



# Inverse Relationship between Sleep Duration and Cardio-Ankle Vascular Index in Children

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**Aim:** Poor sleep has been shown to be associated with the development of cardiovascular risk factors, such as obesity, in both adults and children. This study aimed to investigate the relationship between sleep duration and arterial stiffness indices in Japanese children and early adolescents.

**Methods:** The data on 102 students (56 males, 46 females; mean age,  $11.9 \pm 1.8$  years) were analyzed. As non-invasive arterial stiffness parameters, the cardio-ankle vascular index (CAVI) and heart-ankle pulse wave velocity (haPWV) were evaluated. Their students' sleep habits (bedtime and wake times on a usual weekday) were investigated using questionnaires, and based on these, their sleep durations were calculated.

**Results:** The CAVI values in the males and females were  $4.8 \pm 0.9$  and  $4.7 \pm 0.9$  (arbitrary unit), respectively. haPWV values in the males and females were  $5.5 \pm 0.6$  and  $5.4 \pm 0.6$  m/s, respectively. Sleep duration in the males, but not in the females, was negatively correlated with CAVI ( $r = -0.356$ ) and haPWV ( $r = -0.356$ ), suggesting that students with short sleep duration could have increased arterial stiffness. After adjusting for confounders, such as age, sex, systolic blood pressure, heart rate, adiposity, and physical fitness, the correlation of sleep duration with CAVI, but not with haPWV, was still significant (partial  $r = -0.253$ ,  $p < 0.05$ ).

**Conclusion:** Our findings suggest that shorter sleep duration influences arterial stiffening even in childhood.

**Key words:** Primary prevention, Adolescent, Vascular stiffness, Cardiovascular risk

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## Introduction

Childhood cardiovascular (CV) risk factors, such as obesity, dyslipidemia, low physical fitness, and high blood pressure (BP), precede arteriosclerotic changes<sup>1-6</sup> and lead to increases in CV event risks and mortality rate in early adulthood<sup>7, 8</sup>. In Japan, the rate of overweight/obesity among children at present is higher than that in the 1980s<sup>9</sup>, and further increases in the percentage of individuals with CV risk factors are

expected. Primary prevention in early life is thus all the more important.

Inadequate sleep is associated with both CV risk factors<sup>10, 11</sup> and CV events in adults<sup>12</sup>. Several studies have reported that children and adolescents with sleep problems, including short sleep duration, had more CV risk factors, such as overweight/obesity and high BP, than children without sleep problems<sup>10, 13-15</sup>. Given that arteriosclerosis progression is aggravated by these CV risk factors, we postulate that arteriosclerotic changes may occur in short sleepers, even in children and/or adolescents.

Brachial-ankle pulse wave velocity (PWV) is an indicator of systemic arterial stiffness and is shown to be related to CV events and mortality<sup>16</sup>. Although relationships between PWV and CV risk factors in

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children have been reported<sup>5, 17, 18</sup>), little is known about the influences of an individual's daily sleep habit on arterial stiffness. In addition, given that the PWV value depends on BP levels during the measurement time<sup>17</sup> and that poor and/or inadequate sleep affects BP increase and body-weight gain<sup>10, 13, 14</sup>), we need to clarify the relationships between BP-independent arterial stiffness indicators and daily sleep habits in children and adolescents.

In this study, we investigated the relationship between sleep duration and arterial stiffness in Japanese children by measuring the heart-ankle PWV (haPWV) and the cardio-ankle vascular index (CAVI)<sup>19-23</sup>), which is a modified parameter of arterial stiffness and is independent of BP levels.

## Methods

### Participants

The study participants were Japanese students who were fourth (15 males; 14 females) and sixth (18 males; 11 females) graders in elementary school and second year students (23 males; 21 females) of junior high school (corresponding to eighth grade in the U.S.). These children and adolescents participated in the Improvement of Fitness in the Hokkaido Children Project, which was designed to identify interference factors for physical fitness, especially the influences of cold and snowfall environments, and to promote healthy growth and development in children and adolescents in Hokkaido, Japan. This research project started in October 2010 and continued until June 2013. Its study protocol was approved by the Research Ethics Committee of Hokkaido University of Education. Written informed consent was obtained from a parent or guardian of all participants.

