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Metabolic syndrome and coronary artery calcification: a community-based natural population study

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Keywords: *metabolic syndrome; cardiovascular risk factor; coronary artery calcification*

Background Little is known about the influence of metabolic syndrome (MetS) on coronary artery calcification (CAC) in China. In this article, we aimed to explore the distribution of CAC in populations with and without MetS, and estimate the influence of MetS and its components on CAC in a community-based population of Beijing.

Methods A total of 1647 local residents of Beijing, age 40-77 years, were recruited for a cardiovascular risk factors survey and were determined fasting plasma glucose (FPG), blood lipids, and 64 multi-detector computed tomography (64-MDCT) coronary artery calcium score (CACS) measurement (Agatston scoring). The distribution of CAC was described, and the influence of MetS components on CAC was evaluated.

Results In this population, the prevalence and extent of CAC increased with increasing age and both were higher in MetS subjects compared to nonMetS subjects (all P <0.05), with the exception of those older than 65 years old. The risk of CAC increased with increasing numbers of MetS components, and the odds ratios for predicting positive CAC in subjects with 1, 2, 3, and ≥4 MetS components were 1.60, 1.84, 2.12, and 3.12, respectively (all P <0.05). Elevated blood pressure, elevated FPG, elevated triglycerides, and overweight increased the risk of CAC, yielding odds ratios of 2.64, 1.67, 1.32, and 1.37, respectively (all P <0.05).

Conclusions In the Beijing community-based population, MetS increases the risk of CAC. The risk of CAC increases with increasing numbers of MetS components. Not only the number, but also the variety of risk factors for MetS is correlated with the risk of CAC. Elevated blood pressure, hyperglycemia, hypertriglyceridemia and overweight increase the risk of CAC.

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Over the past two decades, a striking increase in the number of people with metabolic syndrome (MetS) has taken place, it is considered one of the important public health challenges in China.[1,2] MetS includes hypertriglyceridemia, abdominal obesity, insulin resistance, glucose intolerance and hypertension, representing a clustering of cardiovascular risk factors.[3] MetS and its components are all associated with increased atherosclerotic burden, and therefore, increased risk of cardiovascular disease.[4]

MetS has been associated with atherosclerosis in some epidemiological studies. It is important to investigate the prevalence of MetS and its components, and study the association of the MetS with subclinical atherosclerosis. The presence and extent of coronary artery calcium (CAC) are strongly correlated with the magnitude of coronary atherosclerosis plaque burden and subsequent coronary events.[5] However there is limited information available on the distribution of CAC and influence of MetS on CAC in China.

In this article, we aimed to explore the distribution of CAC in populations with and without MetS, and estimate the influence of MetS and its components on CAC in a community-based population of Beijing, a major city of North China.

METHODS

Study population

From September 2008 to June 2009, the Shou-Gang community and Xi-Shan machinery community of Beijing Shi-Jing-Shan district were selected. A total of 2438 residents, age 40-77 years old, who lived in the two communities, were given written notices about participating in the Beijing study. Among 2438 residents, 2118 answered

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(answer rate 86.9%) the field epidemiology investigation, including questionnaire for risk factors and medical history, and anthropometric measurements.

We excluded 248 subjects who had a medical history of cerebrovascular disease (CVD, *n*=122), known coronary artery disease (CAD, *n*=112), or peripheral arterial disease (PAD, *n*=14). CVD was defined as physician diagnosed stroke or transient ischemic attack. CAD was defined as equal or more than 50% stenosis found in at least one coronary. There was no subject with implantation of a pacemaker or artificial cardiac valves, congenital heart diseases, durative atrial fibrillation, pregnancy, or malignant tumor. At last, 1647 residents (participation rate 88.1%) participated in blood tests and coronary CT calcium scans. This study protocol was approved by the Institutional Review Board of Human Research Ethics Committee and was funded by the Ministry of Science and Technology of China. All participants gave written informed consents.

