Additive Effect of Low Skeletal Muscle Mass and Abdominal Obesity on Coronary Artery Calcification

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Abstract

Background Reduced skeletal muscle mass and obesity worsens cardiometabolic risk factors. However, the combined effect of pre-sarcopenia and obesity on overt and subclinical cardiovascular disease (CVD) has yet to be explored. We aimed to investigate the interaction of reduced skeletal muscle mass and abdominal obesity on coronary artery calcification (CAC).

Methods A total of 19,728 adults free of CVD who contemporaneously underwent cardiac tomography for estimating CAC scores and bioelectrical impedance analysis (BIA) at baseline were enrolled in the cross-sectional study. Among them, 5,401 subjects who had one and more follow-up CAC score were included in the longitudinal analysis. Skeletal muscle mass was presented using the skeletal muscle mass index (SMI) [SMI (%) = total appendicular muscle mass (kg)/body weight (kg) x 100] according to sex. CAC presence or incidence was defined as CAC score > 0, and CAC progression was defined as the square root-transformed difference between baseline and follow-up CAC scores > 2.5. Pre-sarcopenia was defined as SMI ≤ −1.0 standard deviation of the sex-specific mean of a young reference group (20-39 years). Abdominal obesity was defined as waist circumference ≥ 90 cm for men and ≥ 85 cm for women. All subjects were further classified into four groups: normal, abdominal obesity alone, pre-sarcopenia alone, and pre-sarcopenic obesity.

Results In total subjects, the normal group was the most common at 57.8%, the abdominal obesity group was 20.4%, the pre-sarcopenic obesity group was 14.3%, and the pre-sarcopenia group was the lowest at 7.5%. The pre-sarcopenic obesity group showed the highest adjusted hazard ratios (AHRs) for CAC presence (AHR 2.16, 95% confident interval [CI]: 1.98-2.36, P <0.001) as well as total events of CAC incidence and progression (AHR 1.54, 95% CI: 1.37 – 1.75, P < 0.001), and the risks were significant compared with those of normal subjects. Pre-sarcopenic obesity significantly increased the risk of CAC incidence and progression compared to either pre-sarcopenia or abdominal obesity alone.

Conclusions The coexistence of pre-sarcopenia and abdominal obesity was significantly associated with a higher risk of CAC presence and increases the risk of CAC incidence and progression independent of traditional CVD risk factors.

Background

Changes in body composition with decreasing muscle mass accompanied by increasing fat mass are associated with advanced age, although weight and body mass index (BMI) may remain relatively unchanged [1, 2]. Reduced skeletal muscle mass and abdominal obesity have a reciprocal influence on each other: low physical activity is associated with sarcopenia, which leads to decreased energy expenditure and increased risk of obesity [3]. Vice versa, visceral obesity is independently associated with future loss of skeletal muscle mass [4]. The loss of skeletal muscle mass and obesity concomitantly worsens cardiometabolic parameters such as hyperglycemia, hypertension, dyslipidemia, and insulin resistance, compared with sarcopenia or obesity alone [5, 6].

However, studies have not shown a consistent association between sarcopenic obesity and cardiovascular disease (CVD) risk. In a prospective study, not muscle mass but strength with obesity was associated with an increased CVD risk [7]. Other cross-sectional studies reported that the subjects with obesity alone have a larger number of CVD risk factors than those with both sarcopenia and obesity [8, 9]. It is unclear that not only overt CVD but subclinical atherosclerosis is associated with sarcopenic obesity. Moreover, the effect of reduced skeletal muscle mass on CVD in relatively younger population has yet to be explored.

As an estimate of coronary atherosclerosis, coronary artery calcification (CAC) has been convenient tool for detection of subclinical CVD and prognostic stratification of asymptomatic individuals [10]. CAC expressed as the Agatstone score can improve discrimination for CVD in the general population beyond established risk prediction tools [11]. Therefore, the objective of this study was to evaluate the combined effect of reduced skeletal muscle mass and abdominal obesity on the presence, incidence and progression of CAC in general population, and to compare it with reduced skeletal muscle mass or abdominal obesity alone.

Methods

Participants

A total of 26,976 adults aged ≥ 20 years contemporaneously underwent baseline or one and more follow-up cardiac CTs for CAC scoring and baseline bioelectrical impedance analysis (BIA) for measuring appendicular skeletal muscle mass (ASM) as a part of voluntary health checkup from January 2006 through December 2013 at the Health Promotion Center at Samsung Medical Center, Seoul, Republic of Korea. The subjects with a past history of CVD such as coronary artery disease, stroke, or heart failure (N = 1,318), those with elevated total bilirubin or liver enzymes more than twice the upper normal limit (N = 817), those with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (N = 369), and those with missing data (N = 4,744) were excluded (Fig. 1). Therefore, 19,728 subjects were included in the cross-sectional study to evaluate the association between skeletal muscle mass index (SMI) and CAC presence. Among them, 5,401 subjects were finally included in the longitudinal analysis study to evaluate the association between SMI and future CAC incidence or progression after excluding 14,327 subjects without follow-up CAC scores (Fig. 1).

Measurements of anthropometric and cardiometabolic parameters

Individual medical history, smoking status, exercise frequency, and current medications were assessed by a structured questionnaire at the first medical checkup. Smoking status was categorized as never, ex-smoker, or current smoker. Exercise status was assessed as none or as frequent exercise if any kind of physical exercise was performed more than three times a week. BMI was defined as body weight (kilograms) divided by the square of body height (meters). Waist circumference (WC) was measured

between the lower border of the rib cage and the iliac crest using a flexible tape. Blood pressure (BP) was recorded to the nearest 2 mmHg by a mercury sphygmomanometer with the arm supported at heart level after sitting quietly for 5 min.

Fasting plasma glucose and insulin levels were measured using the hexokinase method with Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany) and an immunoradiometric assay (DIAsource Co., Louvain-la-Neuve, Belgium), after fasting for at least 12 h. Hemoglobin A1c (HbA1c) levels were measured by automated glycohemoglobin analyzer (TOSOH, Yokkaichi, Japan). Total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine were measured using a Modular D2400 (Roche Diagnostics, Basel, Switzerland). High-sensitivity C-reactive protein (hs-CRP) was determined using the CRP (II) Latax X2 turbidimetric method (Hitachi Corporation, Tokyo, Japan). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [12].

The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated from the following formula: fasting insulin (μIU/mL) x fasting glucose (mg/dL)/405 [13]. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or current antidiabetic drug use. Hypertension was defined as BP greater than or equal to 140/90 mmHg or current antihypertensive drug use.

Measurements of SMI and definitions of different body composition groups

ASM for both arms and legs and body fat were assessed by multifrequency BIA (InBody 720; Biospace, Seoul, Korea). Skeletal muscle mass index (SMI) was calculated by dividing the sum of the ASM in the bilateral upper and lower four limbs (kg) by body weight (kg) and expressed as a percentage [14].

Pre-sarcopenia was characterized by low muscle mass without any decrease in muscle strength or physical performance [15], and defined as an SMI less than − 1.0 standard deviation (SD) of the sex-specific mean of a young reference group (20 to 39 years old) who did not have chronic medical disease (Supplementary Table 1); men 33.6 ± 2.8% and women 29.5 ± 2.9%, 1 SD cut-off: men 30.9% and women 26.7%. Abdominal obesity was defined as a WC ≥ 90 cm for men and ≥ 85 cm for women, according to WC cutoff points for central obesity in Korean adults [16, 17]. Therefore, pre-sarcopenic obesity was defined as the presence of both pre-sarcopenia and abdominal obesity. All enrolled subjects were classified into four groups: normal (neither pre-sarcopenia nor abdominal obesity), abdominal obesity alone, pre-sarcopenia alone, and pre-sarcopenic obesity.

Measurements of CAC

CAC was evaluated using a Brilliance 40 (Philips Medical Systems), VCT LightSpeed 64 (GE Healthcare), or Discovery 750HD (GE Healthcare) multidetector CT scanner. Analysis of the scans was performed on an Extended Brilliance Workspace (Philips Medical Systems) or Advantage (GE healthcare) workstation. The quantitative CAC score was calculated and classified according to the method described by Agatston

et al., and considered as severity [18] none: 0; minimal: <10; mild: 10–100; moderate: 101–400; severe: >400 [15]. CAC presence was defined as detectable CAC (CAC score > 0) at baseline examination. CAC incidence was defined as CAC score > 0 at the follow-up examination in the subjects without detectable CAC (CAC score = 0) at baseline [19]. CAC progression was defined as a square root-transformed difference > 2.5, and the square root-transformed difference between baseline and follow-up CAC scores was calculated [√CAC score (follow-up) − √CAC score (baseline)] in subjects with detectable CAC at baseline [20].

