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Original Article

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Cumulative Cigarette Consumption is Associated with Cardio-Ankle Vascular Index (CAVI) Mediated by Abdominal Obesity Assessed by A Body Shape Index (ABSI): A Cross-Sectional Study

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Aim: To elucidate the mechanism by which cigarette smoking causes vascular damage, we examined the relationship between cumulative cigarette consumption and abdominal obesity, and the possible mediating effect of smoking on arterial stiffness.

Methods: Cross-sectional data from 19499 never smokers and 5406 current smokers receiving health screening was analyzed. Abdominal obesity was assessed by ABSI, and arterial stiffness by CAVI. High CAVI was defined as CAVI ≥ 9.0.

Results: Current smoker showed higher ABSI than never smokers after propensity score matching. Cumulative cigarette consumption expressed in pack-years correlated with ABSI (R_s: 0.312 in men, 0.252 in women), and was also extracted as an independent factor associated with ABSI by multiple regression analysis. A linear relationship between pack-year and CAVI was observed (R_s: 0.544 in men, 0.423 in women). Pack-year had almost equal discriminatory power in predicting high CAVI in both sexes (C-statistic: 0.774 in men, 0.747 in women), and the best cut-offs of pack-year for high CAVI were 24.5 in men and 14.7 in women. Bivariate logistic regression models revealed that the association between pack-year higher than cut-off and high CAVI was independent of traditional risks. A mediating effect of ABSI (mediation rate: 9.9% in men and 11.2% in women), but not waist circumference (WC), on the association of pack-year with CAVI was observed, after adjusting for traditional risks.

Conclusion: Cumulative cigarette smoking in pack-years was independently associated with ABSI. ABSI partially mediates the association between pack-year and CAVI, suggesting that abdominal obesity partially mediates smoking-related vascular dysfunction.

Key words: Cigarette smoking, Abdominal obesity, A body shape index, Cardio-ankle vascular index

Introduction

Cigarette smoking is a well-known risk factor of vascular damage, through activating several mechanisms that predispose to atherosclerosis, including thrombosis, systemic inflammation and oxidative stress, as well as loss of endothelial homeostasis and regeneration[1-3]. Smoking addiction

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is therefore a leading preventable cause of cardiovascular disease (CVD) mortality worldwide. Because nicotine increases energy expenditure in the short term, smokers initially tend to weigh less than non-smokers. In the long term, however, smoking can induce abdominal obesity with insulin resistance[4, 5], leading to adverse changes in body composition and shape, even though the weight may remain comparable to that of non-smokers. Indeed, a meta-analysis of prospective studies suggests that smoking is associated with the development of the metabolic syndrome (MetS)[6].

Overweight and obesity are defined as excessive accumulation of fat that may impair health[7]. Body mass index (BMI) normalizes body weight to height, and does not necessarily reflect abdominal obesity, which is an important factor in metabolic disorders. Anthropometric indices of abdominal obesity for the assessment of visceral adiposity have attracted much research interest[8]. Waist circumference (WC) is the basic and most widely used measure to assess abdominal obesity. However, WC correlates strongly with BMI, making it epidemiologically almost identical to BMI, and does not necessarily reflect visceral fat accumulation much better than BMI[9]. Subsequent research led to the development of a body shape index (ABSI) that normalizes WC to height and weight, thereby minimizing the correlation with BMI. This index potentially identifies BMI-independent body composition and shape associated with abdominal obesity. ABSI was derived from the United States National Health and Nutrition Examination Survey (NHANES) 1999-2004 mortality data[10] and is calculated by dividing WC by an allometric regression of weight and height, which represents the expected value of WC. An increase in ABSI reflects abdominal bulging beyond that expected for a given BMI, or a geometric change from cylindricity to conicity[11].

Systemic arterial stiffness reflects vascular ageing and loss of arterial elasticity, and is used as a predictor of cardiovascular (CV) events[12]. The Cardio-Ankle Vascular Index (CAVI), an arterial stiffness parameter, has been developed to assess the stiffness of the arterial tree from the aortic origin to the ankle independent of blood pressure (BP)[13]. This parameter is positively associated with several CVD risk factors[14, 15], CVD severity[16] and future CV events[17]. Appropriate therapeutic interventions to reduce CAVI may help prevent future CV events[18]. Furthermore, CAVI increases acutely or chronically after smoking[19] and improves after smoking cessation[20]. Individuals with MetS have higher CAVI and smoking rates than those without MetS[21], although the detailed relationship between cumulative cigarette consumption and CAVI warrants further investigation. We have reported that ABSI is the abdominal obesity index most strongly associated with CAVI independent of obesity-related metabolic disorders[9]. Indeed, a retrospective cohort study demonstrated the association between ABSI and the development of aortic diseases including dissection, aneurysm and rupture[22]. Meanwhile, a study of middle-aged Lithuanian men reported that smokers had a higher prevalence of elevated ABSI[23]. However, there have been no consistent attempts to elucidate the effect of smoking on abdominal obesity and how this effect may impact vascular function.

