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Much lower prevalence of coronary calcium detected by electron-beam computed tomography among men aged 40-49 in Japan than in the US, despite a less favorable profile of major risk factors

Akira Sekikawa, MD, PhD, **Hirotsugu Ueshima, MD, PhD, FFPHM**, **Wahid Riad Zaky, MD**, **Takashi Kadowaki, MD, PhD**, **Daniel Edmundowicz, MD, FACC**, **Tomonori Okamura, MD, PhD**, **Kim Sutton-Tyrrell, DrPH**, **Yasuyuki Nakamura, MD, PhD**, **Katsuya Egawa, MD, PhD**, **Hideyuki Kanda, MD**, **Atsunori Kashiwagi, MD, PhD**, **Yoshiyuki Kita, PhD**, **Hiroshi Maegawa, MD, PhD**, **Kenichi Mitsunami, MD, PhD**, **Kiyoshi Murata, MD, PhD**, **Yoshihiko Nishio, MD, PhD**, **Shinji Tamaki, MD, PhD**, **Yoshiki Ueno, MD, PhD**, and **Lewis H. Kuller, MD, DrPH**
Department of Epidemiology, Graduate School of Pubic Health, University of Pittsburgh, Pittsburgh USA (A.S., W.R.Z., K. S., L. H. K.), the Department of Health Science, Shiga University of Medical Science, Otsu, Japan (H.U., T.K., T.O., H.K., Y.K., T. K.), Cardiovascular Institute, University of Pittsburgh, Pittsburgh, USA (D. E.), the Department of Internal Medicine: Endocrinology and Metabolism, Shiga University of Medical Science, Otsu, Japan (K.E., A. K., H.M., Y.N.), Medical Coordination Center, Shiga University of Medical Science, Japan (K. M.), the Department of Radiology, Shiga University of Medical Science, Japan (K. M.), and the Department of Internal Medicine: Cardiology, Shiga University of Medical Science, Japan (Y. N., S.T., Y.U.)

SUMMARY

Background—Since World War II (WWII), exposures to westernized lifestyle have occurred in many non-Western countries, including Japan. National surveys showed that risk factor profiles for atherosclerosis around 1990 were similar in men in the post WWII birth cohorts in the United States (US) and Japan. We compared the degree of coronary calcium and other factors in men in the post WWII birth cohort: men aged 40-49 between the US and Japan.

Methods—We conducted a cross sectional study examining randomly selected 100 men from Kusatsu, Japan, and 100 men from Allegheny County, US. Coronary calcium was assessed using electron-beam computed tomography.

Results—Systolic blood pressure, total cholesterol, LDL-cholesterol and smoking rates were higher among the Japanese (122.6 ± 14.1 versus 113.7 ± 9.6 mmHg, $p<0.01$; 5.72 ± 0.90 versus 4.99 ± 0.81 mmol/l (220.9 ± 34.6 versus 192.8 ± 31.3 mg/dl), $p<0.01$; 3.52 ± 1.01 versus 3.10 ± 0.78 mmol/l (136.0 ± 39.0 versus 119.7 ± 30.0 mg/dl), $p<0.01$; and 48 versus 15%, $p<0.01$, respectively). Triglycerides and fibrinogen were similar. HDL-cholesterol was higher among the Japanese. Body mass index, fasting insulin, and C-reactive protein were higher among the Americans. Prevalence of coronary artery calcium score > 0 was strikingly lower among the Japanese than the Americans (13 % versus 47 %, $p <0.01$).

Conclusions—Much lower prevalence of coronary calcium despite a less favorable profile of many major independent risk factors in the Japanese might imply that there are strong protective factors against atherosclerosis in the Japanese. Further investigation is of critical importance.

Address for correspondence Dr. Akira Sekikawa Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh 3512 Fifth Avenue, Pittsburgh, PA 15213, USA Tel: 412-383-1042 Fax: 412-383-1020 akira@pitt.edu.

