



Longitudinal Associations Between Metabolic Risk Burden and the Cardio–Ankle Vascular Index (CAVI) in Japan Using Health-Check Cohort

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Purpose: The cardio–ankle vascular index (CAVI) is a blood pressure-independent indicator of arterial stiffness. Although CAVI is associated with metabolic risk factors, longitudinal evidence clarifying their relative impact remains limited. This study aimed to examine longitudinal associations between metabolic abnormalities and CAVI in a Japanese health check-up population, focusing on MetS components and waist circumference (WC) status.

Patients and Methods: A total of 13,724 adults (7060 men and 6664 women) who underwent annual health check-ups at the International University of Health and Welfare Narita Hospital between 2020 and 2024 were included. Linear mixed-effects models were used to evaluate longitudinal changes in CAVI according to MetS components (blood pressure, glucose, lipids, and WC). Secondary analyses examined CAVI changes by MetS status, WC strata (WC (+)/WC (-)), metabolic risk count (0–3) and sex.

Results: Older age and male sex were independently associated with higher CAVI. Blood pressure and glucose abnormalities showed the strongest associations with elevated CAVI, whereas lipid risk had a modest effect and WC was inversely associated with CAVI. CAVI increased annually overall, but increased more slowly among participants with blood pressure risk. Time interactions for glucose, lipid and WC risk were not significant. MetS was associated with higher baseline CAVI, but longitudinal time interactions did not differ significantly by MetS status. In WC-stratified analyses, baseline CAVI increased stepwise with accumulation of metabolic risk factors in both WC (+) and WC (-) groups, including a substantial WC (-)-subgroup—particularly women—with multiple metabolic risks and elevated CAVI.

Conclusion: Longitudinal follow-up revealed modest CAVI progression with attenuated slopes among participants with high-baseline CAVI, indicating that baseline CAVI captures cumulative vascular injury rather than accelerated short-term change. CAVI may complement WC-centered screening by identifying non-obese individuals—especially women—with elevated longitudinal vascular risk.

Keywords: arterial stiffness, cardio–ankle vascular index, metabolic syndrome, blood pressure, glucose metabolism, waist circumference

Introduction

The cardio–ankle vascular index (CAVI) developed in 2004 is a noninvasive indicator of arterial stiffness that reflects the stiffness of the vascular segment from the heart to the ankle, independent of blood pressure levels.¹ Compared with conventional pulse wave velocity (PWV), CAVI shows greater measurement stability and higher sensitivity for detecting functional changes in the arterial wall. PWV is known to be influenced by blood pressure at the time of measurement, whereas CAVI incorporates the stiffness parameter β to reduce blood pressure dependency, which leads to better reflection of intrinsic arterial stiffness.^{1–3} The large-scale prospective CAVI-J cohort study demonstrated that elevated CAVI values are significantly associated with the incidence of cardiovascular disease (CVD) and stroke.⁴ Furthermore,



previous studies have shown that CAVI serves as an integrated marker of systemic atherosclerotic burden, correlating with both subclinical vascular damage and future cardiovascular risk.^{5,6}

Because of its simplicity and clinical applicability, CAVI has attracted increasing attention in Japan as a screening tool for subclinical atherosclerosis. Nonetheless, while CAVI is also increasingly recognized as a predictor of cardiovascular outcomes, the extent to which conventional metabolic abnormalities—particularly metabolic syndrome components and waist circumference (WC)—contribute to longitudinal changes in CAVI remains unclear. Beyond Japan, several studies have demonstrated that metabolic syndrome and its components are associated with increased CAVI, with evidence suggesting sex- and age-specific differences. However, most of these studies are cross-sectional in design.^{7–9} Therefore, longitudinal evaluation of CAVI in relation to metabolic risk accumulation remains an important unmet need. This knowledge gap partly reflects the nature of available data: although CAVI is associated with metabolic abnormalities and cardiovascular risk,^{7,10} most evidence to date is derived from cross-sectional analyses, with only limited longitudinal data available. Hence, comprehensive longitudinal data comparing the relative effects of individual metabolic risk factors on changes in CAVI remain limited. Moreover, participant retention across consecutive years is often limited by job changes, workplace transfers, insurance changes or health check-ups conducted at different institutions, reducing the availability of consistent repeated measurements. In addition, because arterial stiffness typically progresses slowly, detecting meaningful changes in CAVI requires long-term observation and large sample sizes.

Meanwhile, metabolic syndrome (MetS) is widely recognized as a cluster of metabolic abnormalities, including elevated blood pressure, impaired glucose metabolism, dyslipidemia, and central obesity, that collectively increase the risk of CVD.¹¹ In Japan, the current diagnostic criteria for MetS require increased WC as an essential component, together with at least two of the following three abnormalities: elevated blood pressure, abnormal glucose metabolism, or dyslipidemia. Although this framework has contributed to cardiovascular risk stratification in Japan, the definition of MetS varies considerably across international guidelines. The International Diabetes Federation (IDF) and Japanese criteria regard WC as a mandatory component, whereas the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) define MetS as the presence of any three or more of these abnormalities, regardless of WC.^{12,13}

Taken together, the limited longitudinal evidence on CAVI and the variability in MetS definitions—particularly with respect to the role of WC—leave an important gap in understanding how individual and clustered metabolic abnormalities drive changes in arterial stiffness over time. Moreover, it remains unclear whether CAVI primarily reflects cumulative vascular burden at baseline or ongoing progression over time, which may have important implications for its clinical interpretation. It is also noteworthy that WC-based MetS definitions may fail to identify individuals with increased vascular risk despite the absence of central obesity. These gaps are especially relevant for individuals without central obesity, in whom metabolic risk may be under-recognized by WC-centered criteria. Accordingly, this study aimed to clarify the longitudinal associations between metabolic abnormalities and arterial stiffness, as assessed by CAVI, in a general health-check population. Specifically, we sought to: (1) identify which metabolic risk factors contribute most strongly to baseline levels and longitudinal progression of arterial stiffness, as assessed by CAVI; and (2) to compare longitudinal changes in CAVI by MetS status stratified by WC-based subgroups, and to evaluate whether the accumulation of metabolic risks (0–3 components), including in non-obese individuals, is associated with progressive increases in CAVI.