Cardiovascular risk factors evaluation

A structured in-person interview was conducted by trained research staff. Demographics and the traditional risk factors were registered and measured. Demographic data were collected on questionnaires, including age, gender, smoking status and personal medical history and current use of prescription medications, and family history of premature CAD. Blood pressure, height, weight and waist circumferences were measured and body mass index (BMI, kg/m^2) was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times with participants in the seated position, with one minute of rest between each measurement. The average of the second and third measurements was used in the analysis. Weight and height were measured in light indoor clothing without shoes to the nearest 0.1 Kilogram (kg) and 0.5 centimeter (cm) respectively. Waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest at minimal respiration to the nearest 0.5 cm.

Blood testing

Five-milliliter (ml) fasting blood samples were taken from each subject. An automatic biomedical analyzer (Beckman DX 800, Beckman-coulter, USA) was used. Total cholesterol (TC) and triglycerides (TG) were obtained using the GPO-PAP methods, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured using the selective melt methods. Fasting plasma glucose (FPG) was measured by the glucose oxidase method.

Definitions

Smoking status was categorized as current smoker, former smoker (defined as no smoking in the past 30 days) and never-smoker (defined as smoking less than 100 cigarettes in lifetime).[6] Hypertension was defined as SBP/DBP >140/90 mmHg (1 mmHg=0.133 kPa) or taking anti-hypertension medication from the questionnaires.[7] Diabetes mellitus (DM) was defined as FPG≥126 mg/dl or taking any anti-diabetic medication as determined from the questionnaires.[7] Participants were considered as dyslipidemia if the lipid test was abnormal or if they were taking lipid-lowering medications.[7] Lipid-lowering medication included HMG-CoA reductase inhibitor (statins), fibrates, bile acid sequestrants and nicotinic acid derivatives.[6] Overweight was defined as a BMI ≥25 kg/m^2. Metabolic syndrome was identified when three or more of the following five components were present:[8] elevated waist circumference: WC ≥90 cm in men, WC ≥80 cm in women; elevated TG: TG ≥150 mg/dl or drug treatment for elevated triglycerides; reduced HDL-C: HDL-C <40 mg/dl in men or <50 mg/dl in women or drug treatment for reduced HDL-C; elevated blood pressure: BP ≥130/85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension; elevated FPG: FPG >110 mg/dl or drug treatment for elevated glucose.

Coronary CT scanning and analysis

Prospective electrocardiographically (ECG)-triggering sequential cardiac MDCT scans were performed by using a 64-detector row spiral computed tomography scanner (Light-Speed VCT; GE Healthcare, Milwaukee, WI, USA) with 2.5 mm section thickness (16×2.5 mm collimation), 0.35-second rotation time, 120 kV, and 200 mA. Images were reconstructed from a data acquisition window (60%–70% RR interval of the cardiac cycle) centered at 70% of the RR interval at ECG gating. The images were transferred to a stand-alone workstation (Deep Blue, ADW4.3, GE Healthcare, Milwaukee, WI, USA) and evaluated for CAC scores independently. The amount of calcification was quantified with the Agatston score method. We first identified each lesion as the hyper-attenuating region with at least four contiguous pixels exceeding the CT density of 130 Houndsfield units (HU). The coronary artery calcium score (CACS) was calculated by multiplying the detectable calcification region with a one to four rating dictated by the maximum CT density within that region (130-199 HU, 200-299 HU, 300-399 HU, >399 HU). A total calcium score was determined by summing individual lesion scores from each of four anatomic sites; left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA).

Statistical analysis

All analyses were performed on SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables from normally distributed data were expressed as mean ± standard deviation (SD) and were compared by using independent samples *t* tests. Positive CAC, in Agatston scores, were expressed as percentage and the distribution of CACS as percentile. The Chi-square test was performed to analyze the difference of risk factors percentages, and positive CAC percentages among LM, LAD, LCX and RCA between groups with MetS and without metabolic syndrome (nonMetS). Mann-Whitney *U* test and Kruskal-Wallis H test were used to analyze CACS in different groups. Logistic regression analysis was carried out with presence or absence of CAC as the dependent variable and risk factors included in MetS as independent variables. A two-tailed *P* value <0.05 was considered statistically significant.

RESULTS

A total of 1647 subjects (819 men and 828 women) enrolled finally and had coronary calcium scans in this study, mean age 53.3 years.

