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Comparative Predictive Value of Three Visceral Adiposity Indices for Cardiovascular Disease: A 17.5-Year Korean Cohort Study

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ABSTRACT

Aims: Cardiovascular diseases (CVD) are the leading cause of death worldwide, with excess visceral adipose tissue (VAT) being identified as an independent indicator of poor cardiovascular outcomes. We examined the association between three indices of VAT, namely, metabolic score for visceral fat (METS-VF), visceral adiposity index (VAI), and lipid accumulation product (LAP), and the development of CVD in a large cohort of middle-aged Korean adults.

Materials and Methods: The study recruited 8192 participants without CVD at baseline from the Korean Genome and Epidemiology Study. METS-VF, VAI, and LAP were calculated using established formulas based on anthropometric and metabolic parameters. Incident CVD was defined based on self-reported physician diagnoses confirmed by trained interviewers. Multivariable Cox proportional hazard regression analyses were performed to estimate the hazard ratio (HR) with a 95% confidence interval (CI) for incident CVD. Heagerty's integrated areas under the receiver operating characteristic curves (iAUC) were used to compare the discriminatory performance of three indices.

Results: The adjusted HRs (95% CIs) for incident CVD in the highest tertile compared with the lowest tertile were 1.62 (1.29–2.03), 1.38 (1.08–1.77), and 1.66 (1.32–2.09) for METS-VF, VAI, and LAP, respectively. METS-VF showed statistically higher discriminatory performance than VAI and LAP for incident CVD ($p < 0.001$), although the overall discriminative ability of indices was modest.

Conclusions: METS-VF, VAI, and LAP were independently associated with an increased risk of CVD events. Among these indices, METS-VF demonstrated relatively better discriminatory performance, suggesting its potential role as a complementary tool for cardiovascular risk stratification.

1 | Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide [1]. Moreover, CVD has emerged as the second most common cause of death in Korea since the early 2000s, and the mortality rate is on a continuous rise [2]. This highlights the significance of identifying individuals at high risk for CVD and conducting early intervention to prevent the disease, reduce

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mortality, and alleviate healthcare burden. Modifiable risk factors impacting the development of CVD include obesity, prediabetes/diabetes, high blood pressure, dyslipidemia, and tobacco smoking [3].

Obesity is one of the major CVD risk factors, and body mass index (BMI) has long been used for evaluating obesity. However, although BMI is a simple and useful measure to define general obesity, it does not reflect adipose tissue distribution [4]. In particular, excess visceral adipose tissue (VAT), largely distributed in the abdominal area, is an independent indicator of poor cardiovascular outcomes [5, 6]. The accumulation of VAT, which secretes free fatty acids, adipokines, and inflammatory markers, induces insulin resistance and systemic inflammation, thereby increasing the risk of CVD [6]. Therefore, research on the association between adiposity indices predicting VAT and the risk of CVD has been increasing.

The most precise methods of estimating VAT are computed tomography (CT), magnetic resonance imaging (MRI), or dual-energy x-ray absorptiometry (DEXA) [7]. However, these imaging modalities are expensive, not routinely available, and impractical for large-scale or routine clinical use. Therefore, simpler and widely available indices that indirectly estimate VAT have been developed. Derived from routinely collected anthropometric and metabolic parameters, these indices provide a practical, cost-effective, and scalable approach for assessing visceral adiposity, particularly in population-based and real-world settings. Simple anthropometric indices, such as waist circumference (WC) and waist-to-hip ratio (WHR), were used [8], and later several calculated indices, such as visceral adiposity index (VAI) and lipid accumulation product (LAP), were developed by combining anthropometric indices and blood lipid values. Bello-Chavolla et al. proposed the metabolic score for visceral fat (METS-VF) as a novel surrogate VAT measurement in 2020 [9].

Previous studies have demonstrated that VAI and LAP were significantly and independently associated with an increased risk of CVD and mortality [10–13]. In addition, several recent studies have demonstrated the positive association of METS-VF with CVD incidence and mortality [14, 15]. Nevertheless, large-scale, long-term prospective studies specifically evaluating and comparing the predictive power of these adiposity indices for CVD incidence are lacking. Thus, this 17.5-year longitudinal study investigated the association between three different indices for visceral adiposity (METS-VF, VAI, and LAP) and the development of CVD, using a large-scale, community population-based Korean prospective cohort. Furthermore, we compared the predictive power of the three indices for CVD incidence.

2 | Materials and Methods

2.1 | Study Population

We used the data from the Korean Genome and Epidemiology Study (KoGES) Ansan and Ansung study, a longitudinal prospective cohort study conducted by the Korea Centers for Disease Control and Prevention, to examine the genetic and environmental risk factors for non-communicable diseases [16]. The data release was approved by the Korea Disease Control and Prevention Agency, and it is available at https://coda.nih.go.kr/frt/index.do (accessed on September 3, 2024).