Materials and Methods

Study Design and Ethical Approval

This longitudinal observational study examined the associations between metabolic abnormalities and arterial stiffness at baseline and over time, as assessed by CAVI. We used annual health check-up data collected at the International University of Health and Welfare (IUHW) Narita Hospital between 2020 and 2024. The study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects¹⁴ and was approved by the Ethics Review Committee of the IUHW, Chiba District (approval number: 25-CC-003). All participant data were de-identified prior to analysis. The requirement for written informed

consent was waived by the Ethics Review Committee, and an opt-out procedure was implemented via the institution's website.

Participants

Participants were selected from individuals who underwent annual health check-ups at the IUHW Narita Hospital between 2020 and 2024. Eligible participants were adults who had at least one valid CAVI measurement available during this period. Participants were excluded if they met any of the following conditions: (1) pregnancy; (2) a ≥ 5 difference between right and left CAVI values; (3) missing data for CAVI or any component required to define MetS status (blood pressure, glucose, lipid parameters, or WC); or (4) a history of myocardial infarction, stroke, type 1 diabetes mellitus, or severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²). After applying these criteria, 13,724 participants (7060 men and 6664 women) were included in the final analysis from 21,612 examinees (Figure 1).

Definitions and Measurements

Metabolic risk factors were defined according to Japanese diagnostic criteria for MetS

- Blood pressure risk was defined as a systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 85 mmHg, or current use of antihypertensive medication.
- Glucose risk was defined as a fasting plasma glucose level ≥ 110 mg/dL or current use of antidiabetic medication.
- Lipid risk was defined as triglycerides (TG) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or current use of lipid-lowering medication.
- WC risk was defined as WC ≥ 85 cm in men or ≥ 90 cm in women.

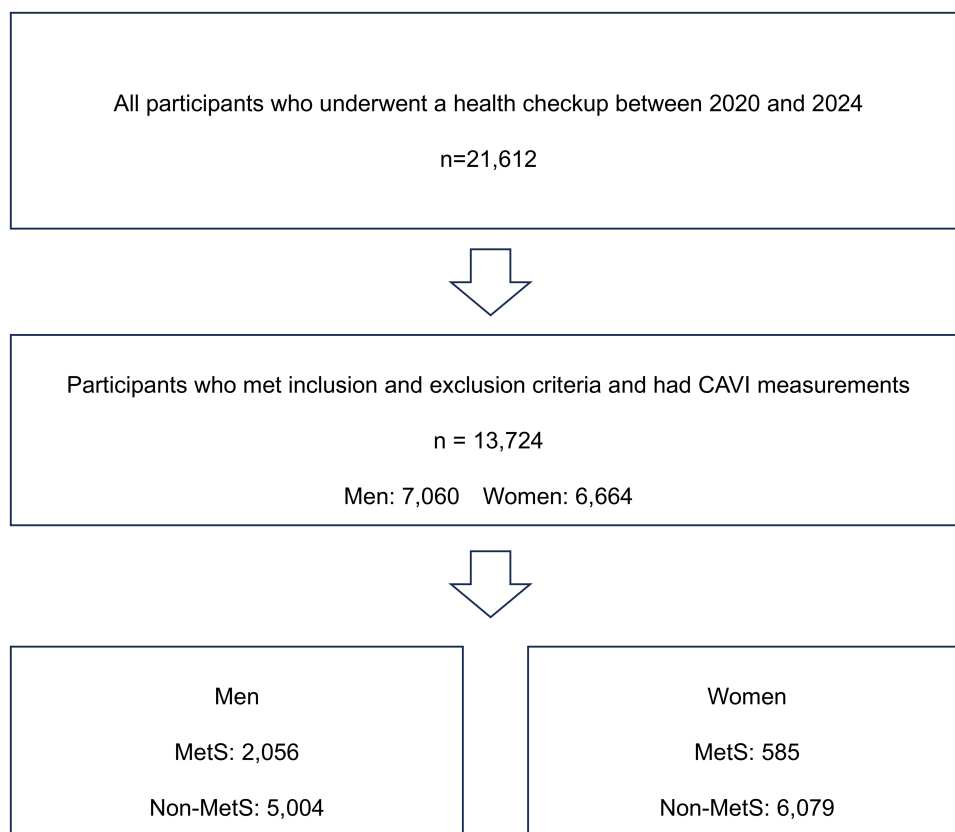


Figure 1 Study flowchart of participant selection.

Metabolic risk count was defined as the number of risk components (0–3) across blood pressure, glucose, and lipid abnormalities. Participants were further stratified into WC (+) and WC (–) groups according to the presence or absence of WC risk, respectively.

Assessment of Arterial Stiffness

CAVI was measured using a VaSera VS-2000 device (Fukuda Denshi Co., Tokyo, Japan) following standardized procedures. CAVI is calculated based on the stiffness parameter β , which incorporates PWV and blood pressure, and reflects arterial stiffness from the origin of the aorta to the ankle, independent of blood pressure at the time of measurement.^{1,2} Measurements were performed in the supine position after a period of rest, using cuffs placed on both arms and ankles, with electrocardiogram electrodes and a phonocardiogram sensor. The mean of right and left CAVI values was used for analysis. Lipid risk was defined according to the Japanese criteria for metabolic syndrome, which include TG and HDL-C as components of dyslipidemia but not low-density lipoprotein cholesterol. Fasting plasma glucose, TG, and HDL-C were measured using standardized laboratory methods at the central laboratory of the IUHW Narita Hospital. Smoking status and current medication use were obtained using standardized self-administered questionnaires. CAVI values were calculated and analyzed to assess the arterial stiffness, and fasting plasma glucose, TG, HDL-C, body mass index, SBP, DBP, current smokers, and WC were measured using standard certified assays.

Statistical Analysis

The primary objective of this study was to examine the effects of individual metabolic risk factors on baseline and longitudinal changes in CAVI. Linear mixed-effects models (LMMs) were applied to evaluate annual changes in CAVI as a function of each metabolic risk factor (blood pressure, glucose, lipid, and WC). To account for within-subject variability across repeated measurements, we fitted LMMs with a random intercept for each participant. Fixed effects included time (Visit 1–5, representing annual measurements), each metabolic risk factor (blood pressure, glucose, lipid, and WC), and the interaction between time and each metabolic risk factor. Baseline age, sex, and current smoking were entered as covariates and adjusted in the model. The reference categories were defined as time = Visit 1 (baseline) and “no risk” for each factor. Regression coefficient derived from the model were used to illustrate annual changes in CAVI across subgroups.

