Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 1774–1781

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Association of the new visceral adiposity index with coronary artery calcification and arterial stiffness in Korean population

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Received 2 November 2020; received in revised form 24 February 2021; accepted 25 February 2021
Handling Editor: A. Siani
Available online 23 March 2021

KEYWORDS
Cardiovascular disease;
Vascular calcification;
Visceral fat

Abstract *Background and aims:* The new visceral adiposity index (NVAI) is an indirect marker of visceral adipose tissue recently developed using a Korean population. Here we examined the association of NVAI with coronary artery calcification and arterial stiffness in asymptomatic Korean patients.

Methods and results: We analyzed data from 60,938 asymptomatic Korean adults. Odds ratios and 95% confidence intervals (CIs) for coronary artery calcification score (CACS) > 100 and brachial–ankle pulse wave velocity (baPWV) ≥14 m/s were calculated across NVAI tertiles using multiple logistic regression analysis. Receiver operating characteristic (ROC) and area under the curve (AUC) analyses were used to assess the ability of NVAI to predict moderate to high risk of cardiovascular disease. The prevalence of moderate and high risk of cardiovascular disease increased significantly as the NVAI tertile increased. The odds ratio (95% CI) of the highest NVAI tertile for CACS >100 was 5.840 (5.101–6.686) for men and 18.916 (11.232–31.855) for women, after adjusting for confounders. All NVAI AUC values were significantly higher than the AUC values for other visceral adiposity markers.

Conclusions: This study provides the evidence that NVAI is independently and positively associated with coronary calcification and arterial stiffness in asymptomatic Korean adults.

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https://doi.org/10.1016/j.numecd.2021.02.032

Introduction

Cardiovascular disease is a major cause of death worldwide. In 2019, the World Health Organization attributed 17.9 million deaths (31% of all deaths) to cardiovascular disease alone. Obesity is a well-known risk factor for cardiovascular disease [1–3]. Indeed, several studies have linked visceral adipose tissue to coronary artery disease and carotid atherosclerosis [4–6]. Although computed tomography (CT) is used to precisely and reliably identify visceral adipose tissue, it is expensive and accompanied by substantial radiation exposure. Anthropometric markers, such as body mass index (BMI), waist circumference (WC), and waist-to-hip ratio, have also been used, but these markers do not distinguish between subcutaneous and visceral fat mass, and their accuracy remains controversial in routine clinical practice.

Considering the limitations of the aforementioned methods for assessing visceral fat, Amato et al. developed the visceral adiposity index (VAI), which considers BMI, WC, triglycerides (TG), and high-density lipoprotein (HDL) cholesterol [7]. They validated the index using abdominal magnetic resonance imaging. VAI has been associated with insulin resistance, cardiovascular disease, cerebrovascular disease, non-alcoholic fatty liver disease, and type 2 diabetes in Caucasian populations [7]. Additional indices have been developed for Asian populations because of differences in fat distributions across ethnic groups. For example, the Chinese VAI (CVAI) was developed for Chinese individuals [8], and our group developed the new VAI (NVAI) for Korean individuals [9]. NVAI was validated using nationally representative data and has more predictive accuracy for atherosclerotic cardiovascular disease risk than previously developed indices [9].

Coronary artery calcification is an important clinical feature of coronary atherosclerosis and implies the presence of cardiovascular disease [10]. The coronary artery calcification score (CACS) is a reliable, noninvasive index for assessing cardiovascular risk and is calculated using cardiac CT [11]. Similarly, brachial–ankle pulse wave velocity (baPWV) is a useful and noninvasive measure of arterial stiffness and another reliable surrogate of vascular damage and early atherosclerosis [12].

Although several studies have demonstrated a link between visceral adipose tissue (measured by abdominal CT) and coronary atherosclerosis or arterial stiffness, most of these studies were limited by their small sample size [13,14]. To date, only one study has reported a significant association between VAI and CACS, which was observed only in men [13]. Furthermore, the association of NVAI with coronary atherosclerosis and arterial stiffness are not fully understood. To address this, we examined whether NVAI is associated with CACS and baPWV in a large group of asymptomatic Korean individuals.