Keywords

Subclinical atherosclerosis; electron-beam computed tomography; US; Japan; epidemiology; risk factors; post Word War II birth cohort; coronary calcium

Since World War II (WWII), exposures to westernized lifestyle have occurred in many non-Western countries, including Japan. The man born after WWII in Japan have had major changes in diet and other lifestyle factors, including heavy cigarette smoking, increase in the levels of total and low density lipoprotein cholesterol (LDL-C), increase in cholesterol intake in diet which is higher than in the United States (US), increase in body weight and obesity, substantial increase in alcohol consumption, and increase in western foods [1]. Comparing the survey data from national representative samples around 1990, risk factor profiles for coronary heart disease (CHD): total cholesterol, and systolic and diastolic blood pressure, were very similar in men in the post WWII birth cohorts in the US and Japan, except for much higher prevalence of cigarette smoking in Japan and much higher prevalence of obesity in the US [2]. We compared CHD mortality in men aged 35-44 between the US and Japan and found that CHD mortality in Japan is still considerably lower than in the US: 23.7/100,000 for the US and 8.7/100,000 for Japan [3]. After careful review, the differences do not appear to be explained by differences in potential misclassification of causes of death [3]. These observations imply that there may be important protective factors that reduce risk of CHD in Japan.

Differences in genetic factors are unlikely to fully explain the difference in CHD mortality because studies of Japanese migrants to the US clearly illustrated the increase in CHD morbidity and mortality in Japanese men in the US [4]. Epidemiological investigations monitoring and comparing CHD morbidity and mortality in the post WWII birth cohorts, i.e. age <50, between the countries would be very important. Such studies are, however, practically impossible to conduct because incidence of CHD is too low in the post WWII birth cohort.

Electron-beam computed tomography (EBT) is a non-invasive method for defining subclinical atherosclerosis of coronary arteries and accurately quantifying coronary artery calcium [5]. Calcification within the coronary arteries is highly correlated with the extent of atherosclerosis. Coronary artery calcification occurs in small amounts in the early lesions of atherosclerosis in the second and third decades of life [5]. It is found frequently in advanced lesions and in older age.

The key question is “Do Japanese men in the post WWII birth cohort with similar risk factor profiles as men in the US have as much or less coronary atherosclerosis?” In this study, we tested the null hypothesis that there is no difference in the prevalence of coronary artery calcium detected by EBT between men aged 40-49 in the US and Japan. We also compared the traditional risk factors and other factors between the two populations.

METHODS

Subjects

Participants were 40-49 years of age and residents in Allegheny County, Pennsylvania (PA) or Kusatsu City, Shiga, Japan. Exclusion criteria included: 1) clinical cardiovascular disease, 2) type 1 diabetes, 3) cancer except skin cancer in the past two years, 4) renal failure, and 5) genetic familial hyperlipidemias.

In Kusatsu City, subjects were randomly selected using the Basic Residents' Register which has each resident's information of name, birth date, address, household, and other details. From the Register, 300 men aged 40-49 were randomly selected and were contacted consecutively via phone. Among 203 men contacted from May 2001 to December 2002, 100 men were agreed to participate in the study and were examined. The rate of participation was 49%. Of 100, two subjects were excluded in the current analyses because EBT images were not obtained appropriately.

In Allegheny County, PA, subjects were volunteers. In May 2002, the study was announced through the University of Pittsburgh Medical Center (UPMC) Health Plan with the eligibility criteria. The UMPC Health Plan is a major health care insurer in the area of Pittsburgh, holding a majority of University workers and students. From June to October 2002, 100 subjects participated in the study. Among them, 99 were Caucasians.

Informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of Shiga University Medical Science, Otsu, Japan, and University of Pittsburgh, Pittsburgh, US.

Study protocol

Participants were instructed to abstain from food or drink beginning at 8 p.m. on the previous day. On the examination day, their body weight and height were measured while they were wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) /height squared (m^2). Waist circumference was measured at the level of the umbilicus while participant was standing erect. Blood pressure was measured in the right arm of seated participants after the participant emptied his bladder and sat quietly for five minutes, using an appropriate-sized cuff, with a standard mercury sphygmomanometer. The average of two measurements of the first (systolic) and fifth (diastolic) Korotkoff sounds was used for the analysis.