For secondary analyses, CAVI was modeled as the dependent variable with fixed effects for time (Visit 1–5), MetS (present vs absent), and their interaction. Baseline age, sex, and current smoking were included as covariates, and sex was additionally included in the overall model but omitted in sex-stratified models. Model-derived regression coefficients were used to illustrate longitudinal changes in CAVI between participants with and without MetS.

Participants were further stratified by WC status (WC (+) vs WC (–)) and sex. Fixed effects for time (Visit 1–5), metabolic risk count (0–3), and the interaction between time and metabolic risk count were entered into the model, with the same covariates as described above.

All statistical analyses were performed using IBM SPSS Statistics, version 30 (IBM Corp., Armonk, NY, USA). A two-sided p -value <0.05 was considered statistically significant.

Results

Baseline Characteristics and Follow-up

Among 21,612 individuals who underwent annual health check-ups at the IUHW Narita Hospital between 2020 and 2024, a total of 13,724 participants (7060 men and 6664 women) met the eligibility criteria and were included in the final analysis (Figure 1).

The numbers of participants contributing data at each visit were 13,724 at Visit 1, 6097 at Visit 2, 4648 at Visit 3, 2995 at Visit 4, and 1045 at Visit 5 (Table 1). Baseline clinical characteristics are summarized in Table 1.

The mean (\pm SD) age was 55.6 ± 13.1 years, and the mean CAVI was 7.72 ± 1.22 . Compared with women, men had higher WC, body mass index, SBP, DBP, fasting plasma glucose, and TG levels, but lower HDL-C. The proportion of current smokers was also higher among men (21.6% vs 5.5%). Baseline CAVI was significantly higher in men than in

Table 1 Baseline Characteristics of the Study Participants

Variable, Mean (SD)	Unit	Total (n=13,724)	Men (n=7060)	Women (n=6664)	P value
Age	Year	55.6 ± 13.1	56.0 ± 13.3	55.2 ± 13.0	0.010
WC	cm	84.9 ± 10.0	87.3 ± 9.4	82.4 ± 10.0	<0.001
BMI	kg/m ²	23.3 ± 3.8	24.2 ± 3.6	22.4 ± 3.8	<0.001
SBP	mmHg	125.4 ± 20.1	127.6 ± 18.8	123.1 ± 21.2	<0.001
DBP	mmHg	77.3 ± 12.4	79.6 ± 12.0	74.9 ± 12.4	0.047
Fasting glucose	mg/dL	103.6 ± 18.3	107.4 ± 20.3	99.6 ± 14.9	<0.001
Triglyceride	mg/dL	104.8 ± 75.3	120.1 ± 89.4	88.5 ± 52.0	<0.001
HDL-C	mg/dL	61.3 ± 15.3	55.8 ± 13.7	67.1 ± 14.9	<0.001
CAVI	–	7.72 ± 1.22	7.95 ± 1.23	7.48 ± 1.15	<0.001
Baseline, n (%)					
Hypertension drug	–	2826 (20.6)	1800 (25.5)	1026 (15.4)	<0.001
Hyperglycemia drug	–	748 (5.5)	563 (8.0)	185 (2.8)	<0.001
Dyslipidemia drug	–	2383 (17.4)	1255 (17.8)	1128 (16.9)	0.008
Current smoker	–	1896 (13.8)	1528 (21.6)	368 (5.5)	<0.001
Visit=1		13,724 (100)	7060 (100)	6664 (100)	–
Visit=2		6097 (44.4)	3188 (45.2)	2909 (43.7)	–
Visit=3		4648 (33.9)	2411 (34.2)	2237 (33.6)	–
Visit=4		2995 (21.8)	1558 (22.1)	1437 (21.6)	–
Visit=5		1045 (7.6)	577 (8.2)	468 (7.0)	–

Abbreviations: WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; CAVI, cardio-ankle vascular index.

women (7.95 ± 1.23 vs 7.48 ± 1.15 , $p < 0.001$). In addition, the proportions of participants receiving treatment for hypertension, hyperglycemia, and dyslipidemia were 20.6%, 5.5%, and 17.4%, respectively.

Longitudinal Changes in CAVI and Associations Between Metabolic Risk Factors and CAVI

The results of the LMMs are presented in Table 2. On average, CAVI increased by 0.286 units over four years, indicating a gradual age-related increase in arterial stiffness. The rate of increase was slower among participants with elevated blood pressure (interaction $\beta = -0.133$, $p = 0.024$), whereas no significant time interactions were observed for glucose, lipid, or WC risks (Figure 2). Older age ($\beta = +0.056$ per year, $p < 0.001$) and male sex ($\beta = +0.387$, $p < 0.001$) were significantly associated with higher CAVI values, whereas non-smoker was associated with slightly lower CAVI ($\beta = -0.119$, $p < 0.001$). Participants with blood pressure, glucose, or lipid risk had significantly higher CAVI ($\beta = +0.238$, $+0.164$, and $+0.035$, respectively; all $p < 0.05$). In contrast, WC risk showed a negative association with CAVI ($\beta = -0.169$, $p < 0.001$), suggesting that non-obese individuals tended to have higher CAVI values.

Sex-stratified analyses (Table 3) revealed that both blood pressure and glucose risks were significantly associated with higher baseline CAVI in men ($\beta = +0.208$ and $+0.176$, respectively, both $p < 0.001$) and women ($\beta = +0.272$ and $+0.140$, both $p < 0.001$).

The effect of lipid risk was significant only among women ($\beta = +0.069$, $p = 0.007$). WC risk was inversely associated with CAVI in both sexes, with a stronger negative association observed in women ($\beta = -0.224$, $p < 0.001$). Interaction analyses revealed significant sex differences in baseline associations for blood pressure, lipid, and WC-related risks (Table 4).