Methods

Study participants

In this retrospective, observational, multicenter registry study, we analyzed data from the Korea Initiatives on Coronary Artery Calcification registry between December 2012 and August 2016. This registry includes data from asymptomatic subjects who underwent a health examination at one of six healthcare centers in a self-referral setting in South Korea. Of the 93,707 people enrolled in the registry during the study period, we excluded individuals with a history of ischemic heart disease or stroke (n = 5237), or no coronary artery calcium scan results (n = 856). Also, we excluded 26,675 individuals with insufficient data for calculating NVAI including those who had no data of WC (n = 26,613), no data of MBP (n = 53), and no data of TG (n = 9). A total of 60,938 patients were included in the final analysis (Fig. 1). The study procedures were approved by the institutional review boards of each participating healthcare center, which waived the need for written informed consent because of the retrospective nature of the study.

Data collection

Data regarding the presence of hypertension, dyslipidemia, and diabetes mellitus, as well as smoking and exercise status, were recorded by an experienced physician. A smoker was defined as a current or previous smoker. An exerciser was defined as a person who exercised at least three times per week. Anthropometric parameters were measured in the standing position with patients wearing light indoor clothing and no shoes. BMI was calculated as weight (kg) divided by height (m)2. WC was measured at the umbilicus. Blood pressure was measured using an automatic manometer after the patient rested for at least 5 min. Mean blood pressure (MBP) was calculated as 1/3 systolic blood pressure + 2/3 diastolic blood pressure. Blood samples were obtained from an antecubital vein after a minimum 8-h fasting period (following relevant guidelines and regulations) and were tested for low-density lipoprotein cholesterol, HDL cholesterol, TG, creatinine, and fasting glucose.

Coronary artery calcification score

The patients underwent coronary artery calcification testing using a >16-slice multi-sensor CT (MSCT) scanner (GE 64-slice Lightspeed, Siemens 16-slice Sensation, Philips Brilliance 256 iCT, or Philips Brilliance 40-channel multi-detector). Horiguchi et al. found a high agreement between 16-slice MSCT scanner and EBCT in CACS [15]. A study by Kopp et al. showed that using MSCT scanners resulted in less inter-scan variability compared to using EBCT [16]. CACS was calculated using the Agatston scoring system [17]. To obtain an accurate score, observers performed a modification procedure to remove calcium

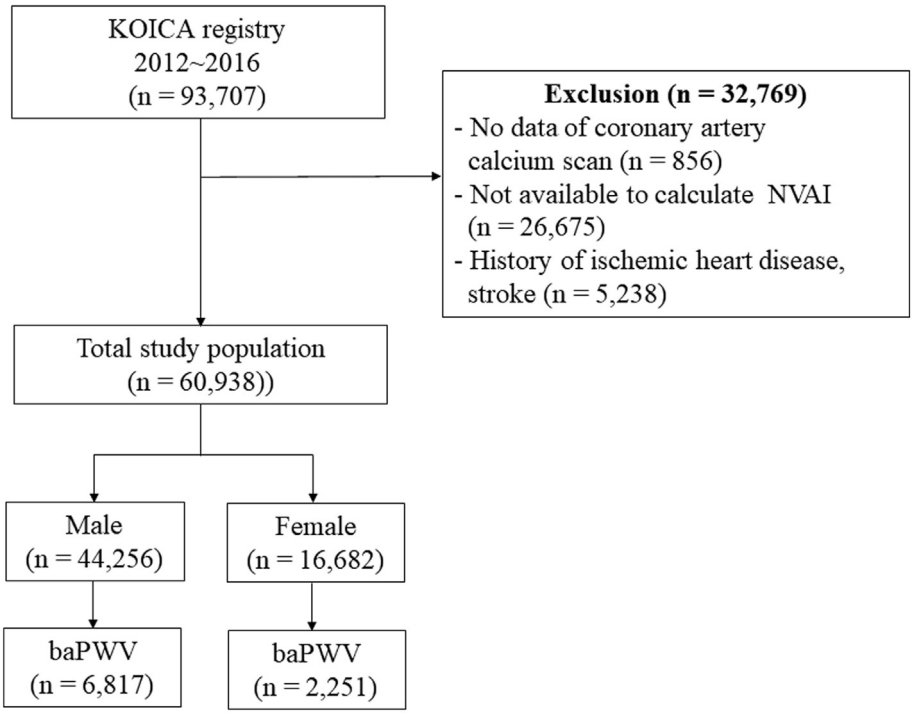

Figure 1 Study flowchart. NVAI, new visceral adiposity index; PWV, pulse wave velocity.

located outside the coronary arteries. CACS was categorized into four groups: very low risk, 0; low risk, 1–100; moderate risk, 101–400; and high risk, ≥401. Also, prior studies have demonstrated excellent inter-scanning reproducibility for Agatston, mass, and volume score [18].