Venipuncture was performed early in the clinic visit after a 12-hour fast. The serum was kept in room temperature for 45 minutes. The plasma was then stored on ice and centrifuged within 60 minutes. Multiple aliquots of plasma or serum were prepared and frozen at −70 °C. Serum samples were shipped on dry ice to the Heinz Laboratory, Department of Epidemiology, University of Pittsburgh, to measure lipids, glucose, and insulin. Serum lipids were measured with the standardized methods according to the Centers for Disease Control and Prevention, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides. LDL-C was estimated by the Friedewald equation [6]. When the value of triglycerides exceeded 4.52 mmol/l (400 mg/dl), LDL-C was measured directly using an automated spectrophotometric assay, LDL Direct Liquid Select (Equal Diagnostics, Exton US). There were two such subjects in each site. Serum glucose was determined using the hexokinase–glucose 6-phosphate dehydrogenase enzymatic assay. Serum insulin was determined using radio immunoassay (Linco Research Inc., St. Charles, US).

Samples were shipped on dry ice to the Laboratory for Clinical Biochemistry Research, University of Vermont, to measure C-reactive protein (CRP) and fibrinogen. CRP was measured by a calorimetric competitive enzyme-linked immunosorbent assay. Fibrinogen was measured in an automated clot-rate assay using the ST4 instrument (Diagnostica Stago, Parsippany, US).

A self-administered questionnaire was used to obtain information on demography, smoking habits, alcohol drinking, fish intake, and other factors. Alcohol drinking was assessed as whether a participant drinks beer, wine, liquor, or sake with the frequency of drinking.

Frequency of fish intake was assessed as less than one time a week, one time a week, two to four times a week, or more than four times a week.

Electron-beam computed tomography (EBT)

The scanning was done using a GE-Imatron C150 Electron Beam Tomography scanner (GE Medical Systems, South San Francisco, US) in both sites. Scanners were calibrated regularly by technologists following a standardized protocol. Measures of water density (0 Hounsfield Unit (HU)), air (-1000 HU), and calcification (threshold 130 HU) were uniform in the two scanners.

Scanning was performed in a standardized protocol to obtain 30-40 contiguous 3 mm thick transverse images from the level of the aortic root to the apex of the heart. Images were obtained during maximal breath holding using ECG triggering so that each 100 m second exposure was obtained during the same phase of the cardiac cycle. The amount of radiation exposure received from the EBT procedure is approximately 0.7 rem to the chest. All scan data were saved to optical disc.

Readings of the scanning were done centrally in the Cardiovascular Institute, Pittsburgh, using a DICOM (Digital Imaging and Communications in Medicine) workstation and software by AccuImage (AccuImage Diagnostic Corperation, San Francisco, US). The software program implements the widely accepted Agatston scoring method [7]. Coronary artery calcium was considered to be present when 3 contiguous pixels (area = 1 mm^2) greater than 130 HU were detected overlying the vessels of interest. A calcium score was then calculated for each region of interest by multiplying the area of all significant pixels by a grade number (1, 2, 3, 4) indicative of the peak computed tomography number (HU). The individual region of interest scores were then summed for a total coronary calcium score. The reading was evaluated by one trained radiology technician. The reproducibility of the EBT scans from this laboratory had an intraclass correlation of 0.99 [8].

Since the distribution of coronary calcium score was very skewed, the data were analyzed in a categorical form. To calculate the prevalence of coronary calcium, two cut points were used: zero and greater than zero as well as less than 10, and 10 or greater.

Statistical analysis

Values are expressed as means ± standard deviation (SD) and were compared with the use of a two-sample t-test. Continuous variables that showed highly skewed distribution (CRP and triglycerides) were compared with the use of the Mann-Whitney U test, and values were expressed as median and inter-quartile range. Dichotomous data (prevalence of coronary artery calcium, cigarette smoking, alcohol drinking, and fish eating) were compared with the use of the chi-square statistics. All p-values were two-tailed. P value less than 0.05 was considered as significant. SPSS software (release 11.5.0, SPSS Inc., Chicago, US) was used for all statistical analyses.