Metabolic Syndrome, Risk Factor Accumulation, and WC

As shown in Table 5 and Figure 3, participants with MetS had significantly higher baseline CAVI than those without MetS ($\beta = +0.079$, 95% CI: 0.040–0.117, $p < 0.001$). Although the MetS group showed a trend toward a slower

Table 2 Baseline and Longitudinal Changes in CAVI by Metabolic Risk Factors

Factor	Baseline Difference (95% CI)	P value	Interaction Difference (95% CI)	P value
BP risk with	+0.238 (0.206 to 0.271) Ref.	<0.001	-0.133 (-0.249 to -0.018)	0.024
Without			Ref	
Glucose risk with	+0.164 (0.126 to 0.202)	<0.001	0 (-0.156 to +0.157)	0.997
Without	Ref.		Ref	
Lipid risk with	+0.035 (0.002 to 0.069)	0.040	-0.078 (-0.203 to +0.048)	0.225
Without	Ref.		Ref	
WC risk with	-0.169 (-0.202 to -0.136)	<0.001	+0.054 (-0.064 to +0.173)	0.369
Without	Ref.		Ref	
Covariates (Fixed effects)				
Age (per 1 year)	+0.056	< 0.001		
Sex (men vs women)	+0.387	< 0.001		
Current Smoker (vs non-smoker)	+0.119	< 0.001		
Time effect (Ref: Visit=1)				
Visit=2	+0.095			
Visit=3	+0.136			
Visit=4	+0.229			
Visit=5	+0.286			

Notes: "+" and "-" indicate the direction of the β coefficient (increase or decrease in CAVI). Models were adjusted for age at first visit, sex, current smoking, and the other three metabolic risk factors.

longitudinal increase in CAVI compared with the non-MetS group, this interaction did not reach statistical significance ($\beta = -0.089$, $p = 0.220$). In sex-specific analyses, men with MetS had higher baseline CAVI than those without MetS ($\beta = +0.094$, $p < 0.001$), while the time interaction between groups was not significant ($\beta = -0.102$, $p = 0.254$). Among women, neither baseline nor longitudinal changes in CAVI differed significantly by MetS status.

Stratified by WC and sex (Table 6, Figure 4), baseline CAVI increased progressively with the number of metabolic risk factors in both WC (+) and WC (-) subgroups among men (Risk 3: WC (+), $\beta = +0.345$, $p < 0.001$; WC (-), $\beta = +0.505$, $p < 0.001$). The time \times risk count interaction reached significance only in men with WC (+) ($\beta = -0.425$, $p = 0.034$). In women, baseline CAVI also increased stepwise with the accumulation of metabolic risk factors, both in the WC (+) and WC (-) subgroups (Risk 3: WC (+), $\beta = +0.311$, $p < 0.001$; WC (-), $\beta = +0.610$, $p < 0.001$). Although time \times risk interactions were not statistically significant, higher-risk groups tended to show weaker time interaction effects for CAVI change.

As shown in Figure 5, metabolic risk clustering patterns differed by sex and WC status: men with WC (+) were more likely to accumulate two or more metabolic risk factors, while a considerable proportion of women with WC (-) also exhibited multiple metabolic risks.

The accumulation of metabolic abnormalities was associated with higher baseline CAVI, including among individuals without abdominal obesity. In contrast, the longitudinal increase in CAVI was smaller over time, particularly in those with higher baseline values.

Discussion

In this longitudinal cohort of 13,724 adults, we gained several insights into the relationship between metabolic abnormalities and arterial stiffness assessed by CAVI. Elevated blood pressure and glucose burden were the strongest determinants of higher baseline CAVI, whereas WC showed an inverse association.