Brachial–ankle pulse wave velocity

Arterial stiffness was assessed by determining baPWV using an automatic waveform analyzer (Omron Healthcare Co, Ltd) and the volume plethysmographic method. Previous study validated the use of automatic waveform analyzer (Omron Healthcare) and demonstrated that this method increases the reproducibility of ABI estimation compared to manual measurement [19]. The highest baPWV value (on either the right or left) was used for analysis. baPWV results were categorized into three groups according to Japanese guidelines [12]: low risk, <14 m/s; moderate risk, 14–17.9 m/s; and high risk, ≥18 m/s.

Visceral adiposity indices

NVAI was calculated as indicated below. For men,

$$1/[1 + \exp\{-(-21.858+(0.099 \times \text{age})+(0.10 \times \text{WC})+(0.12 \times \text{MBP})+(0.006 \times \text{TG})+(-0.077 \times \text{HDL}))\}].$$

For women,

$$1/[1 + \exp\{-(-18.765+(0.058 \times \text{age})+(0.14 \times \text{WC})+(0.057 \times \text{MBP})+(0.004 \times \text{TG})+(-0.057 \times \text{HDL}))\}].$$

VAI was calculated as

$$[\text{WC}/\{39.68+(1.88 \times \text{BMI})\}] \times (\text{TG}/1.03) \times (1.31/\text{HDL}),$$ for men and $$[\text{WC}/\{36.58+(1.89 \times \text{BMI})\}] \times (\text{TG}/0.81) \times (1.52/\text{HDL})$$, for women.

For men, CVAI was calculated as

$$-267.93+(0.68 \times \text{age})+(0.03 \times \text{BMI})+(4.00 \times \text{WC})+(22 \times \text{logTG})-(16.32 \times \text{HDL}).$$

For women, CVAI was calculated as

$$-187.32+(1.71 \times \text{age})+(4.23 \times \text{BMI})+(1.12 \times \text{WC})+(39.76 \times \text{logTG})-(11.66 \times \text{HDL}).$$

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as number (percentage). Men and women were classified into tertiles (T1 to T3) based on their NVAI (men: T1, ≤0.27; T2, 0.28–0.75; and T3, >0.75; women: T1, ≤0.02, T2, 0.03–0.18; and T3, >0.18). Patient characteristics according to NVAI tertiles were analyzed using weighted one-way analysis of variance for continuous variables and Chi-squared test for categorical variables. Pearson correlation was conducted between visceral fat markers and PWV or log-transformed CACS for the overall study population. Odds ratios (ORs) and 95% confidence intervals (CIs) for moderate to high risk CACS and PWV were calculated after adjusting for confounding variables, including BMI, diabetes mellitus, smoking status, exercise

status, and serum creatinine, across NVAI tertiles using multiple logistic regression analysis. Receiver operating characteristic (ROC) and area under the curve (AUC) analyses were performed without adjustment to compare the predictability of moderate to high risk coronary artery calcification and arterial stiffness between NVAI and previous indicators, such as BMI, WC, VAI, and CVAI. Comparison of ROCs was performed using the DeLong method. Statistical analyses were performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA) and R (version 3.1.3) software. P values < 0.05 were considered statistically significant.

Results

A total of 44,256 men and 16,682 women were included in the analysis (Table 1). In both men and women, WC, BMI, lipid profile values, fasting glucose, and prevalence of hypertension, diabetes mellitus, and dyslipidemia were higher in the highest NVAI tertile compared with the lowest NVAI tertile. Prevalence of moderate to high risk CACS, as well as moderate to high risk baPWV, also increased significantly as NVAI tertile increased (Fig. 2). On Pearson correlation analysis, age, WC, VAI, CVAI, and NVAI were significantly correlated with both baPWV and log-transformed CACS (Table 2). Age, WC, and NVAI positively correlated with both baPWV and log-transformed CACS, whereas VAI and CVAI were negatively correlated with log-transformed CACS.

Compared with the lowest tertile (reference group), the OR (95% CI) of the highest NVAI tertile for CACS >100 was 5.840 (5.101–6.686) for men and 18.916 (11.232–31.855) for women. These ORs were adjusted for BMI, diabetes mellitus, smoking status, exercise status, and serum creatinine (Table 3). The OR (95% CI) of the highest NVAI tertile compared with the lower tertile for baPWV ≥14 m/s was 7.594 (6.298–9.156) for men and 12.465 (8.366–18.571) for women, after adjusting for the same confounding factors.

