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The mid-upper arm circumference is associated with an increased cardiometabolic risk in middle aged and elderly Chinese population

Running title: Upper body fat and cardiometabolic risk

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Abstract

Objectives: Upper body fat is suggested to be associated with increased cardiometabolic risk. We aimed to investigate the associations of mid-upper arm circumference (MUAC) with the cardiometabolic risk factors or biomarkers and subclinical atherosclerosis, which was indicated as elevated carotid intima media thickness (CIMT) in Chinese population.

Methods: A cross-sectional analysis was conducted in 6570 middle aged and elderly participants who were from a well-defined community in 2014, Shanghai, China. We assessed the association of MUAC with adiposity, blood glucose, lipids, insulin resistance and blood pressure levels, and as well as the CIMT. An average value of the both sides of the carotids greater than 0.8 mm was defined as subclinical atherosclerosis.

Results: MUAC was positively associated with body mass index (BMI), waist circumference, systolic blood pressure, insulin resistance index and CIMT; while inversely related to fasting plasma glucose. MUAC was also positively associated with risk of multi cardiometabolic disorders, such as central obesity, hypertension, hypertriglyceridemia and low HDL cholesterol. As compared to quartile one of MUAC, quartile 2 to 4 of MUAC was significantly associated with an increased risk of subclinical atherosclerosis (OR = 1.31, 95% CI [1.09-1.58], 1.33 [1.10-1.62], and 1.45 [1.16-1.80], respectively; $P_{for\ trend} = 0.005$), after adjustments for the confounding factors. Moreover, these associations were more prominent in women who are older, more obese and with insulin resistance, diabetes, and hypertension than that in men.

Conclusion: The MUAC was significantly and independently associated with an increased risk of cardiometabolic disorders and subclinical atherosclerosis in women.

Keywords: cardiometabolic risk, mid-upper arm circumference, subclinical atherosclerosis, upper body fat

Strengths and limitations of this study:

• The strength of the current study was evidenced by a well-defined community setting, fair sized sample volume, and desirable population homogeneity.

• We comprehensively determine the association of MUAC with a wide spectrum of cardiometabolic risk profile including subclinical atherosclerosis.

• Although our finding supported that it can be a reliable surrogate of upper body adiposity, MUAC is a measure comprised of both adipose and lean tissue rather than a direct indicator for adiposity

• As body composition changes over time, the narrow range of age for the participants enrolled could affected the outcome.

• Since our study was performed in a Chinese population, it should be cautiously to generalize the results to the other ethnicities.

Introduction

Cardiometabolic disease describes a spectrum of interconnected pathological alterations in the cardiovascular system and metabolic organs that symbiotically increase risk of cardiovascular disease (CVD).[1] Most of the common metabolic disorders, including obesity, diabetes, insulin resistance, dyslipidemia, and hypertension contribute to development of CVD that made CVD became a major cause of mortality and burden of healthcare expenditure worldwide, accounting for 17.3 million deaths per year.[2-5] Early identification and personalized prevention to curb CVD become a big challenge.

As a common contributor of CVD goes through a protracted subclinical phase, atherosclerosis could only be detected at an advanced stage of CVD.[6,7] Thus, identification of subclinical atherosclerosis in the asymptomatic period is critical for early prevention of CVD progression. Noninvasive ultrasonography measured carotid intima media thickness (CIMT) is a well-established clinical index for early arteriosclerosis detection and therefore has been extensively adopted around the world.[8]

Meanwhile, fat distribution, specifically upper body and visceral adiposity, is proven highly relevant with cardiovascular risk.[9,10] In addition to the conventional body fat indices such as body mass index (BMI) and waist circumference (WC), mid-upper arm circumference (MUAC), as a novel anthropometric measurement, was widely used for diagnosing malnutrition, adiposity and chronic diseases.[11] A cross-sectional study using data from the 1999 to 2006 National Health and Nutrition Examination Survey (NHANES) reported that MUAC was positively associated with insulin resistance in the non-obese subjects; while no significant association in obese ones.[9] Another follow up

study from the British National Diet and Nutrition Survey, which were included 1054 participants aged ≥ 65 years and followed up for more than 15 years, demonstrated that MUAC was significantly and inversely associated with risk of all-cause mortality.[12]

To our knowledge, few studies have been systematically and comprehensively evaluated the association of cardiovascular risk factors with MUAC in East Asian populations. Hence, our study aimed to explore the association of MUAC with a spectrum of cardiometabolic risk factors.

Methods

Study population

This is a population-based cross-sectional analysis based on one of the follow-up circle of our previous community-based cohort study.[13,14] The study participants were enrolled from Jiading district, Shanghai, China, from August 2014 to May 2015. A total of 6570 participants aged 40 years or above were invited and participated in this examination, which including a questionnaire to collect the lifestyle information, the disease history and medicine use, etc, anthropometry measurements, blood sampling and measurements to assess the early indicators of atherosclerosis. 283 individuals were excluded from the final analysis due to missing information on MUAC or CIMT. Thus, 6287 participants were finally included in our study. The study was approved by the Institutional Review Board of Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. All participants provided the written consents.

Data collection and biochemical measurements

Detailed information on sociodemographic characteristics, family history, medical history, physical activity and health-related lifestyle were obtained using a standard questionnaire by trained personnel. Anthropometric measurements such as height, weight, waist circumference, and MUAC were assessed by well-trained physician according to a standard protocol. Body height and weight were measured with participants wearing light clothes without shoes to the nearest 0.1 centimeter (cm) and 0.1 kilogram (kg). BMI was calculated as body weight in kilograms divided by body height squared in meters (kg/m^2). MUAC was measured on the upper left arm (halfway between the acromion process and the olecranon process) with subject's bilateral arms hanging down naturally.[15] WC was measured at the level of the umbilicus with the patient in the standing position. Systolic and diastolic blood pressures were measured in the non-dominant arm with an automated electronic sphygmomanometer (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China) three times (averaged for analysis) consecutively with 1 min intervals after at least 5 min rest in a seated position.

All individuals underwent a 75-glucose tolerance test (OGTT) after an overnight fasting (nothing by mouth after midnight), of whom fasting plasma glucose and OGTT 2-hour plasma glucose were measured using hexokinase method on a clinical chemistry diagnostic system (Beckman coulter AU5800). Serum concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol were measured by an autoanalyzer (Beckman coulter AU5800). High sensitive C-reactive protein concentration was determined by highly sensitive

competitive immunoassay (antigens and antibodies from Beckman coulter IMMAGE800). Serum insulin was measured by using the electrochemiluminescence methods on an Immunology analyzer (Roche cobas e 60, Roche Diagnostics, Switzerland). Insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting plasma glucose (mmol/L) / 22.5, and insulin resistance was defined as HOMA-IR ≥ 2.8, which is the cut-off point for the highest quartile of the total participants.

Definitions

Type 2 diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L or OGTT 2-hour plasma glucose ≥ 11.1 mmol/L or use of anti-diabetic agents.[16] Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or current taking an antihypertensive medication.[17] Central obesity was defined as WC ≥ 102 cm for men and ≥ 88 cm for women. Hypertriglyceridemia was defined as triglycerides ≥ 2.26 mmol/L; Low HDL cholesterol was defined as HDL-C < 1.04 mmol/L. Cardiometabolic disorders was defined as status with central obesity, diabetes, hypertension, hypertriglyceridemia, or low HDL cholesterol. Current smokers or drinkers were those who consumed any kinds of cigarettes or alcohol regularly in the past 6 months, respectively. Physical activity in term of MET hour/week was acquired and calculated according to the short form of the International Physical Activity Questionnaire (IPAQ) including both during leisure time and at work.[18]

CIMT measurement were conducted by a trained sonographer using a high-resolution

B-mode tomographic ultrasound system (Esaote Biomedica SpA, Genoa, Italy) with a linear 7.5 MHz transducer.[19] The position of CIMT measurement was recorded on the far wall of both right and left common carotid arteries, 1.5 cm proximal to the bifurcation. CIMT was measured on-line at the end of diastole as a distance from the leading edge of the first echogenic line to that of the second. These two lines represent the lumen-intima interface and collagen-contained upper layer of tunic adventitia, respectively. Individuals with a bilateral CIMT average greater than 0.8 mm was defined as subclinical atherosclerosis, which is the highest quartile of the total participants.

Statistical analyses

SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) was used for data management and statistical analysis. Continuous variables were described as means ± standard deviation (SD) or median (inter-quartile ranges), and categorical variables as numbers (percentages). HOMA-IR, TG, and C-reactive protein were normalized by logarithmic transformation before analysis because of skewed distribution.

All participants were divided into four groups according to quartiles of MUAC. The quartiles of MUAC were as follows: Q1 (15.5-27.1 cm), Q2 (27.2-29.1 cm), Q3 (29.2-31.2 cm) and Q4 (31.3-43.3 cm). Linear regression analysis was used to test for trend across the MUAC quartiles for continuous variables and the Cochran-Armitage trend chi-square test was used for categorical variables. Multivariate linear regression was conducted to study the association of MUAC with a wide spectrum of cardiometabolic

risk factors or biomarkers. There models were also created to evaluate the association of MUAC with risk of subclinical atherosclerosis in multivariate logistic regression analysis. Model 1, unadjusted. Model 2, adjusted for age, sex, BMI, current smoking, current drinking, physical activity, and WC. Model 3, further adjusted for C-reactive protein, total cholesterol, HDL-C, LDL-C, triglycerides, fasting plasma glucose, and systolic blood pressure. Stratified analysis by metabolic indictors such as age, BMI, waist circumference, diabetes, insulin resistance, and hypertension were then performed to verify those associations. *P* for interaction was tested by adding these metabolic indictors in the multivariate adjusted logistic regression models simultaneously.

Statistical significance was set to a two-sided P value of less than 0.05.

Patient and public involvement

The study was conducted without patient and public involvement. No patients were invited to take participate in the development of the research question and outcome measures, the study design and the interpretation of the results. The findings from this study will be disseminated to the participants after the results are published in a peer-reviewed journal.

Results

Characteristics of the study participants

The study sample consisted of 2310 (36.7%) men and 3977 (63.3%) women with an average age of 62.2 ± 8.78 years. Detailed sociodemographic and clinical characteristics

of the study participants according to MUAC quartiles were displayed in Table 1. As expected, BMI, WC, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HOMA-IR, LDL-C, triglycerides, C-reactive protein and CIMT were increased with MUAC quartiles as well as the prevalence of insulin resistance, hypertension, diabetes, and subclinical atherosclerosis (all *P* value < 0.05). However, age and HDL-C gradually decreased from the lowest quartile to the highest quartile (both *P* value < 0.0001) (Table 1). Physical activity and total cholesterol were not different among the quartile of MUAC.

Association of MUAC with cardiometabolic profiles.

Table 2 shows the linear regression analysis of association of MUAC with cardiometabolic profiles. MUAC was positively associated with BMI, WC, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HOMA-IR, LDL-C, triglycerides, C-reactive protein, CIMT (all *P* value < 0.01), except for total cholesterol (*P* value = 0.30). Whereas, age and HDL-C were negatively associated with MUAC (all *P* value < 0.01). After adjustment for age, sex, BMI, current smoking, current drinking, physical activity, the results did not change appreciably. Further adjusted for WC, MUAC was positively associated with systolic blood pressure, HOMA_IR and CIMT. The subgroup analysis showed similar results that MUAC was associated with HOMA_IR, C-reactive protein and CIMT in women after adjustment for multiple confounding factors (Supplementary Table 1), but not in men (Supplementary Table 2).

Association of MUAC with risk of the cardiometabolic disorders.

In the multivariable adjusted logistic regression model, we found that MUAC was positively and significantly associated with central obesity, diabetes, hypertension, hypertriglyceridemia and low HDL cholesterol, after adjustment for age, sex, BMI, current smoking, current drinking, physical activity (all *P* value < 0.001). And each one-SD increase in MUAC (3.13 cm) was associated with a 5%, 9%, 21%, and 26% increased risk in central obesity, diabetes, hypertension, and low HDL cholesterol, respectively. Further adjustment for WC, MUAC remained positively associated with these cardiometabolic disorders (all *P* value ≤ 0.03), except for diabetes and hypertriglyceridemia (both *P* value > 0.05). The analysis for the association of each 1-SD increase in MUAC with the metabolic disorders showed similar results. (Table 3). In addition, the association between MUAC and hypertension was more significantly in women, but not in men after adjustment for WC and other confounding (Table 3).

Association of MUAC with risk of subclinical atherosclerosis

In the total study samples, each SD or quartile specific increment in MUAC was significantly associated with an increased risk of subclinical atherosclerosis after adjustment for traditional confounding factors (model 2). Moreover, these associations were not prominently attenuated when further adjustment for C-reactive protein, serum lipids, fasting plasma glucose, and systolic blood pressure. Compared with the lowest quartile of MUAC, the second, third and highest quartiles were associated with a 31% (95% CI [1.09-1.58]), 33% (95% CI [1.10-1.62]) and 45% (95% CI [1.16-1.80])

increased risk of subclinical atherosclerosis, respectively, after adjustment for age, sex, BMI and other confounders ($P_{\text{for trend}}$= 0.005). Stratified analysis by sex revealed that MUAC was positively associated with subclinical atherosclerosis in women but not in men (women, OR=1.54, 95% CI [1.24-1.93] in the second quartile; 1.42 [1.11-1.83] in the third quartile; 1.66 [1.26-2.20] in the highest quartile, $P_{\text{for trend}}$ = 0.002, $P_{\text{for interaction}}$ = 0.20, Table 4).

Stratified analysis of the association of MUAC with subclinical atherosclerosis

We also examined the relationship between MUAC and subclinical atherosclerosis stratified by the traditional cardiometabolic risk factors. Among women, it was found that MUAC was significant and positive associated with subclinical atherosclerosis in participants with age ≥ 62 years, BMI ≥ 25 kg/m^2 or waist circumference < 88 cm (Figure 1A), and those women who with diabetes, insulin resistance, or hypertension (Figure 1B). Moreover, there existed significant interactions between diabetes and insulin resistance with MUAC on the risk of subclinical atherosclerosis, *P* for interaction=0.04 and 0.01, respectively. However, these relationships were disappeared when stratified analysis were performed in men (Supplementary Figure 1).

To further evaluate whether the association of MUAC with subclinical atherosclerosis was influenced by BMI and waist circumference, we conducted a similar multivariable logistic regression analysis in different BMI-WC categories. Among women, individuals were divided into 4 groups based on their BMI and WC (the BMI limits were set at < 25 kg/m^2 and ≥ 25 kg/m^2; the WC limits were set at < 88 cm and ≥

88 cm). We found that MUAC increased from the lower WC subgroups to the higher WC subgroups within each BMI subgroup. (Figure 2A). It was also found that MUAC was independently associated with subclinical atherosclerosis in subgroup of WC < 88 cm independent of BMI, after adjustment of age, BMI and other confounders (OR=1.22, 95% CI [1.05-1.43] in the subgroup of BMI < 25 kg/m^2 and 1.40 [1.11-1.77] in the subgroup of BMI ≥ 25 kg/m^2, respectively). However, no significant association were found when WC ≥ 88 cm (Figure 2B).

Discussion

In this cross-sectional investigation including 6287 community dwelling Chinese adults, we found that MUAC was significant associated with cardiometabolic disorders and subclinical atherosclerosis as well, which was assessed by elevated CIMT, after adjusted for the confounding factors. In sex-specific sub-analyses, the association between MUAC and subclinical atherosclerosis remained significant in women, not in men. The association was more prominent in those who were much older, obese, insulin resistant, and have diabetes and hypertension, the status that were more likely to have subclinical atherosclerosis.

MUAC was widely used for assessing obesity and malnutrition in children and adolescents;[20, 21] several previous studies highlighted its predictive value for endings of cardiovascular events in both Asian and Caucasian populations.[21] A retrospective observational study from the National Health and Nutrition Examination Survey III founding that MUAC is inversely associated with 28% lower in risk of all-cause

mortality in non-obese individuals, but not in obese individuals.[21] Another study using data from Health Effects of Arsenic Longitudinal Study (HEALS) reported that there was no relationship between MUAC and CIMT.[22] Our study indicated that MUAC increment is associated with an increased risk of cardiometabolic disorders and subclinical atherosclerosis as well.