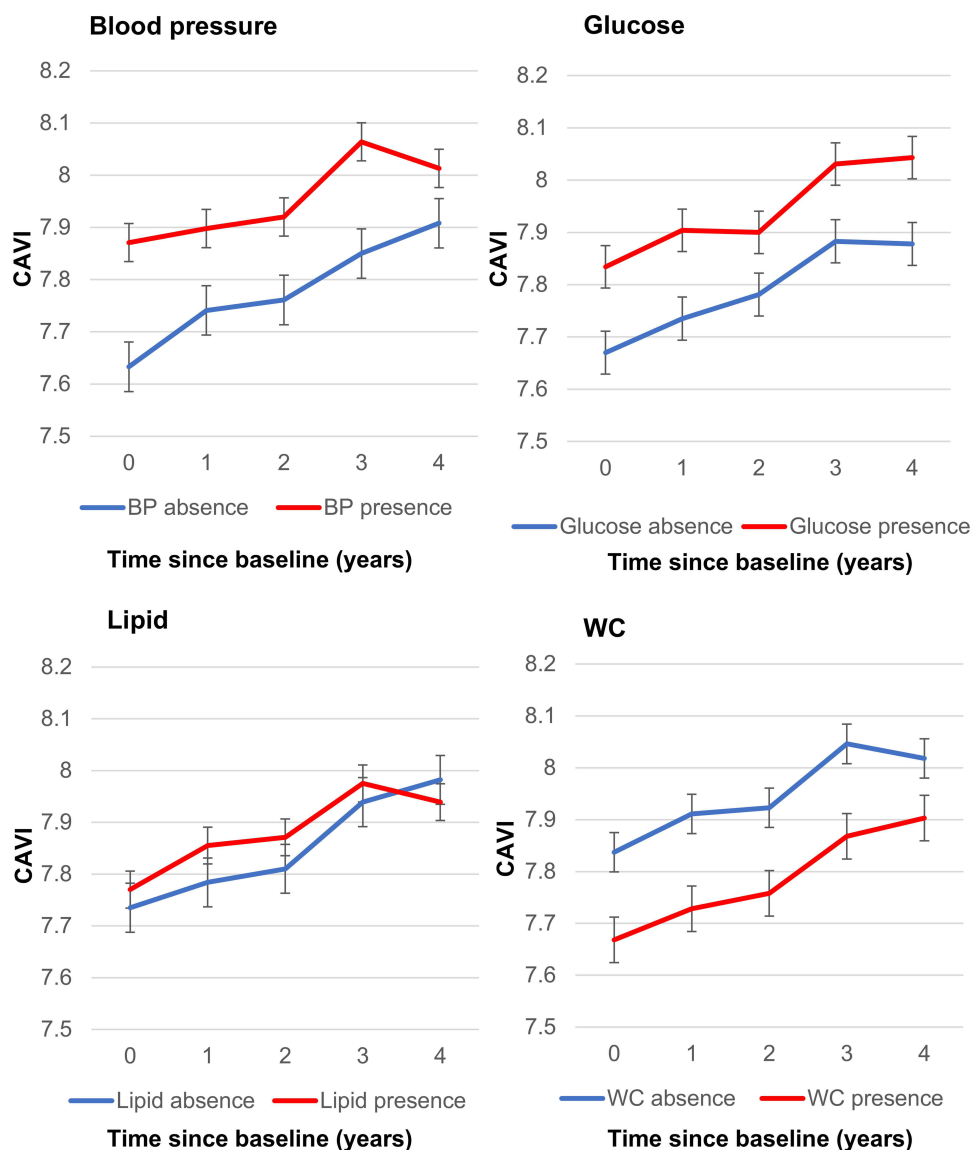


Figure 2 Estimated longitudinal changes in CAVI according to each metabolic risk factor. Models were adjusted for age, sex, smoking status and the other three metabolic risk factors. Blood pressure and glucose risks were more strongly associated with higher baseline CAVI than lipid and WC risks. A significant time interaction was observed only for blood pressure. The y-axis represents CAVI, and the x-axis represents time since baseline (years), where 0 indicates baseline and subsequent values represent years since baseline.

Metabolic Drivers of CAVI and Longitudinal Progression

We found that, among MetS components, elevated blood pressure and glucose burden showed the greatest impact on CAVI, whereas lipid abnormalities had a smaller and less consistent effect, and WC was inversely associated with CAVI. These findings align with previous studies demonstrating that hypertension and impaired glycemic control are key contributors to increased CAVI.⁷⁻⁹ In contrast, the inverse association between WC and CAVI observed in this study is consistent with prior reports, suggesting that WC alone may not adequately capture subclinical vascular risk.^{8,15}

In longitudinal analysis, CAVI increased annually across the cohort, while individuals with blood pressure risk showed a slower rate of increase. This likely reflects their higher baseline CAVI values, leaving limited room for further progression, a pattern consistent with previous reports demonstrating that CAVI progression is inversely correlated with baseline levels.¹⁶ This divergence may partly reflect regression to the mean related to the limited follow-up duration. Accordingly, in longitudinal health-check settings with limited follow-up duration, baseline CAVI level may provide more clinically meaningful prognostic information than short-term slope estimates alone.

Table 3 Baseline and Longitudinal Changes in CAVI by Metabolic Risk Factors, Stratified by Sex

Men	Baseline Difference (95% CI)	P value	Interaction Difference (95% CI)	P value
BP risk with	+0.208 (0.161 to 0.255)	<0.001	-0.108 (-0.269 to 0.054) Ref.	0.191
Without	Ref.			
Glucose risk with	+0.176 (0.126 to 0.225)	<0.001	-0.018 (-0.211 to +0.174) Ref.	0.853
Without	Ref.			
Lipid risk with	+0.013 (-0.034 to 0.059)	0.588	-0.135 (-0.303 to +0.033) Ref.	0.114
Without	Ref.			
WC risk with	-0.136 (-0.182 to -0.091)	<0.001	+0.134 (-0.033 to +0.3) Ref.	0.115
Without	Ref.			
Women	Baseline difference (95% CI)	P value	Interaction difference (95% CI)	P value
BP risk with	+0.272 (0.227 to 0.317)	<0.001	-0.162 (-0.328 to 0.003)	0.055
Without	Ref.		Ref.	
Glucose risk with	+0.140 (0.080 to 0.199)	<0.001	+0.073 (-0.218 to +0.363)	0.623
Without	Ref.		Ref.	
Lipid risk with	+0.069 (0.019 to 0.120)	0.007	-0.009 (-0.205 to +0.186) Ref.	0.924
Without	Ref.			
WC risk with	-0.224 (-0.275 to -0.172)	<0.001	+0.094 (-0.291 to +0.104) Ref.	0.351
Without	Ref.			

Notes: “+” and “-” indicate the direction of the β coefficient (increase or decrease in CAVI). Models were adjusted for age at first visit, current smoking, and the other three metabolic risk factors. Analyses were conducted separately for men and women.

Table 4 Sex Interactions Between Metabolic Risk Factors and CAVI

Risk factor	β (95% CI)	P value
BP Risk \times sex	+0.084 (0.041 to 0.128)	<0.001
Glucose Risk \times sex	-0.019 (-0.074 to 0.037)	0.505
Lipid Risk \times sex	+0.056 (0.008 to 0.104)	0.023
WC Risk \times sex	-0.088 (-0.136 to -0.040)	<0.001

Notes: “ \times ” indicates an interaction term between sex and each metabolic risk factor. “+” and “-” indicate the direction of the β coefficient (increase or decrease in CAVI). Models were adjusted for age at baseline, smoking status, and the other metabolic risk factors.

Table 5 Baseline and Longitudinal Changes in CAVI According to MetS Status

Population	Model ITEM	Baseline Difference (95% CI)	P value	Interaction Difference (95% CI)	P value
All participants	MetS (Ref: Non-MetS)	+0.079 (+0.040 to +0.117)	<0.001	-0.089 (-0.230 to +0.053)	0.220
Men	MetS (Ref: Non-MetS)	+0.094 (+0.046 to +0.142)	<0.001	-0.102 (-0.277 to +0.073)	0.254
Women	MetS (Ref: Non-MetS)	+0.025 (-0.047 to +0.098)	0.492	-0.062 (-0.35 to +0.226)	0.687

Notes: “+” and “-” indicate the direction of the β coefficient (increase or decrease in CAVI). Models were adjusted for age at first visit and current smoking status. In analyses including all participants, sex was additionally included as a covariate.