RESULTS

Comparison of the major independent risk factors between men in the US and Japan

Levels of many major independent risk factors were less favorable among the Japanese men than among the American men (Table 1). Levels of systolic blood pressure were significantly higher among the Japanese men by about 10 mmHg. Prevalence of hypertension defined as levels of systolic blood pressure >=140 mmHg, or levels of diastolic blood pressure >=90, or on anti-hypertensive medication was 19.4 % for the Japanese and 11.0% for the Americans. Levels of total cholesterol as well as LDL-C were significantly

higher among the Japanese men by about 0.73 mmol/l (28 mg/dl) and 0.41 mmol/l (16 mg/dl), respectively. Prevalence of current cigarette smoking was substantially higher among the Japanese men. Levels of HDL-C, in contrast, were significantly higher among the Japanese men by about 0.23 mmol/l (9 mg/dl).

Comparison of other factors between men in the US and Japan

Differences were observed in obesity, levels of insulin, CRP and glucose, and some lifestyle factors, which may relate to major independent risk factors or atherosclerosis (Table 1). Anthropometry data showed that the American men were much more obese and had greater waist circumferences. Levels of insulin as well as CRP were much higher among the American men. Levels of triglycerides as well as fibrinogen were similar between the two populations. Levels of glucose were significantly higher among the Japanese men by about 0.44 mmol/l (8 mg/dl). Prevalence of diabetes defined as levels of fasting blood sugar >= 6.0 mmol/l (126 mg/dl) or on anti-diabetic medication was 2.0 % for both the Japanese and the Americans.

Almost a half of the Japanese men drank alcohol every day, while only small percentage of the American men drank alcohol every day (46% versus 16%; $p<0.01$). All the Japanese men ate fish two times a week or more, while only 17% of the American men did.

Prevalence of subclinical atherosclerosis detected by EBT in men in the US and Japan

Prevalence of coronary artery calcium score > 0, or >=10 was strikingly lower among the Japanese men than the American men. Prevalence of coronary calcium score > 0 was 47 % among the American men, which is very similar to other reports in men in this age group in the US, while it was only 13% among the Japanese men. Similarly prevalence of coronary calcium score >=10 was 26% among the American men, and it was only 5% among the Japanese men. Among the American men, four subjects had coronary calcium score >=100, while only one subject did among the Japanese men (Figure).

Comparison of major independent risk factors and other factors by the presence of coronary calcium in each population

Table 2 shows the comparison of factors by the presence of coronary calcium (coronary calcium score > 0 versus coronary calcium score = 0) in the American men as well as in the Japanese men. The American men with coronary calcium score > 0 had significantly higher levels of fasting glucose, BMI, and waist circumference than those with coronary calcium score = 0. Levels of total cholesterol, HDL-C, or LDL-C did not appear to be different between the two groups in the American men. The Japanese men with coronary calcium score > 0 had higher levels of total cholesterol, LDL-C, CRP, fibrinogen, lower levels of HDL-C, and higher prevalence of cigarette smoking than those with coronary calcium score = 0, although most of the differences did not reach statistical significance, due to a small number of subjects. We did the same analyses using the cut-point of calcium score 10 (coronary calcium score 10 or greater versus less than 10). The results were very similar with those in the table 2, except the differences in the levels of both systolic and diastolic blood pressure reached statistical significance in both the Americans and the Japanese.

DISCUSSION

We observed strikingly lower prevalence of coronary artery calcium among the Japanese men than the American men despite a less favorable profile of several major independent risk factors: levels of systolic blood pressure, total cholesterol, and LDL-C, and the rate of cigarette smoking. The reason for this striking difference is largely unknown. Much higher levels of HDL-C among the Japanese in part account for the difference. Observed

differences in obesity, especially central obesity, alcohol consumption, and fish intake may to some extent account for the difference in atherosclerosis formation.

