

District Differences in the Measured Values of Arterial Stiffness in Japan

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Background: In Japan, district differences in the prevalence of cardiovascular disease (CVD) are well-known. This study examined district differences in Japan in measured values of arterial stiffness, an independent risk factor for CVD.

Methods and Results: Local residents participating in health checkups conducted in the Wakayama ($n=461$) and Nagano ($n=186$) prefectures in 2018 were recruited to the study. Brachial-ankle pulse wave velocity (baPWV) was evaluated as an index of arterial stiffness. After multivariate adjustment, baPWV was significantly higher in the Wakayama than Nagano district in subjects aged ≥ 70 years (mean \pm SE) $1,912 \pm 25$ vs. $1,763 \pm 30$ cm/s; $P < 0.01$), but not in subjects aged < 70 years. Multivariate linear regression analysis demonstrated that the Wakayama/Nagano district difference was significantly ($P < 0.01$) associated with baPWV.

Conclusions: District differences were observed in the measured values of arterial stiffness in Wakayama and Nagano. The Wakayama and Nagano prefectures are representative areas with a relatively high and relatively low prevalence of CVD, respectively, in Japan. Therefore, based on the results of the present study, we propose to conduct a study to examine whether district differences in arterial stiffness underlie district differences in the prevalence of CVD.

Key Words: Arterial stiffness; Cardiovascular disease; Elderly people; Epidemiology

Cardiovascular disease (CVD) risk is closely related to aging, with early vascular aging suggested to be an underlying factor in promoting the early onset of vascular damage and CVD.¹ Arterial stiffness, as a core characteristic of vascular aging, is an independent risk marker for the development of CVD.^{2,3} In Japan, district (prefecture) differences in the prevalence of CVD are well known.⁴ However, whether such differences may also be associated with similar differences in measured values of arterial stiffness among districts has not yet been fully clarified. Therefore, we conducted this study to examine district differences in the measured values of arterial stiffness in Japan.

Methods

Ethics Statement

The study protocol was approved by the ethics committees of Wakayama Medical University (Approval no. 92) and

Tokyo Medical University (Approval no. T2019-0075). All participants provided written informed consent before the examinations. All procedures were followed in accordance with the Declaration of Helsinki.

Study Subjects

The study subjects were selected from local residents participating in a population-based health study, which was conducted based on the annual health checkups managed by the city administration, held in both Wakayama and Nagano prefectures in Japan. Nagano Prefecture is known as the “Longevity Prefecture”. In contrast, the average life span of individuals in Wakayama Prefecture is in the 30th percentile group in Japan.⁵ The present study was conducted in subjects aged ≥ 60 years (Wakayama, $n=559$; Nagano, $n=219$) in 2018. Participants without any information on blood pressure, anthropometric data, and blood examinations, as well as those with atrial fibrillation or an ankle-brachial pressure index (ABI) < 0.95 were excluded.⁶

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Table 1. Clinical Characteristics of Subjects Aged ≥ 60 Years From the Nagano and Wakayama Districts in Japan

	Nagano (n=186)	Wakayama (n=461)	P value
Clinical variables			
Age (years)	78 \pm 8	70 \pm 6	<0.01
Sex			0.08
No. males/females	73/113	210/251	
% Males	39	46	
BMI (kg/m ²)	22.5 \pm 3.0	23.0 \pm 3.1	0.07
SBP (mmHg)	137 \pm 16	125 \pm 16	<0.01
DBP (mmHg)	75 \pm 9	74 \pm 10	0.18
MBP (mmHg)	96 \pm 10	91 \pm 11	<0.01
HR (beats/min)	65 \pm 10	71 \pm 11	<0.01
LDL-C (mg/dL)	107 \pm 23	119 \pm 32	<0.01
HDL-C (mg/dL)	64 \pm 15	60 \pm 15	<0.01
TG (mg/dL)	90 \pm 60	114 \pm 89	<0.01
HbA _{1c} (%)	6.0 \pm 0.5	5.8 \pm 0.5	<0.01
Creatinine (mg/dL)	0.78 \pm 0.30	0.81 \pm 0.18	0.20
baPWV (cm/s)	1,829 \pm 349	1,673 \pm 385	<0.01
Lifestyle habits			
Current smoker	10 (5)	7 (2)	0.01
Alcohol drinking daily	53 (28)	132 (29)	0.53
Medication			
Hypertension	125 (67)	201 (44)	<0.01
Diabetes	23 (12)	55 (12)	0.49
Dyslipidemia	72 (39)	147 (32)	0.10
History of CVD			
	17 (9)	45 (10)	0.88

Unless indicated otherwise, values are given as the mean \pm SD or as n (%). baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; MBP, mean blood pressure; SBP, systolic blood pressure; TG, triglycerides.