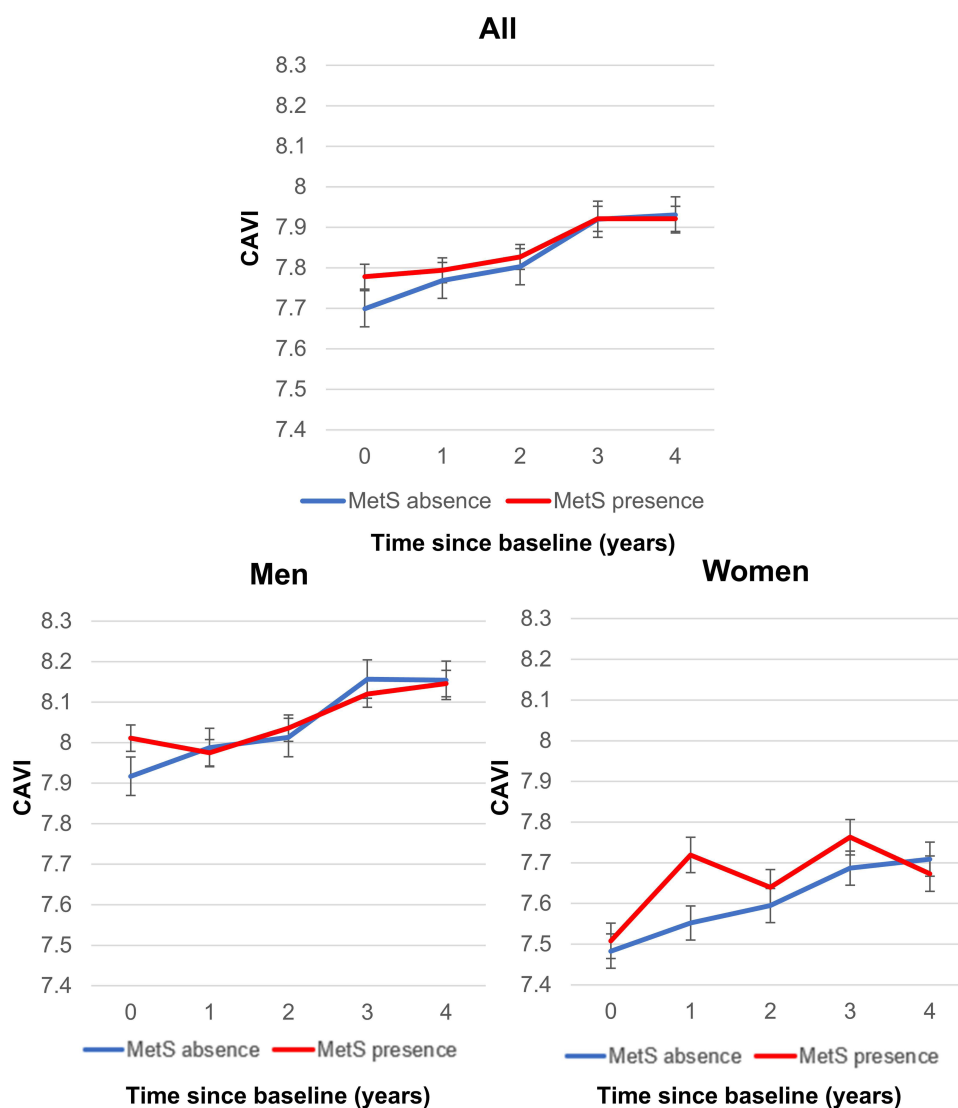


Figure 3 Estimated longitudinal changes in CAVI based on MetS status. Models were adjusted for age at first visit and current smoking status. Sex was additionally included as a covariate in the overall analysis. The y-axis represents CAVI, and the x-axis represents time since baseline (years), where 0 indicates baseline and subsequent values represent years since baseline.

The clinical importance of elevated baseline CAVI is supported by prospective evidence from the TRIPLE-A-Stiffness study, which reported that each 1-unit increase in CAVI was associated with ~25% higher cardiovascular morbimortality risk (adjusted HR ~1.25 per 1-unit increase in subjects ≥ 60 years) and identified age-specific CAVI thresholds (9.25 for ≥ 60 years and 8.30 for < 60 years).¹⁶ Together with the heterogeneous associations observed across metabolic risk factors, these findings substantiate the clinical relevance of the elevated baseline CAVI observed in our cohort. Moreover, metabolic factors exert heterogeneous effects on baseline CAVI, supporting a cumulative and continuous vascular risk interpretation rather than a binary MetS framework. Prior work also shows that CAVI stratified by quartiles and metabolic severity identifies vascular risk more sensitively than MetS classification alone.^{7,17} From a public health perspective, these findings indicate that data-driven vascular risk scoring could therefore complement existing health-check screening to improve early identification and the timing of preventive intervention.

Metabolic Vascular Burden Beyond WC

At baseline, participants clinically diagnosed with MetS exhibited significantly higher CAVI, consistent with prior evidence that CAVI is elevated in individuals with MetS.⁸ However, longitudinal CAVI trajectories during follow-up

Table 6 Baseline and Longitudinal Changes in CAVI According to Total Metabolic Risk Counts, Stratified by Sex and WC

Population	Model Term	β (95% CI)	P value
Men with WC (+) Baseline difference Ref: Risk0	Risk count = 3	+0.345 (+0.241 to +0.448)	<0.001
	Risk count = 2	+0.228 (+0.137 to +0.320)	<0.001
	Risk count = 1	+0.138 (+0.048 to +0.228)	0.003
Men with WC (+) Interaction difference Ref: Time×Risk0	Time×Risk3	-0.425 (-0.819 to -0.032)	0.034
Men with WC (-) Baseline difference Ref: Risk0	Risk count = 3	+0.505 (+0.360 to +0.650)	<0.001
	Risk count = 2	+0.335 (+0.242 to +0.427)	<0.001
	Risk count = 1	+0.179 (+0.106 to +0.252)	<0.001
Men with WC (-) Interaction difference Ref: Time×Risk0	Time×Risk3	-0.077 (-0.576 to +0.421)	0.760
Women with WC (+) Baseline difference Ref: Risk0	Risk count = 3	+0.311 (+0.142 to +0.479)	<0.001
	Risk count = 2	+0.210 (+0.068 to +0.351)	0.004
	Risk count = 1	+0.072 (-0.061 to +0.205)	0.289
Women with WC (+) Interaction difference Ref: Time×Risk0	Time×Risk3	-0.153 (-0.713 to -0.407)	0.589
Women with WC (-) Baseline difference Ref: Risk0	Risk count = 3	+0.610 (+0.489 to +0.730)	<0.001
	Risk count = 2	+0.351 (+0.280 to +0.422)	<0.001
	Risk count = 1	+0.233 (+0.181 to +0.286)	<0.001
Women with WC (-) Interaction difference Ref: Time×Risk0	Time×Risk3	-0.261 (-1.036 to +0.514)	0.760

Notes: WC (+) and WC (-) indicate the presence and absence of abdominal obesity, respectively, based on the defined WC criteria. "+" and "-" indicate the direction of the β coefficient (increase or decrease in CAVI). Models were adjusted for age at first visit, current smoking, and time (Visit 1–5).

did not differ significantly by MetS status, and the difference between groups tended to narrow over time. Although we could not disentangle the effects of medication use and lifestyle changes during follow-up, these findings reinforce the interpretation that baseline CAVI captures the cumulative burden of metabolic vascular injury, which may not be fully reflected by subsequent short-term change.