Plausible mechanisms of the association of central obesity with atherosclerosis include small dense LDL, low HDL-C, large VLDL, high triglycerides, high systolic blood pressure, glucose intolerance, elevated CRP, abnormal coagulation/fibrinolytic profile, impaired endothelial function and others [9]. Although levels of LDL-C were higher among the Japanese men, it is possible that the American men had a greater proportion of small dense LDL particles because they had much greater waist circumference and higher insulin levels [10].

Higher levels of systolic blood pressure among the Japanese men and similar levels of triglycerides and fibrinogen in the two populations are inconsistent with the profile related to central obesity described above. The much higher alcohol consumption in the Japanese men may in part relate to higher levels of blood pressure [11]. Much higher intake of salt among the Japanese than Americans in general also may be in part responsible for the higher systolic blood pressure [1,12]. Similar levels of fibrinogen may be in part due to much higher prevalence of cigarette smoking among the Japanese men.

Much more frequent intake of alcohol among the Japanese than the Americans may in part relate to the lower prevalence of coronary calcium among the Japanese through the increase in HDL-C, reduction in blood clotting and platelet aggregation, increase in insulin sensitivity, and other mechanisms [13].

The National Nutrition Survey in Japan showed that the Japanese eat fish more than 100 g/day; men aged 40-49 eat fish about 120 g/day on average [1]. Average fish consumption in epidemiological studies examining its association with CHD in western and some non-western countries ranged from 14g/day to 60g/day [14,15]. This substantially higher fish consumption in the Japanese may exert some protective mechanisms against atherosclerosis, such as increasing the particle size of LDL [16], or reducing the levels of CRP [17].

Reported variation in cholesterol ester transfer protein polymorphisms may affect both HDL-C levels and atherosclerosis [18]. Variations in lipoprotein size, distribution, and particle concentration are related to atherosclerosis and CHD, independent of lipid levels [18]. These factors may be affected by genetic polymorphisms of enzymes such as lipoprotein lipase or hepatic lipase and may be influenced by certain environmental factors such as lack of exercise and diets leading to central obesity [19].

Very high consumption of isoflavonoids from soy products in the Japanese in general may in part account for the difference [1,20], although we did not examine soy consumption in this study.

Varying “lag time” between exposure to risk factors and disease occurrence is unlikely to explain the difference because levels of total cholesterol in this post WWII birth cohort of US Caucasian men and Japanese men in Japan were very similar in the 1970s [2]. Prevalence of cigarette smoking in this birth cohort in Japan was already much higher than in the US in the 1980s [1,12].

Various minimal numbers of pixels have been used in different studies for distinguishing true foci of calcium from noise, raging from 1 pixel to 4 adjacent pixels [8,21-24]. We employed a conservative threshold in this study: three adjacent pixels in our study. We also measured the coronary calcium using a calcium-volume score [25] in our study, which has higher reproducibility between scans than coronary calcium score by Agatston methods. The correlation coefficient between a coronary calcium score and a calcium volume score was

0.997. Body size per se may possibly be related to increased prevalence of small lesions simply due to increased random scatter of the electron beam. If the prevalence of small lesions increases due to increased random scatter of the electron beam, there is a statistically significant positive correlation between a coronary calcium score and body mass index, especially when a coronary calcium score is less than 10. There was, however, no significant correlation between coronary calcium score and body mass index (correlation coefficient −0.26, p = 0.895).

Risk factor profiles of the examined population in Japan do not seem to be much different from those in the general population in Japan. The levels of total cholesterol and HDL-C as well as the rates of alcohol drinking and cigarette smoking in this population were very similar to the numbers reported from the National Nutrition Survey [1].

There are several limitations of the study. First, the study was cross-sectional in design and we can not establish causal relationship. Second, the sample size of the study was too small to conduct robust multi-variable analyses. Third, the subjects in the Pittsburgh site were not randomly selected but volunteers. The results of the Pittsburgh site, therefore, can not be generalized to the US population.