Possible explanations for the positive association between MUAC and cardiometabolic risk are multifactorial, including change of body composition over time, accumulation of upper body subcutaneous adipose, sarcopenia obesity, and race. First, aging is a critical factor in changing process of metabolism and body composition. Substantial fat-free mass and muscle mass reduced as the age growing, while substantial visceral fat rather than subcutaneous fat increased with the growth of age, even under the condition of body weight unchanged. Individuals with age > 65 suffer a reduction rate over 25 percent per year for muscle mass; and this rate can be accelerated to 50 percent per year for those older than 80.[22-24] Our study indicated that MUAC levels tend to decrease with aging and there exists a stronger magnitude of association between MUAC and subclinical atherosclerosis in those aged ≥ 62 years in women. Second, upper body subcutaneous adipose tissue is not only a unique fat depot but also an active endocrine organ, which may confer additional risk for metabolic risk factors over generalized and central adiposity.[25] It can release free fatty acids and is more lipolytically active than lower body adipose tissue. Meanwhile, free fatty acids are directly related with hepatic very low-density lipoprotein production, insulin resistance and endothelial dysfunction, thus lead to cardiovascular and metabolic consequences.[26]

Third, sarcopenia obesity is also a critical factor. Sarcopenia obesity is a phenomenon that muscle mass is gradually decreased with age, even if body fat mass or body weight is unchanged or slightly increased. It continually occurred in the elderly as well as young or middle-aged adults with chronic disease.[27,28] It is widely held that sarcopenia obesity is a well-correlated risk factor for hypertension.[29] Subjects with this phenotype may be more inclined to develop metabolic and CVD than subjects with the opposite phenotype.[27-28] A study has shown that decreased muscle mass in lower extremity may result in atherosclerosis; while increased muscle mass through weight training may reduce the risk of atherosclerosis and CVD.[29] Furthermore, the decrease of muscle mass will not only result in reduction in muscle strength but also a strong impact on metabolism.[22] Finally, compared with Caucasians, the East Asians tend to have a higher percentage of body fat, a weaker willingness on body build, and less muscle mass as well as connective tissue.

MUAC was associated with subclinical atherosclerosis in a sex-specific manner. One plausible explanation for the sex difference in MUAC-subclinical atherosclerosis relationship is biological differences between men and women, such as hormones effect, immune system responses, muscle capacity and physical function. For instance, men tend to have greater muscle capacity and higher muscle mass than their women counterparts due to higher levels of testosterone.[21]

The strength of the current study was evidenced by a well-defined community setting, fair sized sample volume, and desirable population homogeneity. We comprehensively determine the association of MUAC with a wide spectrum of cardiometabolic risk

profile including subclinical atherosclerosis. However, we acknowledge the following limitations in our study. Firstly, the cross-sectional nature of present study means no causal inference can be drawn. Further prospective study is needed to investigate the efficacy of MUAC in predicting atherosclerosis and CVDs. Secondly, although our finding supported that it can be a reliable surrogate of upper body adiposity, MUAC is a measure comprised of both adipose and lean tissue rather than a direct indicator for adiposity. Thirdly, as body composition changes over time, the narrow range of age for the participants enrolled could affected the outcome. Lastly, since our study was performed in a Chinese population, it should be cautiously to generalize the results to the other ethnicities.

In conclusion, our study provides evidence of a positive association of MUAC with cardiometabolic risk and subclinical atherosclerosis. Given the accelerating rise rate of atherosclerosis in China, MUAC might act as a valuable indicator for early prevention of CVD.

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Footnotes

Contributors: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TW, MX, YB and WW. Acquisition of data: YH, XJ, LX, WZ, CD, LW, ZZ, ML, JL, YX, and YC. Analysis and interpretation of data: YH, TW, MX, YB and WW. Drafting of the manuscript: YH. Critical revision of the manuscript: TW, MX, YB and WW. Statistical analysis: YH and XJ.

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Figure legends

Figure 1. Stratified analysis of the association of mid-upper arm circumference with risk of subclinical atherosclerosis in women. A: All subjects were divided into subgroups based on their average age (age < 62 years, age ≥ 62 years), body mass index (BMI < 25 kg/m^2, BMI ≥ 25 kg/m^2), or waist circumference (WC < 88 cm or WC ≥ 88 cm). B: All subjects were divided into subgroups based on diabetes (yes or no), insulin resistance (yes or no), or hypertension (yes or no). Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Figure 2. A: MUAC in the BMI and WC subgroups in women. B: Association of MUAC with risk of subclinical atherosclerosis in the BMI and WC subgroups in women. MUAC: mid-upper arm circumference, BMI: body mass index, WC: waist circumference. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Table 1. Characteristics of study participants according to quartiles of mid-upper arm circumference in total samples

	Mid-upper arm circumference, cm				
	Quartile 1 (15.5-27.1)	Quartile 2 (27.2-29.1)	Quartile 3 (29.2-31.2)	Quartile 4 (31.3-43.3)	*P* for trend
n	1510	1570	1582	1625	
Age (years)	63.4 (9.2)	62.2 (8.8)	61.7 (8.6)	61.6 (8.4)	< 0.0001
Female, n (%)	1110 (27.9)	1048 (26.4)	922 (23.2)	897 (22.6)	
Body mass index (kg/m^2)	22.3 (2.8)	24.2 (3.8)	25.5 (3.2)	27.9 (7.5)	< 0.0001
Waist circumference (cm)	75.6 (8.5)	81.4 (7.9)	85.5 (8.3)	91.6 (9.2)	< 0.0001
Systolic blood pressure (mmHg)	132.6 (18.0)	133.4 (17.3)	136.0 (17.2)	137.0 (16.4)	< 0.0001
Diastolic blood pressure (mmHg)	74.2 (9.5)	75.7 (9.3)	77.2 (9.2)	78.0 (9.8)	< 0.0001
Current smoking, n (%)	196 (13.0)	279 (17.8)	346 (21.9)	393 (24.2)	< 0.0001
Current drinking, n (%)	151 (10)	195 (12.4)	256 (16.2)	290 (17.9)	< 0.0001
Physical activity (MET-h/wk)	21.0 (6.0-21.0)	15.3 (3.0-21.0)	15.0 (3.0-21.0)	15.0 (3.0-21.0)	0.30
Fasting plasma glucose (mmol/L)	5.99 (1.36)	6.06 (1.34)	6.21 (1.57)	6.28 (1.61)	< 0.0001
HOMA-IR	1.42 (0.99-2.15)	1.75 (1.20-2.57)	1.95 (1.35-2.86)	2.43 (1.69-3.55)	< 0.0001
Total cholesterol (mmol/L)	5.28 (0.95)	5.31 (0.98)	5.26 (1.04)	5.24 (1.08)	0.20
LDL-C (mmol/L)	3.56 (0.75)	3.62 (0.77)	3.62 (0.83)	3.63 (0.81)	0.02
HDL-C (mmol/L)	1.42 (0.33)	1.35 (0.29)	1.31 (0.29)	1.27 (0.27)	< 0.0001
Triglycerides (mmol/L)	1.33 (0.98-1.84)	1.49 (1.07-2.12)	1.58 (1.12-2.25)	1.66 (1.19-2.30)	< 0.0001
C-reactive protein (mg/L)	0.19 (0.14-0.28)	0.21 (0.16-0.31)	0.23(0.17-0.35)	0.25(0.18-0.39)	< 0.0001
CIMT (mm)	0.69 (0.16)	0.70 (0.15)	0.70 (0.14)	0.72 (0.14)	< 0.0001
Insulin resistance, n (%)	203 (13.5)	313 (20.0)	410 (26.0)	655 (40.5)	< 0.0001

Hypertension, n (%)	747 (49.5)	862 (52.7)	978 (61.9)	1108 (68.3)	< 0.0001
Diabetes, n (%)	368 (24.7)	403 (25.9)	457 (29.2)	533 (33.2)	< 0.0001
Subclinical atherosclerosis, n (%)	472 (31.3)	541 (34.5)	555 (35.1)	590 (36.3)	0.0035

Data are presented as means ± standard deviation (SD), or medians (inter-quartile ranges) for skewed variables, or number (proportions) for categorical variables.

P values were calculated from one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables.

Subclinical atherosclerosis was defined as CIMT ≥ 0.8 mm, which is the cut-off point for the highest quartile of the total participants.

Insulin resistance was defined as HOMA-IR ≥ 2.8, which is the cut-off point for the highest quartile of the total participants.

Abbreviations: MET, metabolic equivalent task; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CIMT, carotid intima-media thickness; HOMA-IR indicates homeostasis model assessment of insulin resistance.

Table 2. The association of mid-upper arm circumference with cardiometabolic profiles in total samples

	Model 1		Model 2		Model 3	
	β ± SE	P value	β ± SE	P value	β ± SE	*P* value
Age (years)	-0.20 ± 0.04	<0.0001	/	/	/	/
Body mass index (kg/m^2)	0.70 ± 0.02	<0.0001	/	/	/	/
Waist circumference (cm)	1.94 ± 0.03	<0.0001	1.62 ± 0.04	<0.0001	/	/
Systolic blood pressure (mmHg)	0.55 ± 0.07	<0.0001	0.49 ± 0.09	<0.0001	0.20 ± 0.10	0.04
Diastolic blood pressure (mmHg)	0.49 ± 0.04	<0.0001	0.32 ± 0.05	<0.0001	0.08 ± 0.06	0.15
Fasting plasma glucose (mmol/L)	0.03 ± 0.01	<0.0001	0.02 ± 0.01	0.01	-0.02 ± 0.01	0.04
HOMA-IR	0.03 ± 0.001	<0.0001	0.02 ± 0.001	<0.0001	0.01 ± 0.002	0.0003
Total cholesterol (mmol/L)	-0.004 ± 0.004	0.30	0.004 ± 0.005	0.48	-0.01 ± 0.01	0.24
LDL-C (mmol/L)	0.009 ± 0.003	0.005	0.01 ± 0.004	0.001	0.001 ± 0.005	0.79
HDL-C (mmol/L)	-0.02 ± 0.001	<0.0001	-0.01± 0.001	<0.0001	-0.003 ± 0.002	0.08
Triglycerides (mmol/L)	0.01 ± 0.001	<0.0001	0.01 ± 0.001	<0.0001	0.001 ± 0.001	0.38
C-reactive protein (mg/L)	0.01 ± 0.001	<0.0001	0.01 ± 0.001	<0.0001	0.002 ± 0.002	0.12
CIMT (cm)	0.003 ± 0.001	<0.0001	0.003 ± 0.001	0.0002	0.002 ± 0.001	0.005

Data are linear regression estimates ± standard error (β ± SE).

P values were calculated from multivariable linear regression model.

Model 1: unadjusted;

Model 2: adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk);

Model 3: further adjusted for waist circumference (cm).

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CIMT, carotid intima-media thickness.

Table 3. Logistic regression analysis of risk of cardiometabolic disorders in relation to mid-upper arm circumference in total and sex-specific samples

		OR (95% CI)					P for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	1-SD (3.13 cm)	
Total cohort							
Central obesity	Model 1	1.00	1.43 (0.99-2.05)	3.44 (2.45-4.82)	7.25 (5.12-10.3)	2.05 (1.85-2.28)	< 0.0001
	Model 2	1.00	1.43 (0.99-2.05)	3.44 (2.45-4.82)	7.25 (5.12-10.3)	2.05 (1.85-2.28)	< 0.0001
Diabetes	Model 1	1.00	1.00 (0.82-1.21)	1.13 (0.93-1.37)	1.26 (1.02-1.55)	1.09 (1.02-1.16)	0.02
	Model 2	1.00	0.87 (0.73-1.06)	0.89 (0.73-1.10)	0.87 (0.70-1.09)	0.96 (0.90-1.04)	0.33
Hypertension	Model 1	1.00	1.04 (0.87-1.24)	1.57 (1.30-1.89)	1.65 (1.34-2.04)	1.21 (1.14-1.30)	< 0.0001
	Model 2	1.00	0.92 (0.77-1.10)	1.29 (1.06-1.56)	1.23 (0.98-1.53)	1.10 (1.03-1.19)	0.006
Hypertriglyceridemia	Model 1	1.00	1.55 (1.25-1.92)	1.78 (1.43-2.21)	1.92 (1.53-2.41)	1.24 (1.15-1.35)	< 0.0001
	Model 2	1.00	1.31 (1.05-1.63)	1.32 (1.05-1.66)	1.19 (0.93-1.54)	1.03 (0.94-1.13)	0.28
Low HDL cholesterol	Model 1	1.00	1.40 (1.06-1.84)	1.80 (1.38-2.35)	2.06 (1.57-2.69)	1.26 (1.16-1.37)	< 0.0001
	Model 2	1.00	1.21 (0.91-1.60)	1.41 (1.06-1.86)	1.38 (1.02-1.88)	1.10 (1.01-1.22)	0.03
Women							
Central obesity	Model 1	1.00	1.49 (1.04-2.15)	3.54 (2.50-4.99)	7.10 (4.97-10.2)	2.01 (1.81-2.25)	< 0.0001
	Model 2	1.00	1.49 (1.04-2.15)	3.54 (2.50-4.99)	7.10 (4.97-10.2)	2.01 (1.81-2.25)	< 0.0001
Diabetes	Model 1	1.00	1.11 (0.89-1.41)	1.29 (1.01-1.65)	1.39 (1.07-1.80)	1.12 (1.03-1.22)	0.007
	Model 2	1.00	0.98 (0.77-1.24)	1.03 (0.80-1.32)	0.97 (0.73-1.29)	0.99 (0.91-1.09)	0.93
Hypertension	Model 1	1.00	1.10 (0.89-1.35)	1.93 (1.54-2.44)	1.80 (1.39-2.33)	1.27 (1.17-1.38)	< 0.0001
	Model 2	1.00	0.96 (0.78-1.18)	1.55 (1.23-1.97)	1.29 (0.98-1.68)	1.14 (1.05-1.24)	0.003

Hypertriglyceridemia	Model 1	1.00	1.63 (1.28-2.01)	1.89 (1.48-2.42)	1.84 (1.42-2.38)	1.25 (1.15-1.37)	< 0.0001
	Model 2	1.00	1.38 (1.08-1.78)	1.43 (1.09-1.86)	1.17 (0.87-1.58)	1.05 (0.94-1.17)	0.33
Low HDL cholesterol	Model 1	1.00	1.67 (1.17-2.38)	1.94 (1.36-2.77)	1.87 (1.29-2.71)	1.21 (1.09-1.35)	0.0007
	Model 2	1.00	1.47 (1.03-2.21)	1.56 (1.07-2.28)	1.32 (0.86-2.01)	1.08 (0.91-1.23)	0.23
Men							
Central obesity	Model 1	1.00	0.38 (0.02-6.61)	3.99 (0.49-32.0)	10.4 (1.33-81.2)	3.08 (1.92-4.95)	< 0.0001
	Model 2	1.00	0.38 (0.02-6.61)	3.99 (0.49-32.0)	10.4 (1.33-81.2)	3.08 (1.92-4.95)	< 0.0001
Diabetes	Model 1	1.00	0.79 (0.56-1.10)	0.85 (0.61-1.18)	0.97 (0.68-1.38)	1.01 (0.90-1.13)	0.84
	Model 2	1.00	0.69 (0.49-0.98)	0.68 (0.48-0.97)	0.69 (0.47-1.01)	0.91 (0.81-1.03)	0.12
Hypertension	Model 1	1.00	0.92 (0.66-1.29)	1.06 (0.76-1.48)	1.29 (0.89-1.88)	1.10 (0.98-1.24)	0.10
	Model 2	1.00	0.84 (0.60-1.17)	0.91 (0.65-1.28)	1.03 (0.70-1.52)	1.03 (0.91-1.16)	0.68
Hypertriglyceridemia	Model 1	1.00	1.37 (0.85-2.21)	1.46 (0.92-2.31)	1.66 (1.03-2.67)	1.13 (0.96-1.32)	0.04
	Model 2	1.00	1.19 (0.73-1.92)	1.15 (0.72-1.84)	1.13 (0.68-1.87)	0.97 (0.81-1.52)	0.81
Low HDL cholesterol	Model 1	1.00	1.01 (0.65-1.58)	1.42 (0.94-2.16)	1.62 (1.04-2.51)	1.21 (1.06-1.38)	0.006
	Model 2	1.00	0.92 (0.59-1.44)	1.22 (0.79-1.86)	1.27 (0.80-2.01)	1.12 (0.97-1.29)	0.13

Data were presented as odds ratio (OR) and 95% confidence interval (CI).

P values were calculated from multivariable logistic regression analysis in quartile of mid-upper arm circumference.

Model 1: adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk);

Model 2: further adjusted for waist circumference (cm), except for central obesity.

Table 4. The association of mid-upper arm circumference with subclinical atherosclerosis in total and sex-specific samples

	OR (95% CI)					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	1-SD (3.13 cm)	*P* for trend
Total cohort						0.20*
Cases/Participants	472 / 1510	541 / 1570	555 / 1582	590 / 1625	2158 / 6287	
Model 1	1.00	1.16 (1.00-1.34)	1.19 (1.02-1.38)	1.25 (1.08-1.45)	1.06 (1.01-1.12)	0.004
Model 2	1.00	1.30 (1.08-1.56)	1.30 (1.07-1.58)	1.35 (1.09-1.67)	1.06 (0.98-1.15)	0.013
Model 3	1.00	1.31 (1.09-1.58)	1.33 (1.10-1.62)	1.45 (1.16-1.80)	1.08 (0.99-1.17)	0.005
Women						
Case/participants	287 / 1110	327 / 1048	275 / 922	282 / 897	1171 / 3977	
Model 1	1.00	1.30 (1.08-1.57)	1.22 (1.00-1.48)	1.32 (1.09-1.60)	1.07 (1.00-1.14)	0.014
Model 2	1.00	1.54 (1.24-1.93)	1.43 (1.18-1.82)	1.53 (1.17-2.02)	1.11 (1.01-1.23)	0.007
Model 3	1.00	1.54 (1.24-1.93)	1.42 (1.11-1.83)	1.66 (1.26-2.20)	1.14 (1.03-1.26)	0.002
Men						
Case/participants	185 / 400	214 / 522	280 / 660	308 / 728	987 / 2310	
Model 1	1.00	0.81 (0.62-1.05)	0.86 (0.67-1.10)	0.85 (0.67-1.09)	0.93 (0.85-1.02)	0.39
Model 2	1.00	0.89 (0.64-1.23)	1.04 (0.75-1.44)	1.00 (0.70-1.45)	0.97 (0.85-1.11)	0.71
Model 3	1.00	0.90 (0.65-1.25)	1.06 (0.76-1.48)	1.05 (0.72-1.52)	0.99 (0.86-1.06)	0.54

Data were presented as odds ratio (OR) and 95% confidence interval (CI).