Importantly, stratified analysis showed that some individuals without central obesity WC (-) still had high CAVI, indicating that WC alone fails to detect a subset of individuals with vascular risk. This observation is also consistent with our previous cross-sectional analysis in the same health-check population, which suggested that WC-centered criteria may overlook non-obese individuals with elevated CAVI.¹⁸ This is consistent with Nagayama et al, who reported that WC alone does not adequately identify individuals with increased arterial stiffness, and that a body shape index (ABSI) demonstrates superior discriminatory capacity compared to WC.^{8,15} In our cohort, this pattern was particularly evident among women, among whom multiple metabolic abnormalities were frequently observed despite WC values below diagnostic thresholds.

Consistent with this observation, interaction analyses revealed significant sex differences, with stronger positive associations of blood pressure, lipid abnormalities with CAVI in women, whereas WC showed a more pronounced inverse association with CAVI in women (Table 4). Notably, women with WC (-) but with ≥ 2 metabolic risk factors showed a greater increase in CAVI compared with the risk-0 reference group than women with WC (+) and the same number of metabolic risk factors. This finding suggests that WC-based screening may overlook a subgroup of women with substantial vascular risk, which is consistent with previous studies indicating that WC alone does not adequately capture arterial stiffness-related risk.^{8,15,18} Further, besides the limitation of WC-based classification, prior studies have shown that the vascular and cardiovascular consequences of metabolic abnormalities tend to be more pronounced in women than in men.^{8,9,19,20} Supporting this sex-specific heterogeneity, prior evidence also shows that CAVI increases

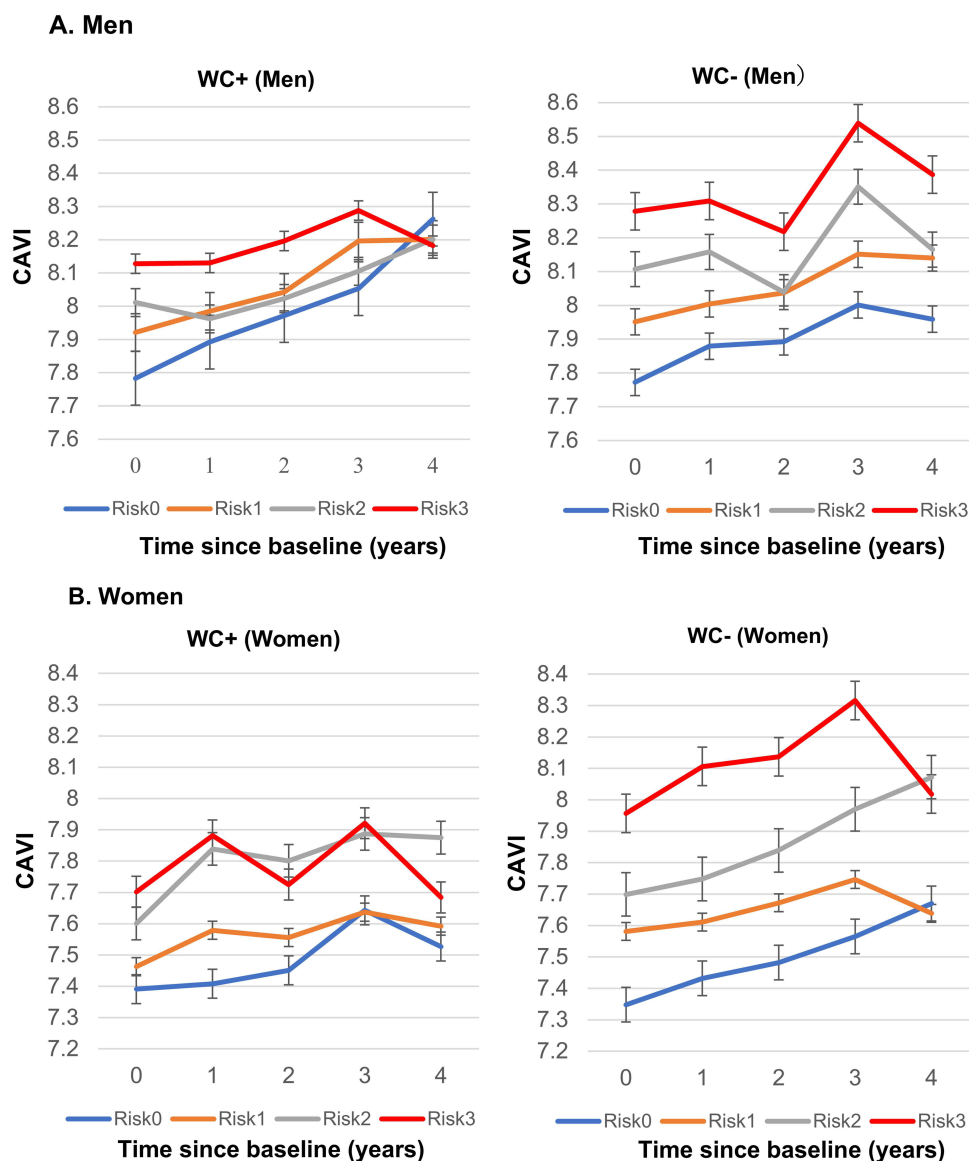


Figure 4 Estimated longitudinal changes in CAVI according to the number of metabolic risk factors, stratified by sex and WC, and adjusted for age and smoking status. **(A)** Men, **(B)** Women The y-axis represents CAVI, and the x-axis represents time since baseline (years), where 0 indicates baseline and subsequent values represent years since baseline.

stepwise with accumulating metabolic syndrome components in women (P -trend < 0.001), whereas no such trend is observed in men (P -trend = 0.427).⁹ Taken together, these findings suggest that CAVI can capture a dimension of vascular risk—particularly among women—that may not be identified by conventional MetS screening.