The distribution of demographics and traditional cardiovascular risk factors in the nonMetS and MetS groups are shown in Table 1. Compared with the nonMetS, the MetS subjects were older, less likely to be male, with a higher prevalence of hypertension, diabetes, hyperlipidemia, higher average BMI and waist circumference (all *P* <0.05).

The prevalence of MetS was 34.7% (572 cases) in this cohort, 31.9% (261 cases) for male and 37.5% (311 cases) for female, age-standardized prevalence was 32% and 36.7% (*P*=0.041). The prevalence of MetS components for men and women were as follows: elevated waist circumference in 68.4% and 52.0%; elevated blood pressure in 54.6% and 60.6%; elevated FPG in 16.1% and 20.9%; elevated TG in 12.8% and 20.3%; reduced HDL-C in 7.1% and 23.8%, as shown in Figure 1.

Table 1. Baseline demographic characteristics and cardiovascular risk factors of studied subjects

Variables	NonMetS (*n*=1075)	MetS (*n*=572)	*P* values
Male (*n* (%))	558 (51.9)	261(45.6)	0.015
Age (years, mean (SD))	52.6 (8.3)	55.0 (8.3)	<0.001
Current smoker (*n* (%))	387 (36.0)	185 (32.3)	0.138
Ever smoker (*n* (%))	81 (7.5)	47 (8.2)	0.623
Never smoker (*n* (%))	607 (56.5)	340 (59.5)	0.245
Hypertension (*n* (%))	335 (31.2)	401(70.1)	<0.001
Anti-hypertension treatment (*n* (%))	182 (54.3)	250 (62.3)	0.163
Family history of premature CAD (*n* (%))	271 (25.2)	151 (26.4)	0.599
Diabetes mellitus (*n* (%))	61 (5.7)	153 (26.7)	<0.001
Anti-diabetes treatment (*n* (%))	34 (55.7)	80 (53.3)	0.648
Dyslipidemia (*n* (%))	177 (16.5)	347 (60.7)	<0.001
Anti-dyslipidemia treatment (*n* (%))	18 (10.2)	31 (8.9)	0.646
BMI (kg/m^2, mean (SD))	24.4 (3.1)	27.8 (6.3)	<0.001
Waist circumference (cm, mean (SD))	84.7 (10.3)	94.4 (8.3)	<0.001

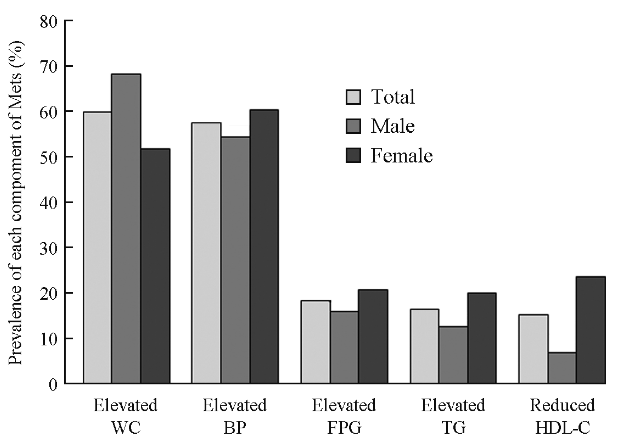

Figure 1. Prevalence of every component of MetS in the total population, males and females.

Among 1647 residents, 33.9% (559 cases) had positive CAC results, the prevalence of CAC were 42.5% (243 cases) and 29.4% (316 cases) in populations with and without MetS. Two hundred and fifty-one (15.2%) were single-vessel calcification, 308 (18.7%) had calcification in more than two vessels. In both the MetS and nonMetS groups, the prevalence of CAC was the highest in the LAD then, in descending order, in the RCA, LCX, and LM coronary artery (both *P* <0.001 for trend). In the LAD, RCA, and LCX, the prevalence of CAC were higher in the MetS than in the nonMetS group (all *P* <0.05). There was no significant difference between groups in CAC in LM (*P*=0.132), as shown in Figure 2.

The prevalence and extent of CAC in each age subgroup with and without MetS for males are shown in Table 2. The prevalence and extent of CAC were significantly higher in the MetS than in the nonMetS in the same age subgroup (all *P* <0.05), except for the >65 years subgroup. In the older than 65 years subgroup, the prevalence of CAC and percentile of CACS were higher in nonMetS than in MetS patients (*P* <0.05).