In this volunteer sample, however, the risk relationship should be similar with that in a randomly selected population, because it is highly unlikely that the participants of this study had previous knowledge of their own coronary calcium score. Based on the levels of total cholesterol and the prevalence of cigarette smoking, the participants could be somewhat healthier than a randomly selected population [26]. If this is the case, the prevalence of coronary calcium in a randomly selected population would be higher and the difference in the prevalence of coronary calcium would be much greater. One population-based study in the US reported that the prevalence of coronary artery calcium among men aged 40-49 was 42% [21]. Two studies in the US reported the prevalence among men in this age group who were either physician-, or self-referred, was around 45% [22,23]. It is, therefore, unlikely that the prevalence of coronary artery calcium in the study population is significantly different from that in a randomly selected population.

Much lower prevalence of coronary calcium despite a less favorable profile of most major independent risk factors in the Japanese might imply that there are strong protective factors against atherosclerosis in the Japanese. Further investigation by evaluating and comparing the extent and severity of subclinical atherosclerosis in these populations and its relation to various factors is of critical importance.

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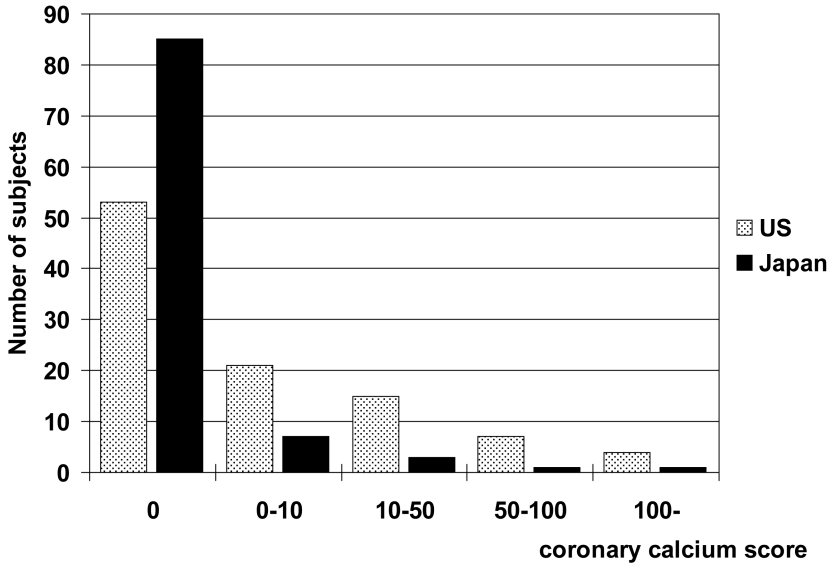

Figure.
Distribution of coronary calcium score (Agatston score) in the American men and Japanese men

Table 1

Comparison of major independent risk factors and other factors between the American and Japanese men

	US (n=100)	Japan (n=98)	p
Age (year)	44.6 ± 2.9	44.7 ± 2.8	0.74
BPsys (mmHg)	113.7 ± 9.6	122.6 ± 14.1	< 0.01
BPdia (mmHg)	78.4 ± 5.8	78.6 ± 10.4	0.99
TC (mmol/l)	4.99 ± 0.81	5.72 ± 0.90	< 0.01
TG (mmol/l)	1.31 (0.89, 1.89)	1.48 (1.02, 2.04)	0.17 *
HDL-C (mmol/l)	1.19 ± 0.30	1.42 ± 0.39	< 0.01
LDL-C (mmol/l)	3.10 ± 0.78	3.52 ± 1.01	0.01
Smoker (%)	15.0	48.0	< 0.01 **
Alcohol (%)	16.0	45.9	< 0.01 **
FBG (mmol/l)	5.29 ± 0.51	5.74 ± 0.49	< 0.01
Insulin (ρmol/l)	86.8 ± 45.8	56.9 ± 26.4	< 0.01
BMI (kg/m^2)	27.0 ± 3.3	23.3 ± 3.1	< 0.01
WC (cm)	96.4 ± 9.8	84.7 ± 8.5	< 0.01
Height (cm)	180.6 ± 6.6	170.2 ± 5.1	< 0.01
CRP (mg/l)	0.9 (0.45, 2.20)	0.43 (0.21, 0.88)	< 0.01 *
FIB (μmol/l)	7.09 ± 1.95	6.95 ± 1.85	0.81