The cohort included 10 030 participants aged 40–69 years, residing in urban (Ansan) or rural (Ansung) areas. The survey was conducted biennially from 2001 to 2002 (baseline) to 2019–2020 (ninth follow-up). Figure 1 presents a flowchart of the selection of the study population. Among the 10 030 participants, we excluded (1) those with CVD at baseline ($n = 325$, 3.2%), (2) those who were lost to follow-up after the baseline

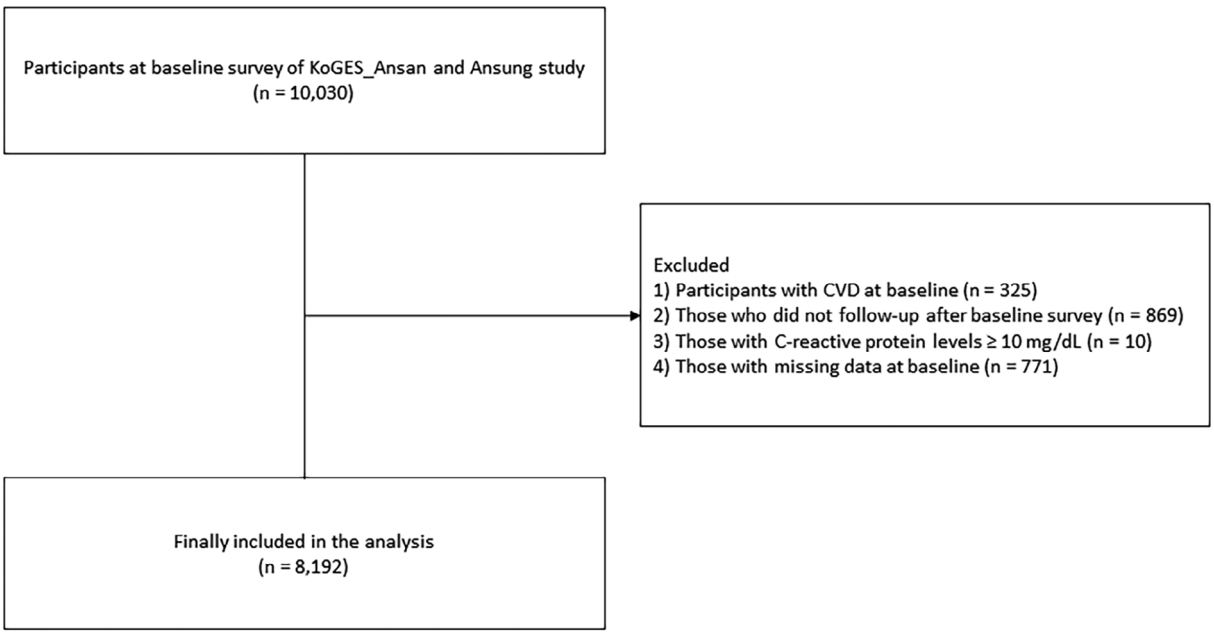

FIGURE 1 | Flow chart of the selection of the study population.

survey ($n = 869$, 8.7%), (3) those with C-reactive protein (CRP) levels ≥ 10 mg/dL ($n = 10$, 0.1%), and (4) those with missing baseline data ($n = 771$, 7.7%), with some overlap between exclusion categories. In total, 1838 participants (18.3%) were excluded. After these exclusions, 8192 participants without CVD at baseline were included in the final analysis. All participants provided written informed consent, and the study protocol conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Institutional Review Board (IRB) of Yongin Severance Hospital (IRB no. 9-2022-0090).

2.2 | Data Collection

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated as the body weight (kg) divided by height squared (m^2). Waist circumference (WC) (cm) was measured midway between the lowest rib and iliac crest with the patient in the standing position. Waist-to-height ratio (WHtr) was calculated as WC (cm) divided by height (cm). Blood pressure (mmHg) was measured after at least 5 min of rest in the sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as the average of the last two of three measurements, with at least a 1-min interval between each.

Blood samples of each participant were collected after at least 8 h of fasting. The fasting glucose, insulin, glycosylated haemoglobin (HbA1c), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and CRP were measured using chemistry analysers (Hitachi 7600; Tokyo, Japan, until August 2002, and ADVIA 1650, Siemens, Tarrytown, NY, since September 2002). Insulin resistance was estimated by calculating the homeostasis model assessment-insulin resistance (HOMA-IR) using the following HOMA-IR formula: (fasting insulin [μIU/mL] × fasting glucose [mg/dL]/405) [17]. Non-HDL cholesterol was calculated as the total cholesterol minus HDL cholesterol [18].

Self-reported questionnaires were used to collect information on smoking status, drinking status, physical activity, and the presence of hypertension, diabetes mellitus, and dyslipidemia. Smoking status was categorized into current smoker, former smoker, and never smoker. Alcohol drinking status was classified into current drinker, former drinker, and non-drinker. Physical activity was quantified as the metabolic equivalent of task (MET) hours per day (METs-h/day), based on the self-reported duration and intensity of activities [19]. Normal glucose tolerance was defined as a fasting plasma glucose level < 100 mg/dL, a plasma glucose level 2 h after the administration of 75 g of oral glucose tolerance test (OGTT) < 140 mg/dL, and an HbA1c level < 5.7%. Prediabetes was defined as a fasting plasma glucose level between ≥ 100 and < 126 mg/dL, a plasma glucose level 2 h after the administration of 75 g of OGTT between ≥ 140 and < 200 mg/dL, or an HbA1c level between ≥ 5.7 and < 6.5%. Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL, plasma glucose level 2 h after the administration of 75 g of OGTT ≥ 200 mg/dL, HbA1c level ≥ 6.5%, or use of an anti-diabetic medication [20]. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of anti-hypertensive medication [21]. Dyslipidemia was defined as the total cholesterol ≥ 240 mg/dL, triglycerides ≥ 200 mg/dL, HDL-cholesterol < 40 mg/dL, or the use of a lipid-lowering medication [22].