Arterial stiffness and other physiological variables of 148 students were measured during the period from late April to early May 2012. The following criteria was applied in the present analysis: (1) the resting heart rate during arterial stiffness measurement was < 100 beats/min; (2) the brachial systolic BP during arterial stiffness measurement was < 130 mmHg; (3) there were no orthopedic injuries in the trunk or lower limbs; (4) sleep duration was > 5 h; and (5) there was no missing data, or the participants completed the fitness tests. The eligible data of 102 students (males,  $n=56$ ; females,  $n=46$ ) were analyzed in this study. All physical and physiological measurements were conducted in the morning.

### Sleep Duration

On a typical weekday school day, the students' sleep duration was assessed using a survey that ques-

tioned the students "what time do you usually go to bed on weekdays" and "what time do you usually get out of bed in the morning on weekdays." These questions were used to compute the average hours of weekday sleep.

### Arterial Stiffness Index

Each student's CAVI, PWV, brachial systolic BP (SBP), brachial diastolic BP, and heart rate (HR) were simultaneously measured by an automatic waveform analyzer (VaSera VS-1000; Fukuda Denshi, Tokyo). The methods used to obtain the values of these parameters were as previously described<sup>19, 24</sup>). Briefly, the measurements were taken with the participant lying in a supine position after resting for at least 5 min. Occlusion and monitoring cuffs were placed around both sites of the participant's upper and lower extremities. The extremity BP was measured by oscillometry. Electrocardiography electrodes were attached to the upper arm. A microphone was placed on the sternal angle for phonocardiography.

PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same wave was transmitted to the ankle, plus the time difference between the second heart sound on the phonocardiogram and the notch of the brachial pulse waves<sup>19</sup>). haPWV obtained from CAVI analysis indicates the velocity of the pulse wave from the heart to the ankle artery and thus differs from the brachial-ankle PWV. CAVI was obtained from the measurement of the participant's BPs and PWV<sup>19</sup>). The means of the right-side and left-side values of haPWV, CAVI, and SBP were used.

### Anthropometric and Fitness Measures

Each participant's height and weight were measured using a standard stadiometer and a digital scale, respectively. The students reported their birth date, and we calculated their ages (in months) at the measurement day. The body mass index (BMI) was calculated from these measures and is expressed as a standard score (z-score) using a spreadsheet program of BMI norms for the students' age (in months) and sex in accordance with the guidelines of the Japanese Society for Pediatric Endocrinology (JSPE program)<sup>25</sup>). The participants' waist circumference was measured at the narrowest torso using a measuring tape. Physical fitness was assessed by a 20-m shuttle run test (20 mSRT) in which the participants ran between two lines 20 m apart until they twice failed to reach the front line within the required time. The initial running speed was 8.5 km/h. The pace of the test was

**Table 1.** Characteristics of subjects

Variable	Male, N=56	Female, N=46
Age, yr	11.9 ± 1.7	11.9 ± 1.8
Height, cm	150.7 ± 12.8	148.9 ± 9.6
Weight, kg	45.8 ± 11.7	43.4 ± 9.7
BMI, kg/m <sup>2</sup>	19.9 ± 3.2	19.4 ± 3.0
BMI z-score	0.42 ± 1.05	0.22 ± 1.03
Waist, cm	68.9 ± 8.9	65.3 ± 6.9
HR, bpm	75.1 ± 10.7	77.9 ± 9.2
SBP, mmHg	114.9 ± 8.7	113.8 ± 6.0
CAVI	4.82 ± 0.90	4.71 ± 0.82
haPWV, m/s	5.51 ± 0.62	5.47 ± 0.64
20mSRT, stage	6.6 ± 2.7	4.8 ± 1.6
Sleep duration, h	8.1 ± 1.1	8.1 ± 1.1

BMI denotes body mass index; SBP, brachial systolic pressure; DBP, brachial diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; CAVI, cardio-ankle vascular index; PWV, pulse wave velocity; 20mSRT, 20-m shuttle run test.

increased by 0.5 km/h every minute, and an audio signal determined whether each lap was completed on time. Total laps were classified by 10 stages, as described by the Ministry of Education, Culture, Sports, Science and Technology of Japan<sup>26</sup>, and we used the stage reached by the participants as a parameter of systemic physical fitness.