P values were calculated from multivariable logistic regression analysis.

*: the interaction of MUAC with sex on subclinical atherosclerosis.

Model 1, unadjusted;

Model 2, adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm);

Model 3, further adjusted for C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

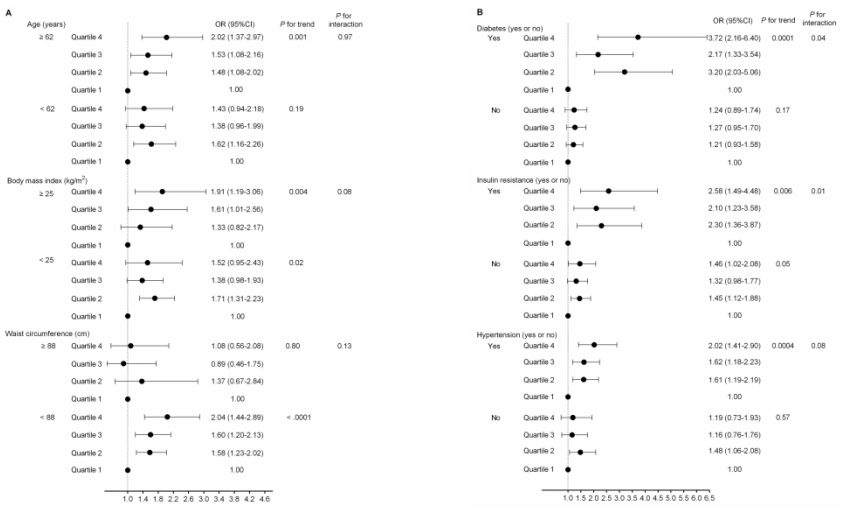


Figure 1

338x190mm (300 x 300 DPI)

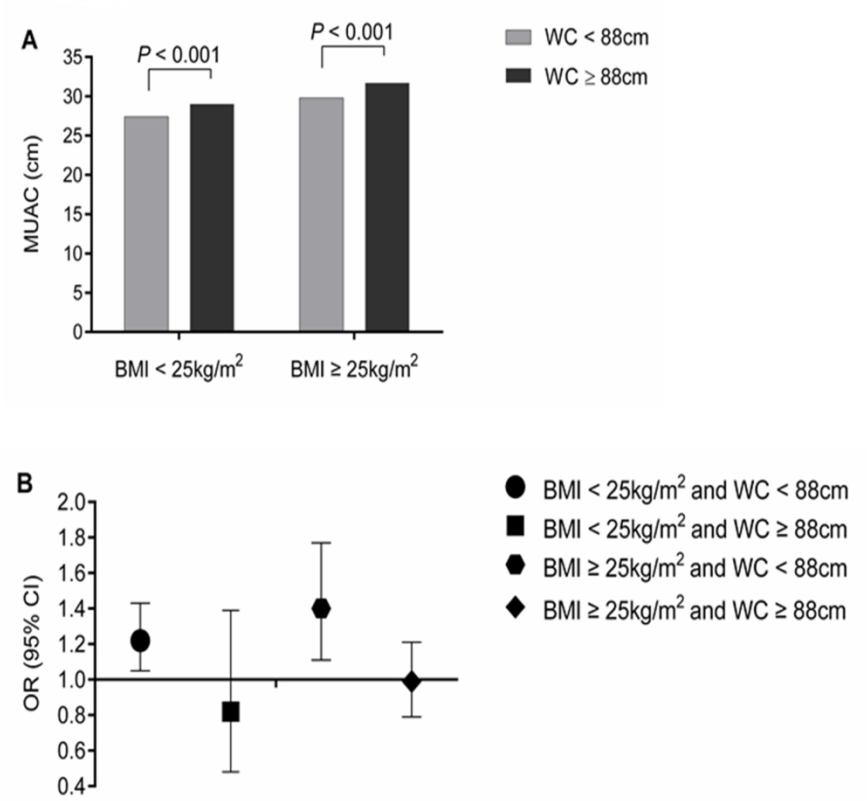


Figure 2

199x176mm (300 x 300 DPI)

Supplemental Information

The mid-upper arm circumference is associated with an increased cardiometabolic risk in middle aged and elderly Chinese population

Supplemental Table 1. The association of mid-upper arm circumference with cardiometabolic profiles in women

Supplemental Table 2. The association of mid-upper arm circumference with cardiometabolic profiles in men

Supplemental Figure Legend

Supplemental Figure 1. Stratified analysis of the association of mid-upper arm circumference with risk of subclinical atherosclerosis in men. A: All subjects were divided into subgroups based on their average age (age < 62 years, age ≥ 62 years), body mass index (BMI < 25 kg/m^2, BMI ≥ 25 kg/m^2), or waist circumference (WC < 88 cm or WC ≥ 88 cm). B: All subjects were divided into subgroups based on diabetes (yes or no), insulin resistance (yes or no), or hypertension (yes or no). Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Supplemental Table 1. The association of mid-upper arm circumference with cardiometabolic profiles in women

	Model 1		Model 2		Model 3	
	β ± SE	*P* value	β ± SE	*P* value	β ± SE	*P* value
Age (years)	-0.10 ± 0.04	0.01	/	/	/	/
Body mass index (kg/m^2)	0.76 ± 0.03	<0.0001	/	/	/	/
Waist circumference (cm)	1.89 ± 0.04	<0.0001	1.71 ± 0.05	<0.0001	/	/
Systolic blood pressure (mmHg)	0.59 ± 0.09	<0.0001	0.54 ± 0.10	<0.0001	0.24 ± 0.12	0.06
Diastolic blood pressure (mmHg)	0.41 ± 0.05	<0.0001	0.33 ± 0.06	<0.0001	0.10 ± 0.07	0.16
Fasting plasma glucose (mmol/L)	0.03 ± 0.007	<0.0001	0.02 ± 0.008	0.003	-0.01 ± 0.01	0.21
HOMA-IR	0.03 ± 0.001	<0.0001	0.02 ± 0.002	<0.0001	0.01 ± 0.002	0.0001
Total cholesterol (mmol/L)	0.01 ± 0.005	0.06	0.01 ± 0.01	0.40	-0.003 ± 0.01	0.64
LDL-C (mmol/L)	0.02 ± 0.004	<0.0001	0.01 ± 0.005	0.006	0.004 ± 0.006	0.49
HDL-C (mmol/L)	-0.01 ± 0.001	<0.0001	-0.01 ± 0.002	<0.0001	-0.002 ± 0.002	0.48

Triglycerides (mmol/L)	0.01 ± 0.001	<0.0001	0.01 ± 0.001	<0.0001	0.001 ± 0.002	0.71
C-reactive protein (mg/L)	0.02 ± 0.001	<0.0001	0.02 ± 0.002	<0.0001	0.006 ± 0.002	0.002
CIMT (cm)	0.003 ± 0.001	<0.0001	0.003 ± 0.001	<0.0001	0.003 ± 0.001	0.0007

Data are linear regression estimates ± standard error (β ± SE). *P* values were calculated from multivariable linear regression model.

Model 1: unadjusted;

Model 2: adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk);

Model 3: further adjusted for waist circumference (cm).

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CIMT, carotid intima-media thickness.

Supplemental Table 2. The association of mid-upper arm circumference with cardiometabolic profiles in men

	Model 1		Model 2		Model 3	
	β ± SE	*P* value	β ± SE	*P* value	β ± SE	*P* value
Age (years)	-0.47 ± 0.06	<0.0001	/	/	/	/
Body mass index (kg/m^2)	0.61 ± 0.02	<0.0001	/	/	/	/
Waist circumference (cm)	1.84 ± 0.06	<0.0001	1.15 ± 0.07	<0.0001	/	/
Systolic blood pressure (mmHg)	0.57 ± 0.12	<0.0001	0.21 ± 0.16	0.18	0.06 ± 0.17	0.73
Diastolic blood pressure (mmHg)	0.51 ± 0.07	<0.0001	0.16 ± 0.09	0.07	0.03 ± 0.10	0.78
Fasting plasma glucose (mmol/L)	0.02 ± 0.01	0.06	0.004 ± 0.02	0.83	-0.03 ± 0.02	0.11
HOMA-IR	0.03 ± 0.002	<0.0001	0.01 ± 0.003	<0.0001	0.002 ± 0.003	0.57
Total cholesterol (mmol/L)	0.003 ± 0.006	0.57	-0.004 ± 0.01	0.65	-0.01 ± 0.01	0.15
LDL-C (mmol/L)	0.02 ± 0.005	0.0007	0.006 ± 0.007	0.40	-0.004 ± 0.008	0.55
HDL-C (mmol/L)	-0.02 ± 0.002	<0.0001	-0.01 ± 0.003	<0.0001	-0.005 ± 0.003	0.08

Triglycerides (mmol/L)	0.01 ± 0.002	<0.0001	0.005 ± 0.002	0.01	0.001 ± 0.002	0.75
C-reactive protein (mg/L)	0.01 ± 0.002	0.0002	0.003 ± 0.003	0.31	-0.005 ± 0.003	0.09
CIMT (cm)	-0.001 ± 0.001	0.33	0.001 ± 0.002	0.48	0.001 ± 0.002	0.69

Data are linear regression estimates ± standard error (β ± SE). *P* values were calculated from multivariable linear regression model.

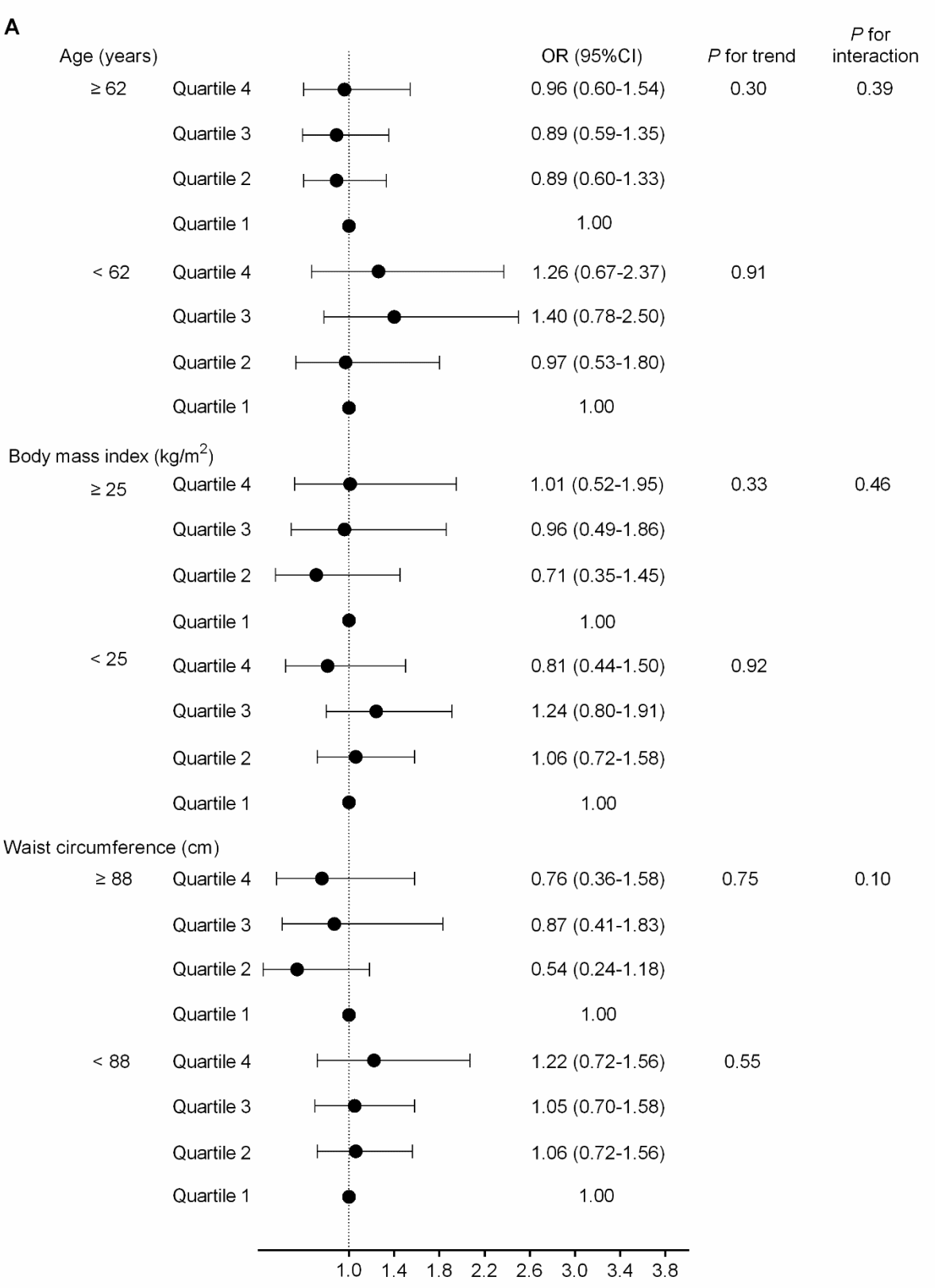
Model 1: unadjusted;

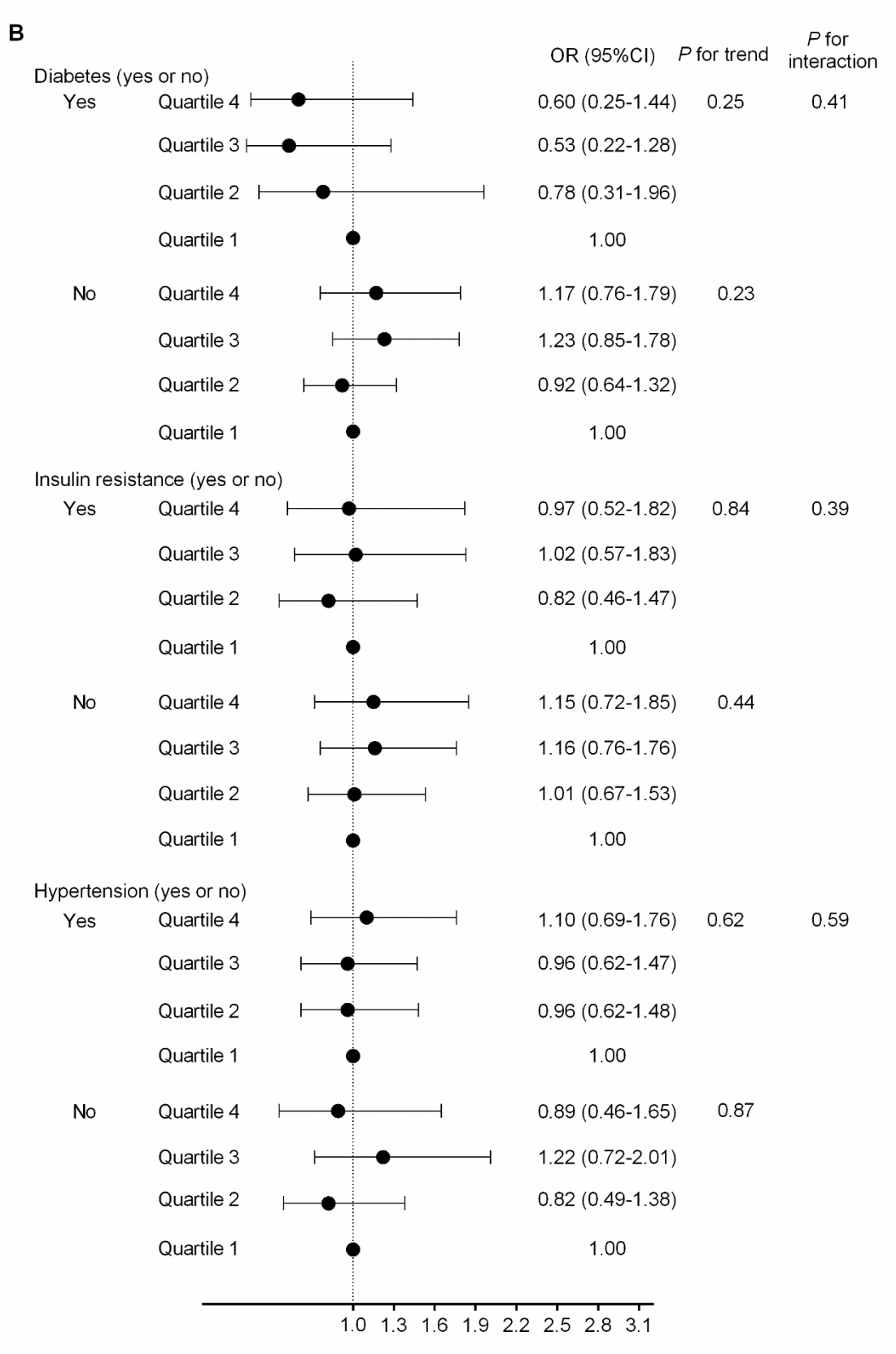
Model 2: adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk);

Model 3: further adjusted for waist circumference (cm).