Statistical analysis

All variables are presented as mean ± SD, median (interquartile range: 25th to 75th percentile), or percentages. Log-transformed (CAC + 1) and log-transformed hs-CRP values were used in the analysis due to skewed distribution. Analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables were used to assess the characteristics according to different body composition groups. If *P*-value of ANOVA was significant, post-hoc analysis was performed using Bonferroni tests.

In a cross-sectional analysis, logistic regression was used to estimate the association with CAC presence. In longitudinal analyses, Cox regression were used to compare the risk of incidence or progression of CAC in different groups, since proportional hazards assumption was not violated. A parametric Cox proportional hazard was calculated to account for interval censoring, where CAC incidence or progression had arisen between two irregular visits [21, 22]. For adjustment for possible covariates, Model 1 was adjusted for age and sex; Model 2 was further adjusted for LDL-cholesterol, diabetes, hypertension, smoking status, and frequent exercise; Model 3 was further adjusted for use of dyslipidemia medication and use of aspirin; and Model 4 was further adjusted for log (baseline CAC + 1). None of the variance inflation factor values exceeded 5.0, which was considered adequate to avoid multicollinearity.

P-values of less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed using STATA version 13.0 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics of study subjects

Among a total of 19,728 subjects, the normal population group was the most common at 57.8% (N = 11,394), the abdominal obesity alone group was 20.4% (N = 4,023), the pre-sarcopenic obesity group was 14.3% (N = 2,825), and the pre-sarcopenia alone group was the lowest at 7.5% (N = 1,486) (Table 1). Approximately 25.3% (N = 1,296) of the subjects were diagnosed with abdominal obesity alone, 13.7% (N = 740) with pre-sarcopenic obesity, and 6.4% (N = 347) with pre-sarcopenia alone among the 5,401 subjects who had follow-up CAC scores (Table 2).

Table 1
Baseline characteristics of total subjects according to body composition group in a cross-sectional cohort.

Variable	Total (N = 19,728)	Normal (N = 11,394)	Abdominal obesity alone (N = 4,023)	Pre-sarcopenia alone (N = 1,486)	Pre-sarcopenic obesity (N = 2,825)	*P* for ANOVA
Age (years)	53.4 ± 8.3	52.7 ± 8.0***	52.9 ± 8.0***	56.7 ± 8.5***	55.2 ± 8.9	< 0.001
Female, n (%)	3793 (19.2)	2235 (19.6)	345 (8.6)***	626 (42.1)***	587 (20.8)	< 0.001
Smoking status, n (%)						< 0.001
Current smoker	5532 (28.0)	3128 (27.5)	1397 (34.7)***	232 (15.6)***	775 (27.4)	
Ex-smoker	6390 (32.4)	3597 (31.5)	1480 (36.8)***	389 (26.2)***	924 (32.7)	
Non-smoker	7806 (39.6)	4669 (41.0)	1146 (28.5)***	865 (58.2)***	1126 (39.9)	
Frequent exercise#, n (%)	11125 (58.0)	6662 (59.9)***	2117 (53.7)	862 (60.5)**	1484 (54.9)	< 0.001
Systolic BP (mmHg)	120.5 ± 16.0	118.3 ± 15.6***	122.0 ± 15.4***	122.9 ± 17.0***	125.5 ± 16.1	< 0.001
Diastolic BP (mmHg)	76.5 ± 10.7	75.4 ± 10.7***	76.0 ± 11.2	78.3 ± 10.3***	78.6 ± 10.5	< 0.001

All values are mean ± standard deviation, and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

***P < 0.001, **P < 0.01, *P < 0.05 for comparing pre-sarcopenic obesity group

#Frequent exercise was defined as any kind of physical exercise performed more than three times a week and was measured in 19,195 subjects.

†Data was measured in 13,319 subjects.

‡Data was measured in 17,345 subjects.

Variable	Total (N = 19,728)	Normal (N = 11,394)	Abdominal obesity alone (N = 4,023)	Pre-sarcopenia alone (N = 1,486)	Pre-sarcopenic obesity (N = 2,825)	*P* for ANOVA
Waist circumference (cm)						
Male	87.6 ± 7.2	83.0 ± 4.5***	93.6 ± 3.3***	85.7 ± 3.7***	96.8 ± 5.7	< 0.001
Female	79.8 ± 7.6	75.8 ± 5.2***	88.4 ± 3.5***	79.1 ± 4.1***	90.6 ± 5.4	< 0.001
Body weight (kg)	69.1 ± 10.6	65.0 ± 8.2***	77.4 ± 8.0	62.5 ± 8.2***	77.4 ± 11.1	< 0.001
Body mass index (kg/m^2)	24.3 ± 2.8	22.9 ± 2.0***	26.0 ± 1.8***	24.3 ± 1.9***	27.8 ± 2.6	< 0.001
ASM (kg)	22.0 ± 4.0	21.5 ± 3.6***	24.9 ± 3.2***	17.6 ± 3.4***	22.0 ± 4.0	< 0.001
ASM/weight (%)	31.8 ± 3.1	33.0 ± 2.6***	32.1 ± 1.7***	27.9 ± 2.4***	28.3 ± 2.3	< 0.001
ASM/BMI	0.90 ± 0.15	0.90 ± 0.17***	0.95 ± 0.13***	0.87 ± 0.08*	0.88 ± 0.08	< 0.001
Total cholesterol (mg/dL)	197.1 ± 34.2	195.8 ± 33.5***	196.9 ± 33.7**	203.4 ± 36.2***	199.2 ± 35.9	< 0.001
HDL cholesterol (mg/dL)	53.6 ± 13.8	55.8 ± 14.3***	49.5 ± 11.9	55.4 ± 13.6***	49.8 ± 12.3	< 0.001

All values are mean ± standard deviation, and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

***P < 0.001, **P < 0.01, *P < 0.05 for comparing pre-sarcopenic obesity group

#Frequent exercise was defined as any kind of physical exercise performed more than three times a week and was measured in 19,195 subjects.

†Data was measured in 13,319 subjects.

‡Data was measured in 17,345 subjects.

Variable	Total (N = 19,728)	Normal (N = 11,394)	Abdominal obesity alone (N = 4,023)	Pre-sarcopenia alone (N = 1,486)	Pre-sarcopenic obesity (N = 2,825)	*P* for ANOVA
LDL cholesterol (mg/dL)	125.4 ± 30.4	123.9 ± 29.8***	126.5 ± 30.3	129.7 ± 31.6	127.9 ± 31.9	< 0.001
Triglycerides (mg/dL)	132.1 ± 78.3	119.4 ± 70.8***	152.3 ± 87.3	131.8 ± 76.8***	154.8 ± 82.8	< 0.001
Glycemic status						
HbA1c (%)	5.67 ± 0.69	5.59 ± 0.65***	5.72 ± 0.69***	5.69 ± 0.62***	5.87 ± 0.82	< 0.001
Fasting plasma glucose (mg/dL)	97.6 ± 18.5	95.5 ± 17.4***	99.8 ± 18.5***	97.5 ± 17.2***	102.6 ± 21.6	< 0.001
Fasting insulin (uIU/mL)†	7.8 ± 4.7	6.5 ± 3.8***	8.8 ± 4.5***	8.2 ± 4.3***	11.0 ± 6.0	< 0.001
Fasting C-peptide (ng/mL)†	1.93 ± 0.90	1.66 ± 0.67***	2.22 ± 0.80***	1.92 ± 0.76***	2.58 ± 1.32	< 0.001
HOMA-IR†	1.9 ± 1.3	1.6 ± 1.0***	2.2 ± 0.8***	2.0 ± 0.8***	2.6 ± 1.3	< 0.001
Diabetes, n (%)	2441 (12.4)	1105 (9.7)***	597 (14.8)***	181 (12.2)***	558 (19.8)	< 0.001
Estimated GFR (mL/min/1.73 m^2)	89.3 ± 13.9	89.1 ± 13.4***	88.1 ± 13.8***	91.9 ± 15.2**	90.4 ± 15.0	< 0.001
Log CRP (mg/dL)‡	-1.16 ± 0.38	-1.22 ± 0.37***	-1.12 ± 0.39***	-1.12 ± 0.39***	-1.02 ± 0.39	< 0.001

All values are mean ± standard deviation, and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

***P < 0.001, **P < 0.01, *P < 0.05 for comparing pre-sarcopenic obesity group

#Frequent exercise was defined as any kind of physical exercise performed more than three times a week and was measured in 19,195 subjects.