The ability of NVAI to predict CACS >100 generated an AUC of 0.717 (95% CI, 0.710–0.723) for the total population, 0.677 (95% CI, 0.669–0.685) for men, and 0.785 (95% CI, 0.770–0.800) for women. These values were significantly higher than those for all other markers (Fig. 3, Table 4). Similar trends were observed for the ability of NVAI to predict baPWV ≥14 m/s: the AUC was 0.679 (95% CI, 0.669–0.690) for the total population, 0.693 (95% CI, 0.681–0.706) for men, and 0.710 (95% CI, 0.689–0.731) for women. These values were also significantly higher than those for all other markers.

Discussion

In this study, NVAI was independently associated with coronary artery calcification and arterial stiffness in an asymptomatic Korean population. NVAI predicted moderate to high risk of cardiovascular disease more accurately than other visceral adipose markers. Moreover, NVAI had the highest AUC among all visceral adipose markers, and the highest NVAI tertile was associated with significantly higher odds of presenting with moderate to high cardiovascular disease risk in both men and women. This trend remained significant after adjusting for confounding variables, including BMI, diabetes

Table 1 Clinical baseline characteristics of NVAI tertiles according to sex.

Characteristics	Males				Females			
	NVAI Tertile 1 (≤0.27)	NVAI Tertile 2 (0.28–0.75)	NVAI Tertile 3 (>0.75)	P-value	NVAI Tertile 1 (≤0.02)	NVAI Tertile 2 (0.03–0.18)	NVAI Tertile 3 (>0.18)	P-value
Number	14,765	14,771	14,765	–	5560	5563	5559	–
Age, y	46.4 ± 8.9	51.7 ± 8.6	55.9 ± 9.3	<0.001	44.5 ± 9.0	53.7 ± 8.0	59.7 ± 8.4	<0.001
WC, cm	82.5 ± 6.2	87.6 ± 5.9	92.3 ± 7.1	<0.001	70.9 ± 5.5	79.1 ± 5.0	88.1 ± 7.3	<0.001
BMI, m/kg^2	23.3 ± 2.3	24.8 ± 2.3	26.2 ± 2.8	<0.001	20.6 ± 2.0	22.6 ± 2.1	25.4 ± 3.1	<0.001
Hypertension, n (%)	1502 (10.2)	3265 (22.1)	5485 (37.1)	<0.001	204 (3.7)	832 (15.0)	1976 (35.5)	<0.001
Dyslipidemia, n (%)	1518 (10.3)	2374 (16.1)	2826 (19.1)	<0.001	274 (4.9)	718 (12.9)	1037 (18.7)	<0.001
DM, n (%)	714 (4.8)	1273 (8.6)	1758 (11.9)	<0.001	49 (0.9)	177 (3.2)	545 (9.8)	<0.001
Smoker, n (%)	8130 (55.1)	8108 (54.9)	7968 (54.0)	0.036	1454 (26.2)	2084 (37.5)	2219 (39.9)	<0.001
SBP (mm Hg)	112.8 ± 11.5	120.4 ± 11.5	131.3 ± 13.4	<0.001	107.6 ± 11.5	116.8 ± 13.7	128.1 ± 15.4	<0.001
DBP (mm Hg)	70.8 ± 8.3	77.6 ± 8.2	84.8 ± 9.3	<0.001	65.5 ± 8.7	71.6 ± 9.7	77.6 ± 10.1	<0.001
LDL-C (mg/dL)	122.2 ± 30.0	126.6 ± 30.7	123.8 ± 31.5	<0.001	110.0 ± 29.0	125.7 ± 31.7	127.7 ± 33.4	<0.001
HDL-C (mg/dL)	57.7 ± 13.0	49.3 ± 10.0	44.0 ± 8.7	<0.001	68.9 ± 14.0	58.4 ± 11.6	50.2 ± 10.2	<0.001
TG (mg/dL)	103.4 ± 46.7	137.5 ± 66.9	185.4 ± 118.9	<0.001	72.6 ± 28.7	95.3 ± 44.8	133.6 ± 77.3	<0.001
Total-C (mg/dL)	196.4 ± 32.9	198.0 ± 34.4	197.2 ± 36.0	0.001	194.1 ± 33.9	203.5 ± 35.4	203.4 ± 37.3	<0.001
Creatinine (mg/dL)	0.97 ± 0.1	0.98 ± 0.2	1.00 ± 0.2	<0.001	0.72 ± 0.2	0.74 ± 0.2	0.76 ± 0.2	<0.001
Fasting glucose (mg/dL)	94.8 ± 16.4	100.7 ± 20.3	106.5 ± 24.9	<0.001	88.4 ± 10.3	93.0 ± 14.4	101.6 ± 23.7	<0.001
CACS >100	657 (4.4)	1466 (9.9)	2611 (17.7)	<0.001	31 (0.6)	158 (2.8)	558 (10.0)	<0.001
baPWV ≥14 m/s	610 (4.1)	1087 (7.4)	1615 (10.9)	<0.001	151 (2.7)	380 (6.8)	488 (8.8)	<0.001