2.3 | Definitions of METS-VF, VAI, and LAP

The METS-VF is a novel surrogate for predicting visceral obesity, which is calculated based on BMI, WHtr, fasting glucose, triglycerides, HDL-cholesterol, sex, and age. The formula for METS-VF was as follows: $\text{METS-VF} = 4.466 + 0.011 \times (\text{Ln}[\text{METS-IR}])^3 + 3.239 \times (\text{Ln}[\text{WHtr}])^3 + 0.319 \times [\text{sex}] + 0.594 \times (\text{Ln}[\text{Age}])$ [9], where sex was a binary variable (male = 1, female = 0) and METS-IR was calculated as (Ln((2 × fasting glucose (mg/dL) + triglycerides (mg/dL)) × BMI))/(Ln[HDL-cholesterol (mg/dL)]).

VAI and LAP have sex-specific equations as follows: VAI in male = WC (cm)/(39.68 + [1.88 × BMI]) × (triglyceride [mmol/L]/1.03) × (1.31/HDL-cholesterol (mmol/L)), VAI in female = WC (cm)/(36.58 + [1.89 × BMI]) × (triglycerides (mmol/L)/0.81) × (1.52/HDL-cholesterol (mmol/L)) [23]; LAP in male = (WC [cm]–65) × triglycerides (mmol/L); LAP in female = (WC [cm]–58) × triglycerides (mmol/L) [24].

2.4 | Definition of CVD

CVD was defined as myocardial infarction, angina pectoris, peripheral artery disease, or stroke based on previous studies [25, 26]. Self-reported questionnaires were obtained for each participant at each biennial follow-up. When a participant reported an incident CVD event in the personal medical history questionnaire, in-depth personal interviews by well-trained examiners were conducted to confirm an incident CVD case.

2.5 | Statistical Analysis

Continuous variables are presented as means ± standard deviation, and categorical variables as numbers (percentages). We conducted the independent *t*-test and the chi-square test to compare the differences of baseline characteristics between the population with or without new-onset CVD for continuous variables and categorical variables, respectively. Kaplan–Meier curves with the log-rank test were used to compare the cumulative incidence rates of new-onset CVD according to the tertiles of METS-VF, VAI, and LAP. The hazard ratio (HR) with a 95% confidence interval (CI) for incident CVD was calculated using multivariable Cox proportional hazard regression analyses. Confounders were determined as variables affecting exposure and outcome: age, sex, smoking status, drinking status, physical activity, CRP level, the presence of hypertension, diabetes mellitus, and dyslipidemia, based on literature review and univariate analysis. To assess multicollinearity among the included covariates, variance inflation factors (VIFs) were calculated. All VIF values were below 5, indicating no significant multicollinearity. Potential nonlinear relationships between METS-VF, VAI, LAP, and the incidence of CVD were examined using restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentiles. The likelihood

ratio test was used to assess departure from linearity by comparing the full spline model to a restricted model retaining only the linear term. Furthermore, we compared the discriminative performance of three indices for CVD incidence using Harrell's concordance index and Heagerty's integrated areas under the receiver operating characteristic curves (iAUC). We additionally compared the discriminative performance of these indices with conventional anthropometric measures, including BMI and WC. Subgroup analyses by age, sex, and glucose tolerance status were performed, and the results are presented as a forest plot. Additional stratified analyses were performed according to drinking and smoking status to assess potential effect modification. All statistical analyses were conducted using the SAS version 9.4 (SAS Institute Inc., Cary, NC) and R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at p value < 0.05.

3 | Results

3.1 | Baseline Characteristics of Study Population

Table 1 shows a comparison of baseline characteristics between the participants who developed CVD and those who did not during the follow-up period. Age, BMI, WC, WHtr, SBP, DBP, fasting glucose, insulin, HbA1c, HOMA-IR, total cholesterol, triglycerides, non-HDL cholesterol, CRP level, and all three adiposity indices, that is, METS-VF, VAI, and LAP, were significantly higher in the participants with new-onset CVD than in those without new-onset CVD, whereas HDL-cholesterol was significantly lower in participants with new-onset CVD. The proportion of current smokers, participants with diabetes, hypertension, and dyslipidemia was significantly higher in the participants with new-onset CVD. No significant differences were noted in the proportion of male sex, physical activity, and drinking status. Baseline characteristics of included and excluded participants are presented in Table S1. Excluded participants were generally older and exhibited a more adverse cardiometabolic profile, including higher blood pressure, worse glycemic indices, and higher levels of triglycerides and inflammatory markers.

3.2 | Incident CVD According to METS-VF, VAI, and LAP

Among 8192 participants without CVD at baseline, 669 (8.2%) developed CVD during a median follow-up of 17.5 years. The incidence rates over follow-up are presented in Table S2. Figure 2 shows the Kaplan–Meier curves of the cumulative rates of incident CVD according to the tertiles of METS-VF, VAI, and LAP. The cumulative incidence of CVD events was higher in the third tertile of METS-VF, VAI, and LAP than in the other tertiles (all log-rank $p < 0.001$). Table 2 summarizes the results of multivariable Cox proportional hazard regression analyses for incident CVD according to METS-VF, VAI, and LAP tertiles. Similar trends were observed in the unadjusted and fully adjusted models. After adjusting for age, sex, physical activity, smoking status, drinking status, CRP level, and the presence of diabetes, hypertension, and dyslipidemia, the adjusted HRs (95% CIs) of incident CVD for the third METS-VF tertile, the third VAI tertile, and the third LAP tertile were 1.62 (1.29–2.03), 1.38 (1.08–1.77), and 1.66 (1.32–2.09), respectively, compared to the referent first tertile of each index. The adjusted HRs (95% CIs) of CVD incidence for each 1-point increase in the METS-VF, VAI, and LAP were 1.37 (1.16–1.63), 1.04 (1.01–1.08), and 1.00 (1.00–1.01), respectively. Restricted cubic spline analyses showed differing dose–response relationships across indices (Figure 3). METS-VF demonstrated a largely linear association with CVD risk (p for non-linearity $= 0.606$), whereas VAI ($p = 0.023$) and LAP ($p < 0.001$) exhibited evidence of non-linear associations, with patterns suggestive of threshold effects. Specifically, LAP showed a steeper increase in risk at lower levels followed by a plateau, while VAI demonstrated a similar but less pronounced pattern.