†Data was measured in 13,319 subjects.

‡Data was measured in 17,345 subjects.

Variable	Total (N = 19,728)	Normal (N = 11,394)	Abdominal obesity alone (N = 4,023)	Pre-sarcopenia alone (N = 1,486)	Pre-sarcopenic obesity (N = 2,825)	*P* for ANOVA
Medications						
Anti-hypertensive medication use, n (%)	4483 (22.7)	1927 (16.9)***	1043 (25.9)***	431 (29.0)***	1082 (38.3)	< 0.001
Lipid-lowering drugs use, n (%)	1559 (7.9)	715 (6.3)***	354 (8.8)***	148 (10.0)*	342 (12.1)	< 0.001
Aspirin use, n (%)	2239 (11.3)	1042 (9.1)***	504 (12.5)***	212 (14.3)*	481 (17.0)	< 0.001
Log (CAC score + 1)	0.59 ± 0.88	0.48 ± 0.79***	0.54 ± 0.81***	0.95 ± 1.08	0.91 ± 1.07	< 0.001

All values are mean ± standard deviation, and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

***P < 0.001, **P < 0.01, *P < 0.05 for comparing pre-sarcopenic obesity group

#Frequent exercise was defined as any kind of physical exercise performed more than three times a week and was measured in 19,195 subjects.

†Data was measured in 13,319 subjects.

‡Data was measured in 17,345 subjects.

Table 2
Baseline characteristics according to body composition group for the development and progression of coronary artery calcification in a longitudinal cohort

Variable	Total (N = 5,401)	Normal (N = 3,018)	Abdominal obesity alone (N = 1,296)	Pre-sarcopenia alone (N = 347)	Pre-sarcopenic obesity (N = 740)	*P* for ANOVA
Age (years)	54.3 ± 7.7	53.7 ± 7.3***	53.5 ± 7.1***	57.6 ± 8.3	56.7 ± 8.8	< 0.001
Female, n (%)	526 (9.7)	253 (8.4)	43 (3.3)***	127 (36.6)	103 (13.9)	0.060
Smoking status, n (%)						0.032
Current smoker	1601 (29.6)	874 (29.0)	453 (35.0)**	53 (15.3)***	221 (29.9)	
Ex-smoker	2082 (38.5)	1178 (39.0)	514 (39.7)	106 (30.5)***	284 (38.4)	
Non-smoker	1718 (31.8)	966 (32,0)	329 (25.4)**	188 (54.2)***	235 (31.8)	
Frequent exercise, n (%)	2326 (43.1)	1258 (41.7)	632 (48.8)**	127 (36.6)	309 (41.8)	0.027
Systolic BP (mmHg)	119.6 ± 15.6	117.4 ± 15.1***	121.3 ± 15.4***	122.6 ± 15.9	124.4 ± 15.9	< 0.001
Diastolic BP (mmHg)	76.1 ± 10.4	75.1 ± 10.2***	77.7 ± 10.4	75.6 ± 11.0**	78.0 ± 10.6	< 0.001
Waist Circumference (cm)						

All values are mean ± standard deviation, median (25th-75th quartile) and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

***P < 0.001, **P < 0.01, *P < 0.05 for comparing SO group

#Data was measured in 3,886 subjects.

†Data was measured in 5,215 subjects.

Variable	Total (N = 5,401)	Normal (N = 3,018)	Abdominal obesity alone (N = 1,296)	Pre-sarcopenia alone (N = 347)	Pre-sarcopenic obesity (N = 740)	*P* for ANOVA
Male	87.7 ± 6.8	83.3 ± 4.3***	93.5 ± 3.3***	85.8 ± 3.8***	96.2 ± 5.0	< 0.001
Female	80.0 ± 7.9	75.5 ± 5.8***	88.5 ± 3.6	78.2 ± 4.7***	90.0 ± 4.5	< 0.001
Body weight (kg)	70.8 ± 9.5	66.8 ± 7.3***	78.2 ± 7.1	63.1 ± 8.0***	77.3 ± 9.9	< 0.001
BMI (kg/m^2)	24.6 ± 2.6	23.3 ± 1.9***	26.2 ± 1.7***	24.3 ± 2.0***	27.7 ± 2.4	< 0.001
ASM (kg)	22.7 ± 3.4	22.3 ± 2.9	25.1 ± 2.7***	18.0 ± 3.3***	22.2 ± 3.4	< 0.001
ASM/weight (%)	32.0 ± 2.7	33.3 ± 2.1***	32.1 ± 1.4***	28.3 ± 2.1*	28.6 ± 2.0	< 0.001
ASM/BMI	0.92 ± 0.13	0.95 ± 0.11***	0.96 ± 0.09***	0.74 ± 0.10***	0.80 ± 0.10	< 0.001
Total cholesterol (mg/dL)	195.4 ± 33.1	194.7 ± 33.0	194.7 ± 32.0	202.2 ± 35.9*	196.3 ± 33.6	0.001
HDL cholesterol (mg/dL)	51.9 ± 12.9	53.7 ± 13.3***	48.5 ± 11.2	54.7 ± 13.8***	49.4 ± 12.0	< 0.001
LDL cholesterol (mg/dL)	124.1 ± 29.1	123.3 ± 28.9	124.8 ± 28.8	127.3 ± 31.4	124.8 ± 29.7	0.046
Triglycerides (mg/dL)	140.9 ± 81.4	128.7 ± 77.6***	157.9 ± 85.7	140.4 ± 78.9***	160.8 ± 81.0	< 0.001
Glycemic status						

All values are mean ± standard deviation, median (25th-75th quartile) and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

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Variable	Total (N = 5,401)	Normal (N = 3,018)	Abdominal obesity alone (N = 1,296)	Pre-sarcopenia alone (N = 347)	Pre-sarcopenic obesity (N = 740)	*P* for ANOVA
HbA1c (%)	5.67 ± 0.73	5.60 ± 0.72***	5.72 ± 0.68***	5.76 ± 0.73	5.86 ± 0.77	< 0.001
Fasting plasma glucose (mg/dL)	98.3 ± 19.5	96.4 ± 19.0***	99.9 ± 18.8*	100.0 ± 20.5	102.6 ± 21.4	< 0.001
Fasting insulin (uIU/mL)#	8.9 ± 4.8	7.8 ± 4.2***	10.1 ± 4.5***	9.0 ± 4.2***	11.8 ± 5.8	< 0.001
Fasting C-peptide (ng/mL)#	2.0 ± 1.0	1.8 ± 0.7***	2.3 ± 0.8***	2.0 ± 0.7***	2.7 ± 1.9	< 0.001
HOMA-IR#	2.2 ± 1.4	1.9 ± 1.3***	2.5 ± 1.2***	2.2 ± 1.2***	2.7 ± 1.9	< 0.001
Diabetes, n (%)	748 (13.8)	341 (11.3)***	194 (15.0)**	61 (17.6)	152 (20.5)	< 0.001
Estimated GFR (mL/min/1.73 m^2)	87.7 ± 13.0	87.1 ± 12.3***	87.6 ± 13.5	90.0 ± 14.9	89.0 ± 13.5	< 0.001
Log CRP (mg/dL)†	-1.15 ± 0.39	-1.19 ± 0.38***	-1.10 ± 0.40**	-1.12 ± 0.37**	-1.04 ± 0.39	< 0.001
Medications						
Anti-hypertensive medication use, n (%)	1424 (26.4)	609 (20.2)***	375 (28.9)***	115 (33.1)	325 (43.9)	< 0.001
Lipid-lowering drugs use, n (%)	693 (12.8)	347 (11.5)**	171 (13.2)	58 (16.7)	117 (15.8)	0.002

All values are mean ± standard deviation, median (25th-75th quartile) and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

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#Data was measured in 3,886 subjects.

†Data was measured in 5,215 subjects.