### Statistical Analyses

We report the data as means ± standard deviations unless otherwise noted. The normality of data distributions was tested using the Kolmogorov–Smirnov test. The correlations between two variables were assessed using Pearson’s correlation analyses. We performed partial correlation analyses after controlling for confounding factors to examine the relationships between arterial stiffness indices and sleep duration. Model 1 was adjusted for age, BMI z-score, HR, and SBP for each gender. In addition, in the total of male and female students (overall), sex (male=1, female=2) was included into the model as control variables. Model 2 was adjusted for the control variables used for model 1 and 20 mSRT. We observed multicollinearity among study variables and therefore performed partial correlation analyses. All statistical analyses were calculated with PASW statistics ver. 18.0 software (SPSS, Chicago, IL), and *P*-values <0.05 were considered significant.

### Results

The students’ characteristics are summarized in **Table 1**. The mean CAVI values were 4.8 ± 0.9 and 4.7 ± 0.8 (arbitrary unit) for the 56 males and 46

females, respectively. haPWV was 5.5 ± 0.6 and 5.5 ± 0.6 m/s in the groups of males and females, respectively. Both males and females slept an average of 8.1 ± 1.1 h. The number (%) of students who slept less than 7.5 h per night (<7.5 sleep duration) was two (6.9%) among the fourth graders, two (6.9%) among the sixth graders, and 25 (56.8%) among the junior high schoolers.

**Table 2** provides the Pearson’s correlation coefficients between arterial stiffness measures and other study variables. In the total sample of males and females, CAVI and haPWV were positively correlated with age and 20 mSRT and negatively correlated with the BMI z-score, HR, and sleep duration. SBP was significantly correlated with haPWV but not with CAVI. **Table 3** shows the correlation coefficients between sleep duration and other variables and between CAVI and other variables for students of each school grade. The correlations between age and sleep duration and between age and CAVI were not significant in any grade. The relationships between CAVI and sleep duration and between the haPWV values and sleep duration are illustrated in **Fig. 1**.

To adjust for confounding factors, we performed a partial correlation analysis using CAVI, haPWV, and sleep duration (**Table 4**). After controlling for age, sex, BMI z-score, SBP, and HR, the partial correlation coefficient of CAVI and sleep duration and of haPWV and sleep duration in overall students was not significant (CAVI,  $r = -0.185$ ; PWV,  $r = -0.101$ ; both  $p > 0.05$ ). As shown in **Table 4**, model 2 analyses after controlling for control variables of model 1 and 20 mSRT demonstrated significant correlations between CAVI and sleep duration in male and overall students.

**Table 2.** Pearson's correlation coefficients between arterial stiffness indices and study variables

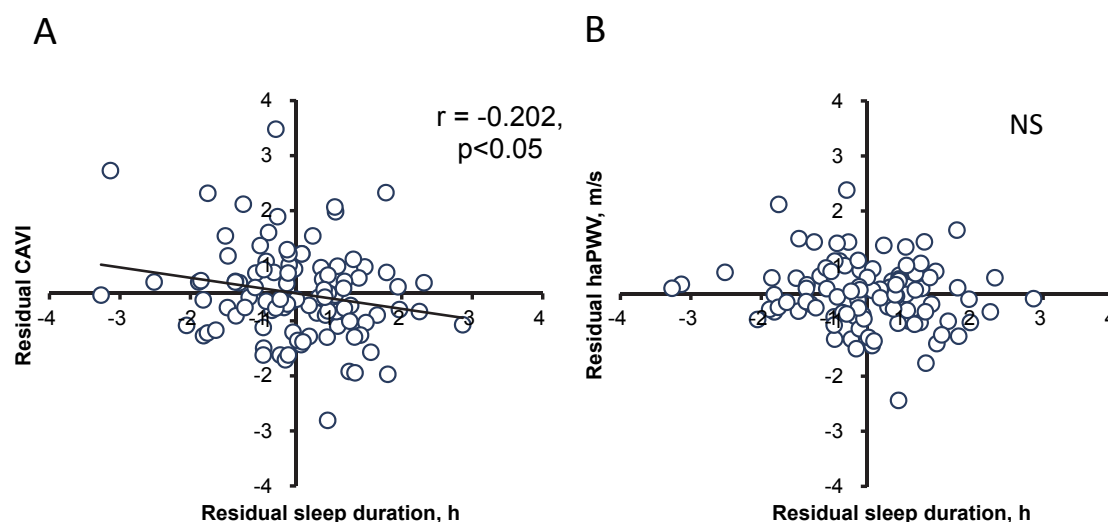
Variable	CAVI			haPWV		
	Male	Female	Overall	Male	Female	Overall
Age, yr	0.391**	0.085	0.252*	0.385**	0.325*	0.355**
BMI z-score	-0.529**	-0.342*	-0.441**	-0.429**	-0.278	-0.356**
Waist, cm	-0.077	-0.277	-0.132	0.066	-0.037	0.032
SBP, mmHg	-0.114	0.085	-0.041	0.239	0.439**	0.308**
HR, bpm	-0.297*	-0.221	-0.273**	-0.190	-0.201	-0.197*
Sleep duration, h	-0.395*	-0.199	-0.309**	-0.406**	-0.220	-0.319**
20 mSRT, stage	0.226	0.301*	0.249*	0.225	0.338*	0.249*