Finally, 461 subjects in Wakayama Prefecture and 186 subjects in Nagano Prefecture were enrolled in the study.

Measurements

Brachial-ankle pulse wave velocity (baPWV) was measured using a volume plethysmographic apparatus (Form/ABI; Omron Healthcare, Kyoto, Japan), as described previously.⁷ Serum concentrations of triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and creatinine, as well as plasma glucose concentrations and HbA_{1c}, were measured using standard enzymatic methods. All blood samples were obtained in the morning after an overnight fast.

Statistical Analysis

Unless indicated otherwise, data are expressed as the mean \pm SD. The significance of differences in mean values between groups was analyzed using Student's t-test or the Mann-Whitney U test, whereas the significance of differences in frequencies was assessed using the Chi-squared test. For group comparisons with the adjustment of covariates, a general linear model regression analysis with post hoc comparisons was performed. Multivariate linear regression analyses were conducted to assess the association of baPWV with variables. The covariates included in the analyses were age, sex, smoking status, body mass index, mean blood pressure, heart rate, LDL-C, HDL-C, triglycerides, HbA_{1c},

creatinine, and medication for hypertension, dyslipidemia, and/or diabetes (not receiving medication=0, receiving medication=1).

All statistical analyses were conducted using SPSS version 25.0 (IBM/SPSS, Armonk, NY, USA). Two-sided P<0.05 was considered statistically significant.

Results

The clinical characteristics of the study subjects are summarized in **Table 1**. Age, the prevalence of current smokers, systolic blood pressure, and blood levels of HbA_{1c} and HDL-C, as well as the proportion of subjects using antihypertensive drugs, were higher in the Nagano than Wakayama district, but serum levels of LDL-C and triglycerides were lower in Nagano. Age and blood pressure are major determinants of arterial stiffness.^{1,8,9} Although crude baPWV was higher in Nagano than in Wakayama (P<0.01; **Table 1**), the adjusted baPWV (adjusted with covariates including age and blood pressure) was lower in Nagano than Wakayama (1,655 \pm 26 vs. 1,744 \pm 15 cm/s, respectively; P<0.01).

Table 2 summarizes clinical characteristics of subjects stratified by age (60–74 vs. ≥ 75 years) and sex from the Nagano and Wakayama districts. Although blood pressure was lower in Wakayama than Nagano, baPWV was similar in both districts.

After adjusting for potential covariates, multivariate linear

Table 2. Clinical Characteristics of Subjects According to Age, Sex, and District

Clinical variables	Age 60–74 years			
	Females		Males	
	Nagano (n=37)	Wakayama (n=211)	Nagano (n=25)	Wakayama (n=163)
Age (years)	69±3	68±4*	68±4	67±4
BMI (kg/m ²)	23.3±2.8	22.4±3.1	22.7±3.1	23.8±3.1
SBP (mmHg)	132±15	124±17*	133±12	126±15*
DBP (mmHg)	74±8	73±10	79±8	77±10
MBP (mmHg)	93±9	90±11	97±8	93±11*
HR (beats/min)	66±10	72±12*	62±10	68±9*
LDL-C (mg/dL)	112±24	128±35*	110±22	110±29
HDL-C (mg/dL)	70±16	66±16	58±13	56±14
TG (mg/dL)	100±84	105±54	118±87	128±128
HbA _{1c} (%)	6.0±0.5	5.7±0.4*	6.2±0.5	5.9±0.6*
Creatinine (mg/dL)	0.69±0.24	0.71±0.11	0.84±0.14	0.94±0.17*
baPWV (cm/s)	1,611±262	1,593±370	1,682±263	1,631±287
Lifestyle habits				
Current smoker	1 (3)	0 (0)	4 (16)	6 (4)*
Alcohol drinking daily	7 (19)	24 (11)*	19 (76)	83 (51)*
Medication				
Hypertension	19 (51)	68 (32)*	17 (68)	78 (48)
Diabetes	3 (8)	19 (9)	5 (20)	24 (15)
Dyslipidemia	17 (46)	71 (34)	9 (36)	42 (26)
History of CVD	3 (8)	8 (4)*	2 (8)	24 (15)