3.3 | Comparison of Discriminative Performance of METS-VF, VAI, and LAP for CVD Incidence

Table 3 shows a comparison of the three indices' discriminative performance for CVD incidence using Harrell's C index and Heagerty's iAUC. Harrell's C index value of METS-VF was significantly higher than those of VAI and LAP (C-index: 0.622, 95% CI: 0.600–0.643 for METS-VF vs. 0.583, 0.560–0.606 for VAI, and 0.600, 0.578–0.622 for LAP, $p = 0.001$ and $p = 0.007$, respectively). Heagerty's iAUC of METS-VF was 0.610 (95% CI: 0.588–0.632), which was significantly higher than those of VAI (Heagerty's iAUC: 0.540, 95% CI 0.527–0.555) ($p < 0.001$) and LAP (Heagerty's iAUC: 0.547, 95% CI 0.534–0.562) ($p < 0.001$). Additional comparisons with conventional anthropometric measures, including BMI and WC, are presented in Table S3. METS-VF demonstrated statistically higher discriminatory performance than BMI and WC; however, the magnitude of improvement was modest.

3.4 | Stratified Analyses for the Association of METS-VF, VAI, and LAP With CVD Incidence

The associations between the tertiles of METS-VF, VAI, LAP and risk for CVD incidence by different subgroups are presented in Figure 4. The third tertile of METS-VF and LAP had a significantly higher risk of CVD events compared to the referent first tertile of each index in the subgroups with age under 65 years, both male and female sex, normal glucose tolerance, and prediabetes. The third tertile of VAI had a significantly higher risk of CVD incidence only in the subgroups with age under 65 years, male sex, and prediabetes. No significant differences were observed in the risk of CVD events among tertiles of all three indices in participants over 65 years old and participants with diabetes. Additional stratified analyses by drinking and smoking status are presented in Table S4. The third tertile of METS-VF, VAI, and LAP showed a significantly higher risk of CVD events compared to the first tertile in the subgroups with never smokers and never drinkers, whereas no significant associations were observed in most former and current smokers and drinkers. However, no statistically significant interaction was observed for smoking or drinking status.

TABLE 1 | Baseline characteristics of the population with or without new-onset CVD.

Variables	Total	Without new-onset CVD	With new-onset CVD	*p*
Participants, *n*	8192	7523	669	
Age, years	51.84 ± 8.81	51.57 ± 8.80	54.91 ± 8.32	< 0.001
Male sex, *n* (%)	3902 (47.6)	3560 (47.3)	342 (51.1)	0.065
BMI, kg/cm^2	24.58 ± 3.15	24.54 ± 3.14	24.98 ± 3.16	< 0.001
Waist circumference, cm	82.51 ± 8.79	82.30 ± 8.79	84.85 ± 8.37	< 0.001
Waist-to-height ratio	0.52 ± 0.06	0.52 ± 0.06	0.53 ± 0.06	< 0.001
SBP, mmHg	120.98 ± 18.21	120.56 ± 18.20	125.71 ± 17.71	< 0.001
DBP, mmHg	80.20 ± 11.41	79.99 ± 11.44	82.58 ± 10.80	< 0.001
Fasting glucose, mg/dL	87.10 ± 20.72	86.72 ± 20.00	91.36 ± 27.21	< 0.001
Insulin, μU/mL	7.61 ± 4.77	7.57 ± 4.72	8.14 ± 5.28	0.007
HbA1c, %	5.72 ± 0.80	5.70 ± 0.77	5.97 ± 1.12	< 0.001
HOMA-IR	1.65 ± 1.15	1.64 ± 1.14	1.85 ± 1.29	< 0.001
Total cholesterol, mg/dL	191.48 ± 35.17	190.96 ± 35.12	197.29 ± 35.21	< 0.001
Triglycerides, mg/dL	160.76 ± 102.97	159.04 ± 102.97	180.07 ± 101.12	< 0.001
HDL-cholesterol, mg/dL	44.76 ± 10.06	44.90 ± 10.12	43.13 ± 9.27	< 0.001
Non-HDL cholesterol, mg/dL	146.72 ± 34.47	146.06 ± 34.36	154.17 ± 34.96	< 0.001
CRP, mg/dL	0.23 ± 0.42	0.22 ± 0.42	0.26 ± 0.39	0.030
METS-IR	37.84 ± 6.66	37.71 ± 6.62	39.35 ± 6.94	< 0.001
METS-VF	6.44 ± 0.59	6.42 ± 0.59	6.63 ± 0.53	< 0.001
VAI	2.65 ± 2.14	2.61 ± 2.13	3.10 ± 2.22	< 0.001
LAP	40.69 ± 35.19	39.93 ± 35.03	49.21 ± 35.94	< 0.001
Smoking status, *n* (%)				0.010
Current smoker	2077 (25.4)	1877 (24.9)	200 (29.9)	
Former smoker	1270 (15.5)	1163 (15.5)	107 (16.0)	
Never smoker	4845 (59.1)	4483 (59.6)	362 (54.1)	
Drinking status, *n* (%)				0.421
Current drinker	3944 (48.1)	3638 (48.4)	306 (45.7)	
Former drinker	501 (6.1)	457 (6.1)	44 (6.6)	
Non-drinker	3747 (45.7)	3428 (45.6)	319 (47.7)	
Physical activity, METs-h/day	23.99 ± 14.89	23.90 ± 14.85	25.06 ± 15.26	0.059
Glucose tolerance status, *n* (%)				< 0.001
Normal glucose tolerance	3871 (47.3)	3609 (48.0)	262 (39.2)	
Prediabetes	3372 (41.2)	3092 (41.1)	280 (41.9)	
Diabetes	949 (11.6)	822 (10.9)	127 (19.0)	
Hypertension, *n* (%)	2544 (31.1%)	2262 (30.1%)	282 (42.2%)	< 0.001
Dyslipidemia, *n* (%)	3771 (46.0%)	3405 (45.3%)	366 (54.7%)	< 0.001