\*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; 20 mSRT, 20-m shuttle run test; CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity.

**Table 3.** Pearson's correlation coefficients between sleep duration or CAVI and study variables in each grade

Variable	Sleep duration			CAVI		
	4th graders	6th graders	Second year students of junior high school	4th graders	6th graders	Second year students of junior high school
Age	-0.261	0.169	0.134	-0.007	-0.104	0.050
BMI z-score	0.207	-0.204	-0.091	-0.296	-0.427*	-0.409**
20 mSRT	-0.060	0.132	-0.129	0.021	0.089	0.206
SBP	-0.041	-0.060	-0.259	-0.333	-0.344	0.063
HR	-0.221	0.215	-0.019	0.056	-0.337	-0.354*
CAVI	-0.378*	-0.172	-0.155	-	-	-
haPWV	-0.145	-0.071	-0.272	0.699**	0.832**	0.922**

\*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; 20 mSRT, 20-m shuttle run test; CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity.

**Fig. 1.** Correlations between the arterial stiffness parameters and sleep duration in the 102 Japanese children and adolescents.

A: The correlation between the residual CAVI and residual sleep duration after adjusting for age and sex. B: The correlation between residual PWV and residual sleep duration after adjusting for age and sex. NS, no significant.

**Table 4.** Partial correlation analyses

		Sleep duration					
		Males		Females		Overall	
		partial <i>r</i>	<i>p</i> value	partial <i>r</i>	<i>p</i> value	partial <i>r</i>	<i>p</i> value
Model 1	CAVI	-0.226	0.106	0.123	0.439	-0.185	0.061
	haPWV	-0.232	0.098	0.085	0.594	-0.101	0.310
Model 2	CAVI	<b>-0.414</b>	<b>0.003</b>	-0.135	0.401	<b>-0.250</b>	<b>0.014</b>
	haPWV	<b>-0.378</b>	<b>0.006</b>	0.081	0.615	-0.137	0.180

CAVI, cardio-ankle vascular index; PWV, pulse wave velocity; model 1 was adjusted by BMI z-score, HR, age, and SBP; model 2 was adjusted by model 1 and 20mSRT. Italic letters are statistically significant.

In model 2, haPWV was negatively associated with sleep duration in male students. After adjusting for age, sex, BMI z-score, HR, and SBP, the 20 mSRT was not significantly correlated with CAVI and haPWV (data not shown).

## Discussion

The main finding from the present study is that there was a significant inverse association between sleep duration and arterial stiffness in Japanese children and early adolescents, even after adjusting for age, HR, BP, adiposity, and physical fitness. Our results suggest that inadequate sleep duration could enhance arterial stiffening in healthy children and may be a behavioral target for primary prevention of early vascular aging.

PWV measurement is a non-invasive and useful tool for assessing arterial stiffness, based on the increasing evidence of PWV as a significant predictor of CV events<sup>16)</sup> and CV mortality<sup>27)</sup>. However, PWV is affected by BP levels at the time of measurement, and thus, when PWV of sensitive persons (e.g., some children and individuals with white coat hypertension) is evaluated, there is a possibility of obtaining an overestimated PWV value. CAVI showed no correlation with BP in previous studies<sup>19, 20)</sup> or in the present study, suggesting that CAVI measurement is a suitable method for assessing the arterial stiffness of such individuals. Although Philip *et al.* (2016)<sup>20)</sup> examined CAVI values in children, recent papers have shown relationships between PWV and intima-media thickness or flow-mediated dilation even in children<sup>28-30)</sup>. Based on the results of these previous studies, it appears that a non-invasive evaluation of arterial stiffness in childhood would be a surrogate marker for vascular health.