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CIMT, carotid intima-media thickness.

Supplemental Figure 1




B
OR (95%CI)
P for trend
P for interaction
Diabetes (yes or no)
Yes
Quartile 4
0.60 (0.25-1.44)
0.25
0.41
Quartile 3
0.53 (0.22-1.28)
Quartile 2
0.78 (0.31-1.96)
Quartile 1
1.00
No
Quartile 4
1.17 (0.76-1.79)
0.23
Quartile 3
1.23 (0.85-1.78)
Quartile 2
0.92 (0.64-1.32)
Quartile 1
1.00
Insulin resistance (yes or no)
Yes
Quartile 4
0.97 (0.52-1.82)
0.84
0.39
Quartile 3
1.02 (0.57-1.83)
Quartile 2
0.82 (0.46-1.47)
Quartile 1
1.00
No
Quartile 4
1.15 (0.72-1.85)
0.44
Quartile 3
1.16 (0.76-1.76)
Quartile 2
1.01 (0.67-1.53)
Quartile 1
1.00
Hypertension (yes or no)
Yes
Quartile 4
1.10 (0.69-1.76)
0.62
0.59
Quartile 3
0.96 (0.62-1.47)
Quartile 2
0.96 (0.62-1.48)
Quartile 1
1.00
No
Quartile 4
0.89 (0.46-1.65)
0.87
Quartile 3
1.22 (0.72-2.01)
Quartile 2
0.82 (0.49-1.38)
Quartile 1
1.00
1.0 1.3 1.6 1.9 2.2 2.5 2.8 3.1

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Association between mid-upper arm circumference and cardiometabolic risk in Chinese population: a cross-sectional study

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Association between mid-upper arm circumference and cardiometabolic risk in Chinese population: a cross-sectional study

Running title: Upper body fat and cardiometabolic risk

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Abstract

Objectives: Upper body fat has been associated with an unfavorable cardiometabolic risk. We aimed to investigate the associations between mid-upper arm circumference (MUAC), a novel indicator of upper body fat, and a wide spectrum of cardiometabolic risk profiles in Chinese population.

Design and setting: Cross-sectional analyses were performed using data from a well-defined community in 2014, Shanghai, China.

Participants: The study population consisted of 6287 participants with complete measurement data (men n=2310, women n=3977).

Outcome measures: Multivariable logistic regression model was used to explore the associations of MUAC with cardiometabolic disorders including central obesity, diabetes, hypertension, hypertriglyceridemia, low HDL cholesterol and subclinical atherosclerosis.

Results: In overall participants, each 1-SD increment in MUAC (3.13 cm) was positively associated with central obesity (OR, 2.05; 95% CI, 1.85-2.28), hypertension (OR, 1.10; 95% CI, 1.03-1.19), and low HDL cholesterol (OR, 1.10; 95% CI, 1.01-1.22), after multivariable adjustment. Multivariable-adjusted ORs for subclinical atherosclerosis was gradually increased across increasing quartiles of MUAC with the lowest quartile as reference (quartile 2: OR, 1.31; 95% CI, 1.09-1.58; quartile 3: 1.33; 1.10-1.62; quartile 4: 1.45; 1.16-1.80, $P_{for\ trend}$ = 0.005) among total participants, and such association was more prominent among women than men. Additionally, MUAC was significantly interacted with diabetes and insulin resistance on subclinical atherosclerosis ($P_{\text{for interaction}}$ = 0.04 and 0.01, respectively).

Conclusion: A greater MUAC was positively associated with several cardiometabolic disorders and subclinical atherosclerosis in Chinese population, and such association patterns were more significant among women.

Keywords: Cardiometabolic risk, mid-upper arm circumference, subclinical atherosclerosis, upper body fat, Chinese adults

Strengths and limitations of this study:

- The strength of the current study was evidenced by a well-defined community setting, fair sized sample volume, and desirable population homogeneity.
- The comprehensive examination of the associations between MUAC and a wide spectrum of cardiometabolic risk profiles including central obesity, diabetes, hypertension, hypertriglyceridemia, low HDL cholesterol and subclinical atherosclerosis.
- Although our findings support that MUAC could be a reliable surrogate of upper body adiposity, MUAC is a measure which comprised both adipose and lean tissue rather than a direct indicator for adiposity.
- As body composition changes over time, the narrow range of age for the participants enrolled could affect the outcome.
- Since our study was performed in a Chinese population, it should be cautiously to generalize the results to the other ethnicities.

Introduction

Cardiometabolic disorders describe a spectrum of interconnected pathological alterations in the cardiovascular system and metabolic organs that symbiotically increase the risk of cardiovascular disease (CVD), which is a major cause of mortality and burden of healthcare expenditure worldwide.[1-5] Several important cardiometabolic disorders, including obesity, diabetes, insulin resistance, dyslipidemia, and hypertension, are major risk factors for CVD and could be served as early targets for early identification and personalized prevention for CVD.[2-5] In addition, as a common contributor of CVD, atherosclerosis goes through a protracted subclinical phase and could only be detected at an advanced stage of CVD.[6,7] Thus, the identification of subclinical atherosclerosis in the asymptomatic period is also critical for prevention of CVD progression. Noninvasive ultrasonography measured carotid intima media thickness (CIMT) is a well-established clinical index for early arteriosclerosis detection and therefore has been extensively adopted to measure subclinical atherosclerosis.[8]

Meanwhile, fat distribution, specifically upper body and visceral adiposity, is proven highly relevant to cardiovascular risk.[9,10] In addition to the conventional body fat indices such as body mass index (BMI) and waist circumference (WC), mid-upper arm circumference (MUAC), as a novel anthropometric measurement, has been widely used for screening of malnutrition, adiposity and chronic diseases.[11] Several epidemiological studies have revealed inconsistent results on the relationship between MUAC and cardiometabolic risk. A cross-sectional study using data from the 1999 to 2006 National Health and Nutrition Examination Survey (NHANES) reported that MUAC was positively associated with insulin resistance in non-obese individuals; while no significant association was found in obese individuals.[9] In a prospective cohort of 1061 European elderly participants with a follow-up of approximately 6 years, a larger

MUAC was associated with elevated risks of all-cause and cardiovascular diseases mortality.[12] In contrast, in the Canada Fitness Survey of 10638 adults, a larger MUAC was independently associated with a lower risk of all-cause mortality.[13] And such inverse association between a larger MUAC and a lower risk of mortality was also documented in the British National Diet and Nutrition Survey of 1054 participants with more than 15 years of followed up.[14]

Most of these previous studies were conducted in European population; so far, comprehensive data on the associations between MUAC and cardiovascular risk profiles in Chinese population are limited. Chinese population tend to have a higher percentage of body fat, a weaker willingness on body build, and less muscle mass as well as connective tissue,[15] as compared with their European counterparts. And these different features may translate into varying susceptibilities to adiposity related cardiometabolic disorders. Therefore, this study aimed to investigate the association between MUAC and cardiometabolic disorders as well as subclinical atherosclerosis in Chinese population.

Methods

Study population

This is a cross-sectional analysis based on one of the follow-up circles of our established community-based cohort.[16,17] Eligible participants aged 40 years or above were identified from the local residence registration records. There was no restriction on ethnicity or gender. Each eligible participant was recruited by trained community staff and local health workers using a door-to-door invitation method. Participants who consented for the study and signed informed consent were scheduled for health examinations. In brief, a total of 6570 participants aged 40 years or above were enrolled

from Jiading district, Shanghai, China, from August 2014 to May 2015. All participants received anthropometric measurements (including height, weight, WC, and MUAC), a standard 75-g oral glucose tolerance test (OGTT), and a standard questionnaire to acquire information regarding lifestyle factors (including smoking and alcohol drinking habits, and physical activity), education, social demographic information, and history of diseases and medicines. Blood samples were collected for biochemical measurements. In the present study, 283 participants were excluded due to missing data on MUAC or CIMT. Thus, a total of 6287 participants were included in the final analysis. This study was approved by the Institutional Review Board of Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from all study participants.

Data collection and biochemical measurements

Detailed information on sociodemographic characteristics, family history, medical history, physical activity and health-related lifestyle were obtained using a standard questionnaire by trained personnel. Current smokers or drinkers were those who consumed any kinds of cigarettes or alcohol regularly in the past 6 months, respectively. Physical activity in term of MET hour/week was calculated according to the short form of the International Physical Activity Questionnaire (IPAQ) including both during leisure time and at work.[18]

Anthropometric measurements such as height, weight, WC, and MUAC were assessed by well-trained physician according to a standard protocol. Body height and weight were measured with participants wearing light clothes without shoes to the nearest 0.1 centimeter (cm) and 0.1 kilogram (kg), respectively. BMI was calculated as body weight in kilograms divided by body height squared in meters (kg/m^2). MUAC

was measured on the upper left arm (halfway between the acromion process and the olecranon process) with subject's bilateral arms hanging down naturally.[19] WC was measured at the level of the umbilicus with the participants in the standing position. Systolic and diastolic blood pressures were measured in the non-dominant arm with an automated electronic sphygmomanometer (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China) three times (averaged for analysis) consecutively with 1 min intervals after at least 5 min rest in a seated position.

All participants underwent a 75-glucose tolerance test (OGTT) after an overnight fasting (nothing by mouth after midnight), of whom fasting plasma glucose and OGTT 2-hour plasma glucose were measured using hexokinase method on a clinical chemistry diagnostic system (Modular P800; Roche, Basel, Switzerland). Serum concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol were measured by an autoanalyzer (Modular E170; Roche). High sensitive C-reactive protein concentration was determined by highly sensitive competitive immunoassay (antigens and antibodies from Beckman coulter IMMAGE800, America). Serum insulin was measured by using the electrochemiluminescence methods on an Immunology analyzer (RIABEAD II; Abbott, Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting plasma glucose (mmol/L) / 22.5, and insulin resistance was defined as HOMA-IR ≥ 2.8, which is the cut-off point for the highest quartile of the total participants.

Definitions of cardiometabolic risk profile

Type 2 diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L or OGTT 2-hour plasma glucose ≥ 11.1 mmol/L or use of anti-diabetic agents.[20] Hypertension was

defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or current taking an antihypertensive medication.[21] Central obesity was defined as WC ≥ 102 cm for men and ≥ 88 cm for women. Hypertriglyceridemia was defined as triglycerides ≥ 2.26 mmol/L. Low HDL cholesterol was defined as a level of HDL-C < 1.04 mmol/L.

CIMT measurement was conducted by a trained sonographer using a high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Genoa, Italy) with a linear 7.5 MHz transducer.[22] The position of CIMT measurement was recorded on the far wall of both right and left common carotid arteries, 1.5 cm proximal to the bifurcation. CIMT was measured on-line at the end of diastole as a distance from the leading edge of the first echogenic line to that of the second. These two lines represent the lumen-intima interface and collagen-contained upper layer of tunic adventitia, respectively. Subclinical atherosclerosis was defined as a bilateral CIMT average greater than 0.8 mm, which is the highest quartile cut-off point of the total participants.

Statistical analyses

SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) was used for data management and statistical analysis. Continuous variables were described as means ± standard deviations (SDs) or medians (inter-quartile ranges), and categorical variables as numbers (percentages). Variables with skewed distributions, such as HOMA-IR, triglycerides, and C-reactive protein, were normalized by logarithmic transformation before analysis.

All participants were divided into four subgroups according to quartiles of MUAC. The ranges of MUAC within each quartile were 15.5 to 27.1 cm for quartile 1, 27.2 to

29.1 cm for quartile 2, 29.2 to 31.2 cm for quartile 3, and 31.3 to 43.3 cm for quartile 4. Linear regression analysis was used to test for trend across the MUAC quartiles for continuous variables and the Cochran-Armitage trend chi-square test was used for categorical variables. Multivariable linear regression and multivariable logistic regression analyses were conducted to assess the associations of MUAC with a wide spectrum of cardiometabolic disorders and subclinical atherosclerosis, with adjustment for age, sex, BMI, current smoking, current drinking, physical activity, WC, C-reactive protein, total cholesterol, HDL-C, LDL-C, triglycerides, fasting plasma glucose, and systolic blood pressure. Stratified analyses by age, BMI, WC, diabetes, insulin resistance, and hypertension were performed. Interactions were tested by adding the respective multiplicative terms in the models simultaneously. Statistical significance was set to a two-sided *P* value of less than 0.05.

Patient and public involvement

This study was conducted without patient and public involvement. No patients were invited to take participate in the development of the research question and outcome measures, the study design and the interpretation of the results. The findings from this study will be disseminated to the participants after the results are published in a peer-reviewed journal.

Results

Characteristics of the study participants

The study sample consisted of 2310 (36.7%) men and 3977 (63.3%) women with an average age of 62.2 years (SD: 8.78). Detailed sociodemographic and clinical characteristics of the study participants according to MUAC quartiles are shown in

Table 1. Participants with a large MUAC were more likely to have higher levels of BMI, WC, systolic and diastolic blood pressures, fasting plasma glucose, HOMA-IR, LDL-C, triglycerides, C-reactive protein, and CIMT, and had higher proportions of insulin resistance, hypertension, diabetes, and subclinical atherosclerosis (all *P* values < 0.05). In addition, participants with a large MUAC were younger and had lower levels of HDL-C (both *P* values < 0.0001) (Table 1). Multivariable linear regression analyses revealed consistent results on the associations between MUAC and these cardiometabolic profiles (Supplemental Table1).

Association between MUAC and cardiometabolic disorders

As shown in Table 2, a large MUAC was positively associated with central obesity, diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol after adjustment for age, sex, BMI, current smoking, current drinking, and physical activity (all *P* values < 0.001). The multivariable-adjusted OR per 1-SD increment in MUAC (3.13 cm) was 2.05 (95% CI, 1.85-2.28) for central obesity, 1.09 (1.02-1.16) for diabetes, 1.21 (1.14-1.30) for hypertension, 1.24 (1.15-1.35) for hypertriglyceridemia, and 1.26 (1.16-1.37) for low HDL cholesterol. Most of these associations were not substantially changed after additional adjustment for WC (all *P* values ≤ 0.03), except for diabetes and hypertriglyceridemia. When stratified by sex, more prominent results were observed among women.

Association between MUAC and subclinical atherosclerosis

In total participants, we observed strong and positive association between MUAC and subclinical atherosclerosis with fully adjustment (Table 3). The OR for subclinical atherosclerosis was 1.31 (95% CI, 1.09-1.58) within quartile 2 of MUAC, 1.33 (95%

CI, 1.10-1.62) within quartile 3, and 1.45 (95% CI, 1.16-1.80) within quartile 4, as compared with the lowest quartile ($P_{\text{for trend}} = 0.005$). When stratified by sex, significant results were observed among women but not among men.

Stratification analyses by traditional cardiovascular risk factors

We further examined the association between MUAC and subclinical atherosclerosis stratified by traditional cardiometabolic risk factors. In women, MUAC was associated with subclinical atherosclerosis among participants who aged ≥ 62 years, with BMI ≥ 25 kg/m^2 or waist circumference < 88 cm (Figure 1A), and among those with diabetes, insulin resistance, or hypertension (Figure 1B). Moreover, there were significant interactions of MUAC with diabetes and insulin resistance on subclinical atherosclerosis ($P_{\text{for interaction}} = 0.04$ and 0.01, respectively). These association patterns were not observed in men (Supplementary Figure 1).

To further evaluate whether the association of MUAC with subclinical atherosclerosis may be influenced by BMI and WC, we replicated the analyses within combinations of BMI and WC. In women, those with higher WC were more likely to have larger MUAC, regardless of BMI levels (Figure 2A). And MUAC was independently associated with subclinical atherosclerosis in the combination of WC < 88 cm and BMI < 25 kg/m^2 (OR, 1.22; 95% CI, 1.05-1.43) and in the combination of WC < 88 cm and BMI ≥ 25 kg/m^2 (OR, 1.40; 95% CI, 1.11-1.77) (Figure 2B).

Discussion

In this cross-sectional investigation of 6287 community dwelling Chinese adults, we found that a large MUAC was positively associated with a series of cardiometabolic disorders including central obesity, hypertension, low HDL cholesterol, and subclinical

atherosclerosis. Such association patterns were independent from traditional cardiovascular risk factors, and were more prominent among women than men. Moreover, we observed significant interactions of MUAC with diabetes and insulin resistance in relation to subclinical atherosclerosis.