Note: Data are presented as mean ± standard deviation or number (%). *p* Values were calculated using the *t*-test for continuous variables and chi-square test for categorical variables.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high density lipoprotein; HOMA-IR, homeostatic assessment model of insulin resistance; LAP, lipid accumulation product; MET, metabolic equivalent of task; METS-IR, metabolic score for insulin resistance; METS-VF, metabolic score for visceral fat; SBP, systolic blood pressure; VAI, visceral adiposity index.

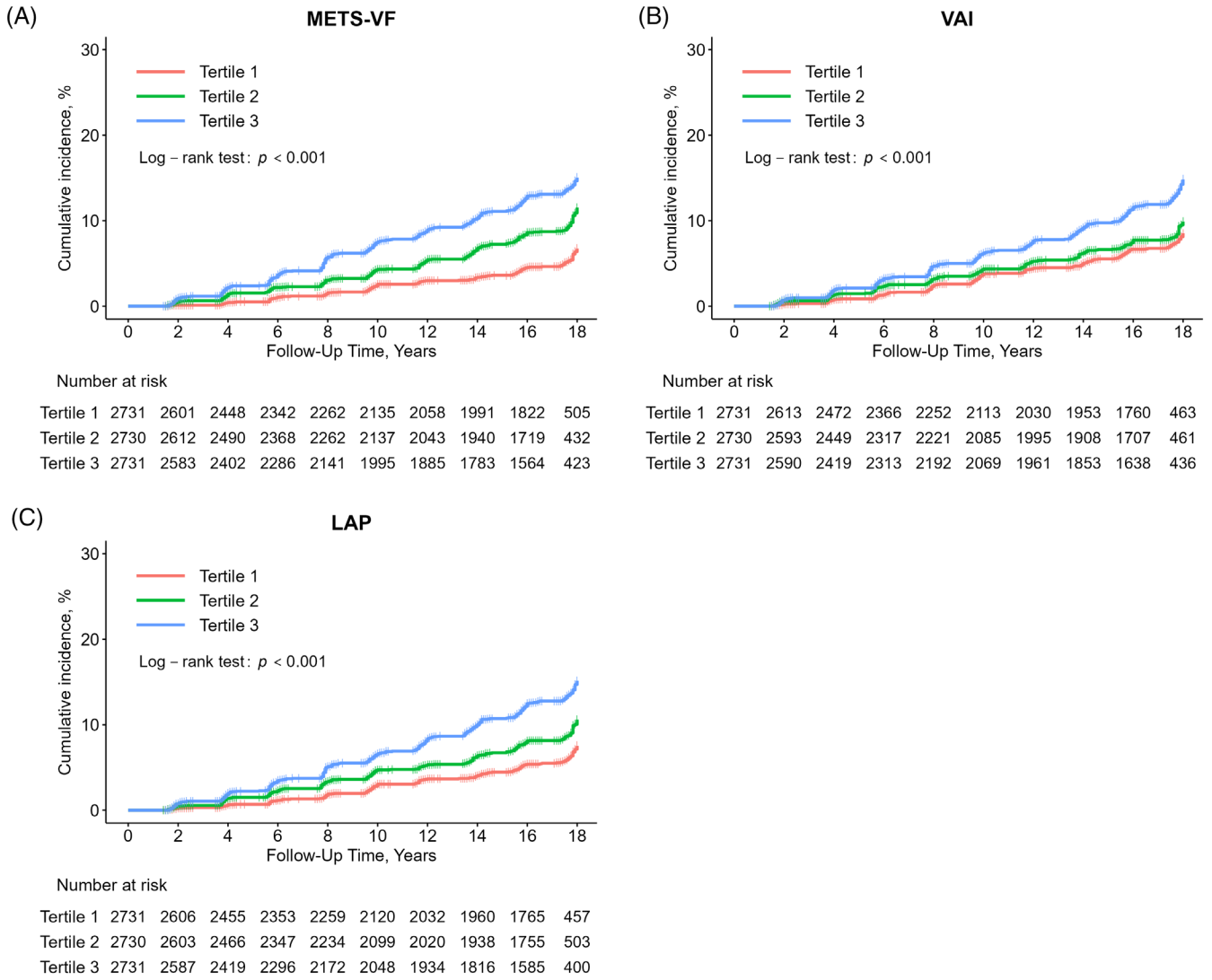

FIGURE 2 | Kaplan–Meier curves for cumulative incidence of CVD according to tertiles of visceral adiposity indices. (A) METS-VF, (B) VAI, and (C) LAP.