Against this background, we conducted a cross-sectional study of Japanese current smokers with the aim to elucidate the detailed relationship of the number of pack-years of cigarette smoking ("pack-year" hereinafter) as an indicator of the cumulative burden of cigarette consumption with ABSI and CAVI. First, differences between current smokers and never-smokers regarding clinical characteristics were examined. Next, the relationship of pack-year with ABSI and CAVI was analyzed. Finally, we conducted a mediation analysis to test for more detailed causal relationship.

Materials and Methods

Subjects and Design

The population-based sample used in this retrospective cross-sectional study consisted of Japanese adults living in major cities nationwide who participated in the annual CVD and cancer screening program organized by the Japan Health Promotion Foundation, and who had undergone annual examinations between 2010 and 2018. Duplicate databases of the same person with multiple visits were deleted, except for first visit. The participants were unpaid volunteers who were not recruited for this study (unlike participants in a dedicated clinical trial). Of the 34662 people who were assessed for eligibility, 4529 people with insufficient data and 5228 former smokers were excluded. In the present study, characteristics of 19499 never smokers and 5406 current smokers were first compared. The relationship of cumulative cigarette consumption with abdominal obesity and arterial stiffness was then examined in the current smokers only.

Data Collection and Laboratory Assay Methods

All parameters were measured using standardized methods. Old age was defined as 65 years of age or older. Height and weight were measured, and BMI (kg/m^2) was calculated as follows: weight (kg) divided

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by square of height (m^2). WC (m) was measured horizontally at the height of the umbilicus, with the participant standing and arms hanging relaxed. ABSI was calculated by the following formula: ABSI = WC/(BMI$^{2/3}$ × Height$^{1/2}$) = WC × Height$^{5/6}$ × Weight$^{-2/3}$ [24]. Currently, an online calculator implementing the derived formula for ABSI and the corresponding anthropometric mortality risk is freely available at https://nirkrakauer.net/sw/ari-calculator.html. BP was measured in a sitting position after 5-minute rest. Hypertension was diagnosed by either systolic BP (SBP) ≥ 140 mmHg and diastolic BP ≥ 90 mmHg, or treatment with BP-lowering agents.

Blood was collected from the antecubital vein in the morning after 12 hours of fasting to measure fasting plasma glucose (FPG), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula: LDL-C = total cholesterol (TC) − (HDL-C) − (TG/5). Since this formula is not valid for patients with TG ≥ 400 mg/dL, individuals with TG ≥ 400 mg/dL (2.8% of all participants) were excluded from the analysis of LDL-C. Diabetes mellitus was diagnosed when FPG ≥ 126 mg/dL or when participant was receiving antidiabetic agent. Dyslipidemia was defined as LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL and/or TG ≥ 150 mg/dL, or treatment with lipid-lowering agents.

Current habitual alcohol consumption and smoking status were assessed by a questionnaire. Habitual alcohol consumption was defined as daily drinking. Cumulative cigarette consumption was assessed by the number of pack-years, which is calculated by multiplying the number of packs of cigarettes smoked per day (20 cigarettes per pack) by the number of years the person has smoked. This index was first reported in the medical literature in the mid-1950s in a study of chronic obstructive pulmonary disease [25] and has since been widely used to quantify cigarette smoke exposure.

Measurement of CAVI as an Arterial Stiffness Parameter

The principle and methods of measurement of CAVI have been described previously [13]. CAVI was calculated using the following formula CAVI = a{(2ρ/ΔP) × ln(Ps/Pd)PWV^2} + b, where Ps is systolic BP; Pd is diastolic BP; ΔP is Ps − Pd; ρ is blood density; PWV is carotid-ankle pulse wave velocity; and a and b are constants. Individuals with an ankle-brachial index less than 0.90 were excluded, because patients with severe arterial occlusive disease may report falsely low CAVI. We defined "high CAVI" as equal to or greater than 9.0 in all participants, which is essentially the cut-off for the presence of coronary artery stenosis [16, 18]. We also defined "high ABSI" as equal to or greater than 0.080, which corresponds to the cut-off associated with both CAVI ≥ 9.0 and eGFR < 60 ml/min/1.73m^2 regardless of sex [26].

Statistical Analysis

The SPSS software (version 11.5, Chicago, IL, USA) was used for statistical processing. All data are expressed as median (interquartile range). When comparing clinical characteristics of participants in two groups with and without smoking, it was necessary to correct for imbalance related to age and gender. Therefore, propensity score matching (PSM) with a 1:1 ratio was performed to match the cases in two groups using the nearest matching method with a caliper width equal to 0.2. Standardized difference < 0.1 of the absolute value was a relatively small imbalance. Sex differences in clinical variables were analyzed by Mann–Whitney *U*-test for continuous variables or Fisher's exact test for dichotomous variables. Spearman's rank correlation coefficient (R_s) was used to evaluate the relationship between two variables. Multiple regression analysis was performed to identify clinical variables that are independently associated with ABSI. The relationship of CAVI with pack-year was determined using one-way analysis of variance. Sensitivity and specificity with respect to high CAVI were analyzed using conventional receiver-operating-characteristic (ROC) curves, and the cut-off was estimated by Youden's J statistic. The relationship between high CAVI and clinical variables was analyzed using bivariate logistic regression analysis. A mediation analysis was carried out using PROCESS (version 4.0) in SPSS [27]. The total effect must be significant to ensure the presence of mediation. Partial mediation exists when indirect and direct effects are both significant. The mediation rate (%) that explains the contribution of mediation to the total effect was calculated using the following formula: indirect effect/total effect × 100. In all comparisons, 2-sided p values < 0.05 were considered statistically significant. The difference between two variables was considered statistically significant if the 95% confidence intervals (CIs) for the correlation coefficients did not overlap.