MUAC is a widely used indicator of upper body adiposity in children, adolescents, and adults.[23, 24] Previous studies have shown mixed results on the associations between MUAC and CVD.[25-28] Findings from a retrospective cohort study of 771 Japanese adults have suggested that MUAC may play a complementary role to BMI in predicting prognosis in patients with heart failure.[25] In addition, a cross-sectional study of 93 pubertal obese adolescents from Brazil have associated a larger MUAC with a higher level of HOMAR-IR and a higher cardiometabolic risk score. [26] In contrast, results from the Health Effects of Arsenic Longitudinal Study of 562 middle-aged participants who were free of CVD in rural Bangladesh have shown no relationship between MUAC and CIMT.[28] Our present study has extended the existing evidence by demonstrating that MUAC increment was associated with an increased risk of a series of cardiometabolic disorders including central obesity, hypertension, low HDL cholesterol, and subclinical atherosclerosis in Chinese population, particularly among women. Central obesity, hypertension, low HDL cholesterol, and subclinical atherosclerosis have been robustly associated with increased risks of CVD. Detecting more effective risk factors for these cardiometabolic disorders is critical to the prevention of CVD. Our findings suggest that paying more attention to women with higher MUAC would be useful in the early identification and prevention of cardiometabolic disorders.

Explanations for the observations between MUAC and cardiometabolic risk are multifactorial. Our study found that MUAC level tended to decrease with age and there was a stronger association between MUAC and subclinical atherosclerosis among

women aged greater 62 years or older. Aging is a critical factor in changing process of metabolism and body composition. Fat-free mass and muscle mass reduced while substantial visceral fat rather than subcutaneous fat increased with aging, even under the condition of body weight unchanged. Individuals with age greater than 65 years suffer a reduction rate over 25 percent per year for muscle mass; and this rate can be accelerated to 50 percent per year for those older than 80 years.[28-30] In addition, we found that MUAC was associated with subclinical atherosclerosis in a sex-specific manner. One plausible explanation for the sex difference in MUAC-subclinical atherosclerosis relationship is biological differences between men and women, such as hormones effect, immune system responses, muscle capacity and physical function. For instance, men tend to have greater muscle capacity and higher muscle mass than women due to higher levels of testosterone.[24] Body fat redistributes to upper body and to a preferential adiposity around the waist with age and this trend was more obvious in women than in men.[30] The sex difference in redistribution of body fat may partly contribute to the observed more predominant associations between MUAC and cardiometabolic disorders among women.

The unique advantage of the present study is that we comprehensively determined the association of MUAC with a wide spectrum of cardiometabolic risk profiles in a well-defined community setting with fair sized sample and desirable population homogeneity. However, several limitations should be considered. Firstly, the cross-sectional nature of present study means no causal inference can be drawn. Secondly, although our finding supported that it can be a reliable surrogate of upper body adiposity, MUAC is a measure comprised of both adipose and lean tissue rather than a direct indicator for adiposity. Thirdly, as body composition changes over time, the narrow range of age for the participants enrolled could affected the outcome. Fourthly,

MUAC measurement was performed on the left arm, though it should be determined on the non-dominant arm. Given the fact that the majority of Chinese population were right-handers, measurement protocol employed in our study for MUAC was acceptable. Finally, since our study was performed in a Chinese population, it should be cautiously to generalize the results to other ethnicities.

In conclusion, our study provides evidence of positive associations of MUAC with cardiometabolic disorders as well as subclinical atherosclerosis in Chinese population. These results suggest that MUAC, as a convenient and inexpensive measurable metric, can be potentially used as a risk stratification tool in cardiometabolic disorders. Given the reliable assessment of MUAC in middle aged and elderly population and the accelerating rise rate of atherosclerosis in China, MUAC may be used as a valuable indicator for early prevention of CVD.

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Footnotes

Contributors: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TW, MX, YB and WW. Acquisition of data: YH, XJ, LX, WZ, CD, LW, ZZ, ML, JL, YX, and YC. Analysis and interpretation of data: YH, TW, MX, YB and WW. Drafting of the manuscript: YH. Critical revision of the manuscript: TW, MX, YB and WW. Statistical analysis: YH and XJ.

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Figure legends

Figure 1. Stratification analysis of the association between MUAC and subclinical atherosclerosis in women. A: All participants were divided into subgroups based on their average age (age < 62 years, age ≥ 62 years), body mass index (BMI < 25 kg/m^2, BMI ≥ 25 kg/m^2), or waist circumference (WC < 88 cm or WC ≥ 88 cm). B: All participants were divided into subgroups based on diabetes (yes or no), insulin resistance (yes or no), or hypertension (yes or no). Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), WC (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Figure 2. Association between MUAC and subclinical atherosclerosis according to combined categories of BMI and WC. A: MUAC in the BMI and WC subgroups in women. B: Association of MUAC with risk of subclinical atherosclerosis in the BMI and WC subgroups in women. MUAC: mid-upper arm circumference, BMI: body mass index, WC: waist circumference. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), WC (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Table 1. Characteristics of study participants according to quartiles of mid-upper arm circumference in total samples

	Mid-upper arm circumference, cm				
	Quartile 1 (15.5-27.1)	Quartile 2 (27.2-29.1)	Quartile 3 (29.2-31.2)	Quartile 4 (31.3-43.3)	P for trend
n	1510	1570	1582	1625	
Age (years)	63.4 ± 9.2	62.2 ± 8.8	61.7 ± 8.6	61.6 ± 8.4	< 0.0001
Female, n (%)	1110 (27.9)	1048 (26.4)	922 (23.2)	897 (22.6)	
Body mass index (kg/m2)	22.3 ± 2.8	24.2 ± 3.8	25.5 ± 3.2	27.9 ± 7.5	< 0.0001
Waist circumference (cm)	75.6 ± 8.5	81.4 ± 7.9	85.5 ± 8.3	91.6 ± 9.2	< 0.0001
Systolic blood pressure (mmHg)	132.6 ± 18.0	133.4 ± 17.3	136.0 ± 17.2	137.0 ± 16.4	< 0.0001
Diastolic blood pressure (mmHg)	74.2 ± 9.5	75.7 ± 9.3	77.2 ± 9.2	78.0 ± 9.8	< 0.0001
Current smoking, n (%)	196 (13.0)	279 (17.8)	346 (21.9)	393 (24.2)	< 0.0001
Current drinking, n (%)	151 (10)	195 (12.4)	256 (16.2)	290 (17.9)	< 0.0001
Physical activity (MET-h/wk)	21.0 (6.0-21.0)	15.3 (3.0-21.0)	15.0 (3.0-21.0)	15.0 (3.0-21.0)	0.30
Fasting plasma glucose (mmol/L)	5.99 ± 1.36	6.06 ± 1.34	6.21 ± 1.57	6.28 ± 1.61	< 0.0001
HOMA-IR	1.42 (0.99-2.15)	1.75 (1.20-2.57)	1.95 (1.35-2.86)	2.43 (1.69-3.55)	< 0.0001
Total cholesterol (mmol/L)	5.28 ± 0.95	5.31 ± 0.98	5.26 ± 1.04	5.24 ± 1.08	0.20
LDL-C (mmol/L)	3.56 ± 0.75	3.62 ± 0.77	3.62 ± 0.83	3.63 ± 0.81	0.02
HDL-C (mmol/L)	1.42 ± 0.33	1.35 ± 0.29	1.31 ± 0.29	1.27 ± 0.27	< 0.0001

Triglycerides (mmol/L)	1.33 (0.98-1.84)	1.49 (1.07-2.12)	1.58 (1.12-2.25)	1.66 (1.19-2.30)	< 0.0001
C-reactive protein (mg/L)	0.19 (0.14-0.28)	0.21 (0.16-0.31)	0.23(0.17-0.35)	0.25(0.18-0.39)	< 0.0001
CIMT (mm)	0.69 ± 0.16	0.70 ± 0.15	0.70 ± 0.14	0.72 ± 0.14	< 0.0001
Insulin resistance, n (%)	203 (13.5)	313 (20.0)	410 (26.0)	655 (40.5)	< 0.0001
Hypertension, n (%)	747 (49.5)	862 (52.7)	978 (61.9)	1108 (68.3)	< 0.0001
Diabetes, n (%)	368 (24.7)	403 (25.9)	457 (29.2)	533 (33.2)	< 0.0001
Subclinical atherosclerosis, n (%)	472 (31.3)	541 (34.5)	555 (35.1)	590 (36.3)	0.0035

Data are presented as means ± standard deviation (SD), or medians (inter-quartile ranges) for skewed variables, or number (proportions) for categorical variables. *P* values were calculated from one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Subclinical atherosclerosis was defined as CIMT ≥ 0.8 mm, which is the cut-off point for the highest quartile of the total participants. Insulin resistance was defined as HOMA-IR ≥ 2.8, which is the cut-off point for the highest quartile of the total participants. Abbreviations: MET, metabolic equivalent task; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CIMT, carotid intima-media thickness; HOMA-IR indicates homeostasis model assessment of insulin resistance.

Table 2. Logistic regression analysis of risk of cardiometabolic disorders in relation to mid-upper arm circumference in total and sex-specific participants

		OR (95% CI)					P for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	1-SD (3.13 cm)	
Total cohort							
Central obesity	Model 1	1.00	1.43 (0.99-2.05)	3.44 (2.45-4.82)	7.25 (5.12-10.3)	2.05 (1.85-2.28)	< 0.0001
	Model 2	1.00	1.43 (0.99-2.05)	3.44 (2.45-4.82)	7.25 (5.12-10.3)	2.05 (1.85-2.28)	< 0.0001
Diabetes	Model 1	1.00	1.00 (0.82-1.21)	1.13 (0.93-1.37)	1.26 (1.02-1.55)	1.09 (1.02-1.16)	0.02
	Model 2	1.00	0.87 (0.73-1.06)	0.89 (0.73-1.10)	0.87 (0.70-1.09)	0.96 (0.90-1.04)	0.33
Hypertension	Model 1	1.00	1.04 (0.87-1.24)	1.57 (1.30-1.89)	1.65 (1.34-2.04)	1.21 (1.14-1.30)	< 0.0001
	Model 2	1.00	0.92 (0.77-1.10)	1.29 (1.06-1.56)	1.23 (0.98-1.53)	1.10 (1.03-1.19)	0.006
Hypertriglyceridemia	Model 1	1.00	1.55 (1.25-1.92)	1.78 (1.43-2.21)	1.92 (1.53-2.41)	1.24 (1.15-1.35)	< 0.0001
	Model 2	1.00	1.31 (1.05-1.63)	1.32 (1.05-1.66)	1.19 (0.93-1.54)	1.03 (0.94-1.13)	0.28
Low HDL cholesterol	Model 1	1.00	1.40 (1.06-1.84)	1.80 (1.38-2.35)	2.06 (1.57-2.69)	1.26 (1.16-1.37)	< 0.0001
	Model 2	1.00	1.21 (0.91-1.60)	1.41 (1.06-1.86)	1.38 (1.02-1.88)	1.10 (1.01-1.22)	0.03
Women							
Central obesity	Model 1	1.00	1.49 (1.04-2.15)	3.54 (2.50-4.99)	7.10 (4.97-10.2)	2.01 (1.81-2.25)	< 0.0001
	Model 2	1.00	1.49 (1.04-2.15)	3.54 (2.50-4.99)	7.10 (4.97-10.2)	2.01 (1.81-2.25)	< 0.0001
Diabetes	Model 1	1.00	1.11 (0.89-1.41)	1.29 (1.01-1.65)	1.39 (1.07-1.80)	1.12 (1.03-1.22)	0.007
	Model 2	1.00	0.98 (0.77-1.24)	1.03 (0.80-1.32)	0.97 (0.73-1.29)	0.99 (0.91-1.09)	0.93

Hypertension	Model 1	1.00	1.10 (0.89-1.35)	1.93 (1.54-2.44)	1.80 (1.39-2.33)	1.27 (1.17-1.38)	< 0.0001
	Model 2	1.00	0.96 (0.78-1.18)	1.55 (1.23-1.97)	1.29 (0.98-1.68)	1.14 (1.05-1.24)	0.003
Hypertriglyceridemia	Model 1	1.00	1.63 (1.28-2.01)	1.89 (1.48-2.42)	1.84 (1.42-2.38)	1.25 (1.15-1.37)	< 0.0001
	Model 2	1.00	1.38 (1.08-1.78)	1.43 (1.09-1.86)	1.17 (0.87-1.58)	1.05 (0.94-1.17)	0.33
Low HDL cholesterol	Model 1	1.00	1.67 (1.17-2.38)	1.94 (1.36-2.77)	1.87 (1.29-2.71)	1.21 (1.09-1.35)	0.0007
	Model 2	1.00	1.47 (1.03-2.21)	1.56 (1.07-2.28)	1.32 (0.86-2.01)	1.08 (0.91-1.23)	0.23
Men							
Central obesity	Model 1	1.00	0.38 (0.02-6.61)	3.99 (0.49-32.0)	10.4 (1.33-81.2)	3.08 (1.92-4.95)	< 0.0001
	Model 2	1.00	0.38 (0.02-6.61)	3.99 (0.49-32.0)	10.4 (1.33-81.2)	3.08 (1.92-4.95)	< 0.0001
Diabetes	Model 1	1.00	0.79 (0.56-1.10)	0.85 (0.61-1.18)	0.97 (0.68-1.38)	1.01 (0.90-1.13)	0.84
	Model 2	1.00	0.69 (0.49-0.98)	0.68 (0.48-0.97)	0.69 (0.47-1.01)	0.91 (0.81-1.03)	0.12
Hypertension	Model 1	1.00	0.92 (0.66-1.29)	1.06 (0.76-1.48)	1.29 (0.89-1.88)	1.10 (0.98-1.24)	0.10
	Model 2	1.00	0.84 (0.60-1.17)	0.91 (0.65-1.28)	1.03 (0.70-1.52)	1.03 (0.91-1.16)	0.68
Hypertriglyceridemia	Model 1	1.00	1.37 (0.85-2.21)	1.46 (0.92-2.31)	1.66 (1.03-2.67)	1.13 (0.96-1.32)	0.04
	Model 2	1.00	1.19 (0.73-1.92)	1.15 (0.72-1.84)	1.13 (0.68-1.87)	0.97 (0.81-1.52)	0.81
Low HDL cholesterol	Model 1	1.00	1.01 (0.65-1.58)	1.42 (0.94-2.16)	1.62 (1.04-2.51)	1.21 (1.06-1.38)	0.006
	Model 2	1.00	0.92 (0.59-1.44)	1.22 (0.79-1.86)	1.27 (0.80-2.01)	1.12 (0.97-1.29)	0.13

Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis in quartile of mid-upper arm circumference. Model 1: adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or

no), current drinking (yes or no), physical activity (MET-h/wk); Model 2: further adjusted for waist circumference (cm), except for central obesity.

Table 3. The association of mid-upper arm circumference with subclinical atherosclerosis in total and sex-specific participants

	OR (95% CI)					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	1-SD (3.13 cm)	*P* for trend
Total cohort						0.20*
Cases/Participants	472 / 1510	541 / 1570	555 / 1582	590 / 1625	2158 / 6287	
Model 1	1.00	1.16 (1.00-1.34)	1.19 (1.02-1.38)	1.25 (1.08-1.45)	1.06 (1.01-1.12)	0.004
Model 2	1.00	1.30 (1.08-1.56)	1.30 (1.07-1.58)	1.35 (1.09-1.67)	1.06 (0.98-1.15)	0.013
Model 3	1.00	1.31 (1.09-1.58)	1.33 (1.10-1.62)	1.45 (1.16-1.80)	1.08 (0.99-1.17)	0.005
Women						
Case/participants	287 / 1110	327 / 1048	275 / 922	282 / 897	1171 / 3977	
Model 1	1.00	1.30 (1.08-1.57)	1.22 (1.00-1.48)	1.32 (1.09-1.60)	1.07 (1.00-1.14)	0.014
Model 2	1.00	1.54 (1.24-1.93)	1.43 (1.18-1.82)	1.53 (1.17-2.02)	1.11 (1.01-1.23)	0.007
Model 3	1.00	1.54 (1.24-1.93)	1.42 (1.11-1.83)	1.66 (1.26-2.20)	1.14 (1.03-1.26)	0.002
Men						
Case/participants	185 / 400	214 / 522	280 / 660	308 / 728	987 / 2310	
Model 1	1.00	0.81 (0.62-1.05)	0.86 (0.67-1.10)	0.85 (0.67-1.09)	0.93 (0.85-1.02)	0.39
Model 2	1.00	0.89 (0.64-1.23)	1.04 (0.75-1.44)	1.00 (0.70-1.45)	0.97 (0.85-1.11)	0.71
Model 3	1.00	0.90 (0.65-1.25)	1.06 (0.76-1.48)	1.05 (0.72-1.52)	0.99 (0.86-1.06)	0.54

Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. *: the interaction of MUAC with sex on subclinical atherosclerosis. Model 1, unadjusted; Model 2, adjusted for age (years), sex, body

mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm); Model 3, further adjusted for C-reactive protein (mg/L), total cholesterol (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