4 | Discussion

We examined the associations between three different indices for visceral adiposity (METS-VF, VAI, and LAP) and incidence of CVD, as well as compared the discriminatory performance of them using the data from a large community-based prospective cohort with a 17.5-year follow-up. Elevated baseline METS-VF, VAI, and LAP were independently associated with an increased risk of CVD events. Notably, these positive associations remained significant even after adjusting for other CVD risk factors. Furthermore, a comparison of the discriminatory performance of METS-VF, VAI, and LAP for CVD incidence demonstrated that METS-VF showed relatively higher discriminatory performance for CVD incidence compared to VAI and LAP.

The ATTICA study, using a large cohort of prospectively followed Caucasian adults, exhibited that baseline VAI and LAP, respectively, had a significant positive association with the 10-year CVD incidence [10, 12]. These studies suggested that VAI and LAP may provide additional information beyond classical anthropometric indices of total and central obesity (e.g., WC, BMI, WHR, and WHtR). METS-VF, the most recently validated VAT indicator, has been demonstrated to be a good predictor of hypertension, diabetes, and metabolic disorders [27–29]. In 2023, Zhu et al. [15] demonstrated a significant independent association between METS-VF and the risk of CVD events and all-cause mortality in a Chinese population. Moreover, this previous study reported that METS-VF may show improved performance compared with other indices, including BMI, WHR, and VAI, in predicting the risk of CVD events. Our results are consistent with those of these previous studies, suggesting that all three VAT indices, METS-VF, VAI, and LAP, are useful indicators of CVD risk. In addition, a comparison of AUCs showed that the METS-VF had higher discriminatory performance than VAI, LAP, and conventional anthropometric indices (BMI and WC) for incident CVD. However, the overall discriminative ability of these indices was modest, suggesting that they may be more appropriately used as complementary tools for risk stratification rather than standalone predictive markers.

To better interpret these findings, it is important to consider the underlying biological mechanisms linking visceral adiposity to

TABLE 2 | Cox proportional regression analysis for incident CVD according to METS-VF, VAI, and LAP tertiles.

	Model 1		Model 2		Model 3	
Category	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
METS-VF						
T1 (< 6.26)	1 (Ref.)		1 (Ref.)		1 (Ref.)	
T2 (6.26–6.76)	1.81 (1.46–2.25)	< 0.001	1.58 (1.27–1.96)	< 0.001	1.43 (1.15–1.79)	0.002
T3 (> 6.76)	2.66 (2.16–3.26)	< 0.001	1.95 (1.57–2.42)	< 0.001	1.62 (1.29–2.03)	< 0.001
Continuous	2.09 (1.79–2.43)	< 0.001	1.61 (1.37–1.89)	< 0.001	1.37 (1.16–1.63)	< 0.001
VAI						
T1 (< 1.58)	1 (Ref.)		1 (Ref.)		1 (Ref.)	
T2 (1.58–2.70)	1.12 (0.91–1.37)	0.274	1.10 (0.89–1.35)	0.377	1.03 (0.83–1.27)	0.817
T3 (> 2.70)	1.74 (1.44–2.10)	< 0.001	1.60 (1.32–1.93)	< 0.001	1.38 (1.08–1.77)	0.012
Continuous	1.08 (1.05–1.11)	< 0.001	1.07 (1.04–1.10)	< 0.001	1.04 (1.01–1.08)	0.017
LAP						
T1 (< 22.3)	1 (Ref.)		1 (Ref.)		1 (Ref.)	
T2 (22.3–43.8)	1.45 (1.18–1.79)	< 0.001	1.38 (1.12–1.70)	0.003	1.29 (1.04–1.60)	0.020
T3 (> 43.8)	2.21 (1.81–2.69)	< 0.001	1.94 (1.59–2.37)	< 0.001	1.66 (1.32–2.09)	< 0.001
Continuous	1.01 (1.00–1.01)	< 0.001	1.01 (1.00–1.01)	< 0.001	1.00 (1.00–1.01)	0.008

Note: Model 1: Unadjusted. Model 2: Adjusted for age, sex, physical activity, smoking status, and drinking status. Model 3: Adjusted for age, sex, physical activity, smoking status, drinking status, CRP, diabetes, hypertension, and dyslipidemia.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LAP, lipid accumulation product; METS-VF, metabolic score for visceral fat; VAI, visceral adiposity index.