Results

Comparison of Clinical and Biochemical Characteristics in Never Smokers and Current Smokers

In the first cross-sectional analysis, clinical and biochemical characteristics were compared between never smokers and current smokers before and after PSM (Table 1).

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Table 1. Comparison of clinical and biochemical characteristics in never smokers and current smokers

Variables	Before PSM		After PSM	
	Never smoker (N=19499)	Current smoker (N=5406)	Never smoker (N= 5065)	Current smoker (N=5065)
Male (%)	29.5	76.6*	76.6	76.6
Age (years)	48 (37–59)	42 (34–52)*	43 (35–54)	43 (35–53)
BMI (kg/m^2)	21.6 (19.7–23.9)	22.7 (20.6–25.2)*	22.6 (20.7–24.8)	22.7 (20.6–25.2)
WC (m)	0.78 (0.72–0.85)	0.82 (0.75–0.88)*	0.81 (0.75–0.87)	0.82 (0.75–0.88)*
ABSI	0.0789 (0.0759–0.0821)	0.0781 (0.0756–0.0808)*	0.0768 (0.0753–0.0804)	0.0782 (0.0757–0.0809)*
CAVI	7.6 (7.0–8.3)	7.4 (6.8–8.1)*	7.3 (6.9–8.1)	7.5 (7.0–8.2)*
Pack-year	0 (0–0)	16.5 (9–29)*	0 (0–0)	16.5 (9.0–29)
Habitual alcohol consumption (%)	51.8	71.0*	68.2	73.9*
SBP (mmHg)	122 (112–132)	124 (114–133)*	123 (114–132)	124 (114–134)*
DBP (mmHg)	70 (64–78)	72 (66–80)*	72 (65–80)	73 (66–80)*
FPG (mg/dL)	85 (80–91)	86 (80–92)*	86 (81–92)	86 (80–92)
TG (mg/dL)	74 (54–108)	99 (68–153)*	85 (59–127)	99 (69–155)*
HDL-C (mg/dL)	70 (59–83)	58 (48–69)*	63 (53–75)	58 (48–69)*
LDL-C (mg/dL)	124 (112–132)	118 (97–141)*	123 (114–132)	118 (114–134)*
Receiving treatment for				
Hypertension (%)	8.8	6.1*	8.0	6.5*
Diabetes mellitus (%)	1.5	1.7	1.7	1.8
Dyslipidemia (%)	6.8	2.8*	4.9	2.9*

Data are presented as median (interquartile range), or percentage. Comparison of two groups was performed using Mann–Whitney *U*-test for continuous variables and Fisher's exact test for dichotomous variables. PSM, propensity score matching; BMI, body mass index; WC, weight circumference; ABSI, a body shape index; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Before PSM, never smokers showed higher age, ABSI, CAVI, HDL-C, LDL-C, prevalence of hypertension and dyslipidemia, and lower male ratio, BMI, WC, drinking habit rate, BP and TG than current smokers. After PSM with age and gender as covariates, current smokers showed higher WC, ABSI, CAVI, drinking habit rate, BP and TG, and lower HDL-C, LDL-C and prevalence of hypertension and dyslipidemia. On the other hand, no significant difference was observed in BMI after PSM.

Clinical and Biochemical Characteristics of Male and Female Participants

A total of 5406 Japanese urban residents who were current smokers (male : female=76.6 : 23.4%; median age 42 years) were analyzed in this cross-sectional study. **Table 2** compares the clinical characteristics between male and female participants. Compared with women, men had significantly higher BMI, WC, pack-year, habitual alcohol consumption, BP, FPG, TG, LDL-C and prevalence of metabolic disorders; and lower age, ABSI and HDL-C. No gender difference in CAVI was observed.

Relationship of Pack-Year with Body Adiposity Indices

We then examined the relationship between cumulative cigarette consumption and general or abdominal obesity indices. **Table 3** shows Spearman's rank correlation coefficients for pack-year versus each adiposity index in male and female participants. The correlations of BMI, WC and ABSI with pack-year were all significant in both men and women, The highest correlation was found for ABSI in men (R_s=0.312).

Correlation between ABSI and Clinical Variables Analyzed by Multiple Regression Model

Next, the independent associations of clinical variables with ABSI were examined using multiple regression analysis, as shown in **Table 4**. In total participants, age, sex, CAVI, SBP, HDL-C, LDL-C, habitual alcohol consumption and pack-year were independently associated with ABSI. When restricted to men, in addition to those variables, FPG was also independently associated with ABSI. On the other hand, when restricted to women, only age and CAVI were independently associated with ABSI.