Variable	Total (N = 5,401)	Normal (N = 3,018)	Abdominal obesity alone (N = 1,296)	Pre-sarcopenia alone (N = 347)	Pre-sarcopenic obesity (N = 740)	*P* for ANOVA
Aspirin use, n (%)	877 (16.2)	418 (13.9)***	217 (16.7)**	83 (23.9)	159 (21.5)	< 0.001
Baseline CAC						< 0.001
None, n (%)	1933 (35.8)	1231 (40.8)***	489 (37.7)***	95 (27.4)***	118 (15.9)	
Minimal to mild, n (%)	2350 (43.5)	1243 (41.2)***	542 (41.8)***	159 (45.8)***	406 (54.9)	
Moderate, n (%)	845 (15.6)	421 (13.9)***	193 (14.9)***	71 (20.5)	160 (21.6)	
Severe, n (%)	273 (5.1)	123 (4.1)***	72 (5.6)***	22 (6.3)*	56 (7.6)	
Duration of follow-up (year)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.056
Number of measurements	2.3 (1.8–3.9)	2.5 (1.9–4.0)	2.3 (1.8–3.9)	2.1 (1.5–3.9)	2.1 (1.5–3.3)	< 0.001

All values are mean ± standard deviation, median (25th-75th quartile) and categorical variables are expressed as percent (%).

BP, blood pressure; BMI, body mass index; ASM, appendicular skeletal muscle mass; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR; homeostatic model assessment for insulin resistance; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; GFR, glomerular filtration rate; CRP, C-reactive protein; CAC, coronary artery calcification; ANOVA, analysis of variance.

***P < 0.001, **P < 0.01, *P < 0.05 for comparing SO group

#Data was measured in 3,886 subjects.

†Data was measured in 5,215 subjects.

In post-hoc analyses (Tables 1 and 2, marked with asterisks), the subjects with pre-sarcopenic obesity were older and had a higher proportion of women or less current smoker compared to those with abdominal obesity alone, while the subjects with pre-sarcopenic obesity were younger and had a smaller proportion of women or more current smoker compared to those with pre-sarcopenia alone. The pre-sarcopenic obesity group had the worst metabolic parameters such as higher BP, worse glycemic parameters, and more increased HOMA-IR and log hs-CRP level, compared to pre-sarcopenia alone or abdominal obesity alone group. The subjects with pre-sarcopenic obesity also had a greater proportion of

using anti-hypertensive drug, lipid-lowering medication, or aspirin than those with pre-sarcopenic obesity alone.

Risk of CAC presence in the pre-sarcopenic obesity group

The prevalence of total CAC was 36.7% (N = 7,248) (Table 3); minimal to mild CAC was 32.9% (N = 6,494), moderate CAC was 2.8% (N = 555), and severe CAC was 1.0% (N = 199). The pre-sarcopenic group had the highest risk for CAC presence in adjusted models (adjusted odds ratio [OR] 2.16, 95% confidence interval [CI] 1.98–2.36, $P < 0.001$) with the normal group as a reference (Table 3). Despite no difference with the pre-sarcopenia alone group, the crude and adjusted ORs of the pre-sarcopenic group for CAC presence were significantly higher than those of the abdominal obesity alone or normal group (Fig. 2A and Supplementary Table 2). In subgroup analyses (Supplementary Table 3), the pre-sarcopenic obesity group had consistently highest risk regardless of diabetes, hypertension, and smoking status (P for interaction > 0.05), but there was an interaction in the age and sex subgroups.

Table 3
Odds ratios of CAC presence among groups with abdominal obesity alone, pre-sarcopenia alone, and pre-sarcopenic obesity.

	Normal (N = 11394)	**Abdominal obesity alone (N = 4023)**		**Pre-sarcopenia alone (N = 1486)**		**Pre-sarcopenic obesity (N = 2825)**		
Presence, n (%)	3598 (31.6)	1465 (36.4)		772 (52.0)		1413 (50.0)		
Severity, n (%)								
None	7796 (68.4)	2558 (63.6)		714 (48.0)		1412 (50.0)		
Minimal - mild	3335 (29.3)	1306 (32.5)		670 (45.1)		1183 (41.9)		
Moderate	205 (1.8)	114 (2.8)		75 (5.0)		161 (5.7)		
Severe	58 (0.5)	45 (1.1)		27 (1.8)		69 (2.4)		
	Normal	**Abdominal obesity alone**		**Pre-sarcopenia alone**		**Pre-sarcopenic obesity**		
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	*P* for trend
CAC presence								
Crude	1 (reference)	1.24 (1.15–1.34)	< 0.001	2.34 (2.10–2.61)	< 0.001	2.17 (1.99–2.36)	< 0.001	< 0.001
Model 1	1 (reference)	1.37 (1.27–1.48)	< 0.001	1.98 (1.77–2.22)	< 0.001	2.18 (2.00–2.37)	< 0.001	< 0.001
Model 2	1 (reference)	1.36 (1.26–1.48)	< 0.001	1.98 (1.76–2.22)	< 0.001	2.16 (1.98–2.36)	< 0.001	< 0.001
Model 3	1 (reference)	1.36 (1.26–1.48)	< 0.001	1.98 (1.76–2.22)	< 0.001	2.16 (1.98–2.36)	< 0.001	< 0.001
Moderate and severe CAC presence								

Model 1: adjusted for age and sex.

Model 2: adjusted for Model 1 plus LDL-cholesterol, diabetes, hypertension, smoking status, and frequent exercise.

Model 3: adjusted for Model 2 plus use of dyslipidemia medication and use of aspirin.

	Normal (N = 11394)	Abdominal obesity alone (N = 4023)		Pre-sarcopenia alone (N = 1486)		Pre-sarcopenic obesity (N = 2825)		
Crude	1 (reference)	1.74 (1.43–2.13)	< 0.001	3.12 (2.47–3.95)	< 0.001	3.75 (3.13–4.50)	< 0.001	< 0.001
Model 1	1 (reference)	1.68 (1.37–2.07)	< 0.001	2.21 (1.72–2.83)	< 0.001	2.90 (2.40–3.51)	< 0.001	< 0.001
Model 2	1 (reference)	1.52 (1.23–1.87)	< 0.001	2.00 (1.55–1.58)	< 0.001	2.45 (2.01–2.98)	< 0.001	< 0.001
Model 3	1 (reference)	1.51 (1.23–1.86)	< 0.001	1.98 (1.53–2.56)	< 0.001	2.42 (1.99–2.94)	< 0.001	< 0.001
Severe CAC presence								
Crude	1 (reference)	2.21 (1.50–3.27)	< 0.001	3.62 (2.28–5.73)	< 0.001	4.89 (3.44–6.96)	< 0.001	< 0.001
Model 1	1 (reference)	2.12 (1.42–3.15)	0.002	2.16 (1.34–3.49)	0.021	3.34 (2.32–4.79)	< 0.001	< 0.001
Model 2	1 (reference)	1.90 (1.27–2.85)	0.002	1.98 (1.21–3.22)	0.006	2.72 (1.87–3.96)	< 0.001	< 0.001
Model 3	1 (reference)	1.90 (1.27–2.86)	0.002	1.95 (1.20–3.18)	0.007	2.71 (1.86–3.94)	< 0.001	< 0.001
Model 1: adjusted for age and sex.								
Model 2: adjusted for Model 1 plus LDL-cholesterol, diabetes, hypertension, smoking status, and frequent exercise.								
Model 3: adjusted for Model 2 plus use of dyslipidemia medication and use of aspirin.								

When we analyzed the risk of CAC by other obesity parameters such as BMI and body fat% (Supplementary Table 4), the pre-sarcopenic obesity group still had the highest risk of CAC presence after adjustment of other cardiometabolic risk factors, even higher than the normal, pre-sarcopenia alone, or abdominal obesity alone group.

Risk of CAC incidence and progression in the pre-sarcopenic obesity group

The total events rate including CAC incidence and progression was 32.8% (N = 990) for the normal group, 38.9% (N = 504) for the abdominal obesity alone group, 44.1% (N = 153) for the pre-sarcopenia alone group, and 56.8% (N = 740) for the pre-sarcopenic obesity group (Table 4). The respective proportion of incidence or progression was also the highest in the pre-sarcopenic obesity group (Table 4). The hazard ratio (HR) of total events was significant and highest in the pre-sarcopenic group in both crude (HR 2.22, 95% CI 1.98–2.49, $P < 0.001$) and adjusted models (adjusted HR 1.54, 95% CI 1.37–1.75, $P < 0.001$) (Table 4). The HR of total events was significantly higher than in the abdominal obesity alone or pre-sarcopenia alone group (Fig. 2B and Supplementary Table 2). Even when CAC incidence and progression were separately analyzed, the risk of the pre-sarcopenic obesity group remained highest. In subgroup analyses (Supplementary Table 5), the pre-sarcopenic obesity group still had the highest risk of CAC incidence and progression regardless of subgroup, although the effects of abdominal obesity alone or pre-sarcopenia alone was modest. However, there was an interaction in the hypertension subgroup.