BPsys: systolic blood pressure, BPdia: diastolic blood pressure, TC: total cholesterol, TG: triglycerides, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, Smoker: current smoker, Alcohol: drink alcohol everyday, FBG: fasting blood glucose, BMI: body mass index, WC: waist circumference, CRP: C reactive protein, FIB: fibrinogen

* Mann-Whitney test;

** Chi-Square test.

Table 2

Comparison of major independent risk factors and other factors between men who showed coronary calcium positive and negative in each of the American and Japanese men

	US			Japan		
CCS	**>0 (n=47)**	**0 (n=53)**		**>0 (n=13)**	**0 (n=85)**	
	Mean ± SD	**Mean ± SD**	**p**	**Mean ± SD**	**Mean ± SD**	**p**
Age (year)	45.1 ± 2.9	44.2 ± 2.8	0.09	45.2 ± 2.4	44.7 ± 2.9	0.42
BPsys (mmHg)	115.6 ± 10.3	112.0 ± 8.7	0.07	125.9 ± 18.8	122.1 ± 13.3	0.30
BPdia (mmHg)	79.3 ± 5.7	77.6 ± 5.9	0.14	81.6 ± 11.9	78.2 ± 10.1	0.26
TC (mmol/l)	4.98 ± 0.84	5.00 ± 0.80	0.90	6.01 ± 1.16	5.68 ± 0.94	0.13
TG (mmol/l)	1.34 (0.89 – 2.08)	1.29 (0.87 – 1.77)	0.42 *	1.75 (1.34 – 2.82)	1.45 (1.01 – 1.98)	0.20 *
HDL-C (mmol/l)	1.17 ± 0.27	1.21 ± 0.33	0.57	1.23 ± 0.26	1.44 ± 0.40	0.07
LDL-C (mmol/l)	3.09 ± 0.83	3.11 ± 0.74	0.88	3.88 ± 1.13	3.47 ± 0.98	0.16
Smoker (%)	17.0	13.2	0.59 **	76.9	43.5	0.03 **
Alcohol (%)	19.1	13.2	0.42 **	46.2	45.9	0.99 **
FBG (mmol/l)	5.43 ± 0.58	5.17 ± 0.39	<0.01	5.80 ± 0.45	5.73 ± 0.49	0.44
Insulin (ρmol/l)	89.3 ± 44.3	84.2 ± 47.1	0.58	64.2 ± 23.7	55.9 ± 27.1	0.28
BMI (kg/m^2)	27.9 ± 3.7	26.3 ± 2.7	0.02	24.2 ± 4.1	23.1 ± 2.9	0.12
WC (cm)	98.7 ± 11.1	94.4 ± 8.1	0.03	87.4 ± 10.7	84.3 ± 8.1	0.14
Height (cm)	180.5 ± 6.7	180.7 ± 6.6	0.85	170.6 ± 4.5	170.2 ± 5.2	0.81
CRP (mg/l)	1.04 (0.5 – 2.31)	0.75 (0.44 – 2.02)	0.53 *	1.02 (0.27 – 1.18)	0.41 (0.21 – 0.73)	0.09 *
FIB (μmol/l)	7.24 ± 2.18	6.96 ± 1.74	0.48	7.76 ± 2.07	6.82 ± 1.79	0.03

CCS: coronary calcium score, SD: standard deviation, BPsys: systolic blood pressure, BPdia: diastolic blood pressure, TC: total cholesterol, TG: triglycerides, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, Smoker: current smoker, Alcohol: drink alcohol everyday, FBG: fasting blood glucose, BMI: body mass index, WC: waist circumference, CRP: C reactive protein, FIB: fibrinogen

* Mann-Whitney test;

** Chi-Square test