Values are mean ± standard deviation or n (%). baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CACS, coronary artery calcium score; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NVAI, new visceral adiposity index; SBP, systolic blood pressure; TG, triglycerides; Total-C, total cholesterol; WC, waist circumference.

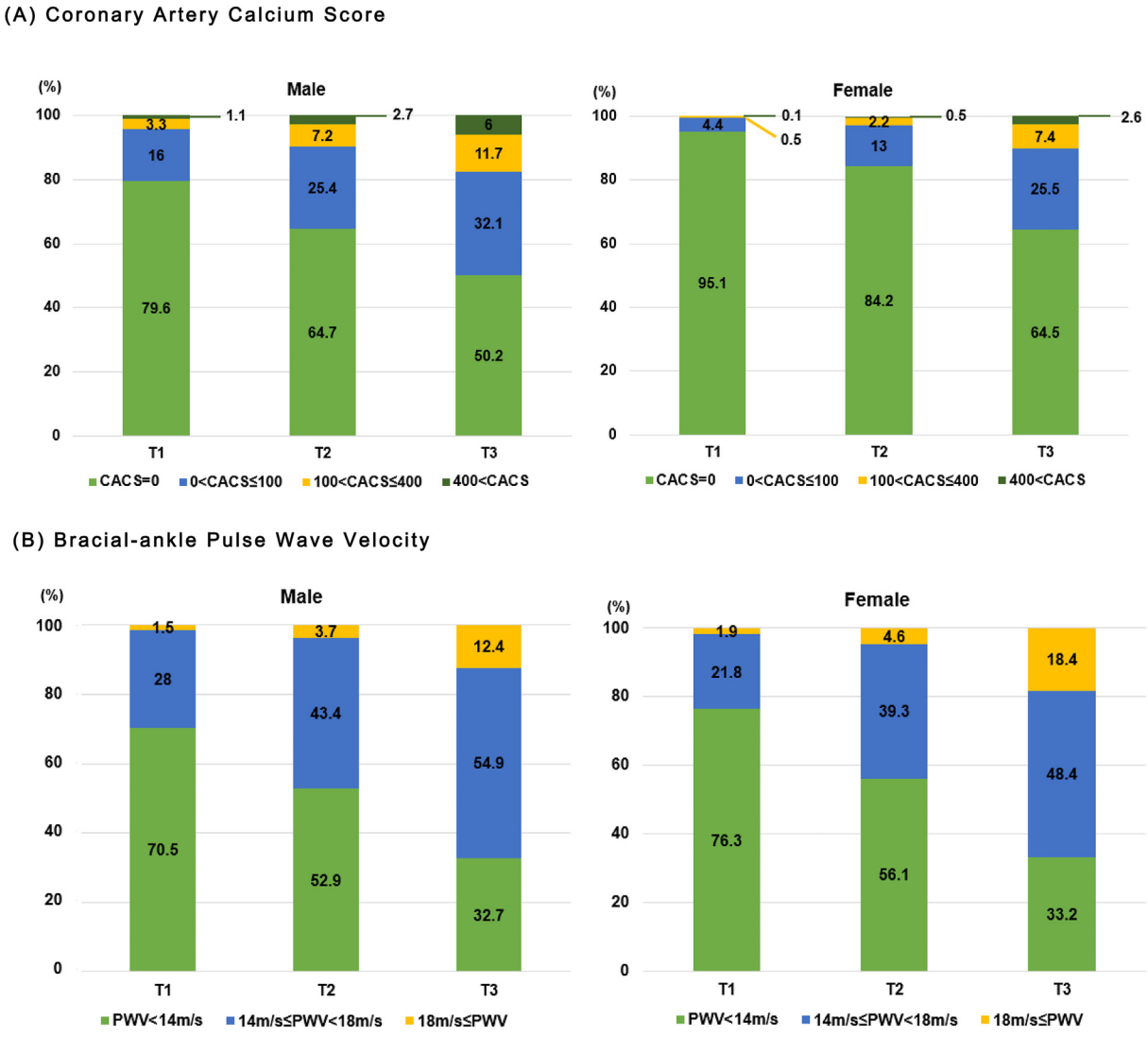

Figure 2 Coronary artery calcification score and brachial–ankle pulse wave velocity according to NVAI tertile. CACS, coronary artery calcium score; NVAI, new visceral adiposity index; PWV, pulse wave velocity.