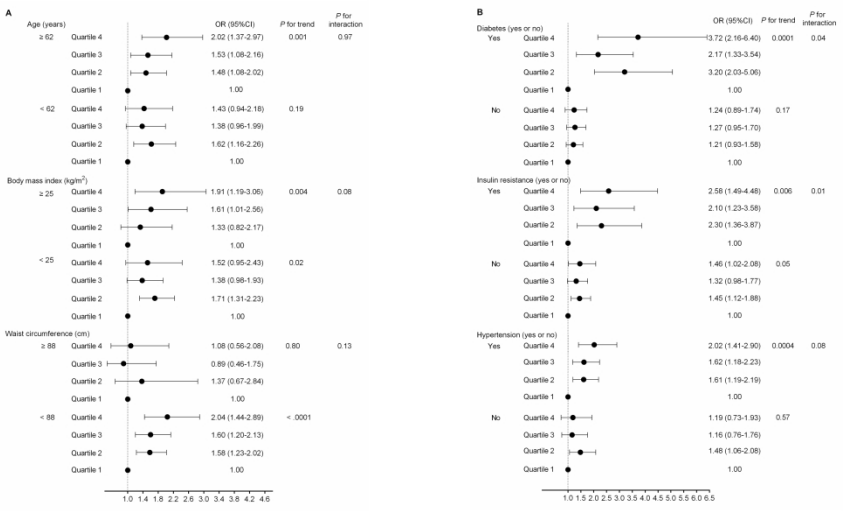

Figure 1

338x190mm (300 x 300 DPI)

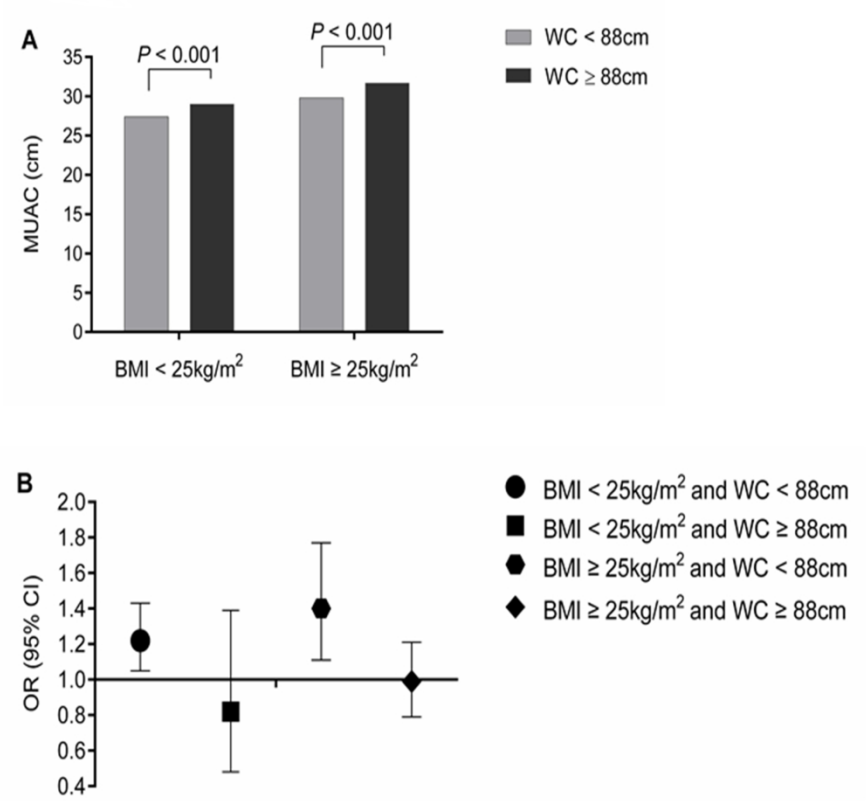

Figure 2

199x176mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-9
Bias	9	Describe any efforts to address potential sources of bias	Page 6-9
Study size	10	Explain how the study size was arrived at	Page 6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	Page 10
		(*c*) Explain how missing data were addressed	Page 7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Page 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 10 Page 22
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10-11
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Page 10-11 Page 22
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Page 11-12

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Page 9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 12
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between mid-upper arm circumference and cardiometabolic risk in Chinese population: a cross-sectional study

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Cardiovascular medicine
Keywords:	cardiometabolic risk, mid-upper arm circumference, subclinical atherosclerosis, upper body fat, Chinese adults

Association between mid-upper arm circumference and cardiometabolic risk in Chinese population: a cross-sectional study

Running title: Upper body fat and cardiometabolic risk

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Abstract

Objectives: Upper body fat has been associated with an unfavorable cardiometabolic risk. We aimed to investigate the associations between mid-upper arm circumference (MUAC), a novel indicator of upper body fat, and a wide spectrum of cardiometabolic risk profiles in Chinese population.

Design and setting: Cross-sectional analyses were performed using data from a well-defined community in 2014, Shanghai, China.

Participants: A total of 6287 Chinese adults (2310 men and 3977 women) aged 40 years or older.

Outcome measures: Multivariable logistic regression model was used to examine the associations of MUAC with cardiometabolic disorders including central obesity, diabetes, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and subclinical atherosclerosis.

Results: In the overall participants, after multivariable adjustment, each 1-SD (3.13 cm) increment in MUAC was positively associated with central obesity (OR, 2.05; 95% CI, 1.85-2.28), hypertension (OR, 1.10; 95% CI, 1.03-1.19), and low HDL cholesterol (OR, 1.10; 95% CI, 1.01-1.22). Multivariable-adjusted ORs for subclinical atherosclerosis were gradually increased across increasing quartiles of MUAC with the lowest quartile as reference (quartile 2: OR, 1.31; 95% CI, 1.09-1.58; quartile 3: 1.33; 1.10-1.62; quartile 4: 1.45; 1.16-1.80; P for trend = 0.005). Similar but more prominent associations were observed among women than men. In addition, MUAC was significantly interacted with diabetes (P for interaction = 0.04) and insulin resistance (P for interaction = 0.01) on subclinical atherosclerosis.

Conclusion: A greater MUAC was positively associated with higher risks of several cardiometabolic disorders and subclinical atherosclerosis in Chinese adults.

Keywords: Cardiometabolic risk, mid-upper arm circumference, subclinical atherosclerosis, upper body fat, Chinese adults

Strengths and limitations of this study:

- The strengths of this study included a well-defined community setting, a fair sized sample size, and comprehensive measurements of cardiometabolic risk profiles.
- The thorough analyses of the associations between MUAC and a wide spectrum of cardiometabolic risk profiles including central obesity, diabetes, hypertension, hypertriglyceridemia, low HDL cholesterol, and subclinical atherosclerosis.
- Although our findings support that MUAC could be a reliable surrogate of upper body adiposity, MUAC is a measurement which reflect both adipose and lean tissue rather than a direct indicator for adiposity.
- Age-related changes in body composition might influence these findings.
- This study was restricted to middle-aged and elderly Chinese adults, and the generalizability of our findings should be cautious to other demographic and ethnic populations.

Introduction

Cardiometabolic disorders describe a spectrum of interconnected pathological alterations in the cardiovascular system and metabolic organs that symbiotically increase the risk of cardiovascular disease (CVD), which is a major cause of mortality and increasing burden of healthcare expenditure worldwide.[1-5] Several important cardiometabolic disorders, including obesity, diabetes, insulin resistance, dyslipidemia, and hypertension, are important risk factors for CVD and could be served as targets for early identification and personalized prevention for CVD.[2-5] In addition, as a common contributor of CVD, atherosclerosis goes through a protracted subclinical phase and could only be detected at an advanced stage of CVD.[6,7] Thus, identification of subclinical atherosclerosis in the asymptomatic period is also critical for the prevention of CVD progression. Noninvasive ultrasonography measured carotid intima media thickness (CIMT) is a well-established clinical index for early arteriosclerosis detection and therefore has been extensively adopted to measure subclinical atherosclerosis.[8]

Fat distribution, specifically upper body and visceral adiposity, has been proven highly relevant to cardiovascular risk.[9,10] In addition to the conventional body fat indices such as body mass index (BMI) and waist circumference (WC), mid-upper arm circumference (MUAC), a novel anthropometric measurement, has been widely used in the screening of malnutrition, adiposity and chronic diseases.[11] However, current epidemiological studies have revealed inconsistent results with regard to the association between MUAC and cardiometabolic risk. A cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2006 circles has reported a positive association between MUAC and insulin resistance in non-obese individuals but no significant association in obese individuals.[9] In a prospective cohort

study of 1061 European elderly participants with a follow-up of approximately 6 years, a larger MUAC was associated with elevated risks of all-cause or CVD mortality.[12] By contrast, in the Canada Fitness Survey of 10638 adults, a larger MUAC was independently associated with a lower risk of all-cause mortality.[13] And such inverse association between a larger MUAC and a lower risk of mortality was also documented in the British National Diet and Nutrition Survey of 1054 participants with more than 15 years of followe-up.[14]

So far, most of the previous studies were conducted in European population. Chinese population tend to have a higher percentage of body fat, a weaker willingness on body build, and less muscle mass as well as connective tissue as compared with their European counterparts.[15] These different features in body composition may translate into varying susceptibilities to adiposity related cardiometabolic disorders. However, comprehensive analyses on associations between MUAC and cardiovascular risk profiles in Chinese population are still limited. Therefore, this study aimed to investigate the association between MUAC and multiple cardiometabolic disorders as well as subclinical atherosclerosis in Chinese population.

Methods

Study population

This is a cross-sectional analysis based on one of the follow-up circles of the established community-based cohort.[16,17] Eligible participants aged 40 years or older were identified from the local residence registration records. There was no restriction on ethnicity or gender. Each eligible participant was recruited by trained community staff

and local health workers using a door-to-door invitation method. Participants who consented for the study and signed informed consent were scheduled for health examinations. Briefly, a total of 6570 participants aged 40 years or older were enrolled from Jiading district, Shanghai, China, from August 2014 to May 2015. All participants received anthropometric measurements including height, weight, WC, and MUAC, a standard 75-g oral glucose tolerance test (OGTT), and a standard questionnaire to collect information regarding social demographic characteristics, education attainment, lifestyle factors, and history of disease and medicine. Blood samples were collected for biochemical measurements. In the present study, 283 participants were excluded due to missing data on MUAC or CIMT, and a total of 6287 participants were included in the final analysis. This study was approved by the Institutional Review Board of Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Written informed consents were obtained from all study participants.

Data collection and biochemical measurements

Detailed information on sociodemographic characteristics, education attainment, and lifestyle factors including smoking and alcohol drinking habits and physical activity, family history, and medical history were obtained by using a standard questionnaire administered by trained personnel. Current smokers or alcohol drinkers were defined as persons who consumed any kinds of cigarettes or alcohol regularly in the past 6 months, respectively. Physical activity in term of metabolic equivalent (MET) hour/week was calculated according to the short form of the International Physical Activity Questionnaire including physical activities both during leisure time and at work.[18]

Anthropometric measurements including height, weight, WC, and MUAC were assessed by well-trained physician according to a standard protocol. Body height and weight were measured with participants wearing light clothes without shoes to the nearest 0.1 centimeter and 0.1 kg, respectively. BMI was calculated as body weight in kilograms divided by body height in meters squared (kg/m^2). MUAC was measured on the upper left arm (halfway between the acromion process and the olecranon process) with the participants' bilateral arms hanging down naturally.[19] WC was measured at the level of the umbilicus with the participants in the standing position. Systolic and diastolic blood pressures were measured in the non-dominant arm with an automated electronic sphygmomanometer (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China) three times (averaged for analysis) consecutively with 1 min interval after at least 5 min rest in a seated position.

All participants were undertaken a 75-g OGTT after an overnight fasting. Fasting plasma glucose and OGTT 2-hour plasma glucose were measured using hexokinase method on a clinical chemistry diagnostic system (Modular P800; Roche, Basel, Switzerland). Serum concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured by an autoanalyzer (Modular E170; Roche). High sensitive C-reactive protein concentration was determined by highly sensitive competitive immunoassay (antigens and antibodies from Beckman coulter IMMAGE800, America). Serum insulin was measured by using the electrochemiluminescence methods on an Immunology analyzer (RIABEAD II; Abbott, Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting plasma glucose (mmol/L) / 22.5, and insulin resistance was defined as HOMA-IR ≥ 2.8, which is the cut-off point for the highest quartile of the total participants.

Definitions of cardiometabolic risk profile

Type 2 diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L or OGTT 2-hour plasma glucose ≥ 11.1 mmol/L or use of anti-diabetic agents.[20] Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or current taking an antihypertensive medication. Central obesity was defined as WC ≥ 102 cm for men and ≥ 88 cm for women. Hypertriglyceridemia was defined as triglycerides ≥ 2.26 mmol/L. Low HDL cholesterol was defined as a level of HDL cholesterol < 1.04 mmol/L.

CIMT measurement was conducted by a trained sonographer using a high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Genoa, Italy) with a linear 7.5 MHz transducer.[21] The position of CIMT measurement was recorded on the far wall of both right and left common carotid arteries, 1.5 cm proximal to the bifurcation. CIMT was measured on-line at the end of diastole as a distance from the leading edge of the first echogenic line to that of the second. These two lines represent the lumen-intima interface and collagen-contained upper layer of tunic adventitia, respectively. Subclinical atherosclerosis was defined as a bilateral CIMT average greater than 0.8 mm, which is the highest quartile cut-off point of the total participants.

Statistical analyses

SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) was used for statistical analysis. Continuous variables were described as means ± standard deviations (SDs) or medians

(interquartile ranges), and categorical variables as numbers (percentages). Variables with skewed distributions, such as HOMA-IR, triglycerides, and C-reactive protein, were normalized by logarithmic transformation before analysis.

Participants were divided into four subgroups according to quartiles of MUAC. The ranges of MUAC within each quartile were 15.5 to 27.1 cm for quartile 1, 27.2 to 29.1 cm for quartile 2, 29.2 to 31.2 cm for quartile 3, and 31.3 to 43.3 cm for quartile 4. Linear regression analysis was used to test the trend of continuous variables across MUAC quartiles and the Cochran-Armitage trend chi-square test was used to test the differences of proportions of categorical variables. Multivariable linear regression and multivariable logistic regression analyses were conducted to assess the associations of MUAC with multiple cardiometabolic disorders and subclinical atherosclerosis, with adjustment for age, sex, BMI, WC, current smoking, current drinking, physical activity, C-reactive protein, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting plasma glucose, and systolic blood pressure. Stratification analyses by age, BMI, WC, diabetes, insulin resistance, and hypertension were also performed. Interactions were tested by adding the respective multiplicative terms in the models simultaneously. Statistical significance was set to a two-sided *P* value of less than 0.05.

Patient and public involvement

This study was conducted without patient and public involvement. No patients were invited to take participate in the development of the research question and outcome measures, the study design and the interpretation of the results. The findings from this study will be disseminated to the participants after the results are published in a peer-reviewed journal.

Results

Characteristics of the study participants

Study participants included 2310 (36.7%) men and 3977 (63.3%) women with an average age of 62.2 years (SD: 8.78). Sociodemographic and clinical characteristics of the study participants according to MUAC quartiles are shown in Table 1. Participants with a large MUAC were younger, had higher levels of BMI, WC, systolic and diastolic blood pressures, fasting plasma glucose, HOMA-IR, LDL cholesterol, triglycerides, C-reactive protein, and CIMT, had higher proportions of insulin resistance, hypertension, diabetes, and subclinical atherosclerosis, and had lower levels of HDL cholesterol (all *P* values < 0.05; Table 1). Consistent linear associations were observed between MUAC and these cardiometabolic profiles (Supplemental Table1).

Association between MUAC and cardiometabolic disorders

As shown in Table 2, the multivariable-adjusted OR per 1-SD increment (3.13 cm) in MUAC was 2.05 (95% CI, 1.85-2.28) for central obesity, 1.09 (1.02-1.16) for diabetes, 1.21 (1.14-1.30) for hypertension, 1.24 (1.15-1.35) for hypertriglyceridemia, and 1.26 (1.16-1.37) for low HDL cholesterol. Most of these associations were not substantially changed after additional adjustment for WC, except for diabetes and hypertriglyceridemia. When stratified by sex, similar but more prominent associations between MUAC and these cardiometabolic disorders were observed among women.

Association between MUAC and subclinical atherosclerosis

In total participants, we observed strong and positive association between MUAC and subclinical atherosclerosis with fully adjustment (Table 3). The OR for subclinical atherosclerosis was 1.31 (95% CI, 1.09-1.58) for quartile 2 of MUAC, 1.33 (95% CI, 1.10-1.62) for quartile 3, and 1.45 (95% CI, 1.16-1.80) for quartile 4 as compared with the lowest quartile (P for trend = 0.005). When stratified by sex, statistically significant results were observed among women but not among men.

Stratification analyses by traditional cardiovascular risk factors

We further examined the association between MUAC and subclinical atherosclerosis across strata of traditional cardiometabolic risk factors. In women, MUAC was associated with subclinical atherosclerosis among participants who aged ≥ 62 years, with BMI ≥ 25 kg/m^2 or waist circumference < 88 cm (Figure 1A), and among participants with diabetes, insulin resistance, or hypertension (Figure 1B). Moreover, there were significant interactions of MUAC with diabetes and insulin resistance on subclinical atherosclerosis (P for interaction = 0.04 and 0.01, respectively). These association patterns were not observed in men (Supplementary Figure 1).

