritis, obesity, breastfeeding, pregnancy and Vitamin D insufficiency (table 2). Furthermore, obesity was a higher risk factor for MetS than CVD.

The present analysis reveals and provides strong evidence for risk factors that are were not previously linked to CVD. Of particular interest is the association of high physical activity with the development of CVD in females. Based on the WHO recommendations, a MET score up to 600 MET-min/week is considered as moderate intensity of physical activity. Our results indicate that intense physical activity, that is, MET ≥600, carried a higher risk of CVD in women, after adjusting all relevant factors (figure 2). This is somehow different from what we expected. The risk of CVD in women with higher physical activity (MET ≥600) should be minimal as one would expect. However, our analysis revealed that in younger women, who were less obese, never pregnant and did not breastfeed, having lower incidence of rheumatoid arthritis, and lower vitamin D insufficiency, a higher physical activity can increase the risk of CVD (table 2).

The inverse relationship between exercise and the risk of CVD has been well established in healthy adults and in those diagnosed with CVD.[29–31] Reports indicate that increased total physical activity was associated with reduced risk of coronary heart diseases in a dose-dependent manner,[32] and the risk is almost doubled in sedentary individuals compared with those performing high-intensity exercise. However,

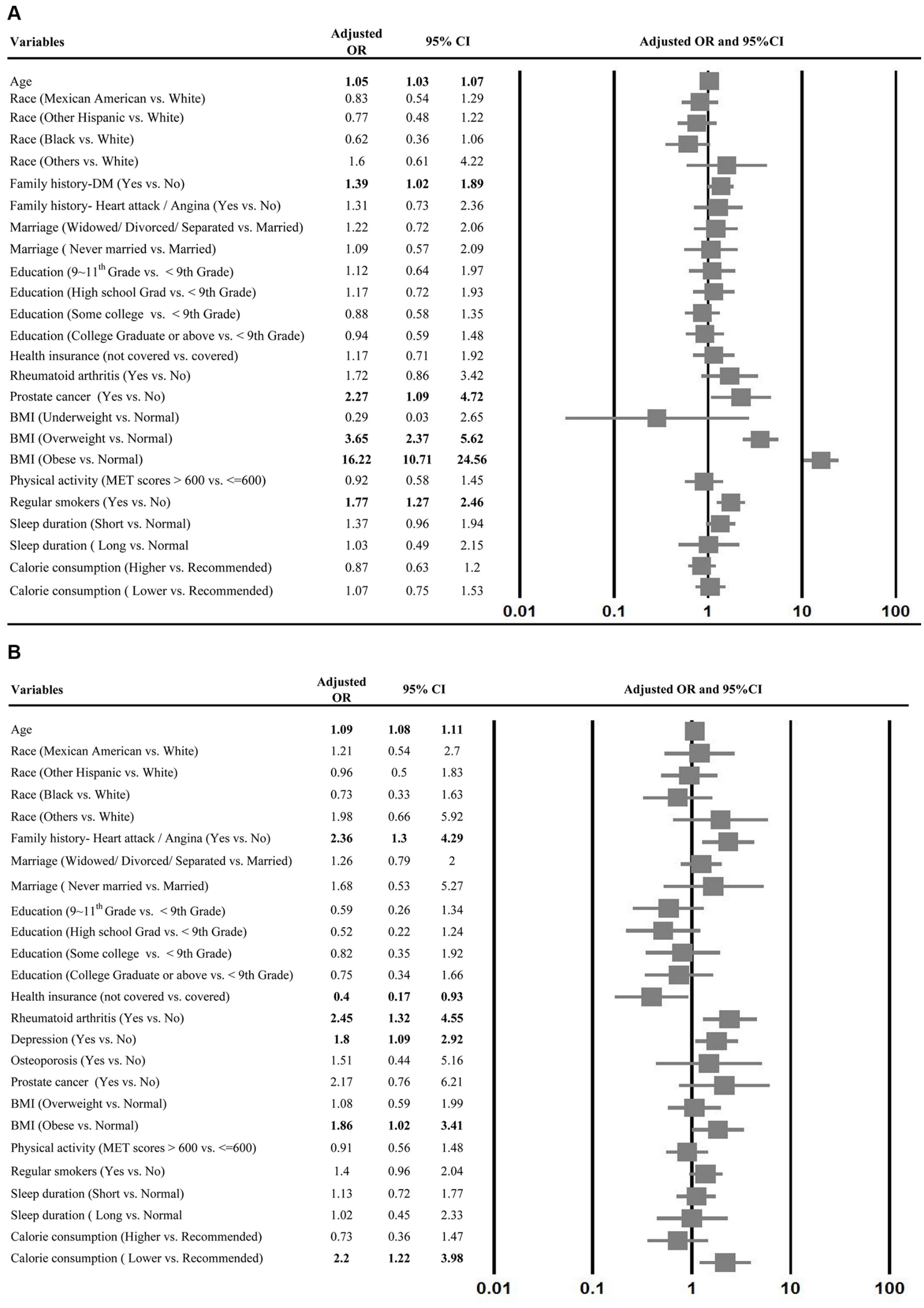

Figure 1 The results of multivariate logistic regression model for the risk factors associated with (A) metabolic syndrome or (B) cardiovascular diseases in males. (A) Associated with metabolic syndrome: age, race, family history of DM and heart attack or angina, marital status, education level, health insurance status, rheumatoid arthritis, prostate cancer, BMI, physical activity, regular smokers, sleep duration, and daily calorie consumption were included in the multivariate logistic regression model. (B) Associated with cardiovascular diseases: age, race, family history of heart attack or angina, marital status, education level, health insurance status, rheumatoid arthritis, depression, osteoporosis, prostate cancer, BMI, physical activity, regular smoking, and sleep duration were included in the multivariate logistic regression model.

what is not clear is that the level of exercise and cardiovascular outcomes is always linear. While compelling evidence indicate that regular and moderate exercise is favorable in healthy subjects and those with CVD, recent data suggest that higher doses of physical and athletic activity are associated with adverse cardiovascular outcomes.[33] Intense and strenuous exercise may have adverse effects in individuals with underlying CV abnormalities[34] and on those with otherwise normal heart.[35] Our results confirm that indeed higher physical activity is associated with increased risk of CVD in women. However, why this association is not seen in men is unclear.