The prevalence and extent of CAC in each age subgroup with and without MetS for females are shown in Table 3. The prevalence and extent of CAC were significantly higher in the MetS than in the nonMetS in the same age subgroup (all *P* <0.05), with the exception of the <45 and >65 years subgroups (both *P* >0.05).

In those subjects with and without MetS, for men and women, the extent of CAC significantly increased with increasing age (all *P* <0.05 for trend).

Logistic regression analysis demonstrated that the risk of CAC increased with the increasing number of MetS components, as shown in Table 4 and Figure 3. Compared with no MetS risk factors, having 1, 2, 3, and ≥4 MetS components increased the risk for positive coronary artery calcification by 1.60, 1.84, 2.12, and 3.12 times respectively (all *P* <0.05). The age and gender adjusted odds ratios

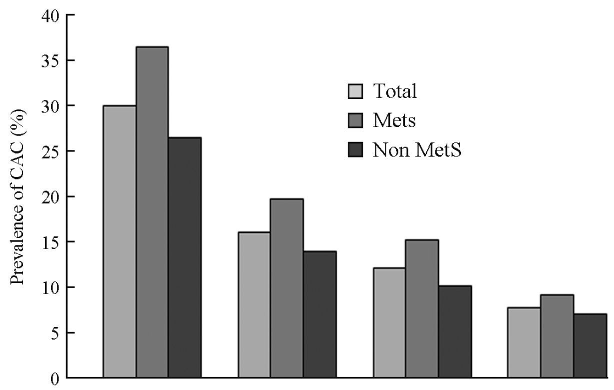

Figure 2. Prevalence of CAC in LAD, RCA, LCX, LM in the total population, MetS and nonMetS patients. LAD, left anterior descending. LCX: left circumflex. RCA: right coronary artery. LM: left main.

Table 2. Prevalence and extent of CAC by age in nonMetS and MetS in male

Age (years)	NonMetS or Mets	Positive CAC *n* (%)	*P* values*	Total CACS 25th	50th	75th	90th	maximum	*P* values†
<45	nonMetS	79 (13.9)		0	0	0	41	249	
	MetS	25 (36.0)	0.021	0	0	12.5	40.8	66	0.031
45–54	nonMetS	283 (30.0)		0	0	7	81.6	898	
	MetS	142 (40.8)	0.026	0	0	32.3	149.3	536	0.026
55–64	nonMetS	130 (50.0)		0	0.5	78.8	396.3	2693	
	MetS	65 (65.2)	0.044	0	22	182.3	651.5	2328	0.024
>65	nonMetS	66 (80.3)		13.8	164.5	565.5	951.4	2203	
	MetS	29 (58.6)	0.027	0	11	212	796	2026	0.010

Positive coronary artery calcification (CAC) in Agatston score were expressed as number and percentage. Extent of CAC were expressed as the 25th, 50th, 75th, 90th percentile and maximum of the total coronary artery calcium score (CACS). **P* values for comparisons of prevalence of CAC between nonMetS and MetS group in each age subgroup. †*P* values for comparisons of CACS between nonMetS and MetS group in each age subgroup.

Table 3. Prevalence and extent of CAC by Age in nonMetS and MetS in female

Age (years)	NonMetS and Mets	Positive CAC *n* (%)	*P* values*	Total CACS 25th	50th	75th	90th	maximum	*P* values†
<45	nonMetS	61 (3.3)		0	0	0	0	103	
	MetS	12 (8.3)	0.421	0	0	0	1.4	2	0.449
45–54	nonMetS	272 (11.0)		0	0	0	1	254	
	MetS	129 (20.9)	0.008	0	0	0	29	759	0.009
55–64	nonMetS	132 (27.3)		0	0	2	73.8	1031	
	MetS	108 (41.7)	0.019	0	0	32.8	150.3	1130	0.015
>65	nonMetS	52 (65.4)		0	39	162.8	363.7	913	
	MetS	62 (71.0)	0.523	0	36	238	780.5	2872	0.415

Positive coronary artery calcification (CAC) in Agatston score were expressed as number and percentage. Extent of CAC were expressed as the 25th, 50th, 75th, 90th percentile and maximum of the total coronary artery calcium score (CACS). **P* values for comparisons of prevalence of CAC between nonMetS and MetS group in each age subgroup. †*P* values for comparisons of CACS between nonMetS and MetS group in each age subgroup.