To further evaluate whether the association of MUAC with subclinical atherosclerosis is influenced by BMI and WC, we replicated the analyses within combinations of BMI and WC. In women, those with higher WC were more likely to have larger MUAC, regardless of BMI levels (Figure 2A). And MUAC was independently associated with subclinical atherosclerosis in the combination of WC <

88 cm and BMI < 25 kg/m^2 (OR, 1.22; 95% CI, 1.05-1.43) and the combination of WC < 88 cm and BMI ≥ 25 kg/m^2 (OR, 1.40; 95% CI, 1.11-1.77) (Figure 2B).

Discussion

In this cross-sectional study of 6287 community dwelling Chinese adults, MUAC was positively associated with a series of cardiometabolic disorders including central obesity, hypertension, low HDL cholesterol, and subclinical atherosclerosis. These associations were independent from traditional cardiovascular risk factors, and were more prominent in women. Moreover, we observed significant interactions of MUAC with diabetes and insulin resistance in relation to subclinical atherosclerosis.

MUAC has been accepted as a widely used indicator of upper body adiposity in children, adolescents, and adults.[22, 23] Previous studies have shown mixed results on the associations between MUAC and CVD.[24-27] Findings from a retrospective cohort study of 771 Japanese adults have suggested that MUAC may play a complementary role to BMI in predicting prognosis in patients with heart failure.[24] In addition, a cross-sectional study of 93 pubertal obese adolescents from Brazil have associated a larger MUAC with a higher level of HOMA-IR and a higher cardiometabolic risk score.[25] On the contrary, results from the Health Effects of Arsenic Longitudinal Study of 562 middle-aged participants who were free of CVD in rural Bangladesh have shown no relationship between MUAC and CIMT.[27] Our study has extended the existing evidence by demonstrating that a greater MUAC was associated with higher prevalent risk of multiple cardiometabolic disorders including central obesity, hypertension, low HDL cholesterol, and subclinical atherosclerosis in Chinese adults, particularly among women. Central obesity, hypertension, low HDL cholesterol, and subclinical

atherosclerosis have been robustly associated with increased risks of CVD, therefore detecting more effective risk factors for these cardiometabolic disorders is critical to the prevention of CVD. Our findings highlight the importance of paying more attention to women with higher MUAC in the early identification and precise prevention of cardiometabolic disorders.

Explanations for the observations between MUAC and cardiometabolic risk are multifactorial. Our study found that MUAC level tended to decrease with age and there was a stronger association between MUAC and subclinical atherosclerosis among women aged 62 years or older. Aging is a critical factor in the changing process of metabolism and body composition. Fat-free mass and muscle mass reduced while substantial visceral fat increased with aging, even under the condition of body weight unchanged.[27] It has been documented that individuals aged greater than 65 years would suffer a reduction in muscle mass over 25% per year; and this rate can be accelerated to 50% per year for those older than 80 years.[27-29] In addition, we found that MUAC was associated with subclinical atherosclerosis in a sex-specific manner. One plausible explanation for the sex difference in MUAC-subclinical atherosclerosis relationship may be due to the biological differences between men and women, such as hormones effect, immune system responses, muscle capacity and physical function. For instance, men tend to have greater muscle capacity and higher muscle mass than women due to higher levels of testosterone.[23] Body fat redistributes to upper body and to a preferential adiposity around the waist with age and this trend was more obvious in women than in men.[29] The sex difference in redistribution of body fat may partly contribute to the observed more predominant associations between MUAC and cardiometabolic disorders among women.

The strength of this study is the comprehensive analyses of the association between MUAC and a wide spectrum of cardiometabolic risk profiles in a well-defined community setting with fair sized sample and desirable population homogeneity. Several limitations should be considered. First, due to a cross-sectional nature of the present study, no causal inference can be drawn. Second, although our findings supported that MUAC could be a reliable surrogate of upper body adiposity, MUAC is a measurement which reflect both adipose and lean tissue rather than a direct indicator for adiposity. Third, although we have carefully adjusted for multiple confounders, age-related changes in body composition might influence these findings. Fourth, MUAC measurement was performed on the left arm, though it should be determined on the non-dominant arm. Given that the majority of Chinese population were right-handers, measurement protocol employed in our study for MUAC was acceptable. Finally, this study was restricted to middle-aged and elderly Chinese adults, and the generalizability of our findings should be cautious to other demographic and ethnic populations.

In conclusion, our study provided novel evidence of positive associations between MUAC and cardiometabolic disorders as well as subclinical atherosclerosis in Chinese population. Our findings suggest that MUAC, as a convenient and inexpensive measurable metric, can be potentially used as a risk stratification indicator in the early detection and prevention of CVD.

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Footnotes

Contributors: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TW, MX, YB and WW. Acquisition of data: YH, XJ, LX, WZ, CD, LW, ZZ, ML, JL, YX, and YC. Analysis and interpretation of data: YH, TW, MX, YB and WW. Drafting of the manuscript: YH. Critical revision of the manuscript: TW, MX, YB and WW. Statistical analysis: YH and XJ.

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Figure legends

Figure 1. Stratification analysis of the association between MUAC and subclinical atherosclerosis in women. A: All participants were divided into subgroups based on their average age (age < 62 years, age ≥ 62 years), body mass index (BMI < 25 kg/m^2, BMI ≥ 25 kg/m^2), or waist circumference (WC < 88 cm or WC ≥ 88 cm). B: All participants were divided into subgroups based on diabetes (yes or no), insulin resistance (yes or no), or hypertension (yes or no). Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), WC (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Figure 2. Association between MUAC and subclinical atherosclerosis according to combined categories of BMI and WC. A: MUAC in the BMI and WC subgroups in women. B: Association of MUAC with risk of subclinical atherosclerosis in the BMI and WC subgroups in women. MUAC: mid-upper arm circumference, BMI: body mass index, WC: waist circumference. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), WC (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

Table 1. Characteristics of study participants according to quartiles of mid-upper arm circumference

	Mid-upper arm circumference, cm				
	Quartile 1 (15.5-27.1)	Quartile 2 (27.2-29.1)	Quartile 3 (29.2-31.2)	Quartile 4 (31.3-43.3)	P for trend
n	1510	1570	1582	1625	
Age (years)	63.4 ± 9.2	62.2 ± 8.8	61.7 ± 8.6	61.6 ± 8.4	< 0.0001
Female, n (%)	1110 (27.9)	1048 (26.4)	922 (23.2)	897 (22.6)	
Body mass index (kg/m2)	22.3 ± 2.8	24.2 ± 3.8	25.5 ± 3.2	27.9 ± 7.5	< 0.0001
Waist circumference (cm)	75.6 ± 8.5	81.4 ± 7.9	85.5 ± 8.3	91.6 ± 9.2	< 0.0001
Systolic blood pressure (mmHg)	132.6 ± 18.0	133.4 ± 17.3	136.0 ± 17.2	137.0 ± 16.4	< 0.0001
Diastolic blood pressure (mmHg)	74.2 ± 9.5	75.7 ± 9.3	77.2 ± 9.2	78.0 ± 9.8	< 0.0001
Current smoking, n (%)	196 (13.0)	279 (17.8)	346 (21.9)	393 (24.2)	< 0.0001
Current drinking, n (%)	151 (10)	195 (12.4)	256 (16.2)	290 (17.9)	< 0.0001
Physical activity (MET-h/wk)	21.0 (6.0-21.0)	15.3 (3.0-21.0)	15.0 (3.0-21.0)	15.0 (3.0-21.0)	0.30
Fasting plasma glucose (mmol/L)	5.99 ± 1.36	6.06 ± 1.34	6.21 ± 1.57	6.28 ± 1.61	< 0.0001
HOMA-IR	1.42 (0.99-2.15)	1.75 (1.20-2.57)	1.95 (1.35-2.86)	2.43 (1.69-3.55)	< 0.0001
Total cholesterol (mmol/L)	5.28 ± 0.95	5.31 ± 0.98	5.26 ± 1.04	5.24 ± 1.08	0.20
LDL cholesterol (mmol/L)	3.56 ± 0.75	3.62 ± 0.77	3.62 ± 0.83	3.63 ± 0.81	0.02

HDL cholesterol (mmol/L)	1.42 ± 0.33	1.35 ± 0.29	1.31 ± 0.29	1.27 ± 0.27	< 0.0001
Triglycerides (mmol/L)	1.33 (0.98-1.84)	1.49 (1.07-2.12)	1.58 (1.12-2.25)	1.66 (1.19-2.30)	< 0.0001
C-reactive protein (mg/L)	0.19 (0.14-0.28)	0.21 (0.16-0.31)	0.23(0.17-0.35)	0.25(0.18-0.39)	< 0.0001
CIMT (mm)	0.69 ± 0.16	0.70 ± 0.15	0.70 ± 0.14	0.72 ± 0.14	< 0.0001
Insulin resistance, n (%)	203 (13.5)	313 (20.0)	410 (26.0)	655 (40.5)	< 0.0001
Hypertension, n (%)	747 (49.5)	862 (52.7)	978 (61.9)	1108 (68.3)	< 0.0001
Diabetes, n (%)	368 (24.7)	403 (25.9)	457 (29.2)	533 (33.2)	< 0.0001
Subclinical atherosclerosis, n (%)	472 (31.3)	541 (34.5)	555 (35.1)	590 (36.3)	0.0035

Data are presented as means ± standard deviation (SD), or medians (interquartile ranges) for skewed variables, or number (proportions) for categorical variables. *P* values were calculated from one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Subclinical atherosclerosis was defined as CIMT ≥ 0.8 mm, which is the cut-off point for the highest quartile of the total participants. Insulin resistance was defined as HOMA-IR ≥ 2.8, which is the cut-off point for the highest quartile of the total participants. Abbreviations: MET, metabolic equivalent task; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CIMT, carotid intima-media thickness; HOMA-IR indicates homeostasis model assessment of insulin resistance.

Table 2. Association between mid-upper arm circumference and multiple cardiometabolic disorders in total and sex-specific participants

		OR (95% CI)					P for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	1-SD (3.13 cm)	
Total							
Central obesity	Model 1	1.00	1.43 (0.99-2.05)	3.44 (2.45-4.82)	7.25 (5.12-10.3)	2.05 (1.85-2.28)	< 0.0001
	Model 2	1.00	1.43 (0.99-2.05)	3.44 (2.45-4.82)	7.25 (5.12-10.3)	2.05 (1.85-2.28)	< 0.0001
Diabetes	Model 1	1.00	1.00 (0.82-1.21)	1.13 (0.93-1.37)	1.26 (1.02-1.55)	1.09 (1.02-1.16)	0.02
	Model 2	1.00	0.87 (0.73-1.06)	0.89 (0.73-1.10)	0.87 (0.70-1.09)	0.96 (0.90-1.04)	0.33
Hypertension	Model 1	1.00	1.04 (0.87-1.24)	1.57 (1.30-1.89)	1.65 (1.34-2.04)	1.21 (1.14-1.30)	< 0.0001
	Model 2	1.00	0.92 (0.77-1.10)	1.29 (1.06-1.56)	1.23 (0.98-1.53)	1.10 (1.03-1.19)	0.006
Hypertriglyceridemia	Model 1	1.00	1.55 (1.25-1.92)	1.78 (1.43-2.21)	1.92 (1.53-2.41)	1.24 (1.15-1.35)	< 0.0001
	Model 2	1.00	1.31 (1.05-1.63)	1.32 (1.05-1.66)	1.19 (0.93-1.54)	1.03 (0.94-1.13)	0.28
Low HDL cholesterol	Model 1	1.00	1.40 (1.06-1.84)	1.80 (1.38-2.35)	2.06 (1.57-2.69)	1.26 (1.16-1.37)	< 0.0001

	Model 2	1.00	1.21 (0.91-1.60)	1.41 (1.06-1.86)	1.38 (1.02-1.88)	1.10 (1.01-1.22)	0.03
Women							
Central obesity	Model 1	1.00	1.49 (1.04-2.15)	3.54 (2.50-4.99)	7.10 (4.97-10.2)	2.01 (1.81-2.25)	< 0.0001
	Model 2	1.00	1.49 (1.04-2.15)	3.54 (2.50-4.99)	7.10 (4.97-10.2)	2.01 (1.81-2.25)	< 0.0001
Diabetes	Model 1	1.00	1.11 (0.89-1.41)	1.29 (1.01-1.65)	1.39 (1.07-1.80)	1.12 (1.03-1.22)	0.007
	Model 2	1.00	0.98 (0.77-1.24)	1.03 (0.80-1.32)	0.97 (0.73-1.29)	0.99 (0.91-1.09)	0.93
Hypertension	Model 1	1.00	1.10 (0.89-1.35)	1.93 (1.54-2.44)	1.80 (1.39-2.33)	1.27 (1.17-1.38)	< 0.0001
	Model 2	1.00	0.96 (0.78-1.18)	1.55 (1.23-1.97)	1.29 (0.98-1.68)	1.14 (1.05-1.24)	0.003
Hypertriglyceridemia	Model 1	1.00	1.63 (1.28-2.01)	1.89 (1.48-2.42)	1.84 (1.42-2.38)	1.25 (1.15-1.37)	< 0.0001
	Model 2	1.00	1.38 (1.08-1.78)	1.43 (1.09-1.86)	1.17 (0.87-1.58)	1.05 (0.94-1.17)	0.33
Low HDL cholesterol	Model 1	1.00	1.67 (1.17-2.38)	1.94 (1.36-2.77)	1.87 (1.29-2.71)	1.21 (1.09-1.35)	0.0007
	Model 2	1.00	1.47 (1.03-2.21)	1.56 (1.07-2.28)	1.32 (0.86-2.01)	1.08 (0.91-1.23)	0.23

Men							
Central obesity	Model 1	1.00	0.38 (0.02-6.61)	3.99 (0.49-32.0)	10.4 (1.33-81.2)	3.08 (1.92-4.95)	< 0.0001
	Model 2	1.00	0.38 (0.02-6.61)	3.99 (0.49-32.0)	10.4 (1.33-81.2)	3.08 (1.92-4.95)	< 0.0001
Diabetes	Model 1	1.00	0.79 (0.56-1.10)	0.85 (0.61-1.18)	0.97 (0.68-1.38)	1.01 (0.90-1.13)	0.84
	Model 2	1.00	0.69 (0.49-0.98)	0.68 (0.48-0.97)	0.69 (0.47-1.01)	0.91 (0.81-1.03)	0.12
Hypertension	Model 1	1.00	0.92 (0.66-1.29)	1.06 (0.76-1.48)	1.29 (0.89-1.88)	1.10 (0.98-1.24)	0.10
	Model 2	1.00	0.84 (0.60-1.17)	0.91 (0.65-1.28)	1.03 (0.70-1.52)	1.03 (0.91-1.16)	0.68
Hypertriglyceridemia	Model 1	1.00	1.37 (0.85-2.21)	1.46 (0.92-2.31)	1.66 (1.03-2.67)	1.13 (0.96-1.32)	0.04
	Model 2	1.00	1.19 (0.73-1.92)	1.15 (0.72-1.84)	1.13 (0.68-1.87)	0.97 (0.81-1.52)	0.81
Low HDL cholesterol	Model 1	1.00	1.01 (0.65-1.58)	1.42 (0.94-2.16)	1.62 (1.04-2.51)	1.21 (1.06-1.38)	0.006
	Model 2	1.00	0.92 (0.59-1.44)	1.22 (0.79-1.86)	1.27 (0.80-2.01)	1.12 (0.97-1.29)	0.13

Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis in quartile of mid-upper arm circumference. Model 1: adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk); Model 2: further adjusted for waist circumference (cm), except for central obesity.