mellitus, smoking status, exercise status, and serum creatinine. The relationship between NVAI and cardiovascular risk factors is more confirmatory than novel. However, because NVAI adjusts for age and blood pressure, it offers enhanced predictability over other visceral adiposity markers. We will continue to improve on this advantage, and research more accurate and more advanced prediction models.

Table 2 Pearson correlation matrix of clinical variables.

	Age	BMI	WC	VAI	CVAI	NVAI	Log (CACS)	baPWV
Age	1							
BMI	0.024[a]	1						
WC	0.177[a]	0.842[a]	1					
VAI	−0.026[a]	0.381[a]	0.343[a]	1				
CVAI	0.109[a]	0.272[a]	0.24[a]	0.514[a]	1			
NVAI	0.377[a]	0.557[a]	0.672[a]	0.478[a]	0.397[a]	1		
Log (CACS)	0.277[a]	0.006	0.056[a]	−0.024[a]	−0.017[b]	0.154[a]	1	
baPWV	0.518[a]	0.015	0.094[a]	0.072[a]	0.043[a]	0.334[a]	0.247[a]	1

baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CACS, coronary artery calcium score; CVAI, Chinese visceral adiposity index; NVAI, new visceral adiposity index; SE, standard error; VAI, visceral adiposity index.
[a] Correlation is significant at the 0.01 level (two-tailed).
[b] Correlation is significant at the 0.05 level (two-tailed).

Table 3 Odds ratios for CACS >100 and baPWV ≥14 m/s according to NVAI tertiles.

	Odds ratio (95% CI) for CACS >100			Odds ratio (95% CI) for baPWV ≥14 m/s		
	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Male						
Unadjusted	1	2.366 (2.152–2.602)	4.613 (4.221–5.042)	1	2.122 (1.873–2.403)	4.921 (4.334–5.588)
Model 1[a]	1	2.638 (2.394–2.907)	5.641 (5.124–6.211)	1	2.693 (2.362–3.070)	8.237 (7.089–9.571)
Model 2[b]	1	2.712 (2.367–3.107)	5.840 (5.101–6.686)	1	2.531 (2.149–2.980)	7.594 (6.298–9.156)
Female						
Unadjusted	1	5.214 (3.541–7.676)	19.900 (13.833–28.629)	1	2.532 (2.020–3.174)	6.530 (5.145–8.286)
Model 1[a]	1	5.605 (3.792–8.284)	23.552 (16.030–34.604)	1	3.254 (2.562–4.132)	13.170 (9.606–18.055)
Model 2[b]	1	4.490 (2.638–7.640)	18.916 (11.232–31.855)	1	2.980 (2.202–4.033)	12.465 (8.366–18.571)

baPWV, brachial–ankle pulse wave velocity; CACS, coronary artery calcium score; CI, confidence interval.
[a] Adjusted for body mass index.
[b] Adjusted for body mass index, diabetes mellitus, smoking status, and serum creatinine.

Visceral adipose tissue plays a key role in the development of atherosclerosis via the inflammatory atherothrombotic pathway [20]. Excess visceral adiposity leads to increased secretion of inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha, plasminogen activator inhibitor type-1) and decreased secretion of the protective adipokine, adiponectin, which is an anti-inflammatory and anti-atherogenic protein [21]. Many studies have demonstrated that visceral adipose tissue is more pathogenic than subcutaneous fat in terms of contributing to cardiometabolic complications [22]. Although CT is the gold standard for distinguishing