Table 4. Logistic regression analysis for number and variety of MetS components associated with presence of coronary calcification

Variables	Crude odd ratio (95% *CI*)	*P* values	Adjusted odds ratio (95% *CI*)*	*P* values
Component number of MetS				
0	–	–	–	–
1	1.60 (1.11–2.31)	0.012	1.40 (0.94–2.10)	0.098
2	1.84 (1.29–2.63)	0.001	1.49 (1.01–2.20)	0.045
3	2.12 (1.46–3.06)	<0.001	1.68 (1.12–2.52)	0.011
≥4	3.12 (2.10–4.62)	<0.001	2.59 (1.68–3.99)	<0.001
Variety of MetS components				
Elevated BP	2.64 (2.12–3.29)	<0.001	1.88 (1.48–2.39)	<0.001
Elevated FPG	1.67 (1.30–2.16)	<0.001	1.32 (1.01–1.74)	0.047
Elevated TG	1.32 (1.06–1.63)	0.012	1.33 (1.05–1.68)	0.018
Elevated WC	1.11 (0.91–1.38)	0.283	1.22 (0.96–1.54)	0.104
Reduced HDL-C	0.94 (0.75–1.19)	0.608	1.03 (0.80–1.33)	0.814
Overweight	1.37 (1.11–1.69)	0.004	1.31 (1.04–1.65)	0.024

BP: blood pressure; FPG: fast plasma glucose; TG: triglycerides; WC: waist circumference; HDL-C: high-density lipoprotein cholesterol; CI: confidence interval; *Adjusted odds ratio was age and gender standardized odds ratio.

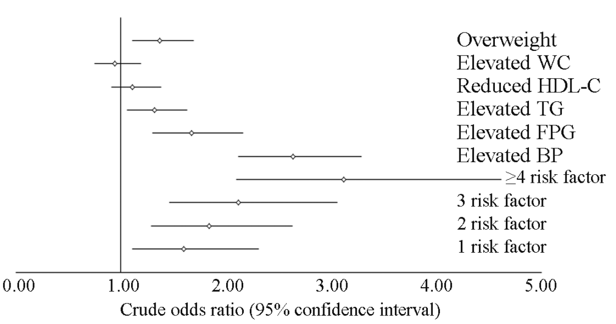

Figure 3. Risks of coronary artery calcification for number and variety of MetS components.

(*ORs*) were still significant for having 2, 3 and ≥4 MetS components. Elevated blood pressure, elevated FPG, elevated TG, and overweight were significant predictors of CAC; the ORs were 2.64, 1.67, 1.32, and 1.37, respectively (all P <0.05). All values were still significant after they were adjusted by age and gender.

DISCUSSION

Metabolic syndrome is a combination of some interconnected cardiovascular risk factors for obesity, insulin resistance and glucose intolerance, dyslipidemia, and hypertension. The increasing prevalence of cardio-metabolic risk factors has resulted in an unprecedented rise in the incidence of cardiovascular disease. The incidence of CAD is predicted to rise by at least 50% in the next 20 years, with an additional 23% increase resulting from increases in cardio-metabolic risk factors.[9]

Coronary artery calcification is strongly correlated with the magnitude of coronary atherosclerosis plaque burden and with the development of subsequent events. The extent of CAC has been shown in several studies to predict cardiac events in asymptomatic individuals.[10] Researching the influence of metabolic syndrome on coronary artery atherosclerosis may provide more information on the risk stratification of patients with metabolic syndrome, and provide more powerful evidence for further early intervention. Reports have shown that considering CAC will markedly improve the predictive value of traditional risk factors in estimating risk of hard CHD events, myocardial infarction or CHD death, and all-cause death.[11,12]