On the other hand, poor sleep habits, including

short sleep duration and low sleep quality, are associated with high BP and increased CV risk factors in children and adolescents<sup>10, 13, 15, 31-34)</sup>. To our knowledge, the present study is the first report of an inverse association between sleep duration and arterial stiffness evaluated using CAVI after controlling for potential confounding factors in 9- to 13-year-old children. Our present findings support the previous studies' results regarding abnormalities in great artery elasticity early in life and also imply that unhealthy sleep habits in childhood can accelerate the process of arteriosclerosis.

We found no correlation between CAVI and physical fitness after adjusting for confounders. Another study also showed no significant association between physical fitness and PWV after adjusting for age, sex, SBP, HR, mean arterial pressure, and adiposity<sup>5)</sup>. With the use of the second derivative of the finger photoplethysmogram, it was demonstrated that low physical fitness was related to higher arterial stiffness parameters in children<sup>35)</sup>. A recent study has revealed that the correlations between arterial stiffness parameters assessed by PWV and the second derivative of the finger photoplethysmogram were only mild<sup>36)</sup>, and the parameters reflected different physiological properties at central and peripheral sites in the arterial system<sup>37, 38)</sup>. In addition, systemic physical fitness assessed using the 20 mSRT is influenced by adiposity because greater body fat would be a load on skeletal muscles of the lower limbs during the repeated stopping and running in this test. Although it is possible that there is an association between arterial stiffness and physical fitness in children, further studies are needed to clarify the influences of physical fitness on arterial stiffness using more precise evaluation methods and/or a longitudinal study design.

The underlying mechanisms whereby short sleep duration may lead to arterial stiffening cannot be



determined using our cross-sectional data. However, one possible explanation is that short sleep duration could induce a sustained activation of the neuroendocrine system. Earlier studies showed that low sleep quality was related to an unhealthy pattern of sympathetic and parasympathetic nervous system activity in 5- to 11-year-old children<sup>32)</sup> and that children with short sleep duration had higher salivary cortisol levels as a biomarker of sympathoadrenal system activity than children with average or long sleep duration<sup>39)</sup>. It was also shown that CAVI was mediated by the  $\alpha$  1-adrenergic receptor pathway<sup>40, 41)</sup>.

Given the results of these previous studies, it appears that short sleep duration could be related to higher sympathetic nervous activity, which may concomitantly mediate alterations in arterial function in children with habitual short sleep durations. On the other hand, CAVI increases with age, especially after middle age, which would be attributed to structural changes in the vascular wall as an inevitable consequence of aging<sup>40)</sup>. Considering that our present participants were 9- to 13-year-old children, there is only a slight possibility of the structural alteration in the vascular wall in children with short sleep duration.

There are several limitations to this study. It had a cross-sectional study design, and thus, our results do not provide a cause-effect relationship between predictors and outcomes. In addition, sleep duration was assessed only by a self-reported questionnaire and not by objective sleep monitors. In previous studies, sleep quality and quantity were assessed using actigraphy monitors worn on the wrist<sup>33, 42, 43)</sup>. Actigraphy methods for sleep assessment showed a tentative low to moderate correlation with sleep polysomnography<sup>44)</sup>, which is a gold standard for evaluating sleep quantity and quality. Given that it is important for students to have self-awareness regarding their sleep habits to improve their daily lifestyle, our results based on self-reported sleep duration could have clinical and/or educational implications. Our results do not show the true effects of childhood obesity and low fitness on arterial stiffness in children and early adolescents because the study's design was cross-sectional. Further research should be performed to determine the relationship between sleep status and arterial stiffness in children and early adolescents in a longitudinal study design using larger sample sizes.

In conclusion, we found that sleep duration was inversely associated with arterial stiffness after adjusting for confounders. Our data suggest that inadequate sleep duration could enhance the process of arterial stiffening in healthy children who are  $\geq 10$  years old. Our findings also suggest that sleep assessments, even by a self-reported questionnaire, may be a useful

screening tool for identifying children with early vascular aging and future CV risks.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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