Clinical variables	Age ≥75 years			
	Females		Males	
	Nagano (n=76)	Wakayama (n=40)	Nagano (n=48)	Wakayama (n=47)
Age (years)	82±5	78±3*	83±5	79±4*
BMI (kg/m ²)	22.1±3.0	23.5±3.4*	22.3±2.9	23.1±3.0
SBP (mmHg)	140±17	132±17*	137±14	127±14*
DBP (mmHg)	75±9	74±10	76±9	70±10*
MBP (mmHg)	97±11	93±12	96±9	87±10*
HR (beats/min)	65±11	74±13*	64±9	71±15*
LDL-C (mg/dL)	107±23	120±30*	102±24	107±23
HDL-C (mg/dL)	67±14	58±12*	59±15	54±14
TG (mg/dL)	79±32	115±80*	85±52	108±51*
HbA _{1c} (%)	6.0±0.5	6.0±0.4	6.0±0.6	5.8±0.6
Creatinine (mg/dL)	0.68±0.13	0.73±0.12*	0.97±0.47	0.95±0.21
baPWV (cm/s)	1,915±368	1,914±311	1,937±323	1,972±559
Lifestyle habits				
Current smoker	0 (0)	0 (0)	5 (10)	1 (2)
Alcohol drinking daily	7 (9)	3 (8)	20 (42)	22 (47)
Medication				
Hypertension	54 (71)	27 (68)	35 (73)	28 (60)
Diabetes	7 (9)	5 (13)	8 (17)	7 (15)
Dyslipidemia	35 (46)	19 (48)	11 (23)	15 (32)
History of CVD	10 (13)	3 (8)	2 (4)	10 (21)*

Values are given as the mean±SD or as n (%). *P<0.05 compared with the Nagano district. Abbreviations as in Table 1.

regression analysis revealed that the Wakayama/Nagano district difference (Wakayama=1, Nagano=0) was significantly associated with baPWV in the total study group ($\beta=0.11$, $P<0.01$) and in subjects aged ≥ 70 years ($\beta=0.20$, $P<0.01$), but not in subjects aged <70 years ($\beta=-0.35$, $P=0.73$). After adjustment, the general linear model regression analysis demonstrated that baPWV was significantly higher in the Wakayama than Nagano district in subjects aged ≥ 70 years, but not in subjects aged <70 years (Figure).

Discussion

This observational study demonstrated significant differences in the measured values of arterial stiffness between 2 districts (Nagano and Wakayama) in Japan.

Arterial stiffness reflects systemic arteriosclerosis at various sites in the vascular tree, most notably in large elastic arteries, and is believed to play a role in the development of CVD.^{2,3} The measurement of baPWV has been used as a simple and convenient method for evaluating arterial stiffness and is considered useful for screening subclinical vascular damage in primary care settings, as well as in large populations.^{7,8} Previous studies revealed that baPWV is closely related to the extent of atherosclerosis and is increased by the presence of various risk factors.⁹ In addition, baPWV has been reported to be a useful surrogate marker for risk prediction of future CVD onset.¹⁰ Every 1-SD increase in baPWV is associated with a 21% increase in CVD risk. An increase in baPWV of 1 m/s is associated with 12%, 13%, and 6% increases in the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively.¹¹

In the present study, mean blood pressure and baPWV were significantly higher in subjects from the Nagano than Wakayama district. The large proportion of elderly people in Nagano Prefecture could explain why values for some clinical characteristics were higher in this district. Thus, we performed multivariate linear regression analysis to confirm the differences in arterial stiffness between the 2 districts. After adjusting for potential confounding factors, the model revealed that the district of residence was a significant predictor of higher baPWV in the total study group, as well as in subjects aged ≥ 70 years. Previously, the IKARIA study in Greece proposed that PWV values in subjects living in a district with greater longevity may be lower than the expected European mean; however, that study did not compare PWV values to those of subjects living in a district with a shorter life span.¹² In the present study, baPWV values were also higher in people residing in a district with a relatively high prevalence of CVD (Wakayama) than in those residing in a district with a relatively low prevalence of CVD (Nagano),⁴ especially in the subgroup of elderly subjects aged ≥ 70 years.