Table 4
The risks of total events including CAC incidence and progression among groups with abdominal obesity alone, pre-sarcopenia alone, and pre-sarcopenic obesity.

	Normal (N = 3018)	**Abdominal obesity alone (N = 1296)**		**Pre-sarcopenia alone (N = 347)**		**Pre-sarcopenic obesity (N = 740)**		
Total events, n (%)	990 (32.8)	504 (38.9)		153 (44.1)		420 (56.8)		
Incidence, n (%)	188 (15.3)	99 (20.2)		17 (17.9)		33 (28.0)		
Progression, n (%)	802 (44.9)	405 (50.2)		136 (54.0)		387 (62.2)		
	HR (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	*P* for trend
Total events								
Crude	1 (reference)	1.27 (1.14–1.42)	< 0.001	1.55 (1.31–1.84)	< 0.001	2.22 (1.98–2.49)	< 0.001	< 0.001
Model 1	1 (reference)	1.28 (1.15–1.42)	< 0.001	1.48 (1.24–1.77)	< 0.001	2.02 (1.80–2.28)	< 0.001	< 0.001
Model 2	1 (reference)	1.19 (1.07–1.33)	0.001	1.38 (1.15–1.65)	< 0.001	1.74 (1.54–1.97)	< 0.001	< 0.001
Model 3	1 (reference)	1.21 (1.08–1.35)	0.001	1.39 (1.16–1.67)	< 0.001	1.78 (1.58–2.01)	< 0.001	< 0.001
Model 4	1 (reference)	1.22 (1.09–1.36)	< 0.001	1.31 (1.09–1.56)	0.004	1.54 (1.37–1.75)	< 0.001	< 0.001
CAC incidence								

Model 1: adjusted for age and sex.

Model 2: adjusted for Model 1 plus LDL-cholesterol, diabetes, hypertension, smoking status, and frequent exercise.

Model 3: adjusted for Model 2 plus use of dyslipidemia medication and use of aspirin.

Model 4: adjusted for Model 3 plus log (CAC + 1).

	Normal (N = 3018)	Abdominal obesity alone (N = 1296)		Pre-sarcopenia alone (N = 347)		Pre-sarcopenic obesity (N = 740)		
Crude	1 (reference)	1.35 (1.06–1.72)	0.016	1.17 (0.71–1.92)	0.546	1.90 (1.31–2.76)	0.001	< 0.001
Model 1	1 (reference)	1.31 (1.03–1.67)	0.031	1.49 (0.85–2.60)	0.162	1.94 (1.33–2.83)	0.001	< 0.001
Model 2	1 (reference)	1.22 (0.95–1.56)	0.116	1.37 (0.78–2.41)	0.271	1.72 (1.17–2.52)	0.005	0.007
Model 3	1 (reference)	1.22 (0.95–1.56)	0.120	1.35 (0.77–2.37)	0.298	1.70 (1.16–2.49)	0.006	0.008
CAC progression								
Crude	1 (reference)	1.25 (1.10–1.41)	< 0.001	1.39 (1.16–1.68)	< 0.001	1.60 (1.42–1.81)	< 0.001	< 0.001
Model 1	1 (reference)	1.25 (1.10–1.41)	< 0.001	1.38 (1.15–1.67)	0.001	1.60 (1.41–1.81)	< 0.001	< 0.001
Model 2	1 (reference)	1.19 (1.05–1.35)	0.007	1.34 (1.10–1.62)	0.003	1.46 (1.28–1.66)	< 0.001	< 0.001
Model 3	1 (reference)	1.19 (1.05–1.35)	0.006	1.34 (1.10–1.63)	0.003	1.48 (1.30–1.69)	< 0.001	< 0.001
Model 4	1 (reference)	1.21 (1.06–1.37)	0.004	1.32 (1.09–1.61)	0.005	1.50 (1.32–1.71)	< 0.001	< 0.001
Model 1: adjusted for age and sex.								
Model 2: adjusted for Model 1 plus LDL-cholesterol, diabetes, hypertension, smoking status, and frequent exercise.								
Model 3: adjusted for Model 2 plus use of dyslipidemia medication and use of aspirin.								
Model 4: adjusted for Model 3 plus log (CAC + 1).								

The pre-sarcopenic obesity group still had a significantly higher risk of CAC incidence and progression than the normal, abdominal obesity alone, or pre-sarcopenia alone group, when we analyzed the risk of CAC using other obesity parameters such as BMI and body fat% (Supplementary Table 6).

Discussion

CAC implies the presence of coronary artery disease regardless of concurrent risk factors or related symptoms [23]. CAC is usually concomitant with advanced atherosclerosis and thus is an established predictor of future cardiac events [24, 25]. In this cross-sectional and longitudinal study, pre-sarcopenic obesity had the highest risk of CAC presence, incidence, and progression among different body composition subtypes, and the risks were significantly higher compared with those of normal subjects. Pre-sarcopenic obesity significantly increased the risk of CAC presence compared to abdominal obesity alone in addition to the risk of CAC incidence and progression compared with either pre-sarcopenia alone or abdominal obesity alone, regardless of other cardiometabolic risk factors.

According to Asian Working Group for Sarcopenia, low ASM with low muscle strength or low physical performance need to diagnose sarcopenia [26]. Therefore, most of the studies on sarcopenia investigated pre-sarcopenia which measured low skeletal muscle mass only. The pre-sarcopenic obesity group defined by ASM/weight < 1 SD and visceral fat area > 100 cm^2 on abdominal CT was more susceptible to insulin resistance and CVD than the obesity or pre-sarcopenia alone group [5]. Individuals with pre-sarcopenic obesity defined by ASM/weight < 1 SD and BMI ≥ 25 kg/m^2 had significantly higher 10-year CVD risk (≥ 20%) determined using the Framingham risk model, whereas pre-sarcopenic non-obese and non-presarcopenic obese individuals were not associated with 10-year CVD risk [27]. Pre-sarcopenic obesity defined by ASM/$height^2$ less than 7.0 kg/m^2 (in men) or 5.4 kg/m^2 (in women) and android to gynoid ratio of higher than the sex-specific median value was significantly and positively associated with incident CVD in subjects with type 2 diabetes, while pre-sarcopenia alone or obesity alone was not [28]. However, pre-sarcopenia with obesity classified according to total adiposity parameter (body fat % or BMI) was not associated with CVD events [28]. A large longitudinal study found that high WC with low muscle strength was modestly associated with CVD risk during 10 years of follow-up, but high WC with low muscle mass was not associated with CVD risk [7]. Low skeletal muscle mass, obesity, and pre-sarcopenic obesity were distinctively associated with a higher risk of CVD events than the reference, but these associations lost statistical significance after adjustment for other covariates [2]. Although there have been conflicting results regarding the association between pre-sarcopenic obesity and CVD, our study to evaluate for the first time that subclinical CVD assessed by CAC presence, incidence, and progression had significant and consistent associations between pre-sarcopenic obesity, suggesting possible connections between incremental risk of pre-sarcopenia and obesity for future CVD. Aside from abdominal obesity, pre-sarcopenic obesity still had a significantly higher risk of CAC presence, incidence, and progression when obesity was defined using BMI or body fat% in this study.

Crucially, pre-sarcopenia defined as SMI less than − 1 SD below the mean value of young individuals represents early stage of the sarcopenia, compared with other definitions using a cut-off value of -2 SD below the mean [29] or using absolute value of men < 7.0 kg/m^2 and women < 5.7 kg/m^2 [26]. If a cut-off value of -2 SD below the mean was used, only 13.7% of total subjects had pre-sarcopenia, and if aforementioned absolute value was used, only 10.2% had pre-sarcopenia. However, even majority of the subjects had modestly low skeletal muscle mass, pre-sarcopenia per se was still associated with an

increased risk of CAC, and additively aggravated the risk of CAC with abdominal obesity. Moreover, in relatively younger subjects (< 60 years) who might preserve enough muscle mass and strength, pre-sarcopenic obesity showed similar risk of CAC incidence and progression, compared with elderly subjects. The additive effect of pre-sarcopenia and abdominal obesity on CAC was still significant in the subjects with and without diabetes.