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Table 2. Clinical and biochemical characteristics of male and female current smokers

Variables	Males	Females	*p* value
Number of individuals	4139	1267	-
Age (years)	41 (34–52)	45 (37–53)	<0.001
Old age (Age ≥ 65y, %)	6.0	4.4	0.036
Height (m)	1.71 (1.67–1.75)	1.58 (1.54–1.61)	<0.001
Body weight (kg)	67.6 (61.0–75.2)	51.9 (47.5–57.4)	<0.001
BMI (kg/m^2)	23.3 (21.3–25.5)	20.8 (19.2–23.0)	<0.001
BMI ≥ 25 kg/m^2 (%)	30.5	13.7	<0.001
WC (m)	0.832 (0.770–0.893)	0.757 (0.703–0.824)	<0.001
ABSI	0.0778 (0.0754–0.0803)	0.0791 (0.0763–0.0827)	<0.001
ABSI ≥ 0.080 (%)	27.8	43.2	<0.001
CAVI	7.4 (6.8–8.1)	7.4 (6.8–8.0)	0.083
CAVI ≥ 9.0 (%)	9.6	5.9	<0.001
Cigarettes/day	20 (10–20)	10 (10–15)	<0.001
Years of smoking	22 (13–30)	20 (12–28)	<0.001
Pack-year	18.0 (10.0–30.8)	10.0 (5.0–18.8)	<0.001
Habitual alcohol consumption (%)	77.3	63.2	<0.001
SBP (mmHg)	126 (116–134)	118 (108–128)	<0.001
DBP (mmHg)	74 (68–82)	68 (62–76)	<0.001
FPG (mg/dL)	86 (81–93)	83 (78–88)	<0.001
TG (mg/dL)	107 (75–165)	75 (55–109)	<0.001
HDL-C (mg/dL)	54 (46–64)	70 (59–81)	<0.001
LDL-C (mg/dL)	119 (98–141)	114 (94–139)	<0.001
Receiving treatment for			
Hypertension (%)	6.6	4.5	0.007
Diabetes mellitus (%)	2.0	0.6	<0.001
Dyslipidemia (%)	2.4	3.9	0.008

Data are presented as median (interquartile range), or percentage. Comparison of two groups was performed using Mann–Whitney *U*-test for continuous variables and Fisher's exact test for dichotomous variables. BMI, body mass index; WC, weight circumference; ABSI, a body shape index; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3. Relationship of pack-year with body adiposity indices in male and female participants

Pack-year vs.	Males Rs (95% CI)	Females Rs (95% CI)
BMI (kg/m^2)	0.138 (0.107 – 0.168)*	0.132 (0.076 – 0.188)*
WC (m)	0.215 (0.185 – 0.245)*	0.215 (0.161 – 0.269)*
ABSI	0.312 (0.283 – 0.340)*	0.252 (0.198 – 0.305)*

*p<0.001. Rs, Spearman's rank correlation coefficient; CI, confidence interval; BMI, body mass index; WC, waist circumference; ABSI, a body shape index.

Relationship of CAVI with Pack-Year

The detailed relationship between cumulative cigarette consumption and systemic arterial stiffness was then examined, as shown in **Fig. 1**. As the distribution of pack-years showed gender difference, scatter plots of CAVI versus pack-year **(Fig. 1A and C)** and bar charts of CAVI stratified by pack-year tiers **(Fig. 1B and D)** were plotted separately for men and women. A positive linear relationship between pack-year and CAVI was observed in both sexes.

Discriminatory Powers and Cut-Offs of Pack-Year for High CAVI (≥ 9.0)

The predictive accuracy of pack-year for high CAVI was examined in both sexes, as shown in **Table 5**. Pack-year showed almost equal discriminatory power for predicting high CAVI in both sexes. In addition, ROC curve analysis identified 24.5 pack-

Advance Publication Journal of Atherosclerosis and Thrombosis
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Table 4. Correlation between ABSI and clinical variables analyzed by multiple regression model

Variables	Total				Male				Female			
	β	SE	*t*	*p* value	*β*	SE	*t*	*p* value	*β*	SE	*t*	*p* value
Age (years)	0.267	<0.001	11.237	<0.001	0.263	<0.001	9.889	<0.001	0.268	<0.001	4.680	<0.001
Male sex	-0.208	<0.001	-14.359	<0.001	-	-	-	-	-	-	-	-
CAVI	0.113	<0.001	5.267	<0.001	0.114	<0.001	4.810	<0.001	0.129	<0.001	2.531	0.012
SBP (mmHg)	0.068	<0.001	4.712	<0.001	0.073	<0.001	4.719	<0.001	0.038	<0.001	1.121	0.263
FPG (mg/dL)	0.023	<0.001	1.693	0.090	0.030	<0.001	2.004	0.045	-0.003	<0.001	-0.080	0.936
HDL-C (mg/dL)	-0.092	<0.001	-6.455	<0.001	-0.097	<0.001	-6.536	<0.001	-0.063	<0.001	-1.903	0.057
LDL-C (mg/dL)	0.062	<0.001	4.569	<0.001	0.067	<0.001	4.533	<0.001	0.017	<0.001	0.486	0.627
Habitual alcohol consumption	0.074	<0.001	5.528	<0.001	0.089	<0.001	6.069	<0.001	0.036	<0.001	1.124	0.261
Pack-year	0.034	<0.001	2.002	0.045	0.043	<0.001	2.301	0.021	0.055	<0.001	1.480	0.139