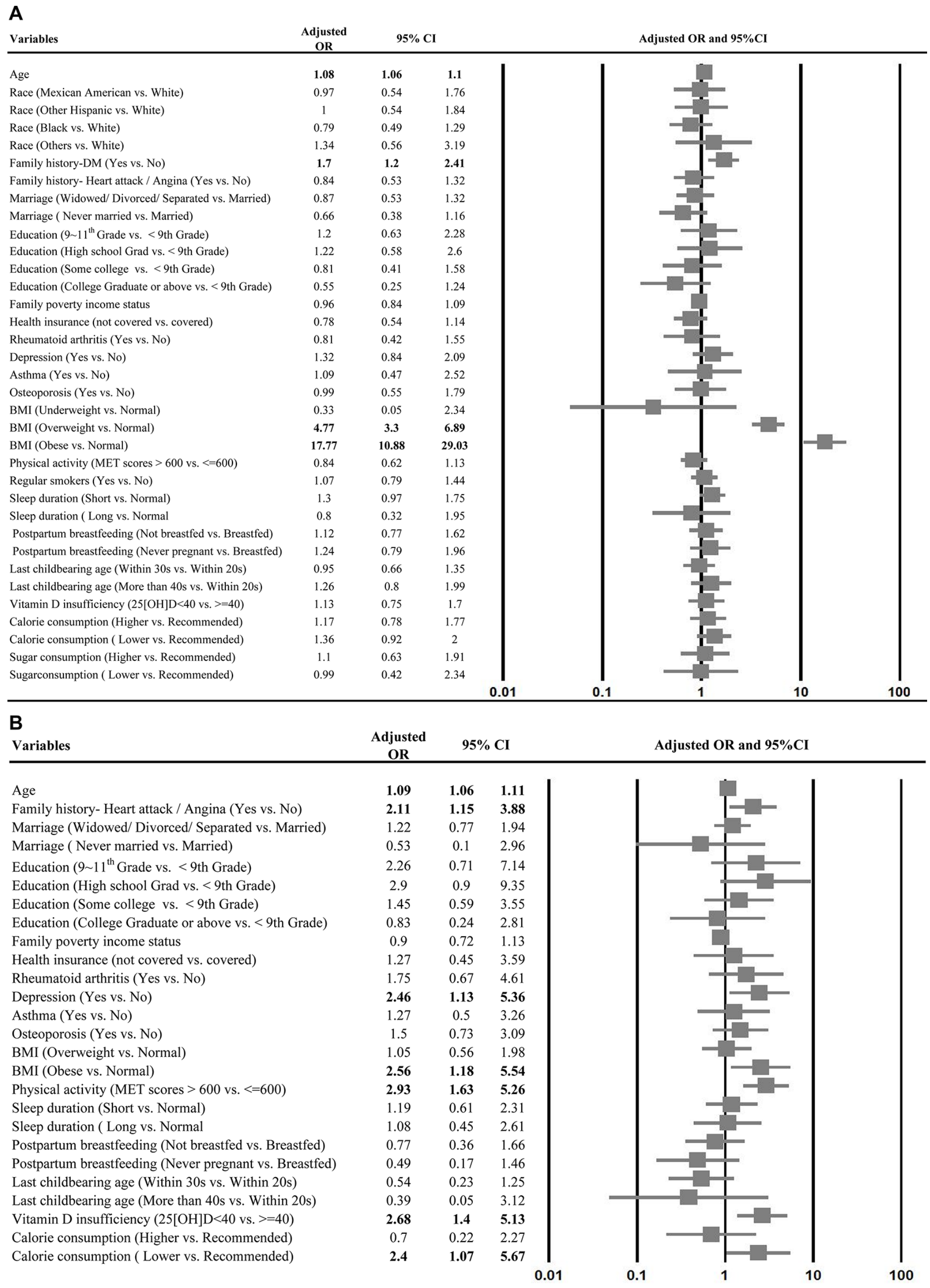

Figure 2 The results of multivariate logistic regression model for the risk factors associated with metabolic syndrome or cardiovascular diseases in females. (A) Associated with metabolic syndrome: age, race, family history of DM and heart attack or angina, marital status, education level, family poverty income status, health insurance status, rheumatoid arthritis, depression, asthma, osteoporosis, BMI, physical activity, postpartum breastfeeding, last childbearing age, sleep duration, and daily calorie and sugar consumption were included in the multivariate logistic regression model. (B) Associated with cardiovascular disease: age, family history of heart attack or angina, marital status, education level, family poverty income status, health insurance status, rheumatoid arthritis, depression, asthma, osteoporosis, BMI, physical activity, sleep duration, postpartum breast feeding, last childbearing age, vitamin D insufficiency, and daily calorie consumption were included in the multivariate logistic regression model. BMI, body mass index.

Another interesting association that emerged from the cross-sectional analysis of NHANES data is the link between low total daily calorie consumption and higher prevalence of CVD, which was evident in subjects, irrespective of their gender. Lifestyle modifications, including dietary change, is the most advocated strategy for the prevention and management of MetS and CVD. A low-calorie, high-fiber diet is often recommended to reduce the risk of diabetes and CVD.[36] Caloric restriction is known to be a strong activator of protective metabolic pathways, thereby leading to lower blood pressure, improved blood lipids, and reduced inflammatory markers,[37] in addition

Table 2 The association between the risk factors associated with cardiovascular disease and physical activity in females, stratified by METS 600.

Variables	MET ≥600	MET <600	p Value
Age (years)	43.9 (0.55)	52.4 (0.53)	<0.001*
Rheumatoid arthritis, n (%)			0.022*
Yes	78 (4.3)	94 (6.8)	
No	1133 (95.7)	989 (93.2)	
BMI, n (%)			<0.001*
Underweight	25 (2.5)	22 (1.8)	
Normal	430 (38.9)	293 (26.5)	
Overweight	409 (29.8)	365 (27.8)	
Obese	440 (28.8)	567 (43.9)	
Postpartum breast feeding, n (%)			<0.001*