The present observational study has several limitations. First, differences in the prevalence of CVD between the Wakayama and Nagano districts in Japan are well known.¹³ However, the participants in this study may not be representative of each district (i.e., there may be selection bias), because it may be that the prevalence of CVD is not homogeneous across each district. Second, in the present study we could not analyze the number of subjects who died of CVD or the number of those who could not present themselves for annual health checkups because of CVD in each district. These issues may plausibly explain the discrepant finding in the present study that although the num-

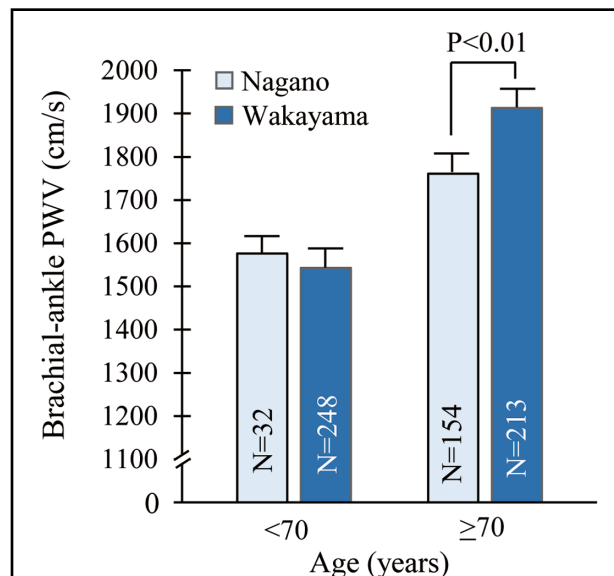


Figure. Brachial-ankle pulse wave velocity (PWV) in the Wakayama and Nagano districts in subjects aged <70 years and ≥ 70 years. Values are the adjusted mean \pm SEM.

bers of subjects with a past history of CVD was similar between the 2 districts, mean baPWV was higher in the Wakayama than Nagano district. Third, the study sample consisted of participants from the general population who underwent health checkups and are therefore considered to be skewed towards a healthier subgroup than the rest of the background population. Fourth, due to the cross-sectional observational design of the study, causation cannot be determined for any of the relationships observed. Fifth, lifestyle modifications are beneficial in improving increased arterial stiffness.¹⁴ The effect of differences in healthy lifestyle between the 2 districts on arterial stiffness needs to be clarified. Sixth, measurement of the baPWV during the annual health checkups was limited to research use, and both Nagano district¹⁵ and Wakayama district¹⁶ conducted the measurements. Therefore, we sought to examine differences in the measured baPWV between the Nagano and Wakayama districts. However, the sample size in both districts was limited. As an example, based on previous reports, Ehime has a relatively high prevalence of CVD,^{13,17} whereas Shiga has a relatively low prevalence of CVD.^{13,18} Thus, the estimated sample size the present was 100 in each group (see <https://clincalc.com/stats/samplesize.aspx>). Finally, although a history of medication for hypertension, dyslipidemia, and/or diabetes was used as a covariate, the detailed medication history of the subjects was not available for this study.

Conclusions

District differences were observed in measured values of arterial stiffness between Wakayama and Nagano. The Wakayama and Nagano prefectures are representative areas with a relatively high and relatively low prevalence of CVD, respectively, in Japan. Therefore, based on the results of the present study, we propose to conduct a study to co examine whether district differences in arterial stiffness

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Disclosures

The authors declare that they have no conflicts of interest to disclose with respect to this manuscript.

IRB Information

The study protocol was approved by the ethics committees of Wakayama Medical University (Approval no. 92) and Tokyo Medical University (Approval no. T2019-0075). All participants provided written informed consent before the examinations.

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