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Age-Related Arterial Stiffening Is Associated with a Body Shape Index and Lean Body Mass Index: A Retrospective Cohort Study in Healthy Japanese Population

Daiji Nagayama[a, b] Yasuhiro Watanabe[b] Kentaro Fujishiro[c] Kenji Suzuki[c] Masahiro Ohira[d] Kohji Shirai[e] Atsuhito Saiki[b]

[a]Department of Internal Medicine, Nagayama Clinic, Tochigi, Japan; [b]Center of Diabetes, Endocrinology and Metabolism, Sakura Medical Center, Toho University, Chiba, Japan; [c]Japan Health Promotion Foundation, Tokyo, Japan; [d]Division of Diabetes, Metabolism and Endocrinology, Ohashi Medical Center, Toho University, Tokyo, Japan; [e]Department of Internal Medicine, Mihama Hospital, Chiba, Japan

Keywords
A body shape index · Body shape age · Abdominal obesity · Lean body mass · Cardio-ankle vascular index

Abstract
Introduction: Several anthropometric indices reflecting cardiometabolic risks have been developed, but the relationship of body composition with arterial stiffness remains unclear. We aimed to determine the interaction between age-related anthropometric changes and progression of arterial stiffness. ***Methods:*** This research analyzed cross-sectional data (N = 13,672) and 4-year longitudinal data (N = 5,118) obtained from a healthy Japanese population without metabolic disorders. The relationship of age with anthropometric indices comprising estimated lean body mass index (eLBMI), body mass index (BMI), waist circumference (WC), and a body shape index (ABSI) was examined. The mediating effects of the indices on the association between age and arterial stiffness assessed by cardio-ankle vascular index (CAVI) were analyzed. ***Results:*** Unlike BMI and WC, ABSI (R_s = 0.284) and CAVI (R_s = 0.733) showed a positive linear relationship with aging in stratified analyses. Especially in the middle-older age groups, eLBMI showed a declining trend with aging. An increase in ABSI was associated with a decrease in eLBMI, whereas increase in BMI or WC was related to increased eLBMI. In cross-sectional analyses, age was associated with CAVI, partially mediated by ABSI or eLBMI after adjusting confounders. Baseline CAVI correlated negatively with 4-year change in (Δ)eLBMI (R_s = −0.120 in men, −0.161 in women). ΔCAVI correlated negatively with ΔeLBMI (R_s = −0.031). ***Conclusion:*** ABSI is a modifiable index that well reflects age-related changes in arterial stiffness and body composition including lean body mass. Since arterial stiffening may cause skeletal muscle loss, potentially creating a vicious cycle, prioritizing CAVI and anthropometric indices in clinical practice may be a useful strategy.

Plain Language Summary
This retrospective cohort study examined the relationship between age and several anthropometric indices in a healthy Japanese population. The results of cross-sectional

karger@karger.com
www.karger.com/ofa

Correspondence to:
Daiji Nagayama, deverlast96071@gmail.com

data analyses revealed that body mass index (BMI) and waist circumference (WC) did not necessarily show a linear relationship with aging. A body shape index (ABSI) showed a positive linear correlation with age, while estimated lean body mass index (eLBMI) showed a declining trend with aging, especially in the middle-to-older age groups. In addition, ABSI correlated inversely with eLBMI, whereas BMI and WC correlated directly with eLBMI. Furthermore, age was associated linearly with cardio-ankle vascular index (CAVI) as a systemic arterial stiffness parameter, and this association was partially mediated by ABSI or eLBMI. In the longitudinal data analysis, baseline CAVI correlated negatively with ΔeLBMI, and a negative correlation between ΔCAVI and ΔeLBMI was observed. These findings suggest that ABSI is an indicator that reflects not only abdominal obesity but also loss of lean body mass with aging. This feature of ABSI may contribute to its superior predictive ability for mortality. Furthermore, vascular function and lean body mass may be related to each other, especially because CAVI increase precedes skeletal muscle loss. Taken together, when managing individuals with high ABSI or high CAVI, it would be appropriate to target imbalance of body composition as a potential cause.

Introduction

Vascular function can be assessed by utilizing the concept of systemic arterial stiffness, and arterial stiffness parameters are useful in the management of cardiometabolic disorders [1]. Cardio-ankle vascular index (CAVI) is an arterial stiffness parameter that includes the entire arterial tree from the aortic valve to the tibial artery [2]. This parameter is theoretically and clinically independent of blood pressure (BP) at the time of measurement. Reports have shown that vascular injury caused by various cardiovascular (CV) risk factors can be detected as increased CAVI and that appropriate therapeutic interventions decrease CAVI. On the other hand, the most prominent independent factor associated with CAVI is aging [3]. Even in a healthy population without any CV risk factor, CAVI shows a linear positive correlation with age [4]. The notion, coined by Georges Cannabis and redefined by William Osler, that "a man (or woman) is as old as his (or her) arteries" remains valid today [5], and the findings of CAVI have demonstrated the concept of "vascular aging."

Like arteries, body composition also changes physiologically with aging. In general, there are three anthropometric changes associated with aging: (1) decreased height, (2) increased waist circumference (WC), and (3) thin extremities [6]. Decreased height indicates a shortened spine; increased WC reflects abdominal obesity, while thin extremities reflect skeletal muscle loss. Skeletal muscle mass can be assessed by lean body mass and is known to decrease from around 50 years of age [7]. We propose to summarize these age-related anthropometric changes with the concept of "body shape aging." However, no index has been established to comprehensively quantify this concept.