Breast fed	568 (48.4)	521 (45.4)	
Not breast fed	348 (28.6)	462 (41.6)	
Never pregnant	201 (23.0)	120 (13.0)	
Last childbearing age, n (%)			<0.001*
Never pregnant	201 (24.3)	120 (13.7)	
Within 20s	460 (41.6)	491 (49.2)	
Within 30s	354 (31.4)	375 (33.2)	
More than 40s	33 (2.7)	57 (3.9)	
Vitamin D insufficiency, n (%)			<0.001*
25(OH)D <40	244 (14.0)	317 (23.9)	
25(OH)D >40	986 (86.0)	827 (76.1)	

*indicates a significant factor, p<0.05.
BMI, body mass index.

to reduction in oxidative damage.[38] Despite the reported positive effect of low calorie intake, our results indicate that low calorie intake was associated with a higher risk of CVD. However, a detailed analysis on the role of each dietary content was not undertaken in this study. In studies elsewhere, it has been shown that vitamin D deficiency in children may increase the risk of CVD.[39] Other reports suggest that associations between vitamin D and cardiometabolic risk among healthy, non-diabetic adults are largely mediated by adiposity.[40] Although a gender difference in MetS was not observed in our study, a report based on the 2012 Korean National Health and Nutrition Examination Survey (KNHANES) data indicate that serum 25 (OH)D levels were inversely associated with MetS in men, while it did not show any association with MetS in women.[41] Regardless, our report is in agreement with others, where regular physical activity along with a healthy eating profile and a better serum vitamin profile is shown to reduce the incidence of MetS and its risk components.[42]

Apart from the nutritional and exercise factors, the present data also highlight the role of psychological characteristics of subjects in the development of MetS and CVD. Remarkably, several recent reports have suggested that psychological characteristics, especially depression, hostility, and anger, may increase risk for the MetS.[10 43] Results from the 2007–2014 KNHANES reveal that MetS was more prevalent in women with a prior diagnosis of depression than those without diagnosed depression (26.20% vs 19.07%, p<0.001).[44] The strong association of depression with MetS and CVD directs our attention to the newly emerging risk factors, in addition to the traditional risk factors.