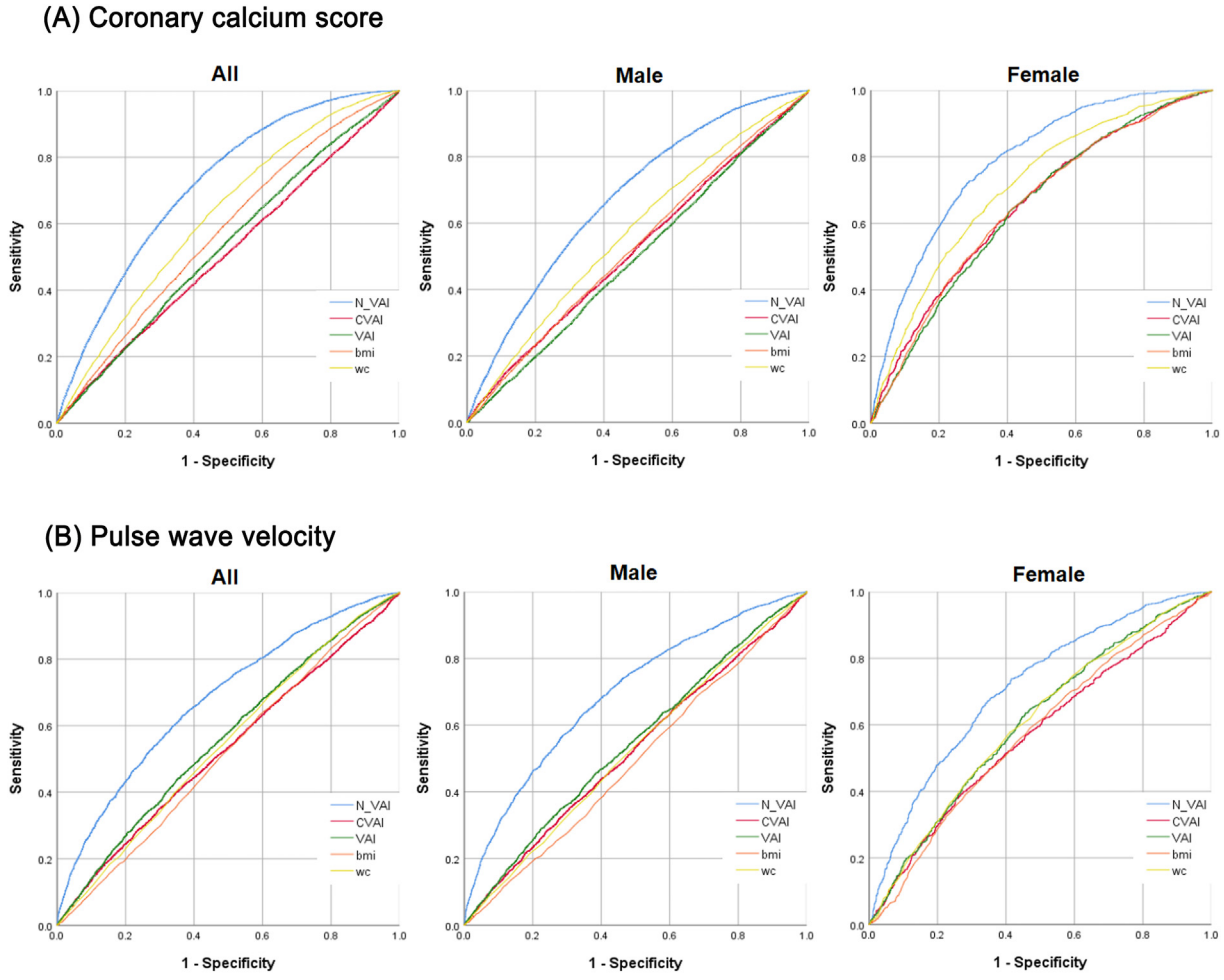

Figure 3 Receiver operating characteristic curves of NVAI and other visceral adiposity markers for coronary artery calcium score and brachial–ankle pulse wave velocity. BMI, body mass index; CVAI, Chinese visceral adiposity index; NVAI, new visceral adiposity index; VAI, visceral adiposity index; WC, waist circumference.

Table 4 Area under the curves of NVAI and other visceral adiposity markers for CACS >100 and baPWV ≥14 m/s.

		All (n = 60,938)		Males (n = 44,256)		Females (n = 16,682)	
		AUC	95% CI	AUC	95% CI	AUC	95% CI
CACS >100	NVAI	0.717	0.710–0.723	0.677	0.669–0.685	0.785	0.770–0.800
	CVAI	0.512	0.504–0.521	0.524	0.515–0.533	0.653	0.633–0.673
	VAI	0.534	0.526–0.542	0.501	0.493–0.510	0.644	0.625–0.663
	BMI	0.574	0.567–0.583	0.530	0.521–0.538	0.650	0.630–0.669
	WC	0.625	0.618–0.633	0.574	0.565–0.582	0.710	0.692–0.728
baPWV ≥14 m/s	NVAI	0.679	0.669–0.690	0.693	0.681–0.706	0.710	0.689–0.731
	CVAI	0.528	0.516–0.540	0.523	0.509–0.537	0.571	0.547–0.594
	VAI	0.560	0.549–0.572	0.544	0.530–0.558	0.607	0.584–0.631
	BMI	0.516	0.504–0.528	0.492	0.478–0.506	0.574	0.550–0.598
	WC	0.545	0.533–0.557	0.524	0.510–0.538	0.607	0.584–0.630