Table 3. Association between mid-upper arm circumference and subclinical atherosclerosis in total and sex-specific participants

	OR (95% CI)					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	1-SD (3.13 cm)	*P* for trend
Total						0.20*
Cases/Participants	472 / 1510	541 / 1570	555 / 1582	590 / 1625	2158 / 6287	
Model 1	1.00	1.16 (1.00-1.34)	1.19 (1.02-1.38)	1.25 (1.08-1.45)	1.06 (1.01-1.12)	0.004
Model 2	1.00	1.30 (1.08-1.56)	1.30 (1.07-1.58)	1.35 (1.09-1.67)	1.06 (0.98-1.15)	0.013
Model 3	1.00	1.31 (1.09-1.58)	1.33 (1.10-1.62)	1.45 (1.16-1.80)	1.08 (0.99-1.17)	0.005
Women						
Case/participants	287 / 1110	327 / 1048	275 / 922	282 / 897	1171 / 3977	
Model 1	1.00	1.30 (1.08-1.57)	1.22 (1.00-1.48)	1.32 (1.09-1.60)	1.07 (1.00-1.14)	0.014
Model 2	1.00	1.54 (1.24-1.93)	1.43 (1.18-1.82)	1.53 (1.17-2.02)	1.11 (1.01-1.23)	0.007
Model 3	1.00	1.54 (1.24-1.93)	1.42 (1.11-1.83)	1.66 (1.26-2.20)	1.14 (1.03-1.26)	0.002

Men						
Case/participants	185 / 400	214 / 522	280 / 660	308 / 728	987 / 2310	
Model 1	1.00	0.81 (0.62-1.05)	0.86 (0.67-1.10)	0.85 (0.67-1.09)	0.93 (0.85-1.02)	0.39
Model 2	1.00	0.89 (0.64-1.23)	1.04 (0.75-1.44)	1.00 (0.70-1.45)	0.97 (0.85-1.11)	0.71
Model 3	1.00	0.90 (0.65-1.25)	1.06 (0.76-1.48)	1.05 (0.72-1.52)	0.99 (0.86-1.06)	0.54

Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. *: the interaction of MUAC with sex on subclinical atherosclerosis. Model 1, unadjusted; Model 2, adjusted for age (years), sex, body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm); Model 3, further adjusted for C-reactive protein (mg/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

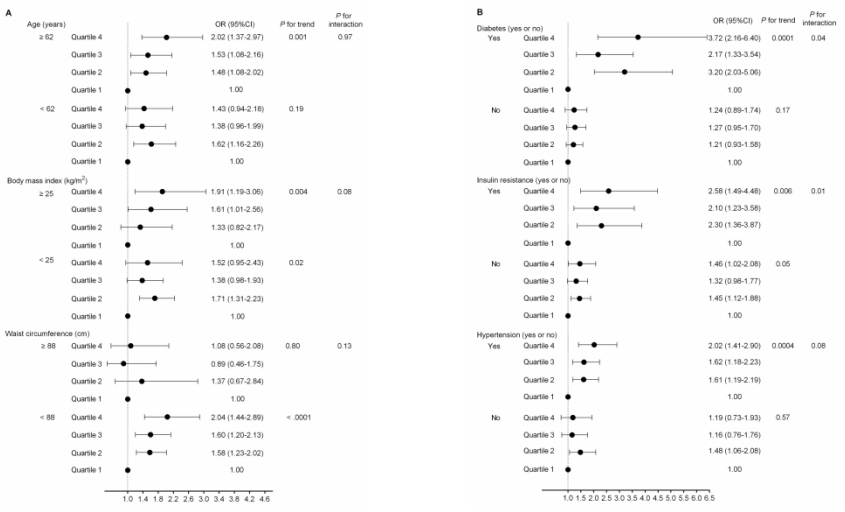


Figure 1

338x190mm (300 x 300 DPI)

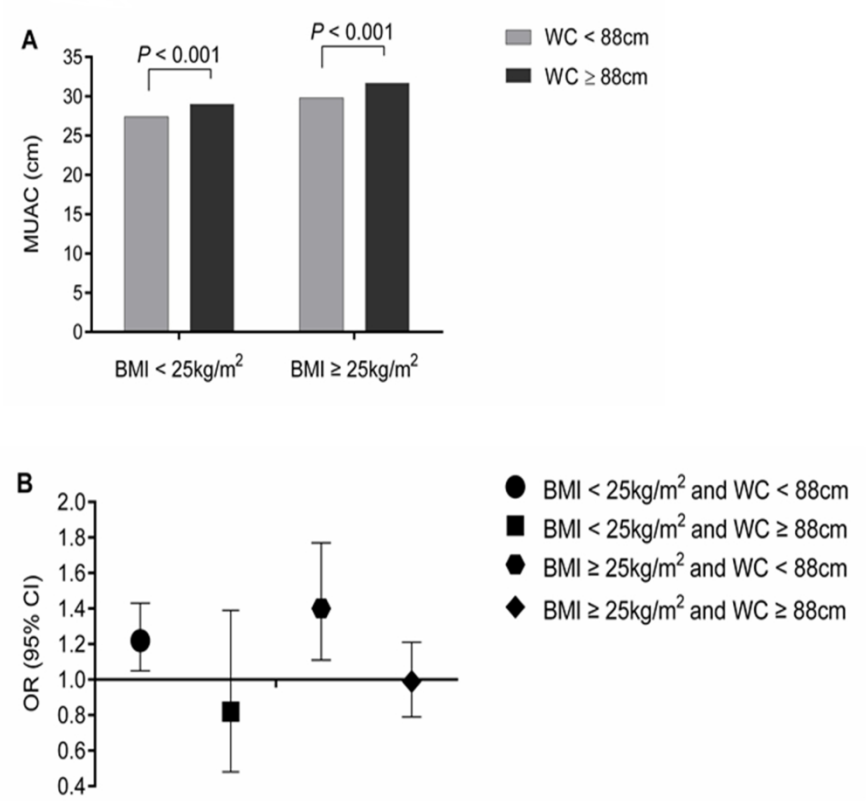


Figure 2

199x176mm (300 x 300 DPI)

Online Supplemental Information

Association between mid-upper arm circumference and cardiometabolic risk in Chinese population: a cross-sectional study

Supplemental Table 1. The association of mid-upper arm circumference with cardiometabolic profiles in total participants

Supplemental Figure Legend

Supplemental Figure 1. Stratified analysis of the association of mid-upper arm circumference with risk of subclinical atherosclerosis in men. A: All subjects were divided into subgroups based on their average age (age < 62 years, age ≥ 62 years), body mass index (BMI < 25 kg/m^2, BMI ≥ 25 kg/m^2), or waist circumference (WC < 88 cm or WC ≥ 88 cm). B: All subjects were divided into subgroups based on diabetes (yes or no), insulin resistance (yes or no), or hypertension (yes or no). Data were presented as odds ratio (OR) and 95% confidence interval (CI). *P* values were calculated from multivariable logistic regression analysis. Adjusted for age (years), body mass index (kg/m^2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk), waist circumference (cm), C-reactive protein (mg/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), triglycerides (mmol/L), fasting plasma glucose (mmol/L), and systolic blood pressure (mmHg).

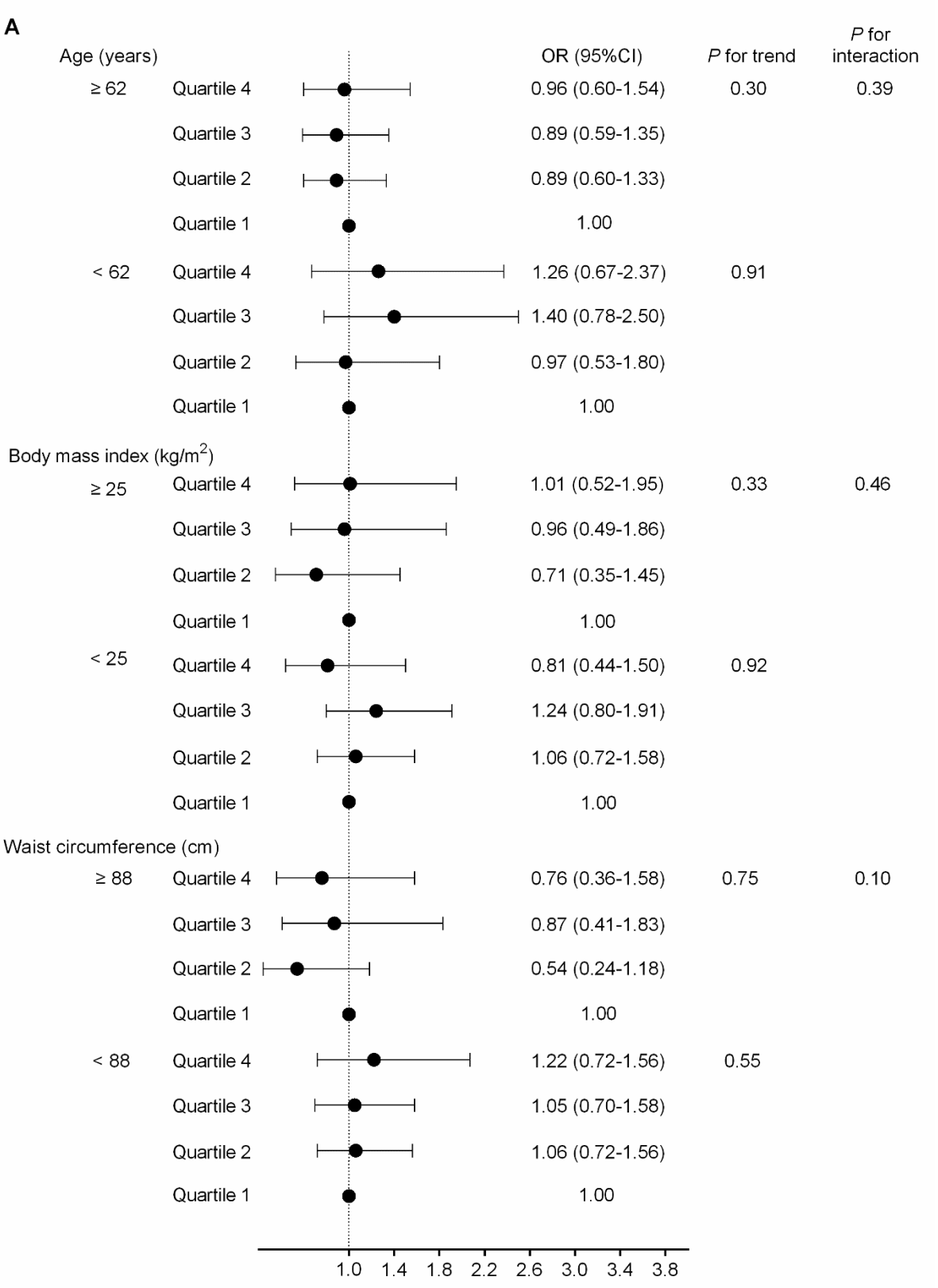
Supplemental Table 1. The association of mid-upper arm circumference with cardiometabolic profiles in total participants

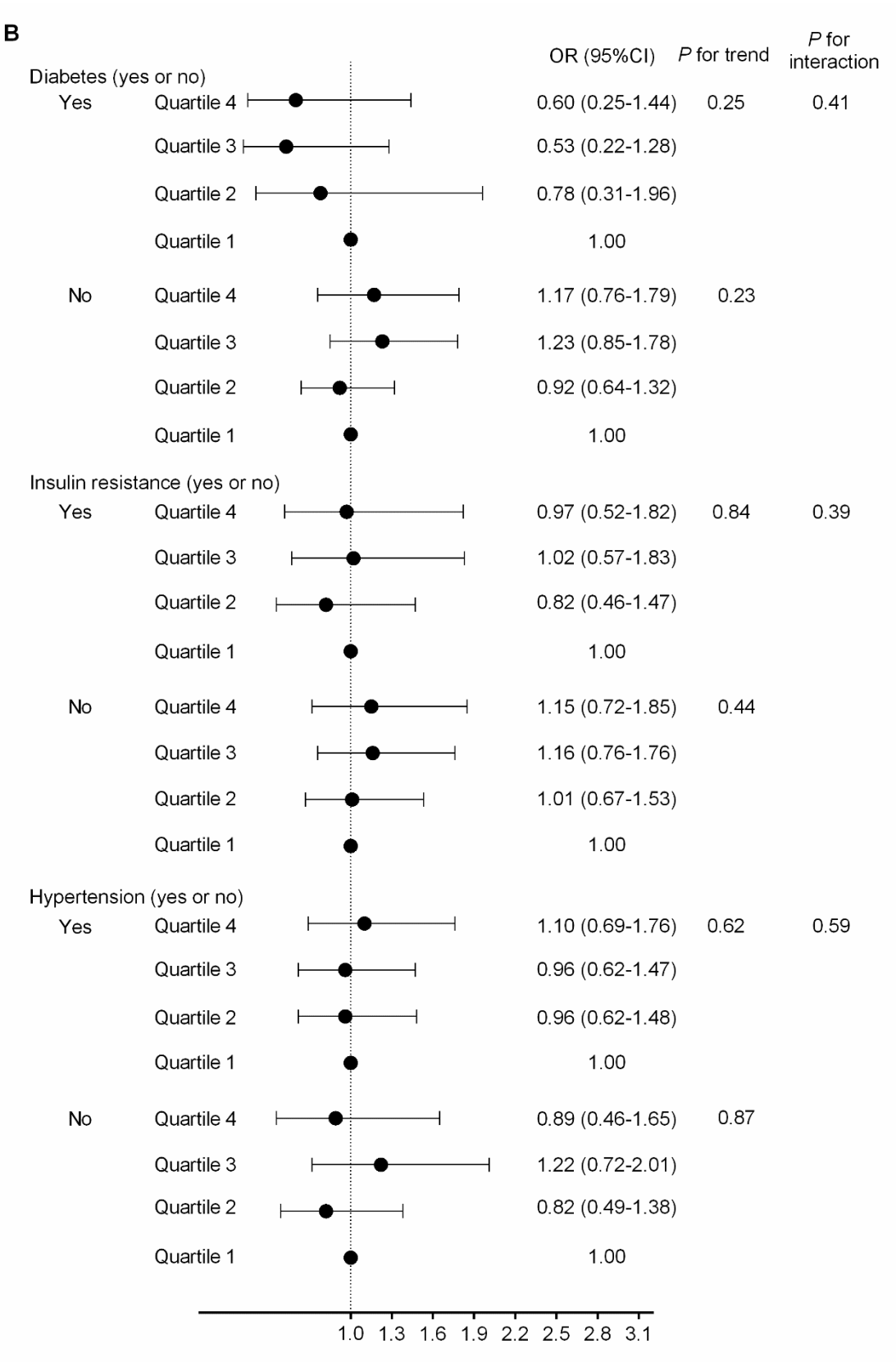
	Model 1		Model 2		Model 3	
	β ± SE	P value	β ± SE	P value	β ± SE	P value
Age (years)	-0.20 ± 0.04	<0.0001	/	/	/	/
Body mass index (kg/m2)	0.70 ± 0.02	<0.0001	/	/	/	/
Waist circumference (cm)	1.94 ± 0.03	<0.0001	1.62 ± 0.04	<0.0001	/	/
Systolic blood pressure (mmHg)	0.55 ± 0.07	<0.0001	0.49 ± 0.09	<0.0001	0.20 ± 0.10	0.04
Diastolic blood pressure (mmHg)	0.49 ± 0.04	<0.0001	0.32 ± 0.05	<0.0001	0.08 ± 0.06	0.15
Fasting plasma glucose (mmol/L)	0.03 ± 0.01	<0.0001	0.02 ± 0.01	0.01	-0.02 ± 0.01	0.04
HOMA-IR	0.03 ± 0.001	<0.0001	0.02 ± 0.001	<0.0001	0.01 ± 0.002	0.0003
Total cholesterol (mmol/L)	-0.004 ± 0.004	0.30	0.004 ± 0.005	0.48	-0.01 ± 0.01	0.24
LDL cholesterol (mmol/L)	0.009 ± 0.003	0.005	0.01 ± 0.004	0.001	0.001 ± 0.005	0.79
HDL cholesterol (mmol/L)	-0.02 ± 0.001	<0.0001	-0.01± 0.001	<0.0001	-0.003 ± 0.002	0.08

Triglycerides (mmol/L)	0.01 ± 0.001	<0.0001	0.01 ± 0.001	<0.0001	0.001 ± 0.001	0.38
C-reactive protein (mg/L)	0.01 ± 0.001	<0.0001	0.01 ± 0.001	<0.0001	0.002 ± 0.002	0.12
CIMT (cm)	0.003 ± 0.001	<0.0001	0.003 ± 0.001	0.0002	0.002 ± 0.001	0.005

Data are linear regression estimates ± standard error (β ± SE). P values were calculated from multivariable linear regression model. Model 1: unadjusted; Model 2: adjusted for age (years), sex, body mass index (kg/m2), current smoking (yes or no), current drinking (yes or no), physical activity (MET-h/wk); Model 3: further adjusted for waist circumference (cm). Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; CIMT, carotid intima-media thickness.

Supplemental Figure 1




B
OR (95%CI)
P for trend
P for interaction
Diabetes (yes or no)
Yes
Quartile 4
0.60 (0.25-1.44)
0.25
0.41
Quartile 3
0.53 (0.22-1.28)
Quartile 2
0.78 (0.31-1.96)
Quartile 1
1.00
No
Quartile 4
1.17 (0.76-1.79)
0.23
Quartile 3
1.23 (0.85-1.78)
Quartile 2
0.92 (0.64-1.32)
Quartile 1
1.00
Insulin resistance (yes or no)
Yes
Quartile 4
0.97 (0.52-1.82)
0.84
0.39
Quartile 3
1.02 (0.57-1.83)
Quartile 2
0.82 (0.46-1.47)
Quartile 1
1.00
No
Quartile 4
1.15 (0.72-1.85)
0.44
Quartile 3
1.16 (0.76-1.76)
Quartile 2
1.01 (0.67-1.53)
Quartile 1
1.00
Hypertension (yes or no)
Yes
Quartile 4
1.10 (0.69-1.76)
0.62
0.59
Quartile 3
0.96 (0.62-1.47)
Quartile 2
0.96 (0.62-1.48)
Quartile 1
1.00
No
Quartile 4
0.89 (0.46-1.65)
0.87
Quartile 3
1.22 (0.72-2.01)
Quartile 2
0.82 (0.49-1.38)
Quartile 1
1.00
1.0 1.3 1.6 1.9 2.2 2.5 2.8 3.1

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Page 5-8
Study size	10	Explain how the study size was arrived at	Page 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 8-9
		(*c*) Explain how missing data were addressed	Page 6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Page 9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10-12
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Page 10-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 10-12

		(*b*) Report category boundaries when continuous variables were categorized	Page 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.