Though the cross-sectional study design is a limitation, the present study has major clinical implications. The key findings that higher physical activity in women and low calorie intake in general are associated with a high risk for CVD is particularly relevant in patient education strategies. Our results reveal that the higher risk of CVD associated with physical activity (MET ≥600) is seen only in women with certain risk factors, suggesting the role of new and emerging risk factors in the development of CVD. Our results also suggest that obesity is a major risk factor in MetS than in CVD, irrespective of gender. The analysis of key risk factors of MetS and CVD will help physicians in identifying patients who need aggressive lifestyle modification or intensive monitoring.

In conclusion, the current results provide cross-sectional evidence for the association of many emerging risk factors, like high physical activity in women and low calorie intake, not previously linked to MetS and CVD. However, prospective studies are necessary to validate these findings.

Contributors X-EZ: guarantor of integrity of the entire study; study concepts; study design; manuscript preparation; and manuscript editing. BC: experimental studies and definition of intellectual content. QW: data acquisition; data analysis; and statistical analysis. J-JW: clinical studies; literature research; and manuscript review.

Competing interests None declared.

Patient consent Meta-analyses do not involve human subjects and do not require IRB review (J Grad Med Educ 2011; 3:5–6).

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REFERENCES

1 Olufadi R, Byrne CD. Clinical and laboratory diagnosis of the metabolic syndrome. *J Clin Pathol* 2008;61:697–706.
2 Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008;28:629–36.
3 Hoang KC, Le TV, Wong ND. The metabolic syndrome in East Asians. *J Cardiometab Syndr* 2007;2:276–82.
4 Hwang LC, Bai CH, Chen CJ. Prevalence of obesity and metabolic syndrome in Taiwan. *J Formos Med Assoc* 2006;105:626–35.
5 Nestel P, Lyu R, Low LP, *et al*. Metabolic syndrome: recent prevalence in East and Southeast Asian populations. *Asia Pac J Clin Nutr* 2007;16:362–7.
6 Lovre D, Mauvais-Jarvis F. Trends in prevalence of the metabolic syndrome. *JAMA* 2015;314:950.
7 Bentley-Lewis R, Koruda K, Seely EW. The metabolic syndrome in women. *Nat Clin Pract Endocrinol Metab* 2007;3:696–704.
8 Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. *Physiol Behav* 2008;94:206–18.
9 Gustafson B, Hammarstedt A, Andersson CX, *et al*. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2007;27:2276–83.
10 Goldbacher EM, Matthews KA. Are psychological characteristics related to risk of the metabolic syndrome? A review of the literature. *Ann Behav Med* 2007;34:240–52.
11 Kahl KG, Schweiger U, Correll C, *et al*. Depression, anxiety disorders, and metabolic syndrome in a population at risk for type 2 diabetes mellitus. *Brain Behav* 2015;5:e00306.
12 Dunbar JA, Reddy P, Davis-Lameloise N, *et al*. Depression: an important comorbidity with metabolic syndrome in a general population. *Diabetes Care* 2008;31:2368–73.
13 Frasure-Smith N, Lespérance F. Reflections on depression as a cardiac risk factor. *Psychosom Med* 2005;67(Suppl 1):S19–25.