Model $r^2 = 0.219$ in Total, 0.215 in Male and 0.188 in Female, $p < 0.001$ in all models. SE, standard error; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

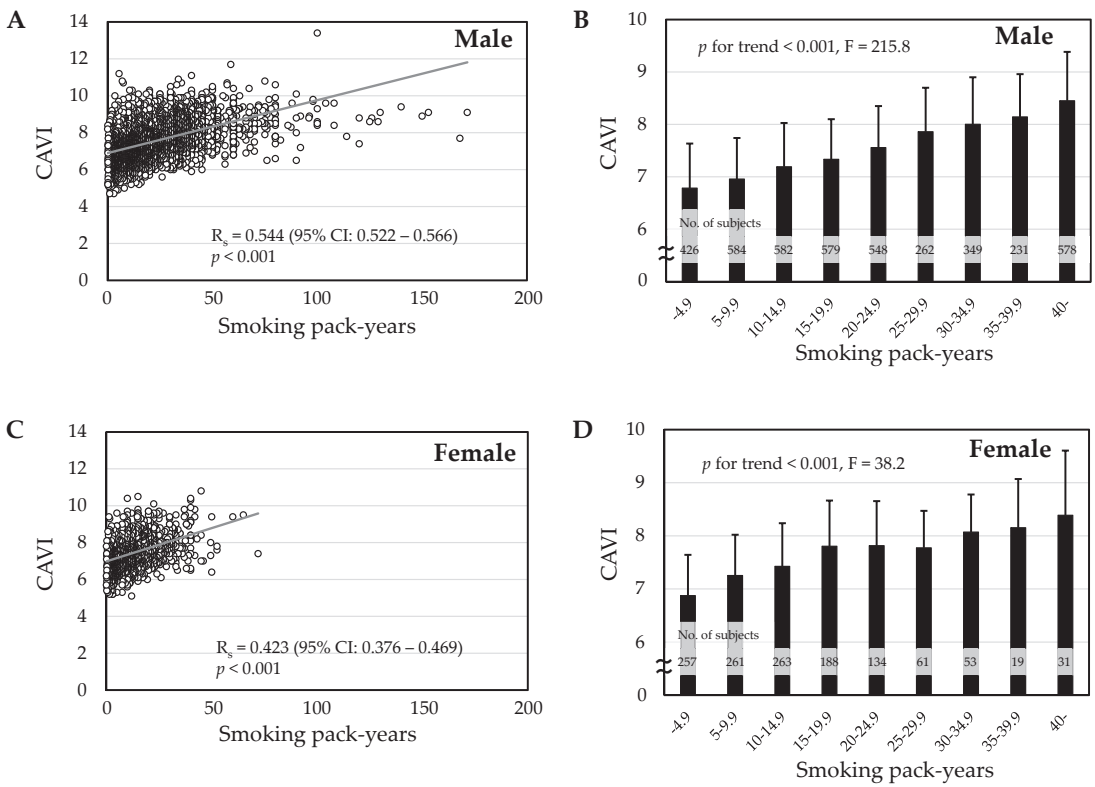

Fig. 1. Relationship of cardio-ankle vascular index (CAVI) with pack-year in male and female participants

Scatter plots of CAVI versus pack-year in (A) males and (C) females were analyzed using Spearman's rank correlation coefficients. Bar charts of CAVI stratified by pack-year tiers in (B) males and (D) females were analyzed using one-way analysis of variance. Data are presented as mean ± standard deviation. CAVI, cardio-ankle vascular index.

Table 5. Discriminating power and cut-off of pack-year for high CAVI (≥ 9.0) analyzed by receiver operating characteristic curve in male and female participants

	C-statistic (95% CI)	*p* value	Cut-off	Sensitivity	Specificity
Males	0.774 (0.750 – 0.798)	<0.001	24.5	0.747	0.699
Females	0.747 (0.692 – 0.802)	<0.001	14.7	0.760	0.639

CAVI, cardio-ankle vascular index; 95% CI, 95% confidence interval.

Advance Publication Journal of Atherosclerosis and Thrombosis
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Table 6. Bivariate logistic regression models for high CAVI (≥ 9.0) in male and female participants

Males		
Variable	Odds ratio (95% CI)	*p* value
Old age (Age ≥ 65 y)	13.611 (9.848 – 18.812)	< 0.001
ABSI ≥ 0.080	1.969 (1.520 – 2.552)	< 0.001
BMI ≥ 25 kg/m^2	0.460 (0.340 – 0.622)	< 0.001
Hypertension	3.675 (2.827 – 4.776)	< 0.001
Diabetes mellitus	2.394 (1.529 – 3.750)	< 0.001
Dyslipidemia	0.918 (0.707 – 1.194)	0.525
Pack-year ≥ 24.5	3.693 (2.806 – 4.861)	< 0.001
Females		
Variable	Odds ratio (95% CI)	*p* value
Old age (Age ≥ 65y)	13.193 (6.586 – 26.427)	< 0.001
ABSI ≥ 0.080	1.382 (0.758 – 2.518)	0.291
BMI ≥ 25 kg/m^2	0.231 (0.093 – 0.574)	0.002
Hypertension	5.143 (2.831 – 9.345)	< 0.001
Diabetes mellitus	5.145(1.128 – 23.479)	0.034
Dyslipidemia	2.175 (1.224 – 3.865)	0.008
The pack-year ≥ 14.7	3.648 (1.990 – 6.685)	< 0.001

Model $r^2 = 0.393$ (males) and 0.351 (females), $p < 0.001$ in both sexes. CAVI, cardio-ankle vascular index; ABSI, a body shape index; BMI, body mass index.

years in men and 14.7 in women as the cut-offs for high CAVI.

Bivariate Logistic Regression Models for High CAVI (≥ 9.0)

We then examined the factors associated with high CAVI by conducting bivariate logistic regression analysis using dichotomous variables, as shown in **Table 6**. The cut-off of pack-year and major CVD risks were entered into the model for men or women. Pack-years higher than the cut-offs (24.5 in men and 14.7 in women) were significantly associated with high CAVI, independent of traditional CVD risk factors including old age, high ABSI, BMI ≥ 25 kg/m^2, hypertension, diabetes mellitus and dyslipidemia. Note that a BMI ≥ 25 kg/m^2 was negatively associated with high CAVI.

The odds ratios of high ABSI (≥ 0.080 in both genders) for high CAVI were 1.97 (95% CI 1.52–2.55, $p < 0.001$) in male, and 1.38 (95% CI 0.76–2.52, $p = 0.291$) in female current smoker. On the other hand, we also performed logistic analyses with identical confounders also in never smokers ($n = 19499$, median 48 years, 29.5% male). Resultantly, the odds ratios of high ABSI for high CAVI were 1.67 (95% CI 1.36–2.06, $p < 0.001$) in male, and 2.02 (95% CI 1.75–2.33, $p < 0.001$) in female (data not shown).

Mediated Associations of the Pack-Year on CAVI via ABSI or WC

The analyses so far showed that high pack-year was independently related to high CAVI **(Table 5)**, and ABSI was independently associated with CAVI **(Table 4)**. We next examined the extent to which the positive association between pack-year and CAVI was mediated by two abdominal obesity indices; ABSI and WC, as shown in **Fig. 2**.

In the mediation analysis, the overall effect of pack-year on CAVI were 0.310 (95% CI; 0.286 — 0.335, $p < 0.001$) in men, and 0.358 (0.289 — 0.428) in women. ABSI partially mediated the positive association between pack-year and CAVI, with a mediation rate of 9.9% in men **(Fig. 2A)** or 11.2% in women **(Fig. 2B)** after adjustment for traditional CVD risk factors. In contrast, WC did not significantly mediate the relationship between pack-year and CAVI in both genders **(Fig. 2C. D)**.

Discussion

This retrospective cross-sectional study showed that current smokers had higher ABSI and CAVI than never smokers, after PSM with age and sex as covariates. The cumulative cigarette consumption expressed in number of pack-years correlated positively with both ABSI and CAVI. The cut-off of pack-year

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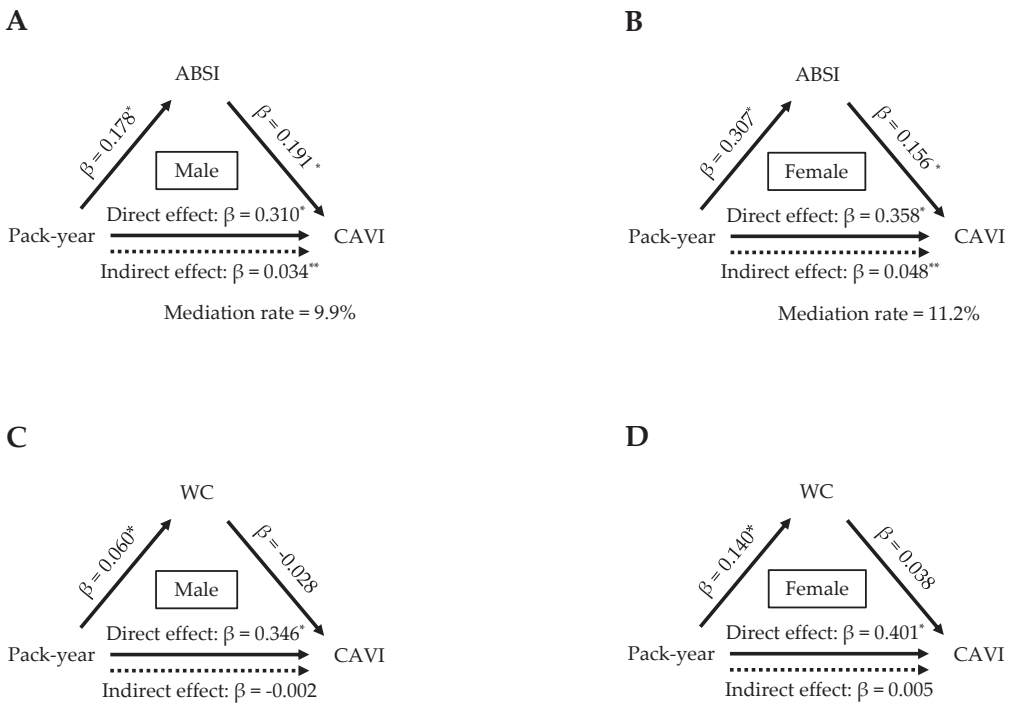

Fig. 2. Mediation analysis of ABSI (A, B) or WC (C, D) as potential mediator of the association between pack-year and CAVI

Mediation analyses restricted to men in (A) and (C), and women in (B) and (D). Analysis was adjusted for confounding factors of old age (≥ 65 years), BMI ≥ 25 kg/m^2, hypertension, diabetes mellitus and dyslipidemia by gender. *$p<0.001$, **$p<0.05$. β, standardized β coefficient. ABSI, a body shape index; WC, waist circumference; CAVI, cardio-ankle vascular index.

for predicting high CAVI was lower in women than in men. Furthermore, the association of pack-year higher than cut-off with high CAVI was independent of traditional CVD risk factors. Mediation analysis indicated that the effect of pack-year on CAVI was partially mediated by ABSI. The novelty of this study is the finding of an association of smoking with abdominal obesity assessed by ABSI as well as with vascular dysfunction assessed by CAVI in the same population.

This study determined the cut-offs of pack-year for predicting high CAVI in men and in women separately. Women may be more prone to smoking-induced vascular dysfunction. However, it should be noted that smoking below the cut-off level is by no means safe. As shown in **Fig. 1**, the relationship between pack-year and arterial stiffening is linear, but not J-shaped. In other words, even individuals with a pack-year lower than the cut-off remain at CVD risk. In fact, even though smoking one cigarette a day has a lower risk of developing CVD, there is still an excess risk of approximately one-half of that by smoking 20 cigarettes a day. To reduce the risk of CVD, smokers should aim to stop smoking, not just reduce the amount of smoking[28]. So why were the pack-year cut-offs estimated in this study? To this question, a similar answer exists to the establishment of the pack-year cut-off for lung cancer, which has been determined to be 20. That is, the cut-off has a reasonable balance between sensitivity and specificity, and may be effective in screening for vascular dysfunctions linking to CVD risk. One study found that the determination of pack-year cut-off could reduce the proportion of people who need to be screened to prevent one death from lung cancer[29]. It is hoped that the pack-year cut-off for arterial stiffening presented in this study will be validated in future longitudinal studies.

As shown in **Fig. 2**, high pack-year was associated with increased CAVI not only directly but also indirectly via increased ABSI, and this pathway was independent of traditional CVD risk factors. This finding is consistent with our previous clinical finding that abdominal obesity may contribute to vascular dysfunction independent of obesity-related metabolic disorders[9]. Furthermore, we have also reported that weight reduction therapy in obese diabetic patients exerted a CAVI-lowering effect, and the change in CAVI correlated with the change in visceral fat area (VFA) measured by computed tomography[30]. In other words, abdominal obesity per se accelerates systemic arterial stiffening, independent of other measures of metabolic disorders. Future longitudinal

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studies are warranted to verify whether smoking cessation contributes to the improvement of CAVI by reducing ABSI.

A positive relationship of smoking with visceral fat accumulation has already been reported. Kim *et al.*[31] reported a linear association of cumulative cigarette consumption with VFA, but not with BMI. Another study also suggested that smoking may be associated with high VFA independent of age and BMI[32]. Several plausible hypotheses have been proposed as the mechanisms by which smoking induces visceral fat accumulation. First, smoking-induced hormonal changes may contribute to visceral fat accumulation. Cortisol has been suggested to be a candidate substance[33]. Additionally, the involvement of both testosterone and androgens in male smokers[34] and estradiol in premenopausal female smokers[35] have been postulated. Second, smoking-induced chronic obstructive pulmonary disease clearly contributes to poor physical activity[36], and inadequate exercise promotes both sarcopenia and abdominal obesity. Indeed, ABSI has also been reported to be an indicator of sarcopenia[37]. Even though ABSI reflects vascular dysfunction[9] and all-cause mortality[38] more strongly than other abdominal obesity indices, the inferior predictive ability of ABSI for visceral fat accumulation[39] and obesity-related metabolic disorders[40] has been reported. This may be because increased ABSI does not necessarily reflect visceral fat accumulation alone, but is also increased in cases of skeletal muscle loss that lack excessive visceral fat accumulation. We recognize that clarifying the relationship between ABSI and body composition is a future challenge. Finally, smokers' dietary and alcohol consumption habits may promote abdominal obesity. For example, heavy drinkers tend to be heavy smokers[41]. However, at least in the current study, the association between pack-year and ABSI was independent of habitual alcohol consumption in male **(Table 4)**. Meanwhile, a clear contribution of high ABSI to high CAVI was observed also in never smokers in the present study. This finding suggests that there are other factors besides smoking that increase ABSI. Smoking may be only one factor that increases ABSI and does not increase the vascular toxicity reflected by ABSI itself.

As mentioned above, female sex hormone has been reported to influence visceral fat metabolism. Visceral fat accumulation has been found to be accelerated after menopause[42], which may alter the effects of smoking on arterial stiffness via abdominal obesity. The women in the study were not assessed for menopausal status. Future studies on smoking and arterial stiffness with menstruation as the focus are required.

In the present study, the significant association between pack-year and ABSI was observed even after adjusting for traditional CVD risks, which were transformed into binary variables **(Fig. 2)**. However, in multiple regression models dealing with continuous variables, the independent relationship between pack-year and ABSI was not significant only for women **(Table 4)**. The much smaller number of subjects and pack-year in women may have reduced the accuracy for analysis.

Visceral fat accumulation as indicated by abdominal obesity occurs early in the pathogenesis of MetS[43]. As mentioned above, smoking is considered to promote both MetS and visceral fat accumulation. A meta-analysis of prospective cohort studies including 56691 participants found a significant positive relationship between active smoking and the risk of MetS (pooled relative risk: 1.26, 95% CI 1.10 – 1.44)[6]. On the contrary, other studies have reported a negative association between MetS and smoking[44, 45]. Since smoking cessation increases caloric intake and decreases basal metabolic rate by reducing the energy required for nicotine metabolism[46, 47], the resulting weight gain may increase the risk of MetS[48]. In general, smokers have lower BMI than non-smokers[49, 50]. The appetite-suppressing effects of smoking may slow the development of MetS, whereas elevated ABSI associated with smoking likely accelerates it. We propose that compared with WC or other WC-derived indices that correlate significantly with BMI, ABSI is a more appropriate index for anthropometric assessment and may promote better understanding of the consequences of smoking and of its cessation on abdominal obesity. As previously reported, VFA is related to pack-year of cigarette smoking independent of BMI[32]. However, since WC correlates closely with BMI, it does not necessarily reflect visceral fat accumulation[51]. Therefore, when WC is used as a criterion for MetS diagnosis, smoking-related weight loss may confound the estimate of abdominal obesity. We have reported that ABSI most strongly reflects vascular dysfunction compared to other anthropometric abdominal obesity indices including WC[9], and that replacement of WC with ABSI in MetS diagnostic criteria improves the predictive ability for arterial stiffening[26] and future renal function decline[21]. The present study supports the adoption of ABSI, based on the observation of a stronger association of ABSI with cumulative cigarette consumption in pack-years, compared with BMI and WC.

We previously investigated the relationship of CAVI with BMI in Japanese urban residents[52]. In the

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result, CAVI adjusted for confounders was negatively and linearly associated with BMI in both sexes. The comparable results were also obtained in other Japanese workers[53] and Korean population[54]. In the present study, obesity was also negatively associated with high CAVI, as shown in **Table 6**. These results suggest that body composition, as reflected in BMI, may be primarily a protective factor for systemic arterial stiffening (i.e. skeletal muscle or subcutaneous adipose tissue). In addition, we have already reported that WC, which is epidemiologically almost identical to BMI, is less associated with CAVI[9]. Accordingly, the suitable abdominal obesity index as a surrogate marker of visceral adiposity exerting vascular toxicity should be independent of BMI, as is ABSI.

A limitation of this study is its cross-sectional nature, which cannot address causal relationship. In addition, the cut-offs of pack-year for the prediction of high CAVI determined for men and women in this study may only be applied to the middle-aged Japanese population. In former smokers, determining the impact of past cumulative smoking on current abdominal obesity seems to be a critical issue. However, the database in the present study did not accurately capture the amount of past cumulative smoking and the duration of smoking cessation in former smokers, which made such an examination impossible. Additionally, the present study showed that the relationship between ABSI and CAVI was independent of old age (≥ 65 years), as shown in **Table 6 and Fig. 2**. However, the relationship between ABSI and CAVI was not significant when adjusted for age as a continuous variable (data not shown), indicating the difficulty of establishing a correlation in two age-dependent factors. Further investigation in a larger number of subjects over a wider age range is warranted.

In conclusion, cumulative cigarette smoking in pack-years was independently associated with ABSI. ABSI partially mediates the association between pack-year and CAVI, suggesting that abdominal obesity partially mediates smoking-related vascular dysfunction. Utilizing ABSI rather than BMI or WC as an adiposity index may be useful in assessing the upstream pathophysiology of smoking-induced metabolic disorders.

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Statement of Ethics

This study was approved by the Institutional Review Board and Ethics Committee of Sakura Hospital, School of Medicine, Toho University (No. S20091). Written informed consent to participate in this study was obtained by opt out method.

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No funding was received for this study.

Conflict of Interest Statement

All authors declare no conflict of interest.

Author Contributions

D.N., J.K., and T.S. contributed to the conception and design of the work. D.N. and K.S. (Kenji Suzuki) acquired the data. D.N. performed data collation and conducted the analysis. K.F., Y.W., and K.S. (Kenji Suzuki) contributed to the interpretation of the data. D.N. wrote the first draft of the paper. J.K., N.K., K.F., Y.W., T.Y., K.S. (Kenji Suzuki), T.S. T.T., K.S. (Kazuhiro Shimizu), A.S., and K.S. (Kohji Shirai) revised the work for content. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants. Further enquiries may be directed to the corresponding author.

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