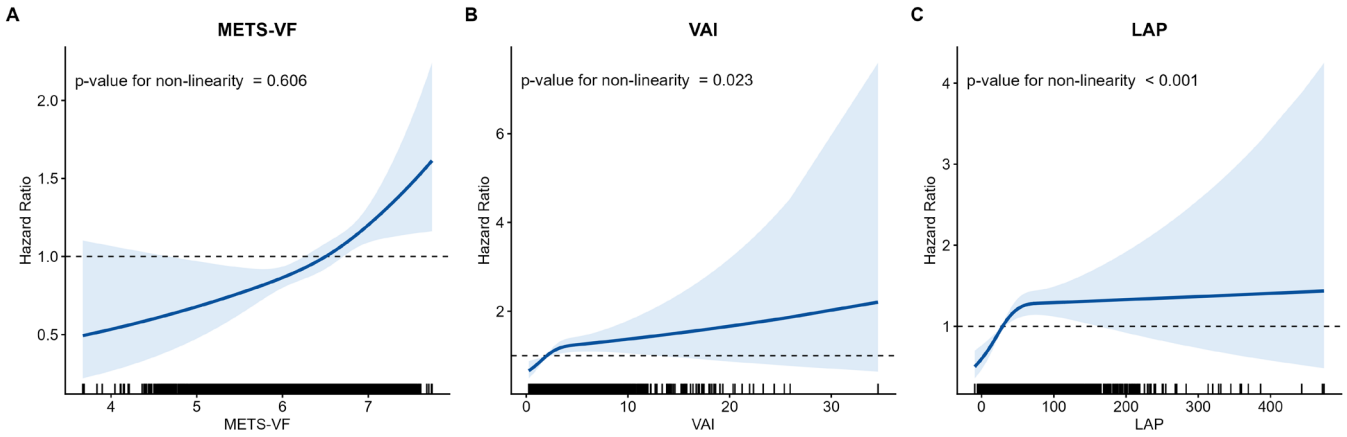

FIGURE 3 | Restricted cubic spline curves for the association between visceral adiposity indices and incident CVD. (A) METS-VF, (B) VAI, and (C) LAP.

CVD. Several possible mechanisms have been proposed to explain the contribution of VAT to the development of CVD [30, 31]. Because most VAT is drained by the portal vein, visceral obesity exposes the liver to excess free fatty acids and glycerol, thus disrupting liver metabolism. These metabolic alterations promote insulin resistance, hyperglycemia, and hypertriglyceridemia [32, 33]. Moreover, expanded VAT induces a chronic inflammatory state due to macrophage infiltration into hypertrophied adipocytes, thus increasing the secretion of pro-inflammatory cytokines (e.g., leptin, tumour necrosis factor-α, and interleukin-6) and reducing the production of anti-inflammatory adipokines such as adiponectin [34]. These pathological changes in VAT play both direct and indirect roles in the development of cardiovascular and metabolic diseases.

Evaluation of dose–response relationships showed a linear association between METS-VF and CVD risk, whereas VAI and LAP exhibited non-linear associations. These findings are consistent with previous studies reporting a non-linear relationship between VAI and cardiovascular outcomes [11], and a study demonstrating a linear association between METS-VF and CVD risk [15]. The linear pattern observed for METS-VF may reflect

TABLE 3 | Comparison of the discriminative performance of METS-VF, VAI, and LAP for incident CVD.

Variables	Harrell's C index	Heagerty's iAUC
METS-VF group, (1)	0.622 (0.600, 0.643)	0.610 (0.588, 0.632)
VAI group, (2)	0.583 (0.560, 0.606)	0.540 (0.527, 0.555)
LAP group, (3)	0.600 (0.578, 0.622)	0.547 (0.534, 0.562)
Difference (1)–(2)	0.039 (0.015, 0.062)	0.069 (0.048, 0.091)
Difference (1)–(3)	0.021 (0.006, 0.037)	0.062 (0.044, 0.081)
Difference (2)–(3)	−0.017 (−0.029, −0.005)	−0.007 (−0.016, 0.002)
p Value: (1) vs. (2)	0.001	< 0.001
p Value: (1) vs. (3)	0.007	< 0.001
p Value: (2) vs. (3)	0.005	0.070

Abbreviations: CVD, cardiovascular disease; iAUC, integrated area under the receiver operating characteristic curve; LAP, lipid accumulation product; METS-VF, metabolic score for visceral fat; VAI, visceral adiposity index.

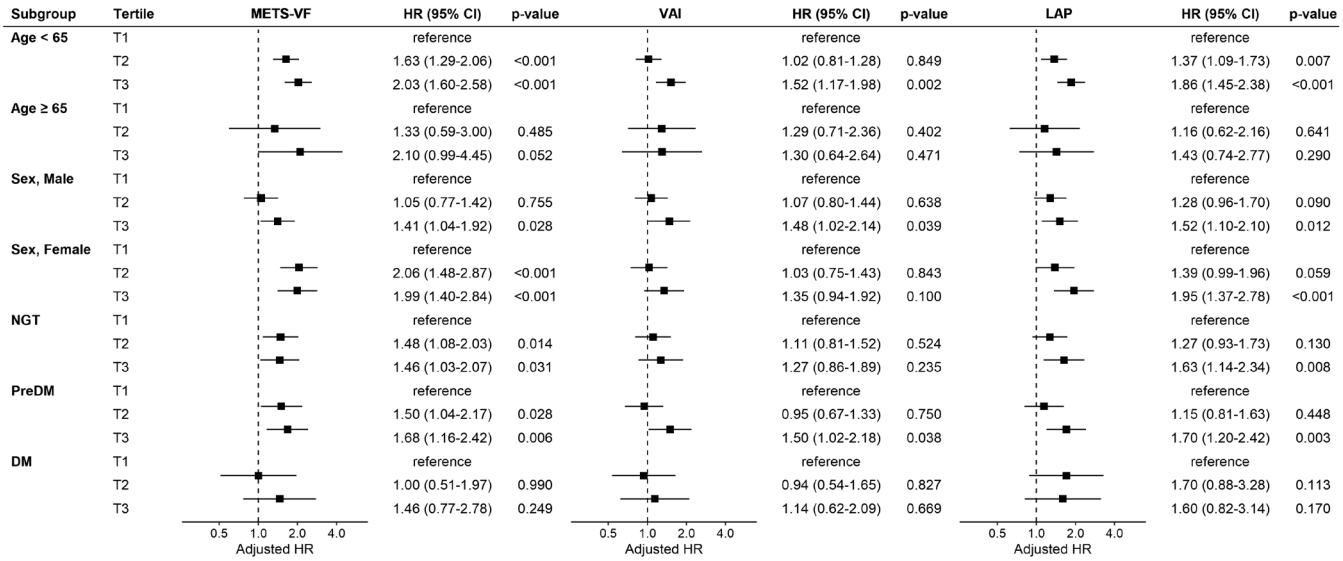

FIGURE 4 | Forest plot of subgroup analyses for the association between METS-VF, VAI, and LAP tertiles and incident CVD.