14 Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998;55:580–92.
15 Goldstein BI, Fagiolini A, Houck P, *et al*. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord* 2009;11:657–62.
16 Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an american Heart Association/National Heart, lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52.
17 NHANES. National Health and Nutrition Examination Survey: 2007 - 2008 Data Documentation, Codebook, and Frequencies. *Mental Health - Depression Screener (DPQ_E) October, 2009 ed: NHANES*.
18 NHANES. National Health and Nutrition Examination Survey: 2007 - 2008 Data Documentation, Codebook, and Frequencies. *Body measures (BMX_E). September, 2009 ed: NHANES*.
19 National Instiute on Alcohol Abuse and Alcoholism. *Helping patients who drink too much: A clinician's guide*: NIH Publication no 053769, 2005. Bethesda, MD.
20 Ainsworth BE, Haskell WL, Herrmann SD, *et al*. 2011 compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;43:1575–81.
21 Hirshkowitz M, Whiton K, Albert SM, *et al*. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 2015;1:40–3.
22 Schleicher RL, Sternberg MR, Lacher DA, *et al*. The vitamin D status of the US population from 1988 to 2010 using standardized serum concentrations of 25-hydroxyvitamin D shows recent modest increases. *Am J Clin Nutr* 2016;104:454–61.
23 Phinney KW. Development of a standard reference material for vitamin D in serum. *Am J Clin Nutr* 2008;88:511S–2.
24 Yetley EA, Pfeiffer CM, Schleicher RL, *et al*. NHANES monitoring of serum 25-hydroxyvitamin D: a roundtable summary. *J Nutr* 2010;140:2030S–45.
25 National Health and Nutrition Examination Survey: 2007 - 2008. *Data documentation, Codebook, and frequencies: dietary Interview - Individual Foods July 2010 ed: nhanes*, 2010.
26 U.S. Department of Agriculture and U.S. Department of Health and Human Services.. *Dietary guidelines for americans, 2010. 7th edition*. Washington: DC: U.S. Government Printing Office. (accessed Dec 2010).
27 Kroenke K, Spitzer RL. The PHQ-9: a New Depression Diagnostic and Severity measure. *Psychiatr Ann* 2002;32:509–15.
28 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
29 Lee IM, Sesso HD, Oguma Y, *et al*. Relative intensity of physical activity and risk of coronary heart disease. *Circulation* 2003;107:1110–6.
30 Rognmo Ø, Moholdt T, Bakken H, *et al*. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation* 2012;126:1436–40.
31 Moholdt T, Madssen E, Rognmo Ø, *et al*. The higher the better? interval training intensity in coronary heart disease. *J Sci Med Sport* 2014;17:506–10.
32 Tanasescu M, Leitzmann MF, Rimm EB, *et al*. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002;288:1994–2000.
33 Kim JH, Baggish AL. Strenuous exercise and Cardiovascular Disease Outcomes. *Curr Atheroscler Rep* 2017;19:1.
34 Manolis AS, Manolis AA. Exercise and arrhythmias: a double-edged sword. *Pacing Clin Electrophysiol* 2016;39:748–62.
35 Merghani A, Malhotra A, Sharma S. The U-shaped relationship between exercise and cardiac morbidity. *Trends Cardiovasc Med* 2016;26:232–40.
36 Mietus-Snyder ML, Shigenaga MK, Suh JH, *et al*. A nutrient-dense, high-fiber, fruit-based supplement bar increases HDL cholesterol, particularly large HDL, lowers homocysteine, and raises glutathione in a 2-wk trial. *Faseb J* 2012;26:3515–27.
37 Gögebakan O, Kohl A, Osterhoff MA, *et al*. Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial. *Circulation* 2011;124:2829–38.
38 Gredilla R, Barja G. Minireview: the role of oxidative stress in relation to caloric restriction and longevity. *Endocrinology* 2005;146:3713–7.
39 Murni IK, Sulistyoningrum DC, Oktaria V. Association of vitamin D deficiency with cardiovascular disease risk in children: implications for the Asia Pacific Region. *Asia Pac J Clin Nutr* 2016;25:S8–19.
40 Mousa A, Naderpoor N, de Courten MP, *et al*. 25-hydroxyvitamin D is associated with adiposity and cardiometabolic risk factors in a predominantly vitamin D-deficient and overweight/obese but otherwise healthy cohort. *J Steroid Biochem Mol Biol* 2016;0760:30347–8.
41 Yoon H, Jeong DK, Park CE, *et al*. The association between gender difference with metabolic syndrome, metabolic syndrome score and serum vitamin D levels in korean adults. *Int J Food Sci Nutr* 2017;68:121–9.
42 Choi JE, Ainsworth BE. Associations of food consumption, serum vitamins and metabolic syndrome risk with physical activity level in middle-aged adults: the National Health and Nutrition Examination survey (NHANES) 2005-2006. *Public Health Nutr* 2016;19:1674–83.
43 Goldstein BI, Carnethon MR, Matthews KA, *et al*. Major depressive disorder and bipolar disorder predispose Youth to Accelerated Atherosclerosis and early Cardiovascular disease: a Scientific Statement from the american Heart Association. *Circulation* 2015;132:965–86.
44 Park SJ, Roh S, Hwang J, *et al*. Association between depression and metabolic syndrome in korean women: results from the korean national health and nutrition examination survey (2007-2013). *J Affect Disord* 2016;205:393–9.