There is no consensus about which skeletal muscle mass or obesity parameters can best predict CVD, particularly among Asians. In regards to the methodology adopted in this study, ASM/weight was used because it is thought to be a better predictor of insulin resistance and cardiometabolic parameters in the Korean population [5, 30]. Our unpublished data also show that weight-adjusted ASM is more closely associated with CAC presence, incidence, and progression compared with other SMI parameters (ASM/BMI and ASM/height^2). In fact, brachial-ankle pulse wave velocity, another marker for reflecting atherosclerotic burden, was also higher in sarcopenic subjects than in normal subjects when sarcopenia was defined by ASM/weight but not by ASM/height^2 [30]. Compared with Western populations, Asian people tend to have lower muscle mass and higher body fat mass with central distribution. With aging, Asian people present with greater increases in fat mass and higher prevalence of abdominal obesity, especially in women [31]. BMI, WC, and waist to hip ratio are strongly correlated with measures of abdominal adiposity. In one Korean study, the best surrogate of abdominal adiposity across a wide age range was WC [40], and WC has been an important predictor of CVD independent of traditional risk factors, including BMI [32, 33]. BMI itself represents both fat mass as well as nonfat, or muscle mass, and cannot detect regional body fat such as visceral fat [34]. Therefore, both ASM/weight and WC may be good indicators for defining pre-sarcopenic obesity compared with other parameters.

The mechanisms underlying pre-sarcopenic obesity are multifactorial. Aging is one of the most crucial factors that contribute to a gradual loss of muscle mass and parallel increase in visceral fat [35]. A reduction in muscle mass and physical activity decreases total energy expenditure and glucose utilization and finally leads to elevated insulin resistance and obesity [36]. Increases in fat mass, particularly visceral fat, promote low-grade inflammation that results in the secretion of tumor necrosis factor (TNF), leptin, and growth hormone [37, 38], which leads to muscle catabolism. Elevated TNF inhibits adiponectin, arresting muscle protein synthesis and mitochondrial processes [39]. Leptin upregulates the pro-inflammatory IL-6 and TNF, which results in a reduction of the anabolic actions of insulin like growth factor-1 (IGF-1) [40]. Reduced growth hormone and IGF-1 decrease anabolic effects of leptin [41] and increase the likelihood of incident fragility [42]. In addition to visceral obesity, aging stimulates fat infiltration into muscle, and thus the deposition of intramyocellular lipids causes lipotoxicity impairing muscle fiber contractility and new muscle tissue growth, which contributes to sarcopenia [43]. Furthermore, higher fat mass at baseline is associated with a further decline in leg lean mass in both sexes [44]. Therefore, a vicious cycle may exist with low skeletal muscle mass and obesity having a reciprocal influence on each other.

The present study has some limitations. First, BIA could not precisely differentiate lipid, water, and fibrous tissue within muscle mass [45]. Considering the higher adiposity of Asian people, the muscle mass

measured by BIA may be overestimated in obese older people with high intramuscular fat infiltration. Second, sarcopenia is also a loss of muscle function in addition to muscle mass. But we could not assess functional outcomes due to the limitations of general health checkups. Third, postmenopausal state or use of estrogen which affects skeletal muscle mass in women could not be assessed due to the limitation of self-report. Finally, the enrolled subjects were all Korean, so our findings may not be generalizable to other ethnic groups, because the interaction between genes and the environment leads to different muscularity and adiposity in different ethnicities [46]. Besides, results could be biased if participants' characteristics at a single medical institute were not representative of the general Korean population.

Conclusions

Reduced skeletal muscle mass with increased adiposity is crucial change in body composition during the aging process. The pre-sarcopenic obesity showed the highest risk of CAC presence, incidence, and progression among different body composition groups, and pre-sarcopenic obesity significantly increased the risk of CAC incidence/progression more than either pre-sarcopenia or abdominal obesity alone. Together with abdominal obesity, pre-sarcopenia even without impact on muscle strength or physical performance may have an additive interaction to aggravate subclinical atherosclerosis. In addition to reducing abdominal fat, increasing skeletal muscle mass might be required to prevent future CVD.

List Of Abbreviations

BMI, Body mass index; SO, sarcopenic obesity; CVD, cardiovascular disease; CAC, coronary artery calcification; BIA, bioelectrical impedance analysis; ASM, appendicular skeletal muscle mass; eGFR; estimated glomerular filtration rate; SMI, skeletal muscle mass index; waist circumference, WC; BP, blood pressure; HbA1c, Hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment index for insulin resistance; SD, standard deviation.

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Review Board (IRB) of Samsung Seoul Hospital (2019-10-023) and was carried out in accordance with the recommendations of the Declaration of Helsinki. The requirement for written informed consent was waived.

Consent for publication:

Not applicable

Availability of data and materials:

Data are available from the the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions

JJK: Conceptualization, methodology, validation, review and editing, supervision; JJE: Conceptualization, data curation, data interpretation, writing – original draft; MK: data acquisition; KK: data interpretation and formal analyses; S-MJ, YCH, KJA, HYC, and I-KJ: review and editing, supervision. All authors contributed to the manuscript for important intellectual contents and approved the submission.

References

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM *et al*: **Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People**. *Age and ageing* 2010, **39**(4):412-423.
2. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG: **Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men**. *Journal of the American Geriatrics Society* 2014, **62**(2):253-260.
3. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V: **Sarcopenic obesity: a new category of obesity in the elderly**. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2008, **18**(5):388-395.
4. Kim TN, Park MS, Ryu JY, Choi HY, Hong HC, Yoo HJ, Kang HJ, Song W, Park SW, Baik SH *et al*: **Impact of visceral fat on skeletal muscle mass and vice versa in a prospective cohort study: the Korean Sarcopenic Obesity Study (KSOS)**. *PloS one* 2014, **9**(12):e115407.

5. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, Kim KW, Lim JY, Park KS, Jang HC: **Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA)**. *Diabetes care* 2010, **33**(7):1652-1654.
6. Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ: **Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity**. *Archives of gerontology and geriatrics* 2013, **56**(1):270-278.
7. Stephen WC, Janssen I: **Sarcopenic-obesity and cardiovascular disease risk in the elderly**. *The journal of nutrition, health & aging* 2009, **13**(5):460-466.
8. Messier V, Karelis AD, Lavoie ME, Brochu M, Faraj M, Strychar I, Rabasa-Lhoret R: **Metabolic profile and quality of life in class I sarcopenic overweight and obese postmenopausal women: a MONET study**. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 2009, **34**(1):18-24.
9. dos Santos EP, Gadelha AB, Safons MP, Nobrega OT, Oliveira RJ, Lima RM: **Sarcopenia and sarcopenic obesity classifications and cardiometabolic risks in older women**. *Archives of gerontology and geriatrics* 2014, **59**(1):56-61.
10. Faggiano P, Dasseni N, Gaibazzi N, Rossi A, Henein M, Pressman G: **Cardiac calcification as a marker of subclinical atherosclerosis and predictor of cardiovascular events: A review of the evidence**. *European journal of preventive cardiology* 2019, **26**(11):1191-1204.
11. Osawa K, Nakanishi R, Budoff MJ: **Is there a role for coronary artery calcification scoring in primary prevention of cerebrovascular disease?** *Atherosclerosis* 2017, **257**:279-287.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T *et al*: **A new equation to estimate glomerular filtration rate**. *Annals of internal medicine* 2009, **150**(9):604-612.
13. Levy JC, Matthews DR, Hermans MP: **Correct homeostasis model assessment (HOMA) evaluation uses the computer program**. *Diabetes care* 1998, **21**(12):2191-2192.
14. Janssen I, Heymsfield SB, Ross R: **Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability**. *Journal of the American Geriatrics Society* 2002, **50**(5):889-896.
15. Pereira FB, Leite AF, de Paula AP: **Relationship between pre-sarcopenia, sarcopenia and bone mineral density in elderly men**. *Archives of endocrinology and metabolism* 2015, **59**(1):59-65.
16. Lee SY, Park HS, Kim DJ, Han JH, Kim SM, Cho GJ, Kim DY, Kwon HS, Kim SR, Lee CB *et al*: **Appropriate waist circumference cutoff points for central obesity in Korean adults**. *Diabetes research and clinical practice* 2007, **75**(1):72-80.
17. Kim YS, Lee Y, Chung YS, Lee DJ, Joo NS, Hong D, Song G, Kim HJ, Choi YJ, Kim KM: **Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the Fourth Korean National Health and Nutritional Examination Surveys**. *The journals of gerontology Series A, Biological sciences and medical sciences* 2012, **67**(10):1107-1113.

18. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R: **Quantification of coronary artery calcium using ultrafast computed tomography**. *Journal of the American College of Cardiology* 1990, **15**(4):827-832.
19. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL: **Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA)**. *Circulation* 2007, **115**(21):2722-2730.
20. Hokanson JE, MacKenzie T, Kinney G, Snell-Bergeon JK, Dabelea D, Ehrlich J, Eckel RH, Rewers M: **Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability**. *AJR American journal of roentgenology* 2004, **182**(5):1327-1332.
21. Royston P, Parmar MK: **Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects**. *Statistics in medicine* 2002, **21**(15):2175-2197.
22. Jun JE, Lee YB, Lee SE, Ahn JY, Kim G, Jin SM, Hur KY, Lee MK, Kang MR, Kim JH: **Elevated serum uric acid predicts the development of moderate coronary artery calcification independent of conventional cardiovascular risk factors**. *Atherosclerosis* 2018, **272**:233-239.
23. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R: **Coronary Artery Calcification and its Progression: What Does it Really Mean?** *JACC Cardiovascular imaging* 2018, **11**(1):127-142.
24. Otsuka F, Sakakura K, Yahagi K, Joner M, Virmani R: **Has our understanding of calcification in human coronary atherosclerosis progressed?** *Arteriosclerosis, thrombosis, and vascular biology* 2014, **34**(4):724-736.
25. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, Carr JJ, Budoff MJ, Allison MA: **Calcium density of coronary artery plaque and risk of incident cardiovascular events**. *Jama* 2014, **311**(3):271-278.
26. Chen L-K, Woo J, Assantachai P, Auyeung T-W, Chou M-Y, Iijima K, Jang HC, Kang L, Kim M, Kim SJJotAMDA: **Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment**. 2020, **21**(3):300-307. e302.
27. Kim JH, Cho JJ, Park YS: **Relationship between sarcopenic obesity and cardiovascular disease risk as estimated by the Framingham risk score**. *Journal of Korean medical science* 2015, **30**(3):264-271.
28. Fukuda T, Bouchi R, Takeuchi T, Tsujimoto K, Minami I, Yoshimoto T, Ogawa Y: **Sarcopenic obesity assessed using dual energy X-ray absorptiometry (DXA) can predict cardiovascular disease in patients with type 2 diabetes: a retrospective observational study**. *Cardiovascular diabetology* 2018, **17**(1):55.
29. Janssen I, Heymsfield SB, Ross RJJotAGS: **Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability**. 2002, **50**(5):889-896.
30. Furushima T, Miyachi M, Iemitsu M, Murakami H, Kawano H, Gando Y, Kawakami R, Sanada K: **Comparison between clinical significance of height-adjusted and weight-adjusted appendicular skeletal muscle mass**. *Journal of physiological anthropology* 2017, **36**(1):15.

31. Wu Y-H, Hwang A-C, Liu L-K, Peng L-N, Chen L-K: **Sex differences of sarcopenia in Asian populations: the implications in diagnosis and management**. *Journal of Clinical Gerontology and Geriatrics* 2016, **7**(2):37-43.
32. Kragelund C, Omland T: **A farewell to body-mass index?** *The Lancet* 2005, **366**(9497):1589-1591.
33. Jee SH, Park SB: **Waist Circumference predicting Cardiovascular Disease in Korean Men and Women**. *Nature Precedings* 2010:1-1.
34. Iozzo P, Rossi G, Michelassi C, Landi P, Carpeggiani C: **Interpretation of the "obesity paradox": a 30-year study in patients with cardiovascular disease**. *International journal of cardiology* 2013, **168**(1):112-116.
35. Polyzos SA, Margioris AN: **Sarcopenic obesity**. *Hormones (Athens, Greece)* 2018, **17**(3):321-331.
36. Nair KS: **Aging muscle**. *The American journal of clinical nutrition* 2005, **81**(5):953-963.
37. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, Ferrucci L: **Sarcopenic obesity and inflammation in the InCHIANTI study**. *Journal of applied physiology (Bethesda, Md : 1985)* 2007, **102**(3):919-925.
38. Batsis JA, Villareal DT: **Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies**. *Nature reviews Endocrinology* 2018, **14**(9):513-537.
39. Lang CH, Frost RA, Nairn AC, MacLean DA, Vary TC: **TNF-alpha impairs heart and skeletal muscle protein synthesis by altering translation initiation**. *American journal of physiology Endocrinology and metabolism* 2002, **282**(2):E336-347.
40. Hamrick MW: **Role of the Cytokine-like Hormone Leptin in Muscle-bone Crosstalk with Aging**. *Journal of bone metabolism* 2017, **24**(1):1-8.
41. Procaccini C, Jirillo E, Matarese G: **Leptin as an immunomodulator**. *Molecular aspects of medicine* 2012, **33**(1):35-45.
42. Yeap BB, Paul Chubb SA, Lopez D, Ho KK, Hankey GJ, Flicker L: **Associations of insulin-like growth factor-I and its binding proteins and testosterone with frailty in older men**. *Clinical endocrinology* 2013, **78**(5):752-759.
43. Carnio S, LoVerso F, Baraibar MA, Longa E, Khan MM, Maffei M, Reischl M, Canepari M, Loefler S, Kern H *et al*: **Autophagy impairment in muscle induces neuromuscular junction degeneration and precocious aging**. *Cell reports* 2014, **8**(5):1509-1521.
44. Koster A, Ding J, Stenholm S, Caserotti P, Houston DK, Nicklas BJ, You T, Lee JS, Visser M, Newman AB *et al*: **Does the amount of fat mass predict age-related loss of lean mass, muscle strength, and muscle quality in older adults?** *The journals of gerontology Series A, Biological sciences and medical sciences* 2011, **66**(8):888-895.
45. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, Maggi S, Dennison E, Al-Daghri NM, Allepaerts S *et al*: **Pitfalls in the measurement of muscle mass: a need for a reference standard**. *Journal of cachexia, sarcopenia and muscle* 2018, **9**(2):269-278.

46. Wulan SN, Westerterp KR, Plasqui G: **Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians**. *Maturitas* 2010, **65**(4):315-319.