In line with prospective evidence demonstrating that elevated baseline CAVI is associated with an increased risk of future cardiovascular events and cardiovascular morbimortality, our results indicate that incorporating CAVI into routine longitudinal health-check screening could enable earlier identification of individuals at elevated prognostic risk who would otherwise be missed by WC-based criteria.^{4,16}

Overall, our findings provide several novel insights into vascular risk stratification. First, we distinguished between baseline CAVI as a marker of cumulative vascular burden and its relatively modest short-term longitudinal progression. Second, we identified a subgroup with elevated CAVI despite not meeting WC-based metabolic criteria, highlighting one limitation of conventional MetS screening. Third, we identified blood pressure and glucose abnormalities as the dominant determinants of arterial stiffness, highlighting a hierarchical and heterogeneous contribution of metabolic risk factors,

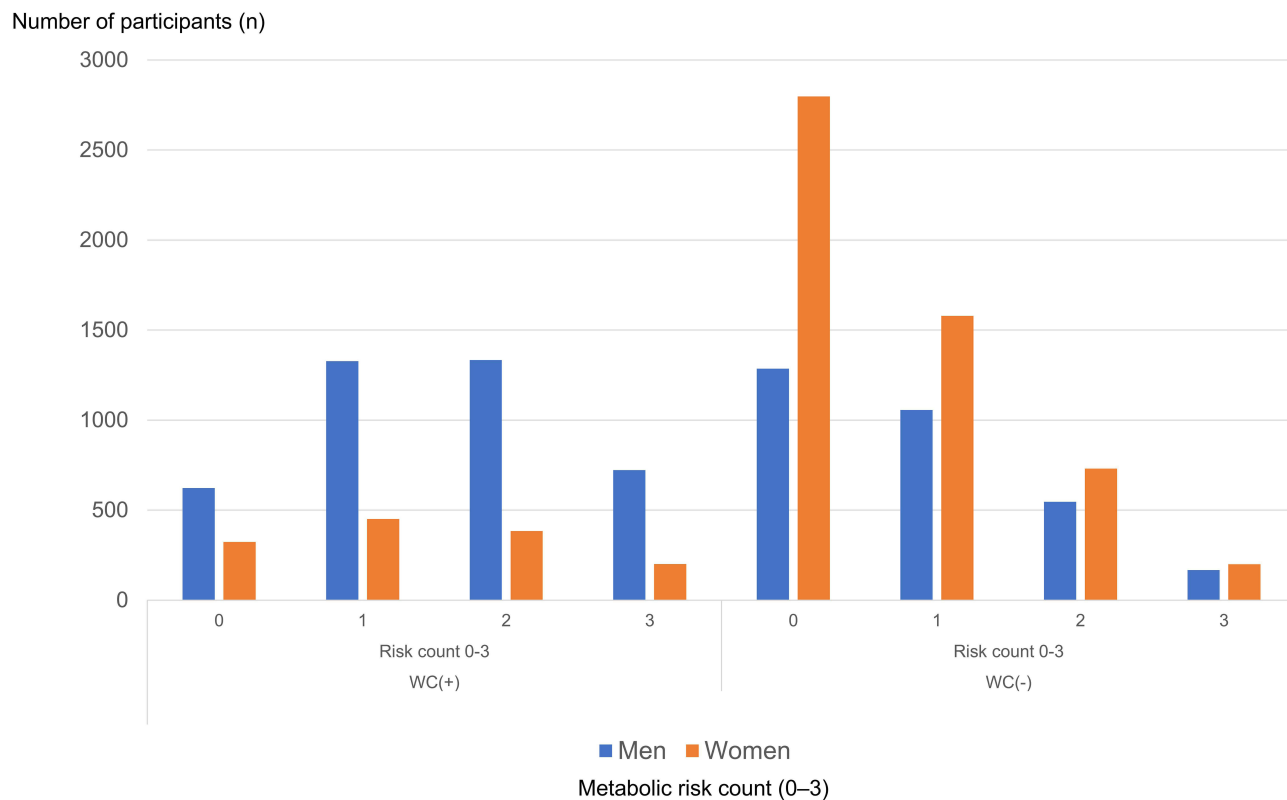


Figure 5 Distribution of metabolic risk counts (0–3) at baseline, stratified by WC and sex. The distribution of participants across risk categories is shown separately for WC (+) and WC (–) groups in men and women. The y-axis indicates the number of participants (n), and the x-axis indicates metabolic risk count (0–3).

including an inverse association for WC. These findings suggest that incorporating CAVI into routine health-check screening may improve the identification of individuals at elevated vascular risk who are not captured by conventional WC-based criteria.

Limitations

Several limitations should be noted. First, this single-center observational study comprised health check-up participants; therefore, selection bias cannot be excluded. Second, CAVI is a surrogate indicator of arterial stiffness and does not directly represent cardiovascular events. Third, follow-up was limited to less than five years, which may restrict assessment of longer-term vascular changes. In addition, regression to the mean, ceiling effects in high-baseline CAVI groups, and the relatively short follow-up duration may have contributed to the attenuation or apparent reversal of progression slopes observed in some metabolic risk categories. Fourth, information on treatment and lifestyle modification during follow-up was not available and may have influenced the results. Finally, residual confounding related to body composition cannot be excluded. Future multicenter studies with longer follow-up and event-based outcomes are warranted to confirm the prognostic utility of CAVI in predicting cardiovascular morbidity and mortality.

Conclusion

In this large longitudinal cohort, CAVI increased modestly during follow-up, whereas progression was attenuated among participants with high baseline CAVI values. This finding suggests that CAVI reflects cumulative vascular injury sustained over time rather than short-term progression alone. Among MetS components, blood pressure and glucose abnormalities were the dominant drivers of elevated CAVI, whereas lipid abnormalities showed weaker effects and WC was inversely associated with CAVI. Importantly, elevated CAVI was also observed in non-obese individuals who would not meet current MetS criteria, revealing a clinically relevant subgroup that may otherwise be overlooked—particularly among women. Together with existing prospective evidence linking CAVI to cardiovascular outcomes, our findings

support the incorporation of CAVI into routine health screening as a quantitative and complementary tool for refined vascular risk stratification.

Acknowledgments

The authors would like to thank Julian Tang for professional English language editing and suggestions to improve the structure and clarity of the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure

Dr Shoichiro Tsugane reports grants or personal fees from Ajinomoto Co., Inc., Meiji Co., Ltd., and Kikkoman Corporation, outside the submitted work. The authors report no other conflicts of interest in this work.

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