The prevalence of MetS in our study was higher than that reported from earlier studies in China. Epidemiological studies have reported that the prevalence of MetS varies widely, from 7.1% to 41.6% across different studies, which might partially be due to the use of different definitions for MetS or different study populations.[13,14] In recent years the prevalence of obesity, diabetes, dyslipidemia, and hypertension has rapidly increased in China due to economic development and its associated changes in lifestyles.[15] As a consequence, MetS has become an emerging epidemic. In this study, abdominal obesity and elevated blood pressure were the most common components of MetS, consistent with other domestic studies.[16,17]

The prevalence and extent of CAC had an ascending trend with increasing age, and they were significantly higher in MetS than in nonMetS patients in the same age subgroup for both males and females. An exception was found for those older than 65 years and women younger than 45 years old. In this study, only a few women younger than 45 years had positive CAC and they were mostly lower CACS. This might be partly due to the age difference of presenting calcification in men and women; it has been reported that calcification is first detected in most men at around age 40, whereas women first show calcification at around age 50.[18] The prevalence and amount of CAC was higher in nonMetS than in MetS patients in the >65 years old males, but there was no significant difference in >65 year old females. This might be related to older subjects who present one or more cardiovascular risk factors related with atherosclerosis, and these risk factors are not being included in the criteria for diagnosing MetS. The presence of these risk factors may balance the influence of MetS. As compared to middle-age adults, the influence of MetS on atherosclerosis probably was attenuated in old subjects. It has been reported that risk factors are only weakly association with the extent of CAC in older adults.[19]

We found that the risk of coronary calcification had an increasing trend with the increasing number of metabolic syndrome components, and the 95% confidence interval (95% *CI*) overlapped, which meant that not only the number, but also the variety of risk factors for MetS is correlated with the risk of coronary calcification. The following components of MetS, elevated triglyceride, elevated blood pressure, elevated FPG, and overweight were risk factors for coronary calcification. Research done in western countries show that metabolic syndrome was associated with an increased risk of CAC.[20] Among 2,735 participants aged 30 to 65 years old, the prevalence of CAC increased from those with neither MetS nor DM (16.6%) to MetS only (24.0%) to DM only (30.2%) to both MetS and DM (44.7%) (P <0.0001). After adjustment, MetS and DM were each independently associated with CAC. Santos reported that in Brazilian low risk participants, the prevalence of CAC increased with the increasing number of metabolic syndrome components (none=29%, 1 or 2=44%, and ≥3=51%, P=0.002 for trend). The risk of CAC was approximately two times (OR=1.94, 95% CI, 1.05-3.61) in those with metabolic syndrome compared to those without metabolic syndrome.[21]

In the Beijing population, we found that overweight instead of abdominal obesity independently increased the risk of coronary calcification. ATPIII-recommended cut-off points waist circumference of abdominal obesity for Asia populations might be inappropriate for Chinese. The Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (2007) recommended waist circumference ≥85 cm for women and ≥90 cm for men as the cut-off values.[22] The cut-off value recommended by ATPIII might overestimate the prevalence of central obesity and thus overestimate the prevalence of metabolic syndrome in Chinese. According to the Chinese Diabetes Society (CDS) definition, BMI was used as one of the five criteria for metabolic syndrome diagnosis, instead of waist circumference.[6] Hou et al[23] studied 46 024 participants ≥20 years old in 2007–2008 and found that the combination of waist circumference and BMI measures were superior to the separate indices in identifying cardio-metabolic disorder and cardiovascular disease risk.

This study has some limitations. Firstly, 1647 enrolled subjects are not sufficient to reduce noise, especially in subgroups of young (<45 years) and old (>65 years) population. Secondly, only Beijing residents were enrolled, it has been reported geographic difference in the prevalence and extent of coronary artery calcification, and in the relationship of risk factors with atherosclerosis.[24,25] Further study with more subjects and more districts and cities need to be conducted. Thirdly, we have to be aware of the radiation dose in the coronary calcium scan, although the radiation dose is low, based on the ALARA ("as low as reasonably achievable") principle, every effort should be made to reduce the radiation dose without reducing the ability to accurately assess CAC burden.

In conclusion, in the Beijing community-based population, MetS increases the risk of CAC, whereas the risk might be different in older residents (>65 years). The risk of CAC increases with an increasing number of MetS components, the number and variety of MetS components are both correlated with the risk of CAC. Elevated blood pressure, hyperglycemia, hypertriglyceridemia, and overweight are significant predictors of CAC.

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