Figures

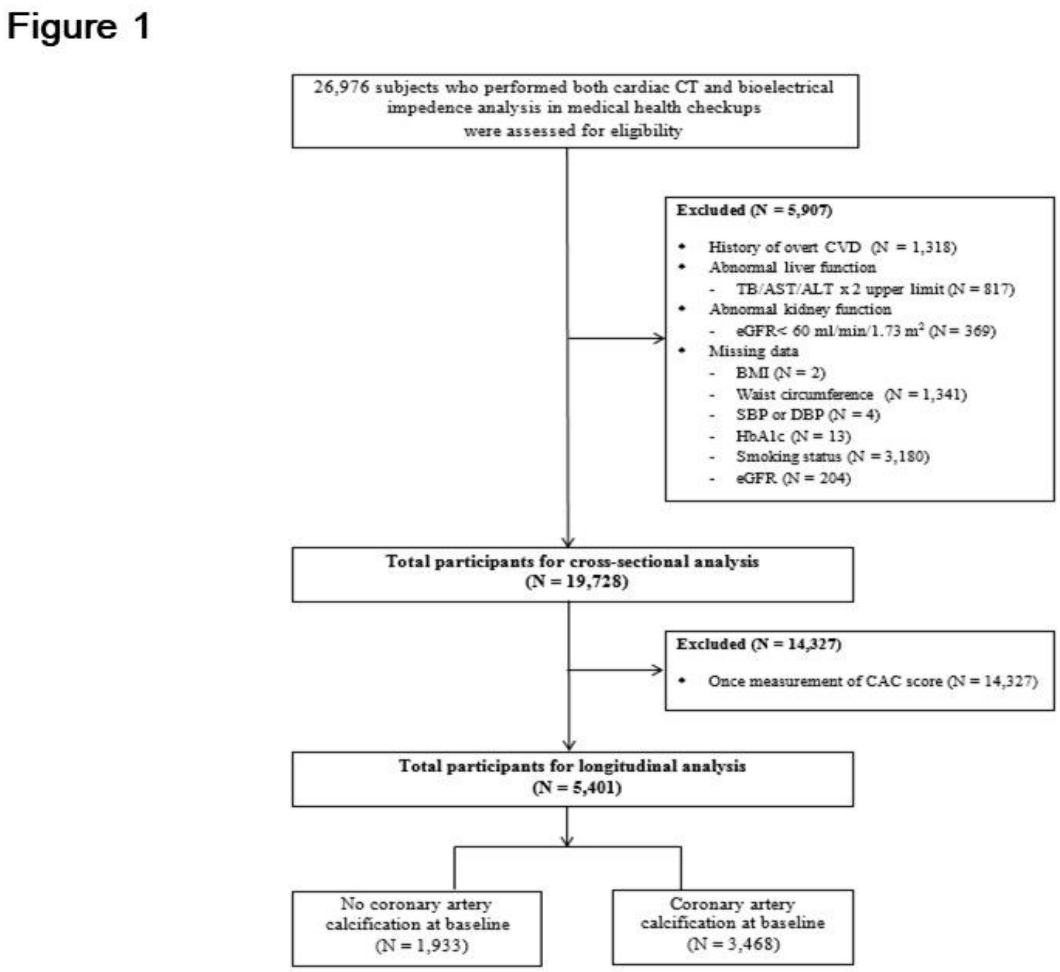

Figure 1

Flow chart of study subjects.

Figure 2A

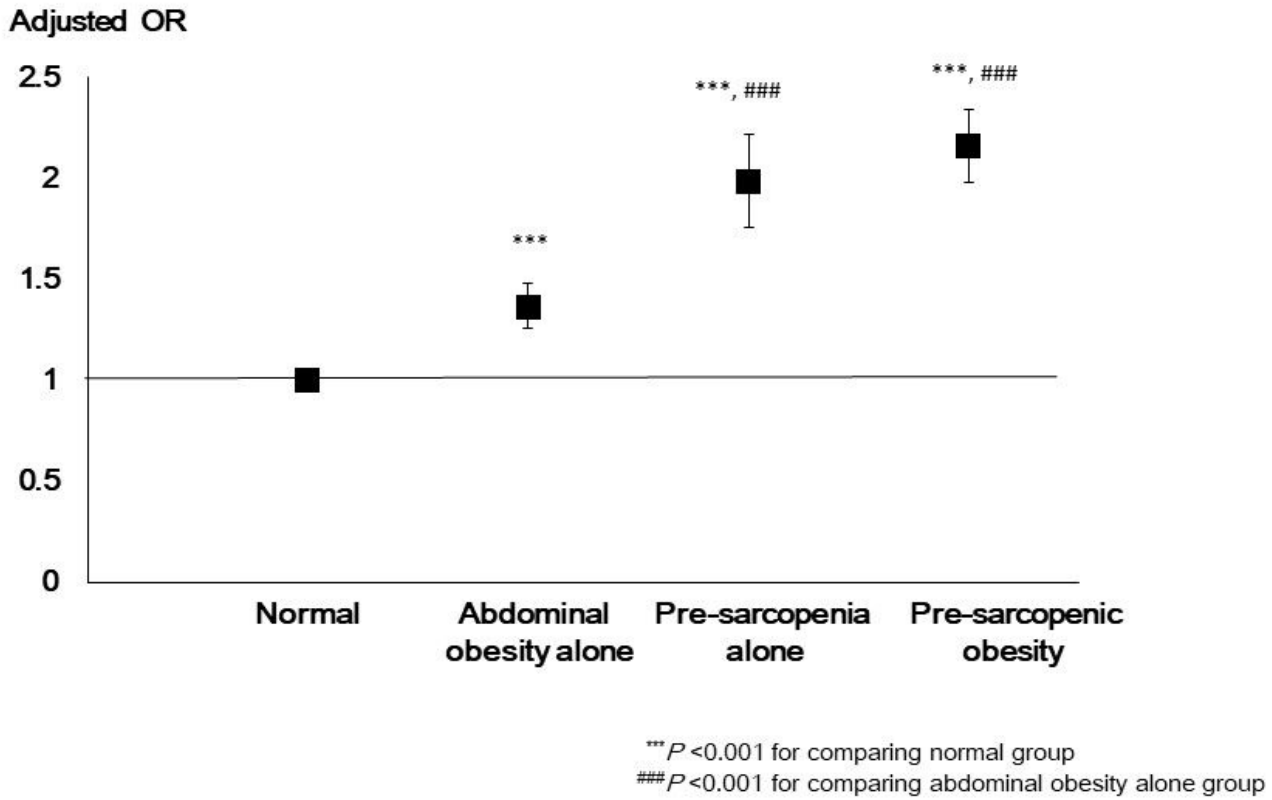

Figure 2

2A. Adjusted odds ratios of CAC presence among different body composition groups. ***P <0.001 for comparing normal group ###P <0.001 for comparing abdominal obesity alone group

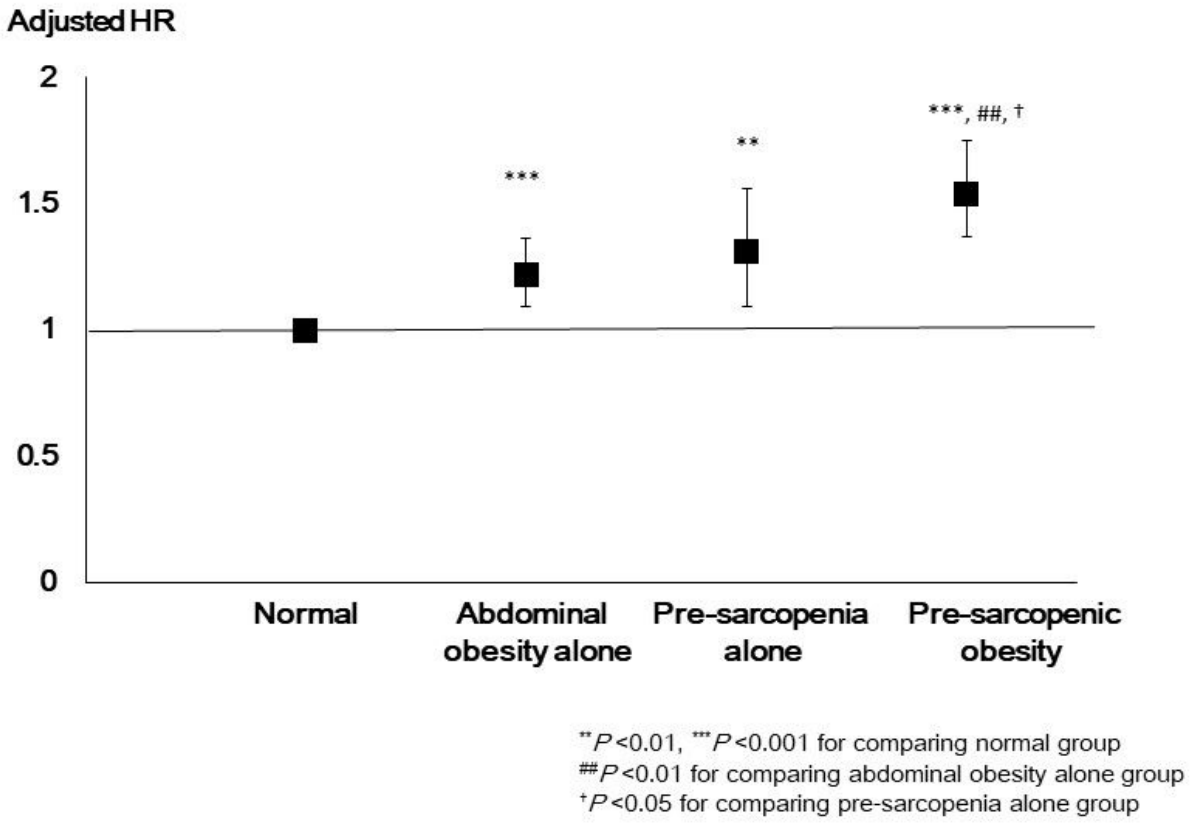

Figure 3

2B. Adjusted hazard ratios of CAC incidence and progression among different body composition groups. **P <0.01, ***P <0.001 for comparing normal group ##P <0.01 for comparing abdominal obesity alone group †P <0.05 for comparing pre-sarcopenia group

Supplementary Files

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