WC is the most widely used basic indicator to assess abdominal obesity. However, WC correlates highly with BMI and consequently is epidemiologically almost identical to BMI and does not necessarily reflect visceral fat accumulation much better than BMI [8]. Therefore, various anthropometric indices have been developed to assess abdominal obesity, and subsequent research led to the development of "a body shape index (ABSI)" [9]. This anthropometric index, which is WC divided by an allometric regression of weight and height, has the potential to identify BMI-independent body shape. According to a meta-analysis of prospective cohort studies, ABSI has superior predictive ability for CV and all-cause mortality compared to other anthropometric indices [10]. Furthermore, we have reported that ABSI is more strongly associated with high CAVI than existing abdominal obesity indices such as WC, WC-to-height ratio, WC-to-BMI ratio, and conicity index [11] and has superior predictive ability for future kidney function decline [12]. On the other hand, it is unclear whether ABSI comprehensively reflects age-related changes in body composition in healthy population. Furthermore, the interaction between body composition and progression of systemic arterial stiffness (i.e., arterial stiffening) with aging is also not fully understood. Against this background, this study aimed to (1) confirm the age-related physiological changes in anthropometric indices and CAVI in healthy individuals; (2) examine whether ABSI is a candidate for quantifying comprehensive physiological change in body composition including lean body mass; and (3) perform a longitudinal analysis to clarify the interaction between body composition and arterial stiffening.

Methods

Study Population and Design

This research was a retrospective study using data from the cardiovascular disease (CVD) and cancer screening program organized by the Japan Health Promotion Foundation. The study population was Japanese residents of major cities in Japan, who had undergone annual

health screenings between 2010 and 2018. Of 34,662 individuals evaluated for eligibility, those with missing data of WC (N = 4,518) and those with previous treatment of any metabolic disorder, CVD, heart failure, peripheral artery disease, and/or past history of cerebral stroke (N = 4,886) were excluded. Next, individuals with untreated hyperglycemia (fasting plasma glucose [FPG] ≥126 mg/dL), hypertension (either systolic blood pressure [SBP] >140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg) or dyslipidemia (low-density lipoprotein cholesterol [LDL-C] ≥140 mg/dL, high-density lipoprotein cholesterol [HDL-C] <40 mg/dL, and/or triglycerides [TG] ≥150 mg/dL) (N = 11,586) were excluded. In addition, individuals with estimated glomerular filtration rate below 60 mL/min/1.73 m^2, corresponding to GFR category 3a or worse, were also excluded. Accordingly, 13,672 metabolically healthy individuals were included for cross-sectional analysis in this study. Furthermore, from this population, 5,118 individuals who participated in the screening program for four consecutive years were also analyzed longitudinally.

Data Collection

All parameters were assessed by standardized methods. Blood was collected from an anterior upper extremity vein in the morning after a 12-h fast to measure FPG (mg/dL), total cholesterol (TC, mg/dL), TG (mg/dL), and HDL-C (mg/dL). LDL-C (mg/dL) was calculated using Friedewald's formula: LDL-C = TC − HDL-C − TG/5.

WC was measured horizontally at the height of the umbilicus, with the participant standing and arms hanging relaxed. We adopted the following anthropometric indices, the usefulness of which has been reported in several major medical journals, and which can be calculated from height, weight, and WC.

$$\text{BMI} = \text{Weight (kg)}/\text{Height (m)}^2,$$

$$\text{A body shape index (ABSI) [13]} = \text{WC (m)} \times \text{Height (m)}^{5/6} \times \text{Weight (kg)}^{-2/3}$$

$$\text{Estimated lean body mass index (eLBMI) [14]} =$$

$$[19.363 + 0.001 \times \text{Age (years)} + 0.064 \times \text{Height (cm)} + 0.756 \times \text{Weight (kg)} - 0.366 \times \text{WC (cm)} - 1.007]/\text{Height (m)}^2 \text{ for males,}$$

$$[-10.683 - 0.039 \times \text{Age (years)} + 0.186 \times \text{Height (cm)} + 0.383 \times \text{Weight (kg)} - 0.047 \times \text{WC (cm)} - 0.34]/\text{Height (m)}^2 \text{ for females.}$$

According to the original article, the coefficients of determination of the prediction equations for LBMI measured by dual-energy X-ray absorptiometry is 0.91 for men and 0.85 for women [14].

Measurement of Arterial Stiffness Parameters and BP

CAVI was measured using a VaSera VS-1500 device (Fukuda Denshi Co., Ltd., Tokyo, Japan) according to the manufacturer's instructions. Cuffs were applied to bilateral upper arms and ankles, with the subject lying supine and the head held in midline position. After resting for 5 min, the examinations were performed. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure of 30–50 mm Hg was used to minimize the effect of cuff pressure on hemodynamics. Thereafter, BP was measured from the cuff of the upper arm. CAVI values were automatically calculated using the following formula [2]:

$$\text{CAVI} = a\{2\rho \times \ln(\text{Ps}/\text{Pd})/\Delta\text{P} \times \text{PWV}^2\} + b$$

where Ps is SBP; Pd is DBP; ΔP is Ps − Pd; ρ is blood density; PWV denotes cardio-ankle PWV; and a and b are constants. Participants remained still and silent during 5 min of measurement. Cuffs were placed on the arms and legs, and a heart sound microphone was attached with double-sided tape to the sternum at the second intercostal space. Subjects with ankle-brachial indices lower than 0.90 were excluded because patients with severe arterial occlusive diseases may give falsely low CAVI.

Statistical Analysis

The SPSS software (version 27.0.1, Chicago, IL, USA) and R software (version 3.4.2) were used for statistical analyses. All data are expressed as median (interquartile range) or mean ± standard deviation. Mann-Whitney U test or Fisher's exact test was performed to examine differences between two groups. The relationship of each anthropometric index with aging was analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni multiple comparison test. Spearman's rank correlation coefficient was used to evaluate the relationship between two variables. Correlation coefficients were compared using the cocor package in R software [15]. A mediation analysis by sex was performed using PROCESS (version 4.0) in SPSS [16] and was adjusted by general confounders including SBP, FPG, LDL-C, HDL-C, and TG. DBP was omitted as a confounder because of the intraclass correlation with SBP (R_s = 0.766). 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, two-sided p values less than 0.05 were considered statistically significant.