AUC, area under the curve; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CACS, coronary artery calcium score; CI, confidence interval; CVAI, Chinese visceral adiposity index; NVAI, new visceral adiposity index; VAI, visceral adiposity index; WC, waist circumference.

visceral adipose tissue, its disadvantages include high cost, radiation exposure, and lack of routine availability. Thus, indirect visceral adipose tissue markers, such as VAI, CVAI, and NVAI, have been developed. VAI was developed using data from 315 healthy Italian adults; it is a useful visceral adiposity marker for assessing cardiovascular disease risk [7]. CVAI was subsequently developed using data from 485 Chinese adults to account for ethnic differences [8]. We previously developed NVAI based on data from 539 healthy Korean adults and validated this index using nationwide population-based cross-sectional survey data (n = 29,235) [9]. NVAI exhibited high accuracy for predicting atherosclerotic cardiovascular events, including myocardial infarction, angina, and stroke, in our previous study [9] and had significantly higher prediction accuracy than CVAI in the present study. However, as NVAI was only recently developed, further studies are required to confirm its efficacy for predicting cardiovascular risk.

In this study, we used CACS and baPWV as markers of cardiovascular disease risk. The existence of calcification at one or more coronary arteries reflects the presence of atherosclerotic cardiovascular disease. Coronary artery calcification provides a reasonable estimate of total coronary atheroma, including noncalcified plaque burden [23]. Moderate to high CACS, defined as >100 in the present study, is associated with moderate atherosclerotic plaque burden [18,24,25]. In a recent study from Hungary, VAI was associated with a CACS >100, but this association was only detected in men [13]. Here, we found a significant association between NVAI and CACS >100 in both men and women. The discrepancy between studies could be attributed, in part, to ethnic differences.

A recent meta-analysis showed that a higher baPWV (as a measure of arterial stiffness) was associated with an increased risk of developing cardiovascular disease [26]. High baPWV is also associated with inflammation, vascular damage, and coronary atherosclerosis [27,28]. Although the reference value for baPWV differs according to blood pressure and age, baPWV ≥14 m/s is an established predictor of cardiovascular disease [12].

This study had limitations. First, because of its retrospective cross-sectional design, caution is advised when inferring causal and temporal relationships. Second, study participants were individuals who self-referred for health promotion screenings; therefore, the study population may not be representative of the general Korean population because of selection bias. Third, the study population consisted of a single ethnic cohort of Korean adults. Therefore, future studies are required to evaluate more heterogeneous populations. Finally, since the data were observational and collected using a cross-sectional design, baPWV was the only tool to assess arterial stiffness. Nevertheless, our study is unique in that we used a Korean-specific visceral adipose tissue measure, NVAI, to predict moderate to high cardiovascular disease risk based on both CACS and baPWV in a large population of asymptomatic adults.

In conclusion, this study provides novel evidence that NVAI is independently and positively associated with coronary calcification and arterial stiffness in asymptomatic Korean adults. Also, NVAI showed better prediction for coronary calcification and arterial stiffness compared to previous surrogate markers such as BMI, WC, VAI, and CVAI in Korean population.

Author contributions

Conceptualization, DH Son and HS Ha.; methodology, HS Lee.; software, DH Son.; validation, HS Ha, HS Lee and DH Han.; formal analysis, DH Son and HS Ha.; investigation, SY Choi, EJ Chun, HW Han, and SH Park.; resources, J Sung and HO Jung; data curation, HJ Chang.; writing—original draft preparation, DH Son and HS Ha.; writing—review and editing, JW Lee and HJ Chang.; visualization, HS Lee; supervision, JW Lee and HJ Chang; project administration, JW Lee and HJ Chang; funding acquisition, JW Lee and HJ Chang. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by an Institute for Information & communications Technology Promotion (IITP) grant funded by the Korean government (MSIT) (2019-31-1293, Autonomous digital companion framework and application), as well as the Technology Innovation Program (20,002,781, A Platform for Prediction and Management of Health Risk Based on Personal Big Data and Lifelogging) funded by the Korean Ministry of Trade, Industry, and Energy.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

We thank all those who conducted the KOICA registry, as well as the participants in the survey.

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