its incorporation of both anthropometric and metabolic components, allowing for a more consistent capture of cardiometabolic risk across its range. In contrast, the non-linear patterns observed for VAI and LAP, particularly the plateau at higher levels, may partly reflect a threshold effect. This pattern may also be influenced by residual selection bias [35], such as the preferential inclusion of individuals who survived despite higher levels of visceral adiposity.

Stratified analyses in our longitudinal cohort study demonstrated that higher METS-VF and LAP were significantly associated with a higher risk of CVD events across most subgroups, excluding participants over 65 years old and participants with diabetes, whereas VAI was significantly associated only in the subgroups of participants under 65 years old, male, and with prediabetes. Our findings are inconsistent with those of previous studies that examined positive correlations between the three adiposity indices and the risk of CVD events among individuals with diabetes [15, 36]. Although previous studies have demonstrated that the associations between adiposity indices and CVD incidence remained significant across the subgroups by age and glucose tolerance status, the associations were stronger in participants of younger age and in those without diabetes [37, 38]. Considering that age and diabetes are crucial risk factors for CVD, the apparent impact of visceral fat accumulation may be less evident in participants of older age and diabetes after stratification. In additional stratified analyses according to smoking and drinking status, the associations between the three indices and CVD risk were observed primarily among never smokers and never drinkers, whereas no significant associations were found in most former and current smokers and drinkers. This pattern may be explained by the strong independent effects of smoking and alcohol consumption on CVD risk, which could mask or attenuate the relative contribution of visceral adiposity. However, no statistically significant interaction was observed for smoking or drinking status, suggesting that these factors did not significantly modify the associations.

Strengths of our study include a large sample size, a long follow-up period (17.2 years) in a prospective cohort, and

standardized measurement methods. To our knowledge, this is the first study to investigate the association between three different indices for visceral adiposity (METS-VF, VAI, and LAP) and the risk of CVD in Korean adults, and further compare their discriminatory performance. Nevertheless, the study has several limitations. First, despite the large sample size, the study population consisted of community-dwelling middle-aged adults, possibly limiting the applicability of our findings to the general Korean population or to other ethnic and age groups. Second, the identification of new-onset CVD cases relied on self-reported physician diagnoses rather than on objective clinical evaluations or confirmatory tests, which may be subject to recall bias and misclassification. Third, a proportion of participants was excluded due to follow-up loss and missing data, and baseline differences between included and excluded individuals may have introduced selection bias and affected the representativeness of the study population. Fourth, only baseline adiposity indices were considered, and changes over time or cumulative exposure were not accounted for. Fifth, we did not validate the consistency between the three adiposity indices and the actual measurement of VAT using CT or DEXA in this study. Finally, although we adjusted for several confounding variables in multivariable analyses, the influence of residual or unidentified confounding factors could not be entirely excluded.

5 | Conclusion

This study demonstrated that METS-VF, VAI, and LAP were independently associated with an increased risk of CVD events, especially in younger adults and those with normal glucose tolerance or prediabetes. Among the three indices, METS-VF displayed relatively better discriminatory performance for CVD incidence. All indices assessed in this study are simple, cost-effective, practical, and reliable indicators of visceral adiposity. Because visceral obesity is a modifiable risk factor, our findings highlight the significance of identification and early intervention in individuals with elevated METS-VF, VAI, and LAP scores. However, the overall discriminative ability of these indices was modest, and they should therefore be considered complementary tools rather than standalone predictive markers.

Author Contributions

A.-R.C., T.H., S.-J.H., and Y.-J.K.: study concept and design; acquisition, analysis, and interpretation of data; drafting of the manuscript. A.-R.C., S.-J.H., and Y.-J.K.: study concept and design; interpretation of data; supervision; revision of the manuscript. A.-R.C., T.H., S.-J.H., and Y.-J.K.: approval of the final manuscript.

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The authors have nothing to report.

Ethics Statement

The KoGES Ansan Ansung Cohort Protocol was reviewed and approved by the Institutional Review Board (IRB) of the Korea Center for Disease Control and Prevention. All participants provided written informed consent and agreed to participate in this study. This study was approved by the IRB of Yongin Severance Hospital (IRB no. 9-2022-0090).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The dataset used in this study was obtained after the review and evaluation of the research plan by the Korea Centers for Disease Control and Prevention. (https://www.kdca.go.kr/contents.es?mid=a40504020100).

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Baseline characteristics of included and excluded participants. **Table S2:** Incidence of CVD during the follow-up study. **Table S3:** Comparison of the discriminative performance of visceral adiposity indices and conventional anthropometric measures for incident CVD. **Table S4:** Stratified analyses for the association of METS-VF, VAI, and LAP with CVD incidence according to drinking and smoking status.