Results

Clinical and Biochemical Characteristics of Males and Females

A total of 13,672 Japanese urban residents without any metabolic disorder, CVD, heart failure, peripheral artery disease, and/or past history of cerebral stroke (male:female = 38.0:62.0) were enrolled in the cross-sectional analysis. Within this study cohort, 5,118 individuals (male:female = 45.7:54.3) who were followed for four consecutive years and had serial data of CAVI and anthropometric indices were further analyzed longitudinally.

Table 1 compares the clinical characteristics between male and female participants. Compared with women, men had significantly higher BMI, WC, BP, FPG, TG, and LDL-C and lower age, ABSI, and HDL-C. Regarding gender differences in FPG and CAVI, the median values were identical, although they showed statistical significant differences. There were little sex differences in longitudinal changes of anthropometric indices, but median eLBMI did not change only in men. For the results presented hereinafter, Table 2 and Figures 1–3 are cross-sectional data, and Table 3 and Figure 4 are longitudinal data.

Relationship between Anthropometric Indices and Age by Sex

Next, we examined the relationship between anthropometric indices and age in men and women, as shown in Figure 1. One-way ANOVA detected a significant trend of change among the stratified age groups for each index in both men and women. With respect to BMI (Fig. 1a) and WC (Fig. 1b), men showed an upward convex curve with aging, whereas women showed an increasing trend. For eLBMI, a linear declining trend was observed for both men and women, especially in the middle-to-older age groups (Fig. 1c). ABSI showed a significant linear increasing trend among the stratified age groups for both men and women (Fig. 1d). Especially, ABSI increased almost linearly in women aged above 50 years. CAVI correlated linearly and positively with age in both men and women (Fig. 1e).

Relationship of eLBMI with Anthropometric Indices by Sex

Next, stratified cross-sectional analyses were performed on the relationship of baseline eLBMI with each anthropometric index, as shown in Figure 2. For both men and women, increase in BMI (Fig. 2a) or WC (Fig. 2b) was associated with increasing eLBMI. In contrast, increase in ABSI group (Fig. 2c) was associated with a decline in eLBMI.

Correlation of Baseline eLBMI or CAVI with Anthropometric Indices

It is known that the human body begins to lose skeletal muscle mass after the age of 50 [17]. In addition, the threshold for obesity in Japan is defined as a BMI of 25 kg/m^2 [18]. To clarify the relationship of systemic arterial stiffness with physiological change in body composition, participants were grouped according to whether they were over or under 50 years or had a BMI over or under 25 kg/m^2. The correlation between anthropometric indices and CAVI was analyzed in age and BMI subgroups, as shown in Table 2.

The positive correlation of eLBMI with BMI and WC was weakened in individuals with obesity for both men and women. In contrast, the negative correlation of eLBMI with ABSI was enhanced in individuals with obesity.

A negative correlation was observed between eLBMI and CAVI in both sexes, and the relationship was enhanced in those above age 50 years and in those with obesity. CAVI correlated weakly and negatively with BMI, and the relationship was enhanced in individuals above 50 years and in those with obesity. Overall, there was a weak positive correlation between CAVI and WC, but the correlation was lost in some subgroups. CAVI correlated positively with ABSI, and the correlation was enhanced, especially in women above age 50.

Mediation Analysis of ABSI or eLBMI as Potential Mediator of Age-CAVI Relationship

Based on the above results, ABSI appeared to be an indicator reflecting both age-related skeletal muscle loss and arterial stiffening. We therefore examined whether the positive relationship between age and CAVI is mediated by ABSI. In addition, the mediation effect of eLBMI on the relationship between ABSI and CAVI was also examined, as shown in Figure 3.

In the mediation analyses after adjusting for confounders, the total effect of age on CAVI was 0.783 (95% CI: 0.763–0.802, $p < 0.001$) for men and 0.753 (95% CI: 0.737–0.770) for women. ABSI partially mediated the relationship between age and CAVI, with mediation rates of 2.2% for men (Fig. 3a) and 2.7% for women (Fig. 3d). Similarly, eLBMI partially and negatively mediated the relationship between age and CAVI, with mediation rates of 2.4% for men (Fig. 3b) and 5.1% in women (Fig. 3e). Furthermore, eLBMI also mediated the

Table 1. Clinical and biochemical characteristics of male and female participants

Variable	Males	Females	*p* value
			males vs. females
Baseline characteristics	*N* = 5,190	*N* = 8,482	–
Age, years	37 (31, 45)	41 (34, 49)	<0.001
Height, m	1.71 (1.67, 1.75)	1.58 (1.55, 1.62)	<0.001
Body weight, kg	64.6 (59.0, 70.8)	50.8 (46.6, 55.5)	<0.001
BMI, kg/m^2	22.0 (20.4, 23.8)	20.2 (18.7, 22.0)	<0.001
WC, m	0.79 (0.74, 0.84)	0.73 (0.68, 0.79)	<0.001
ABSI, ×10^2	7.68 (7.45, 7.91)	7.82 (7.53, 8.13)	<0.001
eLBMI, kg/m^2	16.83 (16.05, 17.65)	13.05 (12.56, 13.66)	<0.001
CAVI	7.2 (6.7, 7.7)	7.2 (6.7, 7.7)	0.004
SBP, mm Hg	115 (108, 123)	108 (101, 116)	<0.001
DBP, mm Hg	71 (66, 77)	67 (61, 73)	<0.001
FPG, mg/dL	85 (80, 89)	85 (80, 85)	<0.001
TC, mg/dL	188 (171, 205)	195 (176, 213)	<0.001
LDL-C, mg/dL	109 (93, 123)	107 (91, 122)	<0.001
HDL-C, mg/dL	62 (54, 73)	77 (66, 89)	<0.001
TG, mg/dL	73 (55, 97)	57 (44, 75)	<0.001
4-year longitudinal changes	(*N* = 2,337)	(*N* = 2,781)	–
ΔBMI, kg/m^2	0.2 (−0.5, 0.9)*	0.2 (−0.5, 0.9)*	0.302
ΔWC, m	0.01 (−0.02, 0.04)*	0.01 (−0.02, 0.04)*	0.404
ΔABSI, ×10^{-2}	0.05 (−0.20, 0.31)*	0.05 (−0.11, 0.21)*	0.539
ΔeLBMI, kg/m^2	−0.01 (−0.39, 0.35)	−0.05 (−0.28, 0.19)*	0.034
ΔCAVI	0.3 (−0.1, 0.6)*	0.3 (−0.1, 0.6)*	0.327

Cross-sectional and longitudinal data are expressed as median (interquartile range). Comparison of two groups was performed using Mann-Whitney U test. BMI, body mass index; WC, waist circumference; ABSI, a body shape index; eLBMI, estimated lean body mass index; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Δ, change in value from baseline to 4th year. *$p < 0.001$, 4th year vs. baseline, Wilcoxon signed-rank test.

relationship between ABSI and CAVI, with mediation rates of 18.0% in men (Fig. 3c) and 19.1% in women (Fig. 3f).

Correlation of Baseline eLBMI and CAVI with Changes in Anthropometric Indices

In Table 2 and Figure 3, an inverse relationship between eLBMI and CAVI was observed. However, the causality between the two is unknown. We then examined the relationship of baseline eLBMI and CAVI with the changes in anthropometric indices in 4-year longitudinal data, as shown in Table 3. Baseline eLBMI correlated positively with ΔABSI and ΔCAVI in both sexes. Baseline CAVI correlated negatively with ΔABSI and ΔeLBMI. Furthermore, the inverse correlation between CAVI and ΔeLBMI was stronger in men without obesity and in women under age 50 years.

Relationship of Change in Each Anthropometric Index with ΔCAVI

Finally, the correlation between 4-year changes in two anthropometric indices and 4-year change in CAVI was examined as shown in Figure 4. No correlation was observed between ΔCAVI and ΔABSI (Fig. 4a), whereas ΔeLBMI correlated negatively with ΔCAVI ($R_s = -0.031$, $p = 0.025$, Fig. 4b).

Table 2. Spearman's rank correlation coefficients for baseline eLBMI and CAVI vs. anthropometric indices

	Number	eLBMI vs.			CAVI vs.			
		BMI	WC	ABSI	BMI	WC	ABSI	eLBMI
Male								
Total	5,190	0.920*	0.611*	−0.191*	−0.039*	0.053*	0.273*	−0.131*
Age <50 years	4,211	**0.930***	0.632*	−0.174*	**−0.061***	**0.008**	0.158*	**−0.111***
Age ≥50 years	979	**0.900*§**	0.569*	−0.248*	**−0.210*§**	**−0.120*§**	0.189*	**−0.274*§**
BMI <25 kg/m^2	4,406	**0.878***	**0.443***	**−0.317***	**0.011**	**0.116***	0.285*	**−0.104***
BMI ≥25 kg/m^2	784	**0.763*§**	**0.132*§**	**−0.543*§**	**−0.177§**	**−0.015§**	0.262*	**−0.337*§**
Female								
Total	8,482	0.959*	0.675*	−0.118*	−0.013	0.119*	0.275*	−0.195
Age <50 years	6,380	**0.982***	0.704*	−0.111*	**−0.042***	0.055*	**0.156***	**−0.133***
Age ≥50 years	2,102	**0.976*§**	0.727*	−0.043	**−0.155*§**	−0.018	**0.238*§**	**−0.250*§**
BMI <25 kg/m^2	7,887	**0.949***	**0.604***	**−0.158***	**0.001**	**0.146***	0.275*	**−0.207***
BMI ≥25 kg/m^2	595	**0.894*§**	**0.373*§**	**−0.306*§**	**−0.129*§**	**0.070§**	0.292*	**−0.406*§**

Cross-sectional data from a total of 13,673 participants (male 38.0%) were analyzed. Bold font denotes significant difference in individual subgroup analysis. CAVI, cardio-ankle vascular index; BMI, body mass index; WC, waist circumference; ABSI, a body shape index; eLBMI, estimated lean body mass index. *$p < 0.001$, Spearman's rank correlation analysis. §$p < 0.001$, comparison of correlation coefficients in individual subgroup analysis.

Discussion

This retrospective cohort study examined the relationship between age and several anthropometric indices in a healthy Japanese population without any metabolic disorder, CVD, heart failure, peripheral artery disease, and/or past history of cerebral stroke. The results of cross-sectional data analyses revealed that BMI and WC did not necessarily show a linear relationship with aging. ABSI showed a positive linear correlation with age, while eLBMI showed a declining trend with aging, especially in the middle-to-older age groups. In addition, ABSI correlated inversely with eLBMI, whereas BMI and WC correlated directly with eLBMI. Furthermore, age was associated linearly with CAVI, and this association was partially mediated by ABSI or eLBMI. In the longitudinal data analysis, baseline CAVI correlated negatively with 4-year ΔeLBMI, and a negative correlation between 4-year ΔCAVI and 4-year ΔeLBMI was observed. These findings suggest the following. First, ABSI is an indicator that reflects not only abdominal obesity but also loss of lean body mass with aging. This feature of ABSI may contribute to its superior predictive ability for mortality. Second, vascular function and lean body mass may be related to each other, especially because CAVI increase precedes skeletal muscle loss. Taken together, when managing individuals with high ABSI or high CAVI, it would be appropriate to target imbalance of body composition as a potential cause.

The detailed pathophysiology of the linkage between body composition and systemic arterial stiffness has not been fully elucidated. This study demonstrated an inverse relationship between eLBMI and CAVI, and this relationship was enhanced in middle-to-older age groups or the presence of obesity. Since skeletal muscle loss is a major cause of sarcopenia, this finding is consistent with a previous report showing higher CAVI in individuals with sarcopenia than in those without [19]. On the other hand, the causality between skeletal muscle loss and arteriosclerosis is controversial. Myokine, a cytokine specifically produced in skeletal muscle tissue, is a candidate mediator for regulating vascular function. For example, follistatin like-1, which is a myokine produced and secreted in skeletal muscle, is known to be associated with improved vascular function by counteracting endothelial dysfunction [20]. Hence, qualitative or quantitative degeneration of skeletal muscle tissue may promote arteriosclerosis via increased insulin resistance, inflammation, and oxidative stress [21]. However, a contrasting pathophysiological mechanism that vascular dysfunction precedes skeletal muscle loss has also been postulated [22]. In the present study, baseline CAVI correlated inversely with ΔeLBMI, suggesting that arterial stiffening may induce muscular atrophy by restricting nutrient supply to skeletal muscle, at least in healthy population. Longitudinal analysis primarily in older individuals with accelerated skeletal muscle loss may be needed to

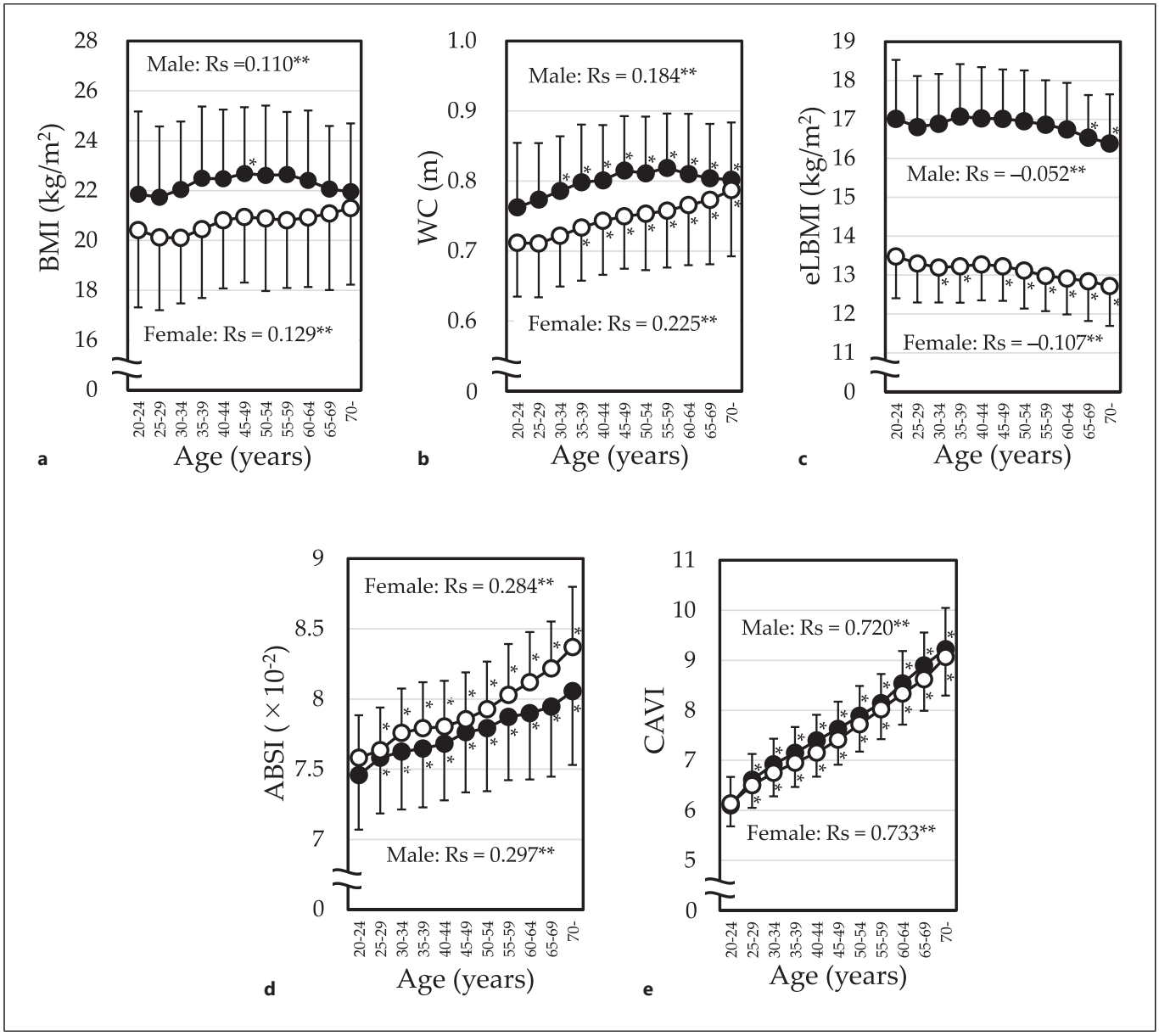
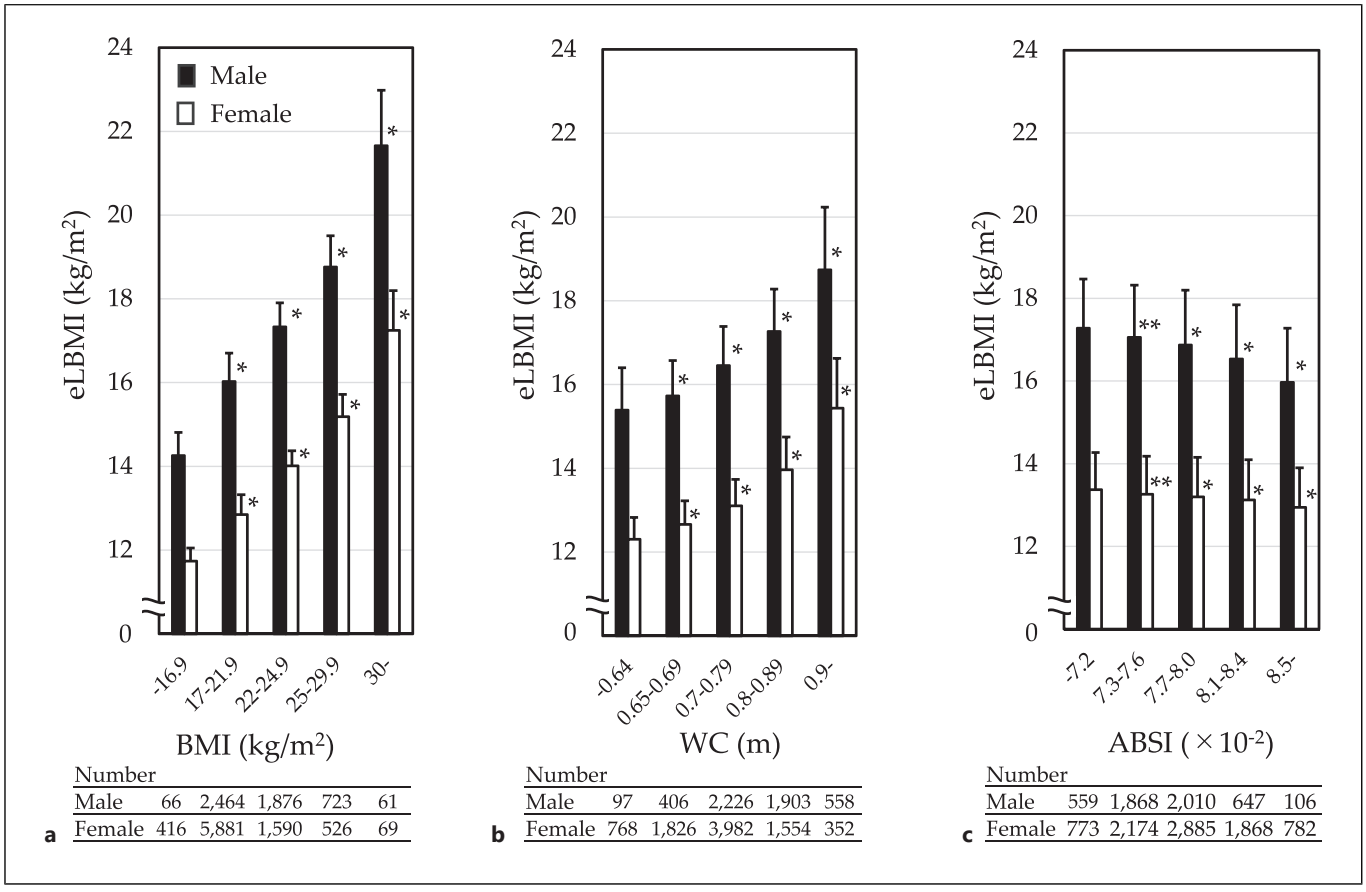


Fig. 1. Relationship of anthropometric indices with aging in male (black circle) and female (white circle) participants. Cross-sectional data from a total of 13,673 participants (male 38.0%) were analyzed. Data are expressed as mean ± standard deviation. Anthropometric indices studied: BMI (**a**), WC (**b**), eLBMI (**c**), ABSI (**d**), and CAVI (**e**). *$p < 0.001$ vs. 20–24 age group, one-way ANOVA followed by Bonferroni multiple comparison test. **$p < 0.001$, comparison of Spearman's rank correlation coefficients in each age group for each index. CAVI, cardio-ankle vascular index; eLBMI, estimated lean body mass index; BMI, body mass index; WC, waist circumference; ABSI, a body shape index; ANOVA, analysis of variance.

confirm whether decreased lean body mass secondarily induces arteriosclerosis.

Recently, the anti-aging benefits of exercise have attracted attention. For example, the NIPPON DATA90 study [23] has revealed favorable impact of exercise habits on long-term mortality risks. However, this study did not include information on the subjects' exercise intensity. It has already been reported that exercise can decrease CAVI accompanied by decreased visceral fat [24]. Considering the longitudinal analysis of this study, exercise may prevent a decrease in LBMI through decreased CAVI. Furthermore, of course, it is speculated



a

Number					
Male	66	2,464	1,876	723	61
Female	416	5,881	1,590	526	69

b

Number					
Male	97	406	2,226	1,903	558
Female	768	1,826	3,982	1,554	352

c

Number					
Male	559	1,868	2,010	647	106
Female	773	2,174	2,885	1,868	782

Fig. 2. Relationship of eLBMI with BMI (**a**), WC (**b**), and ABSI (**c**) by sex. Cross-sectional data from a total of 13,673 participants (male 38.0%) were analyzed. Data are expressed as mean ± standard deviation. *$p < 0.01$, **$p < 0.05$ vs. the lowest stratum, one-way ANOVA followed by Bonferroni comparison test. eLBMI, estimated lean body mass index; BMI, body mass index; WC, waist circumference; ABSI, a body shape index; ANOVA, analysis of variance.

that exercise would reduce ABSI through decreased visceral fat and/or increased skeletal muscle. Therefore, it is highly likely that exercise can suppress the unfavorable age-related changes in CAVI and anthropometric indices.

ABSI was developed as an anthropometric index, and the superior predictive ability for CV mortality has been reported [10]. However, an unresolved paradox regarding ABSI is that it is inferior to existing abdominal obesity indices in identifying abdominal obesity-related metabolic disorders [25]. In addition, ABSI has also been reported to have a relatively weak association with visceral fat area evaluated by computed tomography [26]. As an explanation for this paradox, we speculate a possibility that high ABSI does not necessarily reflect excess visceral fat accumulation. An increased ABSI reflects abdominal bulging beyond that expected for a given BMI or a geometric change from cylindricity to conicity [27]. In other words, decreased skeletal muscle mass relative to WC may also result in high ABSI. As shown in this study, ABSI correlated inversely with eLBMI. This finding is consistent with previous reports that high ABSI also reflects the risk of sarcopenia including decreased hand grip strength [28, 29]. Since ABSI is an indicator that reflects decreased height, abdominal obesity, and skeletal muscle loss, the evaluation of "body shape age" using ABSI is probably useful in health screening and daily clinical practice. The reason is that high "body shape age" deviating from chronological age signifies a risk factor for abdominal obesity-related metabolic disorders, sarcopenia, or CVD. The concept of "early body shape aging" (i.e., high ABSI) could be utilized in health education, with the aim to contribute to health consciousness. In the present study, however, ΔCAVI correlated with ΔeLBMI,

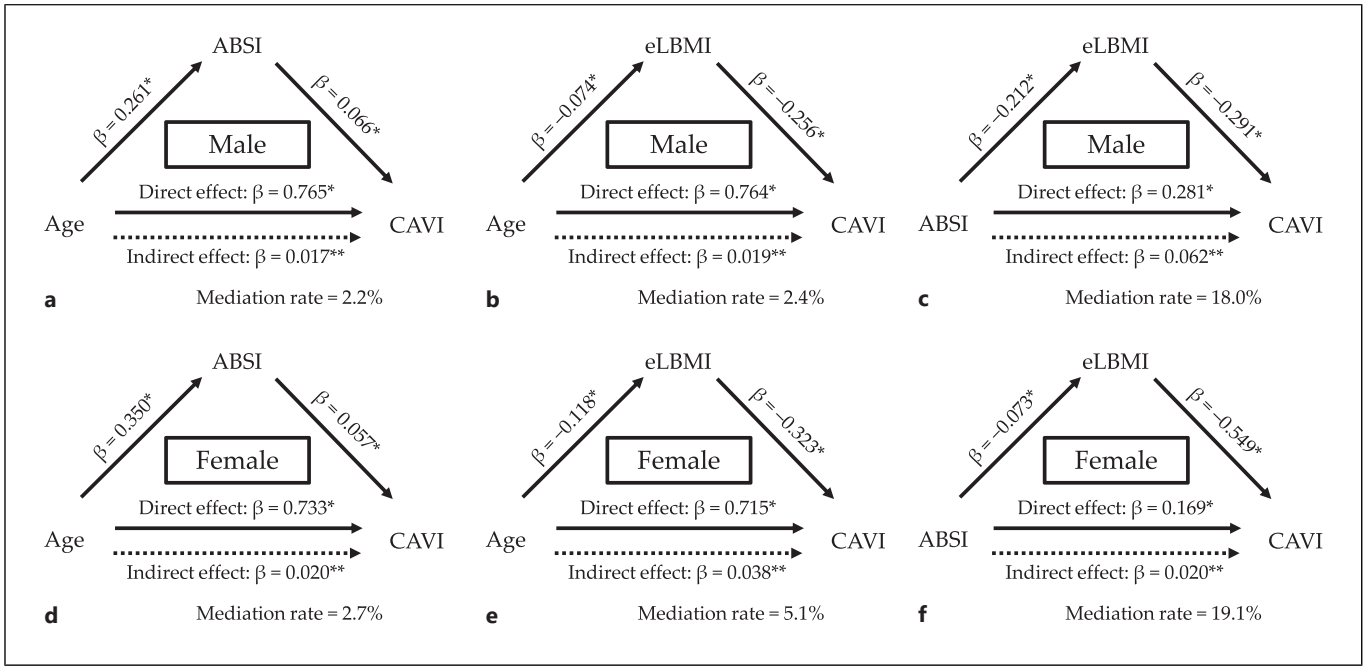


Fig. 3. Mediation analysis of ABSI or eLBMI as potential mediator of the association between age and CAVI. Cross-sectional data from a total of 13,673 participants (male 38.0%) were analyzed. Mediation analyses for men (**a–c**) and for women (**d–f**) are shown. *$p < 0.001$, **$p < 0.05$. Analyses were adjusted for confounders comprising SBP, FPG, LDL-C, HDL-C, and TG. β, standardized β coefficient; ABSI, a body shape index; CAVI, cardio-ankle vascular index; eLBMI, estimated lean body mass index; SBP, systolic blood pressure, FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table 3. Spearman's rank correlation coefficients for baseline eLBMI and CAVI vs. changes in anthropometric indices

	Number	Baseline eLBMI vs.		Baseline CAVI vs.	
		ΔABSI	ΔCAVI	ΔABSI	ΔeLBMI
Male					
Total participants	2,337	0.080*	0.077*	−0.056*	−0.120*
Age <50 years	1,557	0.059	0.076*	−0.046	−0.080*
Age ≥50 years	780	0.104*	0.098*	0.020	−0.051
BMI <25 kg/m^2	1,698	0.127*	0.017	−0.061*	**−0.166***
BMI ≥25 kg/m^2	639	0.155*	0.058	−0.051	**−0.041**§
Female					
Total participants	2,781	0.052*	0.084*	−0.009	−0.161*
Age <50 years	1,428	0.080*	0.078*	−0.014	**−0.067***
Age ≥50 years	1,353	0.031	0.090*	−0.050	**0.026**§
BMI <25 kg/m^2	2,418	0.042	0.048	0.003	−0.173*
BMI ≥25 kg/m^2	363	0.109	0.050	−0.075	−0.130*

Four-year longitudinal data from a total of 5,118 participants (male 45.7%) were analyzed. Bold font denotes significant difference in individual subgroup analysis. CAVI, cardio-ankle vascular index; ABSI, a body shape index; eLBMI, estimated lean body mass index; Δ, change in value from baseline to 4th year. *$p < 0.001$, Spearman's rank correlation analysis. $^{\S}p < 0.001$, comparison of correlation coefficients in individual subgroup analysis.

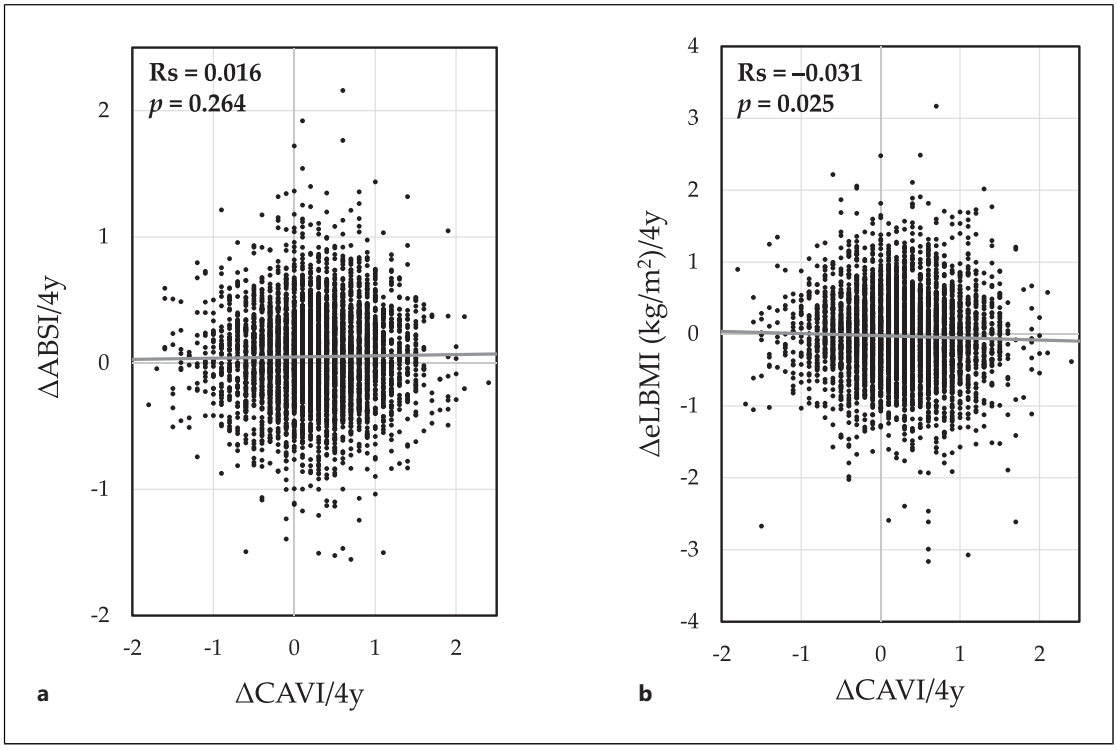


Fig. 4. Relationship of 4-year ΔABSI (**a**) and ΔeLBMI vs. 4-year ΔCAVI (**b**). Longitudinal data from a total of 5,118 participants (male 45.7%) were analyzed. R_s, Spearman's rank correlation coefficients; BMI, body mass index; WC, waist circumference; ABSI, a body shape index; eLBMI, estimated lean body mass index; CAVI, cardio-ankle vascular index; Δ, change in value from baseline to 4th year.

but not with ΔABSI. This indicates that although ABSI is associated with eLBMI, it is not as closely related to arterial stiffness as eLBMI, at least in healthy individuals. Long-term observational studies are warranted to clarify whether ΔABSI is associated with ΔCAVI in individuals with cardiometabolic risk factors.

Our results suggest that CAVI may increase with aging in association with ABSI or eLBMI. In addition, enhanced association between eLBMI and CAVI in individuals with BMI ≥25 kg/m^2 or age ≥50 years was the common finding in both sexes. On the other hand, the greater increase in ABSI in women compared to men after age 50 years was a finding different from the age-related increase in CAVI, which showed little sex difference. At the very least, sex and age may need to be considered in the interpretation of ABSI. Why does the relative increase in ABSI in women after middle age not contribute to the relative increase in CAVI? This discrepancy may be due to the fact that subcutaneous fat mass does not decrease with aging in women, unlike in men [30]. In other words, the relatively increased subcutaneous fat in middle-older-aged women may attenuate the vascular toxicity associated with increased ABSI. Recently, the vasoprotective effects of subcutaneous adipose tissue have drawn attention [31]. Indeed, we have previously reported that lipoprotein lipase derived from subcutaneous adipose tissue may suppress the progression of arteriosclerosis [32]. However, the lack of an indicator of subcutaneous fat mass in this study hindered our ability to analyze the mechanism in detail. Therefore, future study should investigate the interaction of subcutaneous adipose tissue with age-related arterial stiffening as well as visceral fat and skeletal muscle.

The present study has several limitations. First, it should be noted that lean body mass assessed by eLBMI is less accurate than dual-energy X-ray absorptiometry. Second, this study recruited healthy individuals at baseline but did not consider any new-onset metabolic disorders during the 4-year study period. Finally, there is the possibility of selection bias in the enrollment of health screening participants. Individuals who participated in health screenings may be more health conscious and have healthier lifestyle than those who did not participate. Therefore, caution should be exercised in generalizing the present results to the general population.

In conclusion, ABSI is a modifiable index that well reflects age-related changes in arterial stiffness and body composition including lean body mass. Since arterial stiffening may cause skeletal muscle loss, potentially creating a vicious cycle, prioritizing CAVI and anthropometric indices in clinical practice may be a useful strategy.

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Statement of Ethics

The protocol of the study was prepared in accordance with the Declaration of Helsinki. The opt-out informed consent protocol was used for use of participant data for research purposes. The study protocol including this consent procedure was reviewed and approved by the Institutional Review Board and the Ethics Committee of Sakura Hospital, School of Medicine, Toho University (No. S24011; date of approval, June 14, 2024).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, data curation, writing – original draft preparation, and formal analysis: D.N.; data acquisition: D.N. and K.S. (Kenji Suzuki); data interpretation: Y.W., A.S., and K.S. (Kohji Shirai); writing – review and editing: Y.W., K.F., K.S. (Kenji Suzuki), M.O., K.S. (Kohji Shirai), and A.S. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

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 inquiries may be directed